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Meta-analysis to Identify and Evaluate Factors Associated with Regulatory Approval of Orphan Drugs (OD) to Develop an Algorithm for Predicting Regulatory Approval (Success) and to Develop a Standardized Tool to Improve Orphan Drug Portfolio Decision-making

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Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Health Sciences
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DEDICATION

This dissertation research is dedicated to all the people in the World who are currently suffering any physical and mental illness.

"He who has health has hope; and he who has hope, has everything"

Thomas Carlyle.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Meta-analysis to identify and evaluate factors associated with regulatory approval of Orphan Drugs (OD) to develop an algorithm for predicting regulatory approval (success) and to develop a standardized tool to improve orphan drug portfolio decision-making.

Background and Purpose of the Study: Developed an algorithm (AODI) for predicting probability of regulatory success (PRS) for new orphan drugs after phase II testing has been conducted with the objective of providing a tool to improve drug portfolio decision-making. *Methods:* Examined 132 studies from recent publications (2005 onwards). Data on safety, efficacy, operational, market, and company characteristics were obtained from public sources. Meta-analysis and meta-regressions were used to provide an unbiased approach to assess overall predictability and to identify the most important individual predictors. *Results:* Found that a simple three-factor model (disease prevalence, clinical trial duration and clinical trial participation) had high specificity for predicting regulatory approval (success). *Conclusion:* smaller clinical trial participation, shorter clinical trials duration and lower rare disease prevalence were found to be highly associated with the Probability of Regulatory Success (PRS) of orphan drugs.

Keywords: meta-analysis, meta-regression, orphan drugs, probability, regulatory success, regulatory approval, predictors, clinical trials, participation, duration, prevalence, research and development, regulatory assessment, policy, legislations

CHAPTER I

INTRODUCTION

Problem Background

In general, an orphan or rare disease is any pathology or condition that affects a small percentage of the population (Wastfelt et al., 2006). Most of the known rare diseases are genetic, and therefore, are present throughout the entire life of an affected individual. Many appear early in life and about 30% of children with rare diseases die before the age of 5 years (Wastfelt et al., 2006). There is no single cut-off number that has been universally agreed upon for which a disease is classified as rare. For instance, in the United States (US) the Orphan Drug Act (ODA) defines a rare disease as any disease or condition that affects less than 200 000 persons in the United States (US), while in Japan for example a rare disease is defined as one that affects fewer than 50 000 patients. The European Commission on Public Health, on the other hand, defines rare diseases as those which are life-threatening or chronically debilitating and are of such low prevalence (1 in 2000 people) that special combined efforts are needed to address them. Additionally, a disease considered rare in one part of the world, or in a particular group of people, could be a common disease in another. The incidence of an individual rare disease may be small however, cumulatively, there are 7,000 known rare diseases that affect about 25 million Americans, or nearly 10% of the US population (Hemphill, 2009). Since the definition of rare diseases refer to treatment availability, resource scarcity and disease severity, rare diseases are also commonly referred to as orphan diseases, especially after the orphan drug movement that began in the United States in 1983. Consequently, the US Orphan Drug Act

of 1983 includes both rare diseases and any non-rare diseases for which there is no reasonable expectation that the cost of developing and making available a drug for such a disease in the United States (US) can potentially be recovered from sales of that drug in the United States (US). About 7,000 rare diseases have been identified, and a list is maintained by the Office of Rare Diseases (ORD) at the National Institutes of Health (NIH). While some of the listed rare diseases are well-known (e.g. cystic fibrosis, Huntington's disease), a majority are less familiar with several disease having patient populations of fewer than a hundred, these are called ultra-rare. Approximately 250 new rare diseases and conditions are identified and described each year (Aarti, 2009). The US Orphan Drug Act (ODA) went into effect to encourage the research and development of orphan drugs to treat rare diseases. The Orphan Drug Act (ODA) evolved in response to the small number of orphan drugs (OD) that were approved in the US in the years prior to the approval of the Orphan Drug Act (ODA) (Mullard, 2012). The development process for orphan drugs is technically the same as that for any other drug developed to treat any disease: very expensive and time consuming (Schieppati et al., 2008). It's key to determine which factors actually contribute the successful approval of orphan drugs (OD).

Problem Statement

Pharmaceutical industry drug development portfolios vary in scope and range. For each company, however the objective of improving the regulatory success rate of their applications is paramount. Orphan drugs are called orphan not only because it impacts a small number of patients in the overall population, but also their name is appropriate as a small number of companies feel less confident in investing in their development (DiMasi et al., 2003). Understanding the key factors associated with regulatory approval (regulatory success) of orphan drugs (OD) may assist pharmaceutical companies in developing more efficient regulatory strategies and predict with a high level of certainty the likelihood of orphan drugs reaching the market.

Purpose of the Study

The purpose of this study is to identify and evaluate factors associated with regulatory approval of Orphan Drug (OD) in addition to systematizing those components in a mathematical formula to determine with a certain degree, the probability of regulatory success and implement it when assessing the risk in developing, registering and marketing orphan drugs.

Research Questions

Is it possible to identify, compare and evaluate the relevant factors associated with orphan drug approval and systematize a workable model that is applicable to the pharmaceutical industry to assess the risk of developing and registering orphan drugs?

I. Do shorter clinical trials increase the probability of regulatory approval (success) of orphan drugs (OD)?
II. Do smaller clinical trials increase the probability of regulatory approval (success) of orphan drugs (OD)?
III. Does prevalence of the disease increase the probability of regulatory approval (success) of orphan drugs?

Research Hypotheses

RQ1: Is it possible to identify the relevant factors associated with the probability of regulatory success of orphan drugs (OD)?

H1a: Yes, it is possible

H1b: No, it is not possible

RQ2: Is it possible to compare the relevant factors associated with the probability of regulatory success of orphan drugs (OD)?

H2a: Yes, it is possible

H2b: No, it is not possible

RQ3: Is it possible to evaluate the relevant factors associated with the probability of regulatory success of orphan drugs (OD)?

H3a: Yes, it is possible

H3b: No, it is not possible

RQ4: Is it possible to develop an algorithm for predicting the probability of regulatory success of orphan drugs (OD)?

H4a: Yes, it is possible

H4b: No, it is not possible

RQ4.1: Do shorter clinical trials increase the probability of regulatory success of orphan drugs (OD)?

H4.1a: Shorter clinical trials increase the PRS for OD.

H4.1b: shorter clinical trials decrease the PRS for OD.

RQ4.2: Do smaller clinical trials increase the probability of regulatory success of orphan drugs (OD)?

H4.2a: Smaller clinical trials increase the PRS for OD.

H4.2b: Smaller clinical trials decrease the PRS for OD.

RQ4.3: Does a lower number of patients worldwide affected by a rare disease (prevalence) increase the probability of regulatory success of orphan drugs (OD)?

H4.3a: Lower prevalence increase PRS for OD.

H4.3b: Lower prevalence decrease PRS for OD.

Significance of the Study

Rare diseases have become a public heath priority in the United States (Cheung et al., 2004). Healthcare professionals lack of proper training and awareness to identify, diagnose and treat rare diseases (Sharma et al., 2010). There is also delay to a correct diagnosis, lack of quality information and scientific knowledge, inequities and difficulties in access to treatment and care making rare diseases a matter of public health in the US (Schieppati et al., 2008). Scholars have reported in early 2000 that the pharmaceutical industry is not incentivized to invest in research and development for orphan drugs, causing limited industry involvement and leaving millions of patients in the US and around the world with no treatments for their diseases (Grabowski, 2003). According to the Orphan Drug Act (ODA), an orphan drug (OD) is a pharmaceutical agent that has been developed specifically to treat a rare medical condition (21 CRF § 316). Orphan drugs can affect both the quality and length patients' lives (Sharma et al., 2010). Effective orphan drugs can extend and improve patients' lives. Prior to the Orphan Drug Act (ODA), the number of annual deaths from rare diseases were growing at a slightly higher rate than that from other diseases (2.0 percent and 1.3 percent, respectively) (Lichtenberg, 2001). In the 10 years following the Orphan Drug Act (ODA), the number of annual deaths from rare diseases declined at a rate of 3.1 percent, while the annual number of deaths from other diseases continued to grow at a rate of 1.2 percent (Lichtenberg, 2001).

Orphan drugs have also the potential to generate large improvements in patients' lives because rare diseases typically have few, if any, effective treatments available (Cheung et al., 2004). According to the National Office of Rare Diseases Research

(NORD) only 289 of the 7,000 identified rare diseases have one treatment option. That means, only four percent of recognized rare diseases have an available treatment (Schieppati et al., 2008).

A recent survey, conducted by the biotechnology company Shire, found that rare diseases take a significant emotional toll on patients. Patients reported suffering from isolation from friends and/or family (65%), depression (75%), anxiety and stress (86%) (The Shire Report, 2013). Patients often have to travel long distances to receive treatment. On average, it takes 7.6 years for rare-disease patient in the United States (US) to receive an accurate diagnosis, and patients may see up to four primary care doctors and four specialists before receiving an accurate diagnosis (The Shire Report, 2013). Orphan drugs (OD) can reduce the emotional toll patients and caregivers face by relieving symptoms and decreasing the burden of inferior treatment options. These improvements may help reduce feelings of depression, isolation, anxiety, and stress patients and caregivers often experience (Sharma et al., 2010).

Orphan drugs (OD) can also deliver a broad set of economic benefits beyond the increased well-being of patients and caregivers (Sharma et al., 2010). Orphan drugs may increase patients' ability to work, reduce net medical expenditures, and lower the total government spending (Schieppati et al., 2008). Those suffering from chronic disease tend to be less productive at work, either through increased absenteeism or limitations imposed by their disease (Schieppati et al., 2008). Patients with rare diseases often find it difficult to remain at their jobs due to the symptoms of their disease (The Shire Report, 2013). As

a result, treatments that help patients to return to work, provide childcare, or participate in other activities may generate benefits beyond improved health.

Operational Definitions

Algorithm: A procedure or formula for solving a problem based on conducting specific steps or actions

Approval: Authorization by the Food and Drug Administration (FDA) for the marketing of a drug (under a New Drug Application), medical device (under a Premarket Approval Application), or biological product (under a Biologics Licensing Agreement)

Benefit: A positive or valued outcome of an action or event.

Biologics Licensing Application (LA): Form used by bio-pharmaceutical companies to request FDA approval to market a new biologic product in the United States (US) based on information about its safety, effectiveness and other requirements.

Clinical trial: A medical study involving human participants that follows a defined protocol to answer specified questions, for example, about the safety and efficacy of a medical product.

a. Phase I trials initiate the study of candidate drugs in humans. Such trials typically assess the safety and tolerability of a drug, routes of administration and safe dose ranges, and the way the body processes the drug (e.g., how it is absorbed, distributed, metabolized, and excreted). They usually involve less

than 100 individuals, often-healthy volunteers.

b. Phase II trials continue the assessment of a drug's safety and dosing but also begin to test efficacy in people with the target disease. These studies may include a range of controls on potential bias, including use of a control group that receives standard treatment or a placebo, the random assignment of research participants to the experimental and control groups, and the concealment (blinding) from participants and researchers of a participant's assignment.

c. Phase III trials are expanded investigations of safety and efficacy that are intended to allow a fuller assessment of a drug's benefits to provide information sufficient to prepare labeling or instructions for the use of the drug. These studies may involve thousands of research participants and multiple sites.

d. Phase IV studies occur after a product is approved for marketing and are highly variable in their design. They are sometimes required by FDA but may be voluntarily undertaken by pharmaceutical companies. They are typically intended to provide further information about outcomes in clinical practice, e.g., in broader populations or over longer periods than studied in the trials used to support FDA approval.

Data exclusivity: A period of time during which pharmaceutical companies of innovative drugs have the exclusive use of the safety and effectiveness data they submitted to obtain FDA approval.

Drugs: As defined in 21 USC 321(g)(1): "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."

Effectiveness: The achievement of desired results in actual clinical practice.

Efficacy: The achievement of desired results in controlled clinical studies.

Market exclusivity: As provided for by the Orphan Drug Act, a 7-year period during which a pharmaceutical company has exclusive rights to market the drug.

Meta-Analysis: An objective and quantitative methodology for synthesizing previous studies and research on a particular topic into an overall finding.

New Drug Application (NDA): Form used by pharmaceutical companies to request FDA

approval to market a new pharmaceutical drug in the United States (US) based on information about its safety and effectiveness and other requirements

Post-market activities: Evaluations, activities, and decisions that occur after regulatory approval, clearance, or registration of a medical product for marketing.

Preclinical studies: Investigations of toxicity, pharmacological activity, and other characteristics of a promising drug candidate that occurs prior to research with human participants.

Prevalence: The number of diagnosed cases of a particular condition or disease existing in a specified population at a given time. It is distinct from incidence, which is the number of new cases of the disease arising in the population over a given time period.

Portfolio decision-making: Act or process of deciding after careful evaluation of factors on whether or not a drug should move forward in the pipeline.

Probability of Regulatory Success (PRS): Likelihood that a government body or health authority will grant drug approval

Rare disease: In the Orphan Drug Act, a disease or condition that affects fewer than 200,000 people in the United States (US).

Regulatory approval: A process conducted by a government body or health authority in a country resulting in pharmaceutical product registration and a valid license for commercialization

Regulatory science: The development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality.

Risk: A potential harm or the potential for an action or event to cause harm.

Safety: There is reasonable assurance that a drug is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Standardized tool: A tool designed in a way that the results and interpretation is consistent.

Orphan drugs: Any “pharmaceutical agent” use to treat or diagnose a rare disease.

CHAPTER II

LITERATURE REVIEW

Rare Disease Definition and Prevalence

A rare disease can also be referred as orphan disease (Wästfelt, Fadeel & Henter, 2006). It is any type of disease that affects a small percentage of the population (21 CFR § 316). Rare disease can be defined by the number of people living with the disease, etiology, mobility, survival rate or incidence rate however the orphan drug acts define it as "*a life-threatening or chronically debilitating disease that affects less than 200,000 people*" (21 CFR § 316). Although rare disease affects only a small percentage of the population, the combined number of patients is large. This is also known as the paradox of rare diseases (Wästfelt et al, 2006). The incidence of an individual rare disease is very small; however collectively there are over 7,000 known rare diseases that affect approximately 30 million Americans: nearly 10% of the US population (Sharma, Jacob, Tandon & Kumar, 2010)

Figure 1. Paradox of Rare Diseases (Sharma, Jacob, Tandon & Kumar, 2010).

Rare Disease Characteristics

- Chronic progressive, degenerative and life threating (Wästfelt et al, 2006).
- Patient's quality of life is compromised by lack or loss of autonomy (Wästfelt et al, 2006).
- High level of pain and suffering for the patient and family members (Sharma et al., 2010).
- No existing effective cure or treatment (Sharma et al., 2010).
- 75% of rare diseases affect children and 30% of patients die before age of 5 (Wästfelt et al, 2006).
- 80% have been identified of genetics origins (Wästfelt et al, 2006)

Orphan Drug Definition and Classification

An orphan drug is *"any pharmaceutical agent that has been developed specifically to treat a rare medical condition"* (21 CFR § 316). Orphan drugs can be classified into two groups according to their patent status. According to Hutt and Merrill, orphan drugs can be classified in two types:

Type I drugs ineligible for any patent rights as these drugs are actually available in the public domain and are not consider novel (a patent requirement). These drugs are already known to treat certain diseases or conditions but the prohibitive cost of developing and receiving regulatory approval for the drugs prevents these treatments from being produced or put on the market by the private sector (Hutt & Merrill, 1991).

Type II drugs that would be patentable, but they do not exist because there has been an absence of research into such treatments (Hutt & Merrill, 1991). Simply, the number of

people who would require the drug is either so small as to be insignificant or such a group does not constitute a major market segment for pharmaceutical companies. It is important to note however that the problem of orphan drugs type II must be understood separately from the problem of insufficient access to medicine and treatments that already exist for certain diseases. Orphan drugs type II refers to the problem of potential treatments that have not yet been developed and do not exist.

United States Patent and Trademarks Office (US PTO)

The United States Patent and Trademark Office (US PTO) is first federal organization involved in the orphan drug registration and approval process. The US PTO is an agency in the US Department of Commerce that issues patents to investors for their inventions, and trademark registration for product and intellectual property identification (21 CFR §393). The USPTO mission is to promote *"industrial and technological progress in the United states and strengthen the national economy"* in order to fulfill objectives outlined in the United States constitution (21 CFR §393).

It is important to define the term *"Patent"*. A patent is a set of exclusive rights granted by a sovereign state, in this case the United States Patent and Trademark Office (US PTO), to an inventor for a limited period of time in exchange for detailed public disclosure of an invention (World Intellectual Property Organization definitions, 2008). *"An invention is a solution to a specific technological problem and is a product"* (WIPO definitions, 2008). Patents are a form of intellectual property (WIPO definitions, 2008). The procedure for granting patents, requirements placed on the patentee, and the extent of the exclusive rights is overseen by the United States Patent and Trademark Office

(USPTO). Typically, a granted patent application must include one or more claims that define the invention. A patent may include many claims, each of which defines a specific property right. These claims must meet relevant patentability requirements: novelty, usefulness, and non-obviousness (WIPO definitions, 2008). The exclusive right granted to a patentee in the United States is the right to prevent others from commercially making, using, selling, importing, or distributing a patented invention without permission (WIPO definitions, 2008). Under the World Trade Organization (WTO) agreement on trade-related aspects of Intellectual Property Rights (IPR), patents should be available in WTO member states for any invention, in all fields of technology, and the term of protection available should be a minimum of twenty years (WIPO, 2008).

To obtain a patent, an application must be filed at the USPTO with the jurisdiction to grant a patent in the geographic area over which coverage is required (WIPO, 2008). Once the patent specification complies with the laws of the office concerned, a patent may be granted for the invention described and claimed by the specification (WIPO, 2008). In most countries, both natural persons and corporate entities may apply for a patent. In the United States, however, only the inventor may apply for a patent although it may be assigned to a corporate entity subsequently and inventors may be required to assign inventions to their employers under an employment contract (Lemley & Shapiro, 2005). The inventors become the proprietors of the patent when and if it is granted. If a patent is granted to more than one proprietor, the laws of the country in question and any agreement between the proprietors may affect the extent to which each proprietor can exploit the patent (WIPO, 2008).

Patents provide incentives for economically efficient research and development (R&D) (Lemley & Shapiro, 2005). A study conducted annually by the Patent Intelligence for Policy Support (PIPS) shows that the 2,000 largest global companies invested more than 430 billion dollars in 2008 in their research and development departments (Lemley & Shapiro, 2005). Supporters of patents argue that without patent protection, research and development spending would be significantly less or eliminated altogether, limiting the possibility of technological advances and breakthroughs (Lemley & Shapiro, 2005). Corporations would be much more conservative about the research and development investments they made, as third parties would be free to exploit any developments (Lemley & Shapiro, 2005).

United States Food and Drug Administration (US FDA)

The second federal organization involved in regulatory approval of orphan drugs (OD) is the Food and Drug Administration (FDA). The FDA was created in 1820 and it is the oldest federal agency in the United States. The FDA is responsible for "*protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over the counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusion, medical devices, electromagnetic radiation emitting devices (ERED) and veterinary products*" (21 CFR § 393). The agency has over 20 offices but the Center for Drug Evaluation and Research (CDER) is considered the main department where drugs approval takes place (21 CFR § 393). The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in the United States are safe and effective (21 CFR § 393). CDER does

not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness (21 CFR § 393). CDER is the largest center at the FDA. It has responsibility for both prescription and nonprescription (Over-The-Counter also known as OTC) drugs. Pharmaceutical companies submit a New Drug Application (NDA) to introduce a new drug product into the U.S. Market (21 CFR § 393). It is the responsibility of the pharmaceutical company seeking to market a drug to test it and submit evidence that it is safe and effective (21 CFR § 393). A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the application containing the data and proposed labeling (21 CFR § 393).

The office of Regulatory Affairs is also considered an important department within the FDA conducting the vast majority of the FDA's work in the field (21 FDAC § 393), however is the Office of Special Medical Program the one that oversees the implementation of the orphan products provisions of the Federal Food, Drug and Cosmetic Act (21 FDAC § 393). The FDA Office of Orphan Products Development (OOPD) is dedicated to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions (21 FDAC § 393). In order to fulfilling that task, OOPD evaluates scientific and clinical data submissions from pharmaceutical companies to identify and designate products as promising for rare diseases and to further advance scientific development of such promising medical products (21 FDAC § 393).In addition, the OOPD works on rare disease issues along with medical and research communities, professional organizations,

academia, governmental agencies, industry, and rare disease patient groups (21 FDAC § 393).

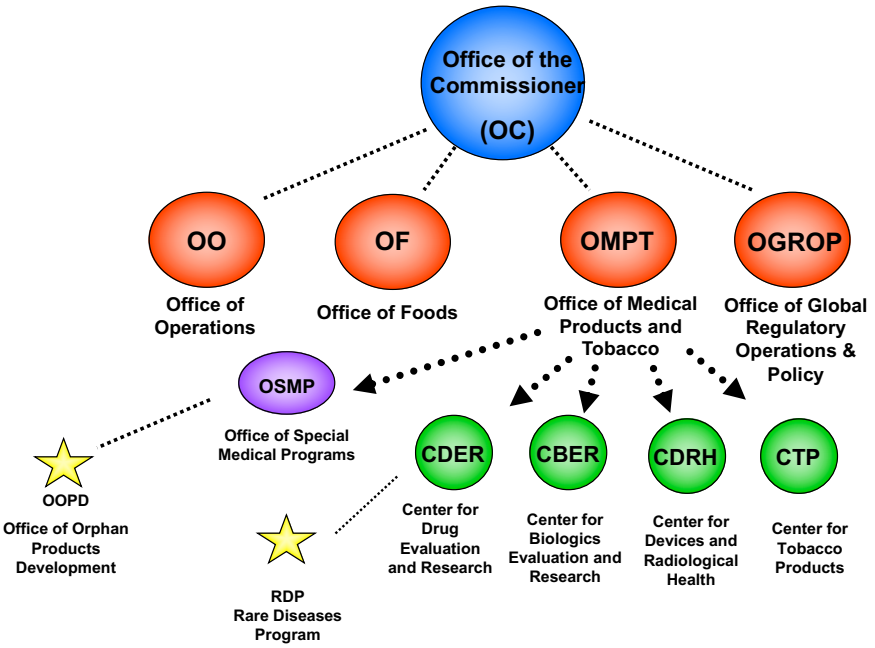

Figure 2. FDA Organizational Chart (FDA Database, 2015 available at https://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm403687.htm).

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) have regulatory responsibility, including pre-market review and continuing oversight over products. They are responsible to ensure that products are safe and effective prior granting regulatory approval for marketing.

The Office of Orphan Products Development (OOPD) is task to advance the evaluation and development of orphan products (drugs, biologics or medical devices) that demonstrate promise for the diagnosis or treatment of rare diseases.

The OOPD oversees two programs: a) the Orphan Drug Designation program which provides orphan status to drugs and biologics which are intended for the safe and effective treatment, diagnosis or prevention of rare diseases that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug (21 FDAC § 393) and b) the Humanitarian Use Device (HUD) program, who designates a device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year as per the Orphan Drug Act (ODA) (21 CFR § 316).

The United States Orphan Drug Act (ODA)

The Orphan Drug Act (ODA) is a law passed in the United States to facilitate development of orphan drugs which affect small numbers of individuals residing in the United States. (Orphan Drug Act, 1983). The Orphan Drug Act (ODA) was passed in large part due to the lobbying efforts of patient's groups and the national Organization for Rare Disorders (NORDs) and many other patients groups frustrated at the lack of drugs approved to treat rare diseases (Cheung, Cohen & Illingworth, 2004). In 1983 the FDA was empowered by the United States Congress to enforce the Orphan Drug Act. During the decade of 1970s, only 10 drugs were marketed for rare diseases indications and by 1982,

36 drugs had ever been approved for the treatment of rare diseases (House of representative Subcommittee Report, 1982). It was found that pharmaceutical companies at times possessed drug with potential benefits for patients suffering from rare diseases however these drugs were not patentable, or their clinical trials were too costly (Cheung, Cohen & Illingworth, 2004). This evidence motivated lobbying efforts of patient groups to pass orphan drug legislation. The ODA includes a number of incentives so pharmaceutical companies can develop orphan drugs and provide access to more than 30 million people in the US suffering from rare diseases (Cheung et al., 2004).

ODA was signed into law on January 4th, 1983; making the United States the first country in the world to provide incentives for developing treatments for rare diseases (H.R.5238). "*The cost of discovering and developing a new drug is often staggering. By definition, an orphan drug is one that treats a disease that affects 200,000 or fewer individuals and, from an economic perspective, groups that small do not now justify the kind of research expenditures those companies must make. The bill that I am signing today helps to cure that problem and consequently, we hope, some of the diseases as well. The bill provides incentives for the private sector to develop drugs to treat these rare diseases*" (Reagan, 1983). Since then, Australia, Japan, and the European Union have instituted provisions similar to the ODA to support the development of orphan drugs in their respective countries (Cheung et al., 2004).

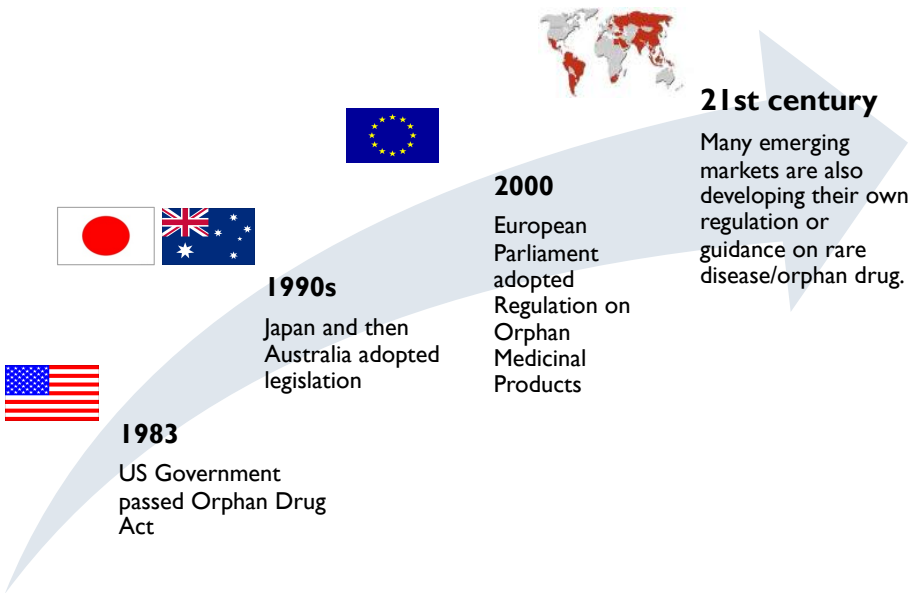

Figure 3. Orphan Drug Legislation Status Worldwide (Cheung et al., 2004).

Japan has extended his orphan drug definition to include medical devices, so all medical device used to treat or diagnosed a rare disease has also protection under the law. All four legislation provides market exclusivity of 7 to 10 years with the exemption of Australia. Market exclusivity is a big incentive for any pharmaceutical companies around the world. It is important to highlight the differences between major legislations in table below specifically in the areas of tax credit, research and development grants and regulatory fee exemption as each market have distinct law and regulation of drug review and approval. Finally, it takes approximately 6-8month after regulatory submission to received orphan drug designation in all markets apart from the European Union (EU) which takes 18 months or more after regulatory submission.

Table I. Orphan Drug Legislation in US and major markets (Cheung, 2004).

	US (1983)	EU (2000)	Japan (1993)	Australia(1997)
Scope	Drugs	Drugs	Drugs and devices	Drugs
Designation criteria	< 200,000 >200,000 but not commercially viable	< 5/10,000 No alternative treatment Unlikely to get financial return	<50,000 Serious and no alternative treatment. Prove high efficacy, safety and development feasibility.	< 2,000 Not commercially viable
Market exclusivity	7 years	10 years	10 years	No
Protocol assistance	Yes	Yes	On request	On request
Priority review	Yes (depends on data and medical need)	Centralized	Yes	Yes
Tax credit	Up to 50% of clinical studies	Member state specific	6% of clinical and non clinical studies	No
R&D grants	Yes	Member state specific	Yes	No
Exemption of regulatory fee	Yes	Reduced	No	Yes
Timeline	6-8motnhs	> 18 months	10 months	Not clear.

Orphan Drug Act Incentives

The Orphan Drug Act (ODA) contains a number of provisions designed to encourage investment in orphan drug research and increase the number of drugs available for patients affected by a rare disease (Cheung et al., 2004). Pharmaceutical companies that developed and successfully register orphan drugs in the US receive: 1) priority review 2) protocol assistance 3) market exclusivity 4) tax credits 5) regulatory fees exemptions and 7) research and development grants. (H.R.5238)

1. Priority review is an orphan drug act incentive, where the time that the FDA takes to review and successfully approve an orphan drug is shorter compared to non-orphan drugs (Hutt & Merrill, 1991). An estimated time for orphan drug

approval is 6-8 months in contrast to non- orphan drugs that require 18- 20 months (Hutt & Merrill, 1991).

2. Market exclusivity is another orphan drug act incentive and represents an economic reward. It provides pharmaceuticals companies with a monopoly over the drug. This incentive is critical to the success of pharmaceutical companies in both profitability and recuperating invested capital (Hutt & Merrill, 1991). Market exclusivity for orphan drugs is very different from non-orphan drugs as the first provides 7 years exclusivity and patent law protection begins once the drug is approved (Hutt & Merrill, 1991).

3. Research and development grants have been reported to be good motivators for pharmaceutical companies when added to the pool of incentives offer by the Orphan Drug Act (Cheung, et al., 2004). Pharmaceutical companies are aware of the risks in investing on orphan drug development. The most obvious risk in drug development is that, despite a long and costly development process, most new drugs candidates will not reach the market (Sharma et al., 2010). Only fractions of one percent of the new drugs that are synthesized and examined in pre-clinical studies make it into human testing. Of these, only 20% of the new drugs entering clinical trials survive development and FDA approval process (Sharma et al., 2010). As part of the ODA of 1983, Congress recognized a need to fund clinical research that test promising new therapies for rare diseases. The FDA and the Office of Orphan Products Development Grants Program (OOPD)

awards grants for clinical trials only for products that have received or could potentially receive orphan status designation (Cheung, et al., 2004). The drug program includes the pre-market review of human drugs and biological products in order to ensure their safety and efficacy and the post marketing monitoring of drug experience (Cote, 2011).

4. Orphan Drug Tax Credit (ODTC) allows pharmaceutical companies to claim a tax credit for up to 50 percent of qualified clinical testing expenses (H.R.5238). Clinical testing costs are a subset of the total cost to bring a new drug to market (Cote, 2011). Qualified expenses for the orphan drug tax credit include human clinical testing costs incurred between orphan designation and drug approval (Cote, 2011). The ODTC also covers expenses related to human clinical testing conducted outside the United States only if an insufficient population of test participants exists domestically (Cote, 2011). Qualified expenses for the ODTC cannot be used toward the research (R&D) tax credit (H.R. 5238). For rare diseases, clinical trial costs alone can total thousands of dollars per person diagnosed with the disease (Sharma et al., 2010). Between 1996 and 2011, the amount of ODTC awarded to orphan drug pharmaceutical companies increased from $31 million to over $750 million (Hay et al., 2014)

For a drug to qualify for provisions contained in the ODA, it must receive an orphan drug designation from the FDA (21CFR §316). Pharmaceutical companies may apply for orphan drug designation at any time before filing a New Drug Application (NDA) or

Biological License Application (BLA) (Hutt & Merrill, 1991). The Office of Orphan Products Development within the FDA reviews applications for orphan drug designation and determines if a drug is eligible to receive the Orphan Drug Tax Credit (ODTC) and other orphan drug act incentives (21 CFR §316). Receiving an orphan drug designation does not change the market approval process nor does it imply that the drug will one day reach the marketplace (Villarreal, 2001).

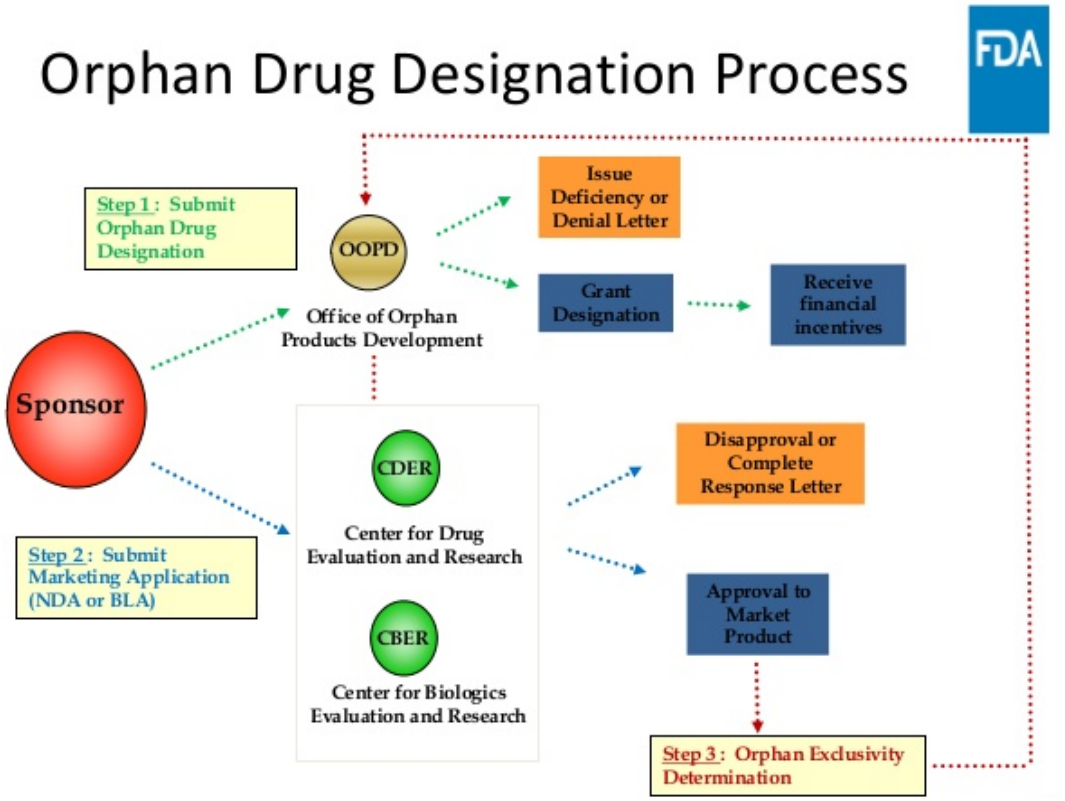

Figure 4. Orphan Drug Designation Process (FDA database, 2015 available at https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/default.htm)

The average review time for an orphan drug designation is 90 days, and between 60 percent and 70 percent of all applications result in drugs receiving orphan drug status (Hutt & Merrill, 1991). A drug can only receive orphan drug designation once it has been determined to diagnose or treat a rare disease (21 CFR §316). Each orphan drug is approved for specific use (21 CFR §316). Each of these uses is called an indication and when granting market approval, the FDA only authorizes a drug for its approved indication (21 CFR §316). It is possible for pharmaceutical companies to obtain a new orphan designation for an existing drug only if a new indication or use is found (21 CFR §316). This encourages pharmaceutical companies to seek new ways for existing drugs to be used to benefit patients with rare diseases (Hutt & Merrill, 1991).

Impact of Orphan Drugs on Orphan Drug Designations

The Orphan Drug Act (ODA) was signed into law in early 1983 and since it had a significant impact on public health. In the 34 years since this pioneering law was passed, more than 500 drugs have become available to patients with rare diseases in the United States, whereas in the 8–10 years prior to the orphan drug legislation, only 1 treatment per year for rare diseases was approved by the FDA and brought to the market.

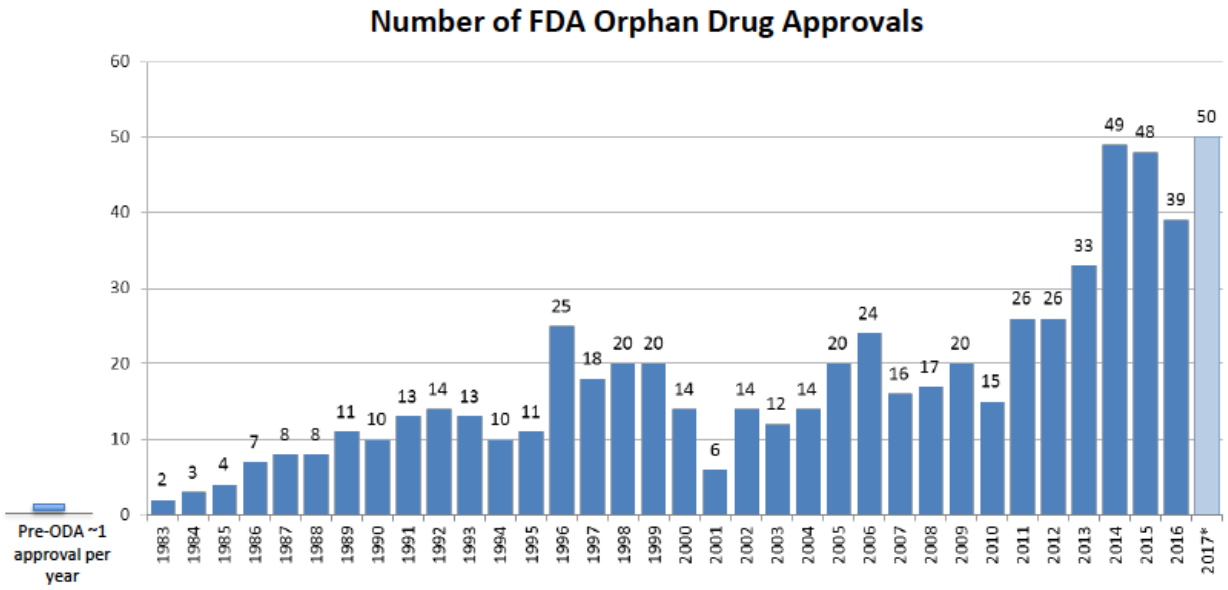

Figure 5. FDA Orphan Drug Approvals 1983-2017 (FDA database, 2017 available at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/Events/ucm598211.htm)

Post ODA, there has been a dramatic increase in the number of new orphan drugs brought to market (FDA database, 2015). The number of new orphan drugs in the development pipeline has increased rapidly as well. "*The enactment of the Orphan Drug*

Act in 1983 has proved to be a very successful venture in public policy, focusing private dollars and intellect on these vexing and often fatal diseases" (Wyden, 1994). Incentives of the ODA have played an important role in the increase in orphan drug manufacturing over the last 30 years (Sharma et al., 2010). Since 1983, 201 new orphan drugs have been brought to market, in part, due to the ODA (FDA database, 2017). The increase in drug innovation and development has been especially strong in recent years; with 50 new orphan drugs approved in 2017 (FDA database, 2017).

The ODA is also used to assist pharmaceutical companies in the re-purposing of existing drugs for the treatment of rare diseases (Villarreal, 2015). A total, 486 orphan products have been approved since ODA was enactment in 1983 (FDA database, 2017). Re-purposing strategy includes a mix of more effective formulations, new indications, dosages, sources of supply, and other changes that have illustrated clinical superiority (FDA database, 2015). While no all approvals represent a new orphan drug, these approvals have the potential to improve outcomes for the patients they were designed to treat. The development pipeline for new orphan drugs also continues to increase. Between 2004 and 2017, the FDA has awarded nearly 2,000 orphan designations (FDA database, 2017).

Risk Associated with Orphan Drug (OD) Research and Development (R&D)

The two most significant market barriers to the development of new orphan drugs are 1) high development costs and 2) limited patient populations (Sharma, et al., 2010). Each new orphan drug requires a substantial investment in research and development with limited chance the drug will make it to market (Hutt & Merrill, 1991). The small pool of potential patients further reduces the ability of a pharmaceuticals company to recover their research investment (Hutt & Merrill, 1991). Drug development costs are high in part because relatively few drugs make it through the development process, by the time drugs enter the preclinical phase of testing, only 1 out of 5 remaining drugs will receive market approval (Hutt & Merrill, 1991). The total research and development cost to produce a single approved drug includes not only the cost to develop the successful approved drug, but also the cost of the unsuccessful drugs (Hutt & Merrill, 1991).

Before the ODA came into effect, academic research began to show rising drug development costs (Hutt & Merrill, 1991). In the 1970s, the total cost of bringing a new drug to market was $182 million (in 2012 dollars), and by the 1980s, that number had risen to $205 million (in 2012 dollars) (Meekings, Williams & Arrowsmith, 2012). Current estimates of the total cost to bring a new drug to market are $1.5 billion (in 2012 dollars) (Meekings, 2012). The total cost of bringing a new drug to market includes: out-of-pocket expenses, the cost of failures and capital cost (Sharma, et al., 2010).

After a drug receives market approval, the pharmaceutical company can begin to recover its investment in the discovery and research process (Sharma, et al., 2010). For orphan drugs, the opportunity is diminished due to the limited pool of potential patients, which is one reason many pharmaceutical companies find it difficult to justify the investment required to develop treatments for rare diseases (Sharma, et al., 2010). According to the ODA, orphan drugs are designed to treat conditions that exist in less than 200,000 patients in the United States, and for many rare diseases, the number of cases may be far less than 200,000 (DiMasi, Hansen & Grabowski, 1991).

In addition to high costs and other market-based disincentives, significant regulatory barriers existed (Sharma, et al., 2010). A robust and comprehensive FDA approval process is important to ensure drugs reaching the market are safe and effective, but it also increases the timeline and cost of drug development (21 CFR §316). It takes an average of 12.5 years and $1.5 billion (in 2012 dollars) to bring a new drug from the preclinical stage through FDA regulatory approval (Cote, 2012). For potential pharmaceutical companies of new orphan drugs, who have a limited patient pool from which to recover these costs, the incentives available under the ODA can be a factor in determining which investments to pursue (DiMasi, et al., 1991).

Once a new potential drug is discovered, it enters preclinical testing during which initial safety assessments take place in a laboratory (21 CFR §316). Before being tested in humans the pharmaceutical company must submit an Investigational New Drug

Application (IND) to the FDA. Once the FDA approves the IND, clinical trials can begin (Hay, Thomas, Craighead, Economides & Rosenthal, 2014).

Clinical testing culminates in Phase III with randomized trials in human volunteers (21 CFR §316). This phase can be particularly challenging for pharmaceutical companies of orphan drugs who may struggle to find the necessary number of trial participants to achieve statistically significant results (Sharma, et al., 2010). If a drug successfully completes each clinical trial phase, the pharmaceutical company can submit a New Drug Application (NDA) or Biologic License Application (BLA) to the FDA for market approval (Cheung, et al., 2004). If the FDA grants market approval, the treatment becomes available to patients. Once a drug becomes available to patients, the costs of development may not end. The FDA can require drug developers to participate in Phase IV post-market monitoring, which may further increase the overall costs of drug development (DiMasi et al., 1991).

The span of time between new drug discovery and market approval means there could be relatively few years remaining of patent protection by the time the drug reaches the market (Cheung, et al., 2004). This is particularly challenging for pharmaceutical companies who already face a limited market from which to recover their research costs. As a result, pharmaceuticals companies can be discouraged from investing in drugs with a potentially limited market value (Meekings et al., 2012). Since the enactment of the Orphan Drug Act (ODA) in 1983, Congress has repeatedly amended the ODA to include additional incentives and support for orphan drug development (Villarreal, 2015). Some changes have

simply improved the clarity and focus of the provisions, such as the 1984 amendments to the ODA, which defined rare diseases as affecting fewer than 200,000 patients in the United States (Villarreal, 2015). Others have strengthened the original Act, such as by extending market exclusivity to patentable, as well as un-patentable products (Meekings et al., 2012). Congress waived certain fees for orphan drug developers in 1992, and in 1997 permanently extended the ODTC (Villarreal, 2015). According to the FDA, fee waivers can total $2 million, which can offer significant assistance, especially for small pharmaceutical companies (Meekings et al., 2012). Research and development (R&D) of new orphan drugs is not concentrated among a few pharmaceutical companies, but is broadly distributed throughout the industry (Cote, 2011). Between 2004 and 2014, 65 separate companies received market approval for at least one new orphan drug. For nearly a third of those companies, approval was for their first successful drug brought to market, orphan or otherwise (FDA database, 2015).

Assessing Risk of Orphan Drug (OD) Regulatory Approval

Drug development portfolios vary in extensiveness and depth. For each company, the objective of improving the success rate of their marketing applications is paramount. Regardless of the many Orphan Drug Act (ODA) incentives, pharmaceutical companies undertake a huge risk when pursing the registration of an orphan drug. Understanding some of the characteristics associated with marketing application success for these special drugs and alternatively some of the pitfalls associated with application failure may assist

pharmaceutical companies in developing more efficient regulatory strategies for orphan drug registration.

Each pharmaceutical company conducts risk assessments using customized algorithms or models. Each company rate or value differently all the factors associated with the probability of regulatory success and subsequently marketing of drugs. The probability of regulatory success also known as PRS provides a qualitative description of uncertainty suffers from vagueness and lack of collective agreement on useful definitions. A subjective probability represents the degree of belief in an event by an individual and the quantification of this uncertainty allows other business metrics to be specified. A careful consideration of technical feasibility is key to portfolio management. Probability is an excellent language for quantifying this uncertainty. PRS assessment is a well-planned process for probability assessment and review that can provide executives with reliable measurements of regulatory feasibility (Maniglia, 2007).

One of the most important risk recently identified associated with orphan drug approval is an accurate and well-constructed probability of regulatory success (PRS). This is a unique and empirical process that helps evaluate the risk associated with orphan drug development. It is confidential by nature and its conducted by a multidisciplinary group within the pharmaceutical company. Each contribution is vital to assets the probability of regulatory success of an orphan drug. Some of the key members are: commercial, clinical, safety, regulatory, finance and forecasting leads chaired by a project manager.

Figure 6. Standard Probability of Regulatory Success (PRS) model (Florent, 2015)

The probability of regulatory success is a systematic evaluation of medical, clinical, nonclinical and regulatory questions that needed to be answered prior to regulatory submission. Probability is an excellent language for quantifying uncertainty. A well-planned process for probability assessment provides executives with reliable measurement of regulatory feasibility. Probability of Regulatory Success (PRS) is multifactorial. The most common factors evaluated in any probability of regulatory success (PRS) model are clinical trial cost, marketing opportunity, competition and marketing cost.

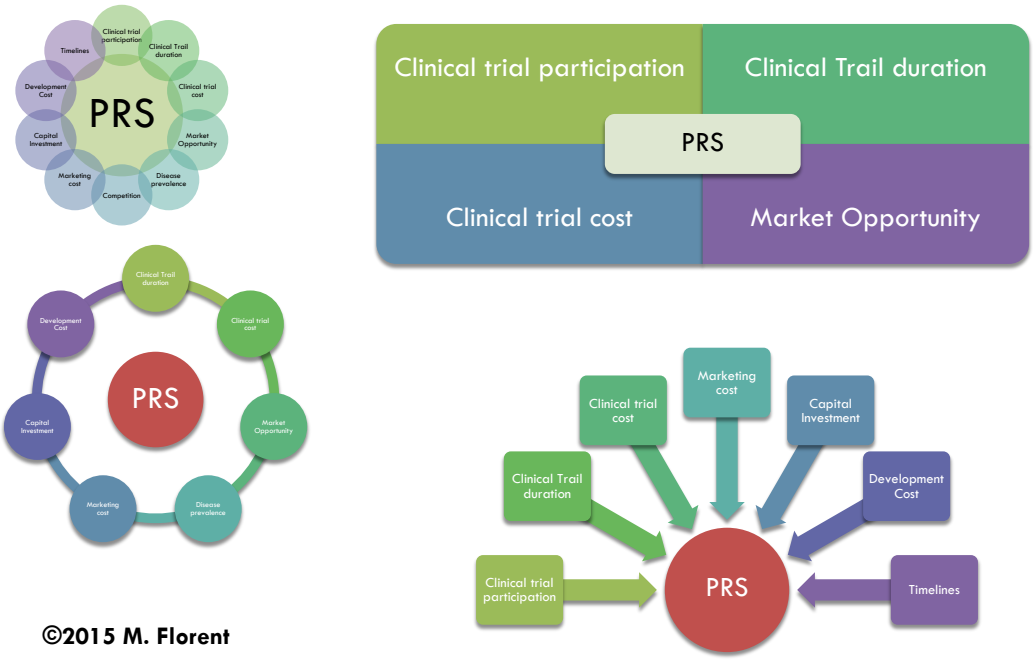

Figure 7. Probability of Regulatory Success (PRS) example (Florent, 2015)

Above figure represents a visual example of how different PRS models look in different organizations and even in departments within the same organization. Probability of regulatory success (PRS) models depends on many factors such as:

- type of pharmaceutical company (ex. pharma v. biotech)
- portfolio type (ex. cardiovascular v. oncology)
- internal processes and practices
- experience and empirical knowledge of the members of the multidisciplinary team.

Net Present Values (NPV)

Currently, the only non-empirical way to evaluate the cost of drugs entering the FDA review process is using the Probability of Regulatory Success (PTRS) together with the Net Present Values (NPV). It is a robust mathematical way to calculate if the drug is worth pursuing based on current expenses and future revenues as Net Present Value (NPV) is the difference between the present value of cash inflows and the present value of cash outflows over a period of time. NPV is used in capital budgeting and investment planning to analyze the profitability of a projected investment or project.

The following formula is used to calculate NPV:

$$NPV = \sum_{t=0}^{n} \frac{Rt}{(1+i)^t}$$

Figure 8. Net Present Value Formula (Kenton, 2015)

In this equation:

R_t = net cash inflow-outflows during a single period t

i = discount rate or return that could be earned in alternative investments

t = number of time periods

NPV = (Today's value of the expected cash flows) – (Today's value of invested cash)

A positive net present value indicates that the projected earnings generated by a project or investment (in present dollars) exceeds the anticipated costs, in present dollars. It is assumed that an investment with a positive NPV will be profitable, and an investment with a negative NPV will result in a net loss. This concept is the basis for the Net Present Value Rule, which dictates that only investments with positive NPV values should be considered. Apart from the formula itself, net present value can be calculated using tables, spreadsheets, calculators, or using NPV calculator.

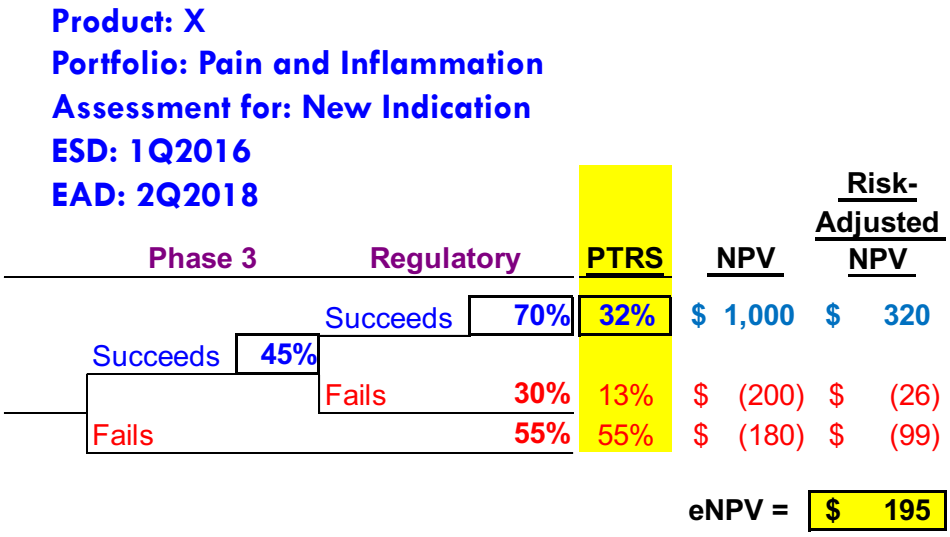

Figure 9. NPV calculation to asses PRS of a non-orphan drug (Florent, 2015).

Figure 9 above presents a decision tree for estimating the NPV of a drug being considered for phase III trials. It requires three (3) probabilities: the probability of technical success for phases I, phase II and phase III. The resolution produced by NPVs depends on these probability estimates answering the question *"How do these probabilities affect a phase's resolution?".* The resolution produced by NPVs depends even more on revenue estimates, but these estimates can be highly erroneous.

THERORETIAL FRAMEWORK

1. Orphan Drug Research and Development.

Competition in the research-based segment of the pharmaceutical industry and it is centered on the discovery and development of drugs that satisfy an unmet medical need or improve upon existing therapies (Sharma et al., 2010). Research and development (R&D) are a complex, costly, risky, and time-consuming process (Cheung et al., 2004). Over the past decade, several economic studies have been undertaken to better understand pharmaceutical R&D process. These studies consider cost and time needed to develop new drugs, the economic returns to drug research and development (R&D) and probability of regulatory success (PRS) (Yin, 2008). They highlight the large technical and commercial risks associated with the pharmaceutical R&D process and the tremendous variability in the economic returns of new drug introduction.

The most evident risk in drug development is that, despite a long and costly development process, most new drug candidates will not reach the market (Grabowski, 2003). Failure can result from toxicity, carcinogenicity, manufacturing difficulties, inconvenient dosing characteristics, inadequate efficacy, economic and competitive factors (Grabowski, 2003). Typically, fractions of one percent (1%) of the drugs that are synthesized and examined in pre-clinical studies make it into human testing (Grabowski, 2003). Of these, only about twenty percent (20%) of the drugs entering clinical trials survive the development and FDA approval process (Grabowski, 2003). The prospect of a long and uncertain development period for a new drug is another source of risk in the drug

development process. Recent new drug approvals have averaged nine years from the beginning of clinical trials to final FDA approval (Fagnan, Gromatzky, Stein, Fernandez & Lo, 2013). The discovery and pre-clinical periods can add another three to five years to this process (Fagnan et al., 2013).

In a study published in the 2003 by the *Journal of Health Economics*, Grabowski examined the representative costs for new drugs whose mean introduction date was in the late 1990s. The average cost estimate incorporates the expenditures for drug candidates that fail in the R&D process, since these costs must be recouped from the revenues of successful drug candidates (Grabowski, 2003). Grabowski found that it requires over $400 million in out of pocket expenditures (in 2000 dollars) to discover and develop the average U.S. new drug introduction. If one also takes account of capital costs utilizing a risk adjusted cost of capital appropriate for the pharmaceutical industry, capitalized R&D costs per new drug introduction are double the out of pocket costs (DiMasi, Hansen & Grabowski, 2003). R&D costs were shown to have increased at an annual rate of 7.4% above general inflation when compared to the costs for new drug introductions of the 1980s (Grabowski, 2003). A major factor accounting for this growth in costs is the size of and number of clinical trials, which have increased significantly in the 1990s compared to earlier periods. Another factor includes the growing complexity of trials (i.e., more procedures per patient), an increased focus on chronic diseases, and greater costs to recruit and maintain patients for these trials (DiMasi, Hansen & Grabowski, 2003).

In a paper published in 2003 by *Pharmaco-economics*, Grabowski examined the distribution of returns for 1990-94 new drug introductions. A key finding was that the sales and returns of new drugs exhibit tremendous variability. In particular, Grabowski found that a small number of drugs provide a disproportionate share of overall revenues. The search for these exceptional drugs, which generally involves significant therapeutic advances over establishing therapies, is a key driver of R&D competition for pharmaceuticals companies. In 2003, Grabowski also found that the distribution of returns is highly skewed, only three (3) of ten (10) new drugs cover the R&D costs incurred by the average new drug (including the costs of failed drugs and discovery costs necessary to generate new product leads) (Grabowski, 2003). Grabowski concluded that the R&D process in very similar to winning the lottery in the sense that most drug candidates taken into testing fail, a small number are marketed commercially and achieves modest financial returns, and only a few drugs succeed in generating very large returns to the pharmaceutical company (Grabowski, 2003).

The highly skewed outcomes reflect the dynamic nature of the R&D process and the large risks that surround the process from a scientific, regulatory and commercial perspective: the long-time delays, the need to obtain regulatory approval from the FDA, and the new drug introductions of competitors and the various scientific and technical risks (Grabowski, 2003). These factors help to explain the great variability in market sales and profitability that has been observed in every cohort since the 1970s. Large pharmaceutical companies, with extensive pipelines of new drug candidates, exhibit great variability in the number of approvals and sales from their R&D investment in a given period (DiMasi et al., 2003). Grabowski performed two studies on the factors that influence the size of a

company's total research and development (R&D) expenditures. The two primary factors found to be economically significant determinants of research and development (R&D) expenditures in these studies were a pharmaceutical company's expected returns and its internally generated funds (Grabowski, 2003). Grabowski found that roughly 25 percent of each million dollar change in cash flow will be directed toward increasing R&D (Grabowski, 2003).

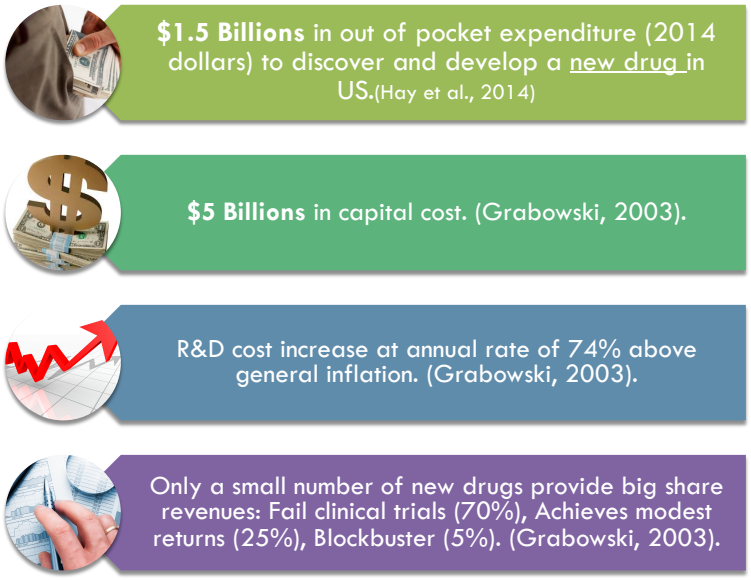

Figure 10. New Drug research and development (R&D) expenditure Grabowski (2003).

In 1993, a study conducted by the office of technology assessment noted that the economics of OD development and approvals might be different than other new drugs candidates. "*These products may have a different cost structure from other New Chemical Entities (NCE), not only because of the tax credit, but also because they may involve smaller and shorter clinical trials than other drugs*" (Grabowski, 2003). Available data sources the number of subjects enrolled in clinical trials and subsequent market sales

suggested that research and development (R&D) cost structure of orphan drugs are indeed different than other NCE (Grabowski, 2003). In addition to protocol assistance from the FDA, many orphan drugs are also eligible for other orphan drug incentives such as priority review, accelerated approval and fast track status (Hutt & Merrill, 1991). Under priority review, the FDA goal is to review new drug applications within six (6) months or less. Priority review is reserved for new drugs that provide a significant improvement in safety or effectiveness. Most orphan drugs qualify for priority review but accelerated approval however was instituted in 1992 to speed the approval of new treatment for serious or life-threatening disease (Villarreal, 2015). This process allows approval to be granted at the earliest phase of development at which safety and efficacy can be reasonably established. This is often done on the basis of a single-phase II trial involving hundreds rather than thousands of patients (DiMasi et al., 2003).

The FDA fast track program was established under the FDA Modernization Act of 1997. It consolidated the expanded FDA's expedited development and accelerated approval regulations to allow fast track designation for drugs with potential to address unmet medical needs for serious or life-threatening conditions (Sharma et al., 2010). Fast track development programs can take advantage of accelerated approval based on surrogate end points, rolling submissions of applications for marketing approval and priority review. Because orphan drugs are targeted to rare disease and illness, it is less likely to enroll large numbers of patients in clinical trials in most instances (Grabowski, 2003). The total number of subjects for orphan drugs approvals is much smaller than the average for all drugs. Grabowski demonstrated that seven orphan drugs marketing approval in 1999 had a mean

of 588 patients with a range between 152 and 1281 total patients in clinical trials compare to an average of more than 5,000 subjects for a typical new drug introduction (Grabowski, 2003).

There were 27 new orphan drugs launched from 1990 to 1994 (FDA database, 2015). The top quintile earned over $500 million in its tenth year on the market (which corresponds to the peak year for most orphan drugs) (Grabowski, 2003). By contrast, the median quintile had ten (10) year sales of only $29.5 million and most of the drugs in the lower two quintiles had tenth year sales of less than $10 million (Grabowski, 2003). Clearly, these results show a tremendous heterogeneity in the sales of orphan drugs. Most of these drugs have very modest sales, but some are just very wealthy (Grabowski, 2003).

The sales data is also strongly supportive that R&D cost structure of orphan drugs is very different in nature from other drugs (Grabowski, 2003). In addition to the possibility of a 50 percent tax credit, the sales of most orphan drugs would not support the large-scale clinical trials involving several thousand patients and which can cost hundreds of millions for the typical new drug approval (Grabowski, 2003). Based on available information on orphan drug sales and the number of subjects listed in the available NDA approval letters, it is reasonable to conclude that the representative orphan drug R&D costs are significantly lower than non-orphan drugs R&D cost (Fagnan et al., 2013).

2. Intellectual Property Strategy for Orphan Drugs

Patents have been found to be critically important to pharmaceutical companies in appropriating the benefits from drug innovation (Bhat, 2005). The reason for this follows directly from the characteristics of the pharmaceutical innovation process. As discussed above, it takes several hundred million dollars to discover, develop, and gain regulatory approval for a new drug (Grabowski, 2003). Absent of patent protection, or some equivalent market barrier, allows imitators to free ride on the innovator's FDA approval and duplicate the drug for a small fraction of the originator's costs (Bhat, 2005). Market exclusivity has been essential in the pharmaceutical industry to allow pioneers to appropriate enough of the benefits from new drug innovation to cover their large R&D costs and earn a risk adjusted return on their overall portfolio of R&D programs (Bhat, 2005).

Economists have demonstrated the importance of patents to pharmaceutical innovation in several studies. Yin in 2008 found that the technology industry for example placed greater stress on factors like time and efficiencies in the production of new products accruing to first movers in comparison to the pharmaceutical industry (Yin, 2008). This reflects the fact that R&D costs and investment periods are larger than average in pharmaceuticals while imitation costs are lower than in other high-tech industries.

Intellectual property rights have emerged as an important policy issue for pharmaceutical companies (Bhat, 2005). The average gross sales margins of the US

pharmaceutical companies during the past few years are nearly twice those of technological companies (Bhat, 2005). Such significant differences in gross margins are primarily attributed to the better track records of pharmaceutical companies in protecting their innovations (Bhat, 2005). Therefore, the protection and dissemination of innovations are great concern to pharmaceutical companies.

Bhat in 2005 argued that very few companies are willing to make huge investments in pharmaceutical R&D without patent protection "*patents support higher economic growth as the pharmaceutical industry provides high paying jobs which in turn lead to higher economic growth*" (Bhat, 2005). Market exclusivity provided by patents yields higher prices and profit margins to brand-name drugs. The longer is the market exclusivity; the higher are the profits (Bhat, 2005) since the profits are typically much higher at the end of the market exclusivity as drugs need minimal advertising and promotion.

However, prior a drug can be marketed in the United States; it needs to be approved by the US Food and Drug Administration (FDA) as safe and effective (21 CFR§ 393). Patent ownership by itself does not provide right to market patented drugs in the United States (Bhat, 2005). In other words, granting patents and drug approval are two different process overseeing by two different institutions.

Table II. Orphan Drug Approval Process in US (Florent, 2015)

Filling	Government Body/Institution	Requirements	Outcome	
Patent Application	USPTO	Patentable Novel Non-Obviousness Useful	Valid Patent	Patent protection of + 25 years
ODD Application	FDA OOPD	Mechanism of action	ODD	Eligible for ODA incentives
NDA/BLA Application	FDA CDER/CBER	Safety Efficacy	Regulatory approval	Legal marketing commercialization

Both patent ownership and drug approval are necessary for a pharmaceutical company to sell drugs without civil or criminal liability in the United States. If a company gets a marketing approval for a drug whose patent is not owned by the company, it could be subjected to liability for patent infringement (Bhat, 2005).

The importance of patent protection in pharmaceuticals is further supported by comparing innovative performance of the pharmaceutical industries in countries with and without strong patent protection. Strong systems of patent protection exist in all countries with strong innovative industries in pharmaceuticals (Grabowski, 2003). This is a major finding of an analysis that Grabowski performed of the distribution of important new global drug introductions categorized by the nationality of the originating companies for the period 1970 and 1985. Similarly, longitudinal studies on the growth of research and development (R&D) expenditures and foreign direct investment in Canada and Japan

associated with changes in their patent systems for pharmaceuticals support the significance of intellectual property rights as incentives for innovation (Fagnan et al., 2013).

Like many other scholars have stated, patent law is considered to be stronger for pharmaceutical companies than for other areas of technology. It seems reasonable that other technologies could advance relatively fast even without patent protection, but in pharmaceuticals, removal of the patent incentive would virtually eliminate private sector drug research (Abramowicz, 2003). Private sector research depends on the patent reward because of the extraordinary costs associated with research into new drugs and the relative easiness with which generic drug manufacturers can copy drugs (Abramowicz, 2003). Abramowitcz's embrace of patent protection for pharmaceutical companies does not imply that the general patent framework is tuned for pharmaceuticals. Indeed, the existence of many exclusivity provisions that are specific to drugs reveals that, because of the importance of drug development, Congress has sought to address inefficiencies and imperfections of the patent system in that context. Pharmaceutical companies clear out of their pipelines drugs that they do not expect to be able to patent, even though these drugs are generally not available on the market (Parchomovsky & Siegelman, 2002). The requirements of patentability, particularly the requirements of novelty and no obviousness make sense to the extent that the goal of patent law is viewed as the conception of drugs that might turn out to be clinically beneficial after a long testing process (U.S.C §102). But if a goal is actually to encourage drug manufacturers to undertake that testing process, patent law will work only so long as the pharmaceutical company that consider a drug proceeds to seek a patent and then undertake the clinical testing process. Nevertheless, if a

third party observes in a scientific publication that a particular compound seems like a very promising drug candidate, it is less likely that an unrelated pharmaceutical company will research that compound, because the company will be concerned that the drug will be un-patentable even if the research turns out to be successful (Parchomovsky & Siegelman, 2002).

3. The Orphan Business Model of Orphan Drugs.

The business model of researching a compound, guiding it through the FDA regulatory approval process, and bringing it to market is an orphan business model. As with other orphan business models, the problem is that second movers can take advantage of information produced by the first mover and dissipate the profits that the first mover could have expected to receive (Abramowicz, 2003). Being first to market and being able to offer the brand-name drug may, as a result of trademark law, provide some first-mover advantages, but at least in many cases these benefits will be insufficient to make the research path appear profitable, even if it would be socially beneficial (Abramowicz, 2003). The type of information on which the second mover is free-riding is different from the relevant information in a typical orphan business model case, where the second mover might wait to see whether there is consumer demand rather than regulatory approval. As with all orphan business models, though, there is a private risk that it will not be feasible to earn a profit providing a good or service, and first movers may not be willing to make expensive investments that have a high chance of producing no profits if second movers can enter the market in the unlikely case success is achieved (Parchomovsky & Siegelman, 2002).

The Orphan Drug Act seeks to protect orphan drugs in this context, drugs that need to be adopted by a pharmaceutical company if they are to be brought to market (Abramowicz, 2003). The title of the statute might at first appear to be a contradiction because it applies to any drug that is for a rare disease, but the definition of rare disease or

condition is expansive. It includes not only any disease that affects less than 200,000 persons in the United States, but also any disease that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (U.S.C §360). In other words, the statute presumes that a drug for a disease affecting a relatively small number of people needs protection because there will generally be reduced incentives to develop drugs for smaller patient populations. The statute, however, in theory also allows pharmaceutical companies to demonstrate that a drug affecting a larger number of people needs protection. For any drug designated for a rare disease the statute provides seven (7) years of marketing exclusivity (U.S.C §360). However, exclusivity can be cancelled if the pharmaceutical company cannot assure the availability of sufficient quantities of the drug (U.S.C §360). Outside the United States, numerous countries and the European Union have adopted statutes similar to the Orphan Drug Act (Sharma et al., 2010).

Most studies of the Orphan Drug Act indicate that it has helped promote further research into drugs for rare diseases. Dr. Yin finds that the Orphan Drug Act promotes drug development, and the effect is greater for more prevalent rare diseases (Yin, 2008). There is an argument, however, about whether the Orphan Drug Act itself provides the primary incentives that induce the development of drugs that are brought to market (Abramowicz, 2003). Other scholars argue that the Orphan Drug Act has in some instances provided protection that was unnecessary to induce drug development. These scholars noted that some orphan drugs have earned more than $1 billion per year, suggesting that they could

have been developed even without an orphan designation (Grabowski, 2003). While incentives provided for pharmaceutical companies by the Orphan Drug Act (ODA) have helped hundreds of treatments for rare diseases enter the market, ethicists, scientists, and many others argue that some pharmaceutical companies have exploited the law to gain profits.

A key provision of the ODA is that each time a medication gets approved by the FDA to treat a rare disease, it gains an additional seven years of market exclusivity for the specified condition, giving companies the ability to charge high fees for an extended period of time. In 2015, a Kaiser Health News (KHN) investigation revealed that a number of pharmaceutical companies gamed the system to sell orphan drugs at astronomical prices by using two key strategies: repurposing commonly used drugs and getting approval to use one product for multiple orphan diseases (KHN, 2015).

Table III. Intellectual Property Strategies (Florent, 2015).

IP Strategy	Definition	Example
OD Development	A drug that has been developed for a yet untreated rare disease.	Lumizyme® (alglucosidase Alfa) for Pompeii disease.
Repurposing	A drug developed to treat a common disease but now it has been repurposed to treat a rare disease.	Viagra® (sildenafil) for Erectile Dysfunction (ED) now for the treatment of pulmonary hypertension (PAH) Revatio® (sildenafil)
Maximizing portfolio	A drugs developed to treat of rare disease that now treats a common disease. ©2015 M. Florent	Ilaris® (Canakinumab) for Muckel-Wells Syndrome (MWS) now for the treatment of Rheumatoid Arthritis (RA)

For example, AbbVie's Humira®, which was FDA-approved in 2003 to treat rheumatoid arthritis, a condition that affects around 1 million adults in the U.S. alone, later gained additional approvals for multiple indications with orphan designation, including juvenile rheumatoid arthritis and pediatric Crohn's disease giving the company market exclusivity for some of these conditions until the early 2020s. Humira® is not a true orphan drug. In fact, Humira® is currently one of the world's best-selling medications as in 2017, it raked in $18 billion in sales. This strategy is well known in the industry as repurposing.

Another technique is to identify additional populations to gain orphan drug approvals in a practice known as maximizing portfolio in which a more common condition is divided into smaller, biomarker-defined categories. A 2016 study found that 13 of the 84 drugs approved with orphan designation between 2009 and 2015 were for subsets of

prevalent diseases and that some of those medications were also approved for other, related conditions (FDA database, 2018). For example, pharma firm Boehringer Ingelheim received FDA approval for Gilotrif® (afatinib) to treat Non-Small Cell Lung Cancer (NSCLC) patients with an EGFR mutation in 2013. Then, in 2016, the company received approval to use the same drug to treat NSCLC patients with squamous histology. The firm was awarded seven years of market exclusivity for both of the specified indications (FDA database, 2018). The ODA doesn't discriminate between genuinely rare conditions where there's usually a hereditary component, almost always in children, versus personalized approaches to cancer where clearly, they still are rare, but they are a different end of the spectrum.

CONCEPTUAL FRAMEWORK

Extracting factors from most theories in the industry and understanding the nature of orphan drugs below in Figure 11. is a proposed conceptual frame of factors associated with probability of regulatory success:

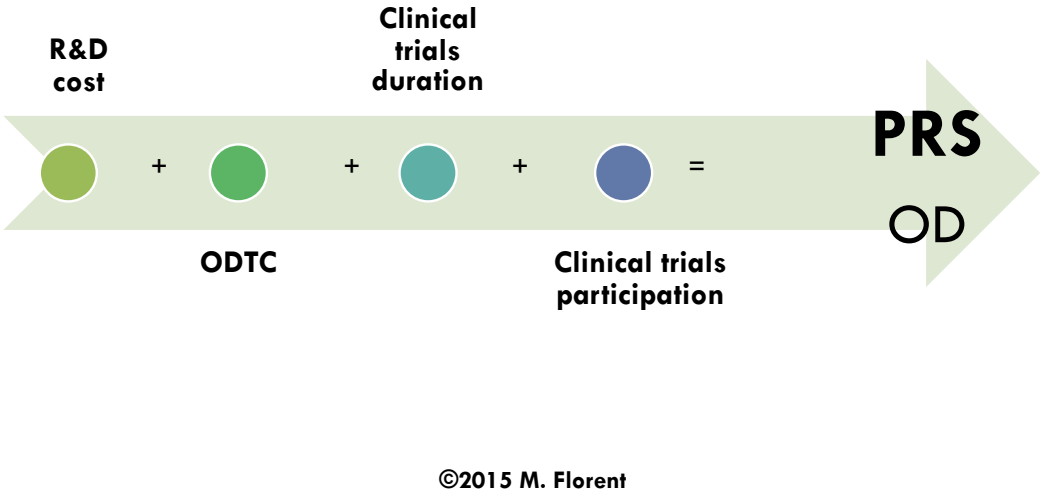

Figure 11. Conceptual Framework for Probability of Regulatory Success of Orphan Drugs (Florent, 2015).

The premise is that factors stated above research and developing (R&D) cost, clinical trial duration, clinical trial participation and Orphan Drug Tax Credit (ODT) are identified factors that are equally associated to probability of regulatory success (PRS) of orphan drugs (OD).

The average cost estimate incorporates the expenditures for drug candidates that fail in the research and development process, since these costs must be recouped from the revenues of successful drug candidates. Using the information from the literature, if pharmaceutical companies look for drugs already approved in their portfolio and apply the repurposing approach (Intellectual Property Theory) it would save more than $400 millions in capital investment and another $200 millions in research and developing cost specifically during discovery phase (in 2012 dollars) (Abramowicz, 2003). A major factor accounting for lower costs is the smaller clinical trials and to low complexity of trials due to fewer participants.

In 1993, a study conducted by the office of technology assessment noted that the economics of orphan drug development and approvals might be different than other new drugs candidates. As explained earlier, these products may have a different cost structure from non-orphan drugs, not only because of the tax credit, but also because they may involve smaller and shorter clinical trials. Available data from FDA sources the number of subjects enrolled in clinical trials and subsequent market sales, suggesting that orphan drugs are indeed different than non-orphan drugs. Because orphan drugs are targeted to rare disease and illness, it may not be feasible to enroll large numbers of patients in clinical trials in most instances. The total number of subjects for orphan drugs approvals is much smaller than the average for non-orphan drugs.

CHAPTER III

METHODOLOGY

Introduction

The Orphan Drug topic has been investigated widely since 1970s and orphan drugs research subject have varied significantly over the last 50 decades. Most of the orphan drugs studies available today focus primarily on qualitative research. The methodology for evaluating factors associated with orphan drugs development and regulatory success is often empirical. There are no standard research methods for this topic in general and researchers are limited to observe and report data from their points of view. Consequently, validity and reproducibility of data is an issue when investigating orphan drugs (Yin, 2016).

Among different methods of data collection commonly used in orphan drug research are observation, interview and questionnaire. Over the last 30 years, scholars have used observation and recorded in narrative or descriptive format to present and analyze the data collected. The tools of research to study orphan drugs can be similar to any other topic in healthcare: observation and description of phenomena; questionnaires seeking data from large numbers of participants, experimental investigation of specific problems, particularly by means of tests; genetic studies; and statistical analysis of the data collected. However, the subject of orphan drugs is so broad and deep that consists in much more than simple applied science; problems which have formed the leading subjects for research fall under one of two main categories: a) orphan drug trends and b) orphan drugs developing cost.

Factors associated with orphan drug regulatory success have not been extensively investigated in the pharmaceutical industry and some companies may claim to have actually quantified how factors affect the probability of regulatory success (PRS) however this information is considered confidential and it is share only internally meaning it is not available in the public domain. Confidential information is also considered property of the disclosing party and for the purpose of this study the disclosing party are the pharmaceutical companies that impose contracts to employees who are bound to honor this agreement.

It is challenging to obtain data to analyze factors that are associated with regulatory success of orphan drugs. Due to trade secret clauses, non-disclosure agreements and confidentiality agreements that pharmaceutical companies impose over its employees, some researches are limited to information available in public databases. For example, many researchers have utilized the US FDA orphan drug product designation website to identify the comprehensive list of drugs which have been approved by the FDA and given orphan status in the US since the establishment of the Orphan Drug Act (ODA) in 1983. Other scholars for example have analyzed the IMS Health MIDAS database to assess orphan drug and total drug expenditures in the US. Some international investigators have used analysis focused on expenditures of orphan drugs that were approved for both orphan and non-orphan indications. In the case of healthcare professional such as physicians, nurses, pharmacist and many others that work closely with patients and families that suffer from any rare diseases, the most common methodology is to apply a survey to a representative sample targeting patients and their families whose experiences can be

generalized to the target universe, even if that universe is small which is the case of rare diseases. However, none of the approaches mentioned above are optimal when evaluating factors associated with regulatory success of orphan drugs therefore a meta-analysis is the proper tool to use since it integrates the results of several independent studies. For this particular topic, a quantitative meta-analysis provides a more precise estimate of the effects of factors that improve the probability of regulatory success (PRS) of orphan drugs than any individual study contributing to the pooled.

Research Design

- Longitudinal (1999-2017).
- Systematic literature review of published literature.
- Quantitative meta-analysis and meta-regression.
- Total population (N= 672) (number of articles used in study)
- Not human subject type of research (IRB exempt)

Institutional Review Board (IRB)

The Institutional Review Board (IRB) is an administrative body established in a teaching or researching institution (hospitals and universities) to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The IRB is charged with the responsibility of reviewing, prior to its initiation, all research involving human participants.

Seton Hall University's Institutional Review Board for Human Subjects Research (IRB) has been established in accordance with federal regulations. This IRB reviews all proposed research involving human subjects in order to ensure that subjects' rights and welfare are adequately protected.

The University's IRB Office is administered and empowered through the Office of the Provost. The IRB is comprised primarily of faculty members from disciplines that conduct research involving human subjects (i.e., nursing, allied health fields, education, psychology, sociology, etc.). Community representatives who have no formal ties to the University also sit on the IRB. The Board's membership, policies and procedures are governed by an Assurance Agreement filed with the United States government.

Under Seton Hall University's Assurance Agreement filed with the U.S. Department of Health and Human Services (HHS), all generalizable research activities involving human subjects, whether federally funded, privately-funded or non-funded, including dissertations, master's theses, pilot studies, class projects, and non-funded faculty-directed research, must be reviewed and approved by the University's IRB prior to conducting the research, if the proposed research meets any of the following conditions:

- the research is sponsored by the University, *or*
- the research is conducted by or under the direction of any University employee, or agent (e.g., faculty member, researcher, or student) in connection with his/her other institutional responsibilities, *or*

- the research is conducted by or under the direction of any University employee or agent (e.g., faculty member, researcher, or student) using any University property or facility, *or*
- the research involves the use of the University's non-public information to identify or contact human research subjects or prospective subjects, *or*
- the research involves the use of the University's students, employees, or facilities.

On November 10th, 2017, this study was submitted to the Institutional Review Board at Seton Hall University. In the application, it was stated that this research involved conducting a quantitative systematic literature review of published literature (Meta-analysis) with no human subjects. On December 6th, 2017 the board requested additional documentation specifically an updated Federal Wide Assurance (FWA) from employer Pfizer, Inc. A Federal Wide Assurance (FWA) is the documentation of an institution's commitment (in this case Pfizer, Inc) to comply with Federal regulations and maintain policies and procedures for the protection of human participants since Pfizer, Inc. does not have an internal IRB process for this type of research study. The IRB at Seton Hall University carefully and fairly evaluated the response in reaching its final determination. On April 16th, 2018 the Director of the Institutional Review Board (IRB) at Seton Hall University responded with a written statement stating the IRB application cannot be review since it does not fall under the purview of the IRB, not even in exempt status as this study does not involved human subjects testing. A systematic literature review and meta-analysis of data is not considered human subject research (U.S. Department of Health and Human Services, 2018). (See Appendices A, B and C).

Data Collection

- Relevant data was be collected regarding the clinical development and approval of orphan drugs that first entered clinical testing anywhere in the world from 1999 to 2017 as published in peer review literature common to the pharmaceutical industry.
- The data elements selected from this larger dataset was generic name, trade name, dates of when clinical testing phases commenced, the development status of the compound, and the indications pursued prior to original marketing or termination of development on the investigational compound. All information can be sourced from the previously mentioned published peer review literature.
- Factors will be grouped into four factor categories: 1) characteristics of the molecule itself, 2) economic factors that relate to potential markets for the drugs and the size of the company developing the drug, 3) features of trial design, and 4) the safety and efficacy outcomes of the clinical trials.

Methodology

1. Systematic Review

On May 21st, 2015 a pilot was conducted in order to understand the length of the work ahead and make a realistic determination of how much time and resources it would be needed to complete this study conducting a full meta-analysis. The literature search was undertaken between May 1st 2015 and March 30th, 2017 to identify published peer-reviewed articles in English. The databases searched use were Medline™, PubMed™ Google™ Scholar, Springer Links™, Scopu™, Cochrane Library Academic™. A search was

also conducted in the following journals: *Health Policy, Pharma-economics, Orphan Drugs: Research and the Orphanet Journal of Rare Diseases*.

A search strategy was developed and implemented under the leadership of the committee. Multiple keywords including but not limiting to the following were used: (“Orphan drugs” or “Orphan drugs clinical trials” or “Clinical trials”) and (“Orphan” or “clinical trial length”) and (“Orphan Medicines” or “Orphan Drugs” or “Orphan Pharmaceuticals”) and (“Drugs” or “Medicines” or “Pharmaceuticals”) and (“Regulation” or “Policy” or “legislation”) (“Pharmaco-economic” or “orphan drug business model” or “orphan research and development”) and (“Orphan” or “clinical trial length”) and (“Orphan Drug Approval ” or “Orphan Drugs designation”) and (“Drugs assessment” or “PRS” or “Probability of regulatory success”) and (“Orphan Drug developing cost” or “R&D developing risk” “R&D cost”) and (“” or “” or “”) and (“” or “”). The keywords were combined and integrated in database and journal searches. Search results (‘hits’) by database and journal were tabulated and printed. The terms used were searched using ‘AND’ to combine the keywords listed and using ‘OR’ to remove search duplication where possible. References of retrieved articles were assessed for relevant articles that our searches may have missed.

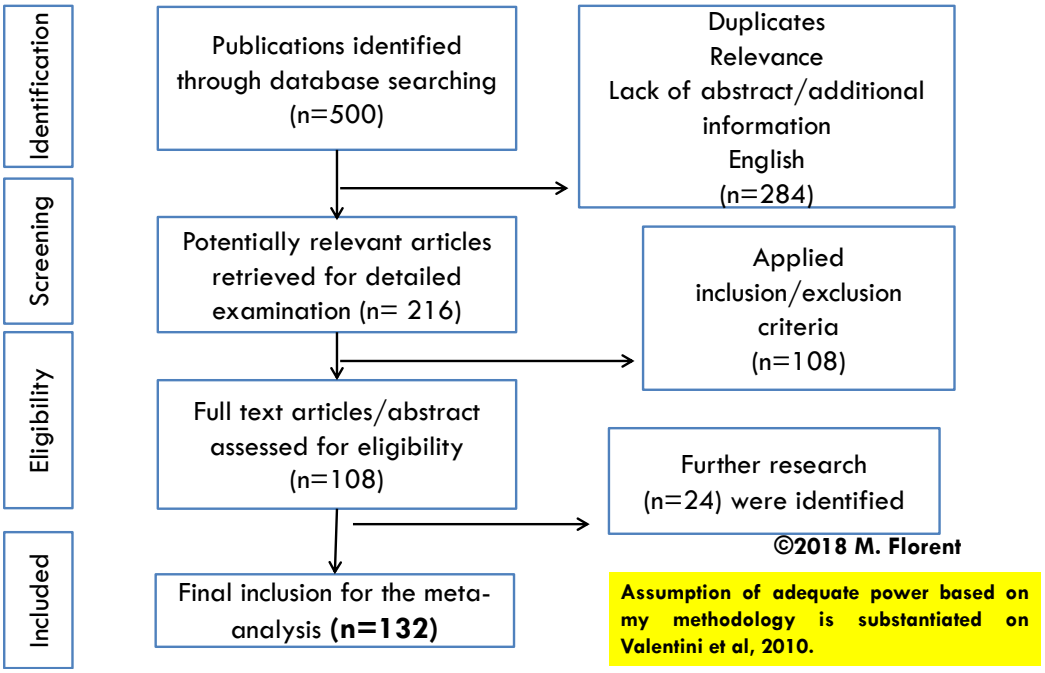

Figure 12. Data Abstraction: PRISMA Flow Chart in Meta-analysis (Florent, 2018)

From the database/journal searches 500 titles/abstracts were retrieved. The title and abstract of all retrieved articles were reviewed for relevance. Subsets of research results were checked by the committee chair. If there was any ambiguity with regards to the paper, the full-text article was retrieved and reviewed for relevance. After removing duplicates and titles/abstracts unrelated to orphan drugs or rare diseases, a total of 216 peer-reviewed English- language articles were identified. Original articles, reviews, commentaries and opinions of they described "key words" for orphan drugs and relevant health services were included. Of these, only 108 articles were relevant to research topic; thus, with guidance from the committee articles in full were read. Six more articles were identified from references of the retrieved articles; thus 24 articles were considered against the study inclusion and exclusion criteria (see Appendix D).

The literature was systematically reviewed to ensure that a narrative synthesis produced was sourced from the most complete collection of relevant literature possible. Thematic analysis of the articles was conducted, and relevant sub-categories were created for examination until no more themes were identified and saturation was deemed to be reached. Using these categories generated by the analysis, the range and types of factors associated with the probability of regulatory success of orphan drugs were described. Once sample of studies (n=132) were collected The Comprehensive Meta-Analysis (CMA) v.3.0 software coded their characteristics and calculated effects sizes.

2. Meta-analysis

Glass first defined meta-analysis in the social science literature as "*the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings"* (Glass, 1976). Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess the results of previous research to derive conclusions about that body of research. Typically, but not necessarily, the study is based on randomized, controlled clinical trials. Outcomes from a meta-analysis may include a more precise estimate of the effect of treatment or factor for disease, or other outcomes, than any individual study contributing to the pooled analysis (Glass, 1976). Identifying sources of variation in responses; that is, examining heterogeneity of a group of studies, and generalizability of responses can lead to more effective treatments or modifications of management. Examination of heterogeneity is perhaps the most important task in meta-analysis (Oxman & Guyatt, 1993).

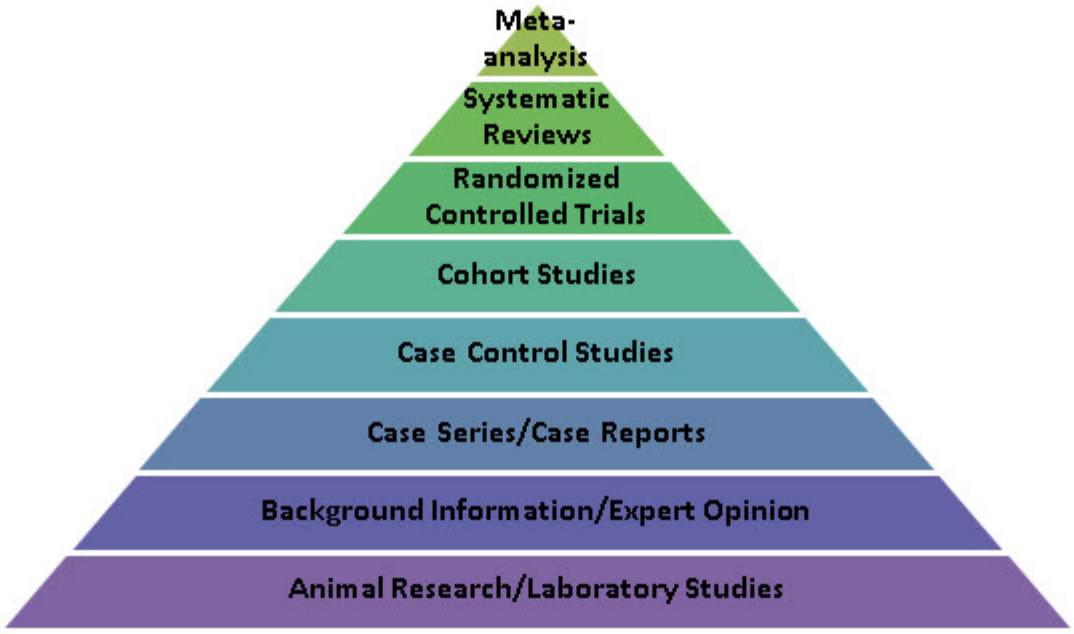

Figure 13. Meta-Analysis in Quantitative Research (Glass, 1976).

Meta-analyses are conducted to assess the strength of evidence present on a disease and treatment. In this particular study one aim to determine whether an effect of factors associated to regulatory success exists and whether the effect is positive or negative. The results of a meta-analysis can improve precision of estimates of effect, answering questions not posed by the individual studies, settle controversies arising from apparently conflicting studies, and generate new hypotheses. In particular, the examination of heterogeneity is vital to the development of new hypotheses (Oxman & Guyatt, 1993).

A sound meta-analysis is characterized by a thorough and disciplined literature search. A clear definition of hypotheses to be investigated provides the framework for such investigation (Oxman & Guyatt, 1993). Studies are chosen for meta-analysis based on

inclusion-exclusion criteria. Inclusion criteria are ideally defined at the stage of initial development of the study protocol. The rationale for the criteria for study selection used should be clearly stated. When studies are excluded from a meta-analysis, reasons for exclusion should be provided for each excluded study (Oxman & Guyatt, 1993). Usually, more than one “assessor” decides independently which studies to include or exclude, together with a well-defined checklist and a procedure that is followed when the assessors disagree (Haidich, 2010). Two people familiar with the study topic perform the quality assessment for each study, independently and this is followed by a consensus meeting to discuss the studies excluded or included (Haidich, 2010).

Although the intent of a meta-analysis is to find and assess all studies meeting the inclusion criteria, it is not always possible to obtain these. There is good reason to be concerned about this potential loss because studies with significant, positive results (positive studies) are more likely to be published and, in the case of interventions with a commercial value, to be promoted, than studies with non-significant or "negative" results (negative studies) (Oxman & Guyatt, 1993). Studies that produce a positive result, especially large studies, are more likely to have been published and, conversely, there has been a reluctance to publish small studies that have non-significant results (Haidich, 2010).

Summary

- Meta-analysis is a statistical technique for combining the findings from independent studies.
- The validity of the meta-analysis depends on the quality of the systematic review on which it is based.
- A good meta-analysis aims for complete coverage of all relevant studies, look for the presence of heterogeneity, and explore the robustness of the main findings using sensitivity analysis.

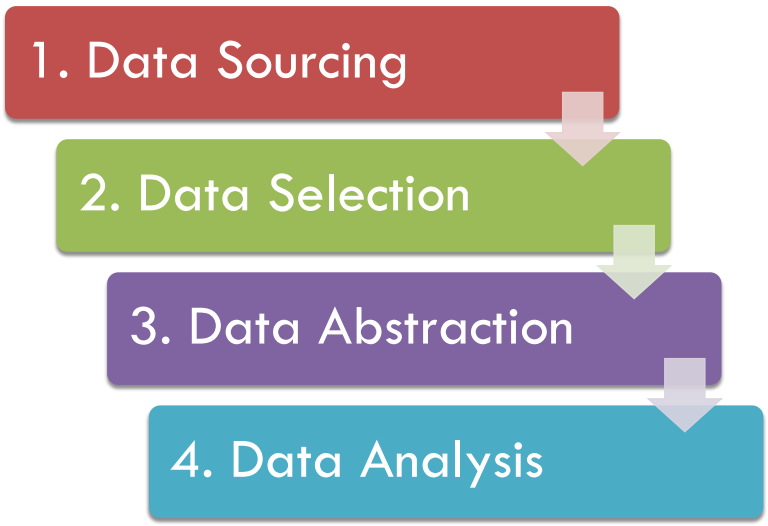

Figure 14. Steps in Meta-Analysis (PRISMA, guidelines, 2018).

There are four steps involved in meta-analysis but first the problem needs to be addressed and specified in the form of clear, unambiguous and structured question before beginning the review work. Once the review questions have been set, modifications to the protocol should be allowed only if alternative ways of defining the populations, interventions, outcomes or study designs become apparent.

Data Sourcing: the search for studies should be extensive. Multiple resources (both computerized and printed) should be searched without language restrictions. The study selection criteria should flow directly from the review questions and be specified *a priori*. Reasons for inclusion and exclusion should be recorded.

Data Selection: Study quality assessment is relevant to every step of a review. Question formulation and study selection criteria should describe the minimum acceptable level of design. Selected studies should be subjected to a more refined quality assessment by use of general critical appraisal guides and design-based quality checklists. These detailed quality assessments will be used for exploring heterogeneity and informing decisions regarding suitability of meta-analysis. In addition, they help in assessing the strength of inferences and making recommendations for future research.

Data Abstraction: data synthesis consists of tabulation of study characteristics, quality and effects as well as use of statistical methods for exploring differences between studies and combining their effects (meta-analysis). Exploration of heterogeneity and its sources should be planned in advance. If an overall meta-analysis cannot be done, subgroup

meta-analysis may be feasible.

Data Analysis: the issues highlighted in each of the four steps above should be met. The risk of publication bias and related biases should be explored. Exploration for heterogeneity should help determine whether the overall summary can be trusted, and, if not, the effects observed in high-quality studies should be used for generating inferences. Any recommendations should be graded by reference to the strengths and weaknesses of the evidence.

2.1 Inclusion and Exclusion Criteria

A meta-analysis carried out on a rigorous systematic review can overcome dangers offering an unbiased synthesis of the empirical data (Oxman et al., 1995). Table 1 below describe main criteria use to select o rejects studies in this meta-analysis.

Table IV. Data Selection: Meta-Analysis Inclusion/Exclusion Criteria. (Florent, 2018)

Inclusion Criteria	Exclusion Criteria
Recent publications 2005 onwards	Older publications
Publications with keys words: number of patients enrolled in clinical trials, length of clinical trial, patent strategy, market exclusivity for OD, size of company, OD legislation, ODD and OD approval	Publications that discuss product specific or disease specific. Publication out of the scope/relevance to this study
Experimental publications, reviews and expert opinions that only discusses ODD	EU, EM study that does not discuss/mention OD Approval
Publications from emerging markets if discuss or analysis ODD and factors associated with designation in the market.	Price and reimbursement, impact on patients and families, funding.
	Articles with unfamiliar/standardized methods
	Publications that lack information about data collection.

2.2 Validity and Reliability

In order to determine if a meta-analysis is valid and reliable, a series of protocols were followed, and tests were conducted:

1. An appropriate systematic review.
2. Cochrane guidance were followed on developing and refining search terms.
3. Clear inclusion/exclusion criteria. A list of validity threats was used as bases for exclusion (Cook & Campbell, 1979) and consider whether each might have influenced studies in my analysis.

A meta-analysis that combines the results from many trials, have more power to detect small but clinically significant effects. Furthermore, they give more precise estimates of the size of any effects uncovered (Oxman et al., 1995). In order to determine if a meta-analysis is valid and reliable, a series of questions need to be asked. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses better known as PRISMA was used. PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions. In addition, the Cochrane Collaboration PRISMA flowchart was utilized to demonstrate screening.

3) Statistical Analysis

A variety of statistical analysis was used to assess a large set of publicly available factors as the basis for creating and testing a straightforward, simple algorithm that would better predict probability of regulatory success of orphan drugs. Such an algorithm would provide a more precise estimate than one can be obtained by utilizing only success rate estimates based on historical industry data for drugs in general, or by therapeutic class.

a) Statistical analysis and inference (associations and logistic regressions): data was be examined by applying a number of statistical inference techniques.

- Identify factors associated with probability of regulatory success of orphan drugs (meta-analysis)
- Linear regression (meta-regression) to evaluate factors associated with probability of regulatory success of orphan drug
- Compare factors previous identity to be associated with probability of regulatory success of orphan drugs (Meta-analysis subgroups). Association statistics between each potential factor and a categorical variable for regulatory approval success or failure.
- Nonparametric X^2 tests (assumption of normality) of association will then applied to determine which factors have statistically significant association with probability of regulatory success of orphan drugs.

b) "AODI" (Approved Orphan Drug Index) algorithm: based on the variety of mathematical and statistical techniques, predictors for a scoring algorithm to three factors will be used. Those factors are: 1) the number of subjects enrolled a clinical trial phase II trial, 2) the length of the clinical trial phase II period and 3) the number of patients affected by the rare disease (prevalence).

Software

Comprehensive Meta-Analysis (CMA) v.3.0 Software

Comprehensive Meta-analysis is an essential tool for efficient problem solving in meta-analysis. Comprehensive Meta-Analysis (CMA) software is user friendly with a simple and clear interface (like an excel sheet) that guides to do complicated meta-analysis. The formats included in the software allow researchers to input data in various ways. It provides clear outputs and high-resolution graphs that can be imported to Microsoft Word®. There is a feature that shows calculation steps and provides advance sub-group analysis, moderator analysis, meta-regression and publication-bias analysis.

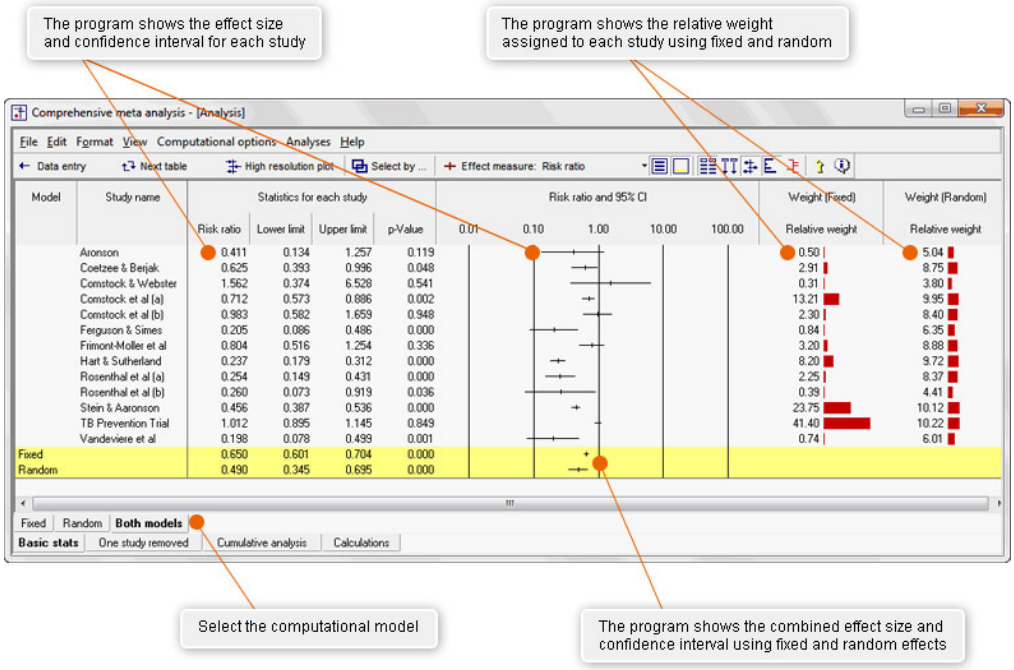

Figure 15. Effect Sizes and Study Weights in Comprehensive Meta-Analysis software (CMA, 2018)

The program was developed partly as an educational tool, and it includes many features that help explain the process of meta-analysis. CMA can be used to create a forest plot which shows each of the individual studies and the combined effect size. CMA also allows manipulation of the studies to see how these modifications impact the weight assigned to each study and how they impact the summary effect. CMA can also see how the selection of a model (fixed-effect vs. random-effects) impacts the analysis.

IBM™ SPSS® Statistics Software v.23

IBM™ SPSS® Statistics is an essential tool of assessment and it is widely used for statistical analysis in social science. SPSS® is also used by marketing, health, government and education researchers. The original SPSS manual has been described as one of sociology's most influential books for allowing ordinary researchers to do their own statistical analysis (Nie, Bent & Hull, 1970). In addition to statistical analysis, IBM™ SPSS® Statistics is ideal for data management (case selection, file reshaping, etc.) and data documentation (data master file).

IBM™ SPSS® Regression Software v.23

IBM SPSS® Regression software predicts categorical outcomes and applies a range of nonlinear regression procedures. This software allows uses regression techniques where research is limited such as a meta-analysis. SPSS Regression software allows expanding the capabilities of IBM™ SPSS® Statistics Base for the data analysis stage in the analytical process.

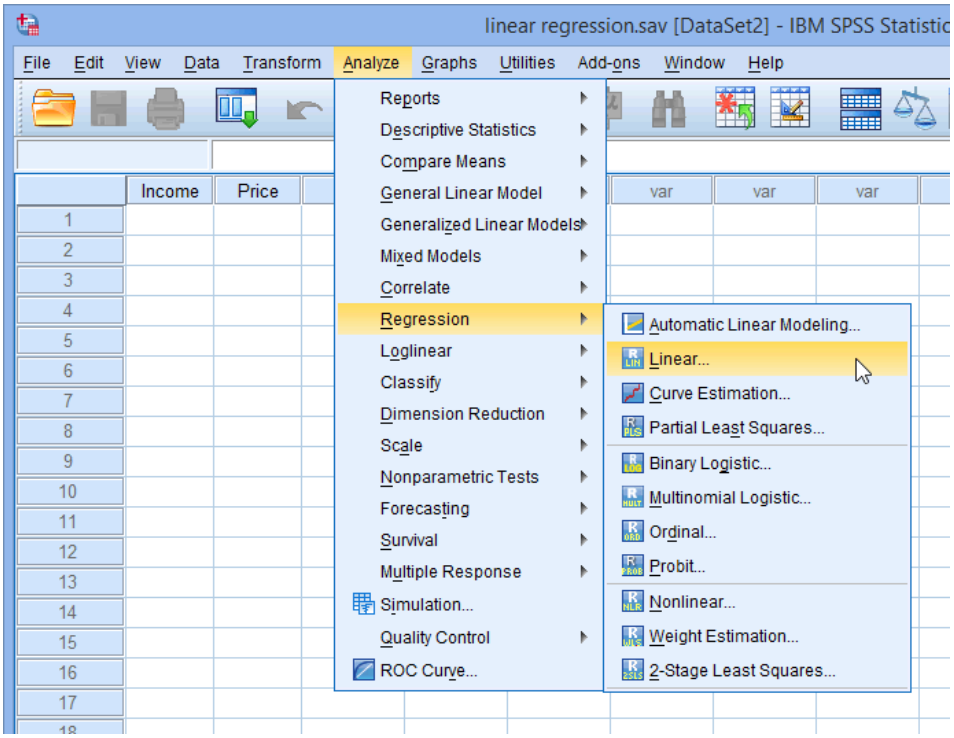

Figure 16. IBM™ SPSS® regression software v.23 (Florent, 2018)

CHAPTER IV

RESULTS

PART 1: Exploratory Research

In the first part, the objective of this study is to identify, compare and evaluate factors associated with probability of regulatory success of orphan drugs (OD).

1. Summary of Findings from Systematic Review

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, frequency percentages are used to combine the results from the individual studies and an overall summary estimate. A systematic review gives weighted values to each of the individual studies according to their size.

Table V. Predominant areas of research in Orphan Drugs Literature (Florent, 2018).

Area of Research	Frequency	%
ODBM	27	20.45
R&D	47	35.60
OD Policy	31	23.48
Clinical Trials	10	7.57
Pharmaco-economics	5	3.78
Intellectual Property	12	9.09
TOTAL	132	100

While the term systematic review typically invokes the process of combining findings across studies to determine the effect, in this study the term describes the selection of studies with a common trait. Table above shows the results of a systematic review also after examining 132 studies. Orphan Drug Business Model (ODBM), Research and Development (R&D) and orphan drug policy were the highest research areas found.

Table VI. Sub-categories within Research and Development (R&D) (Florent, 2018)

Area of Research	**Sub-categories (factors)**	**%**
Research and development (R&D)	Research and development (R&D)	7
	Orphan drug (OD) development cost	35
	Competition	55
	Orphan drug tax credit (ODT)	3

When looking at sub-category Research and Development (R&D); competition and Orphan Drug (OD) development scored very high with 55% and 35% respectively.

Table VII. Sub-category within Orphan Drug Policy (Florent, 2018).

Area of Research	**Sub-categories**	**%**
Orphan Drug (OD) Policy	Prevalence	59
	Market Exclusivity	25
	Policy framework review	16

When looking at sub-category OD policy: prevalence and market exclusivity scored very high with 59% and 25% respectively.

Table VIII. Sub-category Orphan Drug Business Model (ODBM) (Florent, 2018).

Area of Research	**Sub-categories**	**%**
Orphan drug business model (ODBM)	Company size	19
	Clinical trial duration	43
	Clinical trial participation	27
	Regulatory approval timelines	11

When looking at sub-category Orphan Drugs Business Model (ODBM); clinical trial duration scored 43% and clinical trial participation scored 27% leaving company size 19% and regulatory approval timelines 11% in 3rd and 4th place respectively.

2. Summary of Findings from Quantitative Meta-Analysis

Meta-analysis is defined as a quantitative synthesis of information from several studies. However, a qualitative meta-analysis, not to be mistaken for a systematic review, can allow for the systematic review of qualitative studies in a way that is more interpretive than aggregative.

Table IX. Factors Associated with Probability of Regulatory Success of Orphan Drug (Florent, 2018).

Factors associated with Orphan Drug Regulatory Success	**%**	**p. value**
Clinical trial duration	36.7	0.0015
Rare disease prevalence	21.1	0.0020
Research and development cost	3.95	0.01
Number of participants in clinical trials	16.1	0.0068
Company size	2	0.0401

p. <0.005 value for statistical significance

This table shows results of factors associated with probability of regulatory success of orphan drugs. The analysis showed that three of out five factors were identified to have statistical association with probability of regulatory success of orphan drugs. Clinical trials duration showed 36.7% of association with probability of regulatory success of orphan drugs with a *p. value* of 0.0015 meaning there is statistical significance in these results. Rare disease prevalence showed 21.1% of association with probability of regulatory success of orphan drugs with a *p. value* of 0.0020 meaning there is statistical significance in these results. Finally, clinical trial participation showed only 3.95% of association with probability of regulatory success of orphan drugs with a *p. value* of 0.0068 meaning there is statistical significance in these results.

3. Summary of Findings from Meta-Regression

The following results were obtained after conducting a meta-regression with the objective of comparing relevant factors associated with probability of regulatory success of orphan drugs that showed significant results in the quantitative meta-analysis.

Table X. Univariate Association (together) between Potential Predictive Factors and the Probability of Regulatory Success (PRS) of Orphan Drugs (OD) (Florent, 2018)

Variable	**Coefficient**	**SE**	***p*. value**	**Odds Ratio**
Intercept	-1.0382	0.6616	0.1166	
Number of patients enrolled in Clinical Trials	-0.6413	0.5386	0.2338	13.606
Prevalence of Rare disease	-0.8858	0.5159	0.0860	0.170
Duration of Clinical Trials	-0.07349	0.5431	0.1760	3.230

Coefficient negative values represent possible inverse association

Odds ratio highlighted represent possible high association

p. <0.005 value for statistical significance

Table X. shows results of a logistic meta-regression. The test is an univariate association (evaluating together) between selected potential predictive factors and probability of regulatory success of orphan drugs. The regression analysis showed an inverse association between probability of regulatory success of orphan drugs and the independent variables. The intercept is -1.0382 with a *p. value* of 0.1166 meaning there is no statistical significance in these results. Also, the results from the logistic regression show an odds ratio of 13.606 for clinical trial participation. After conducting the statistical

inference of logistic regressions linking three of the factors: clinical trial participation, clinical trial duration and rare disease prevalence; none of them provided a useful basis for predictive purposes as they didn't show significant statistical results to hold up as useful predictors however the results from this meta-regression provide information regarding the weights and directionality of each factors as they associate with probability of regulatory success of orphan drugs .

After identifying and comparing factors associated with probability of regulatory success of orphan drugs, the next step is to evaluate the factors associated with the probability of regulatory success of orphan drugs in an isolation univariate association.

Table XI. Univariate Association (in isolation) between potential predictive factors and the Probability of Regulatory Success (PRS) of Orphan Drugs (OD) (Florent, 2018).

Factor	**Factor value**	**Percentage Approved (%)**	***p.* value**
Clinical trial duration	<18 months	46.7	0.0015
	18-36 months	14.8	
	>36 months	8	
Rare disease prevalence	<50,000	39.1	0.0020
	50,000-200,000	23.8	
	> 200,000	8.3	
Orphan drug development cost	<25,000MM	16.3	0.0401
	>25,000MM	36.7	
Clinical trial participation	<500 subjects	45.7	0.0010
	> 500 subjects	16.1	

p. <0.005 (value for statistical significance)

Table XI. above shows the results of the univariate associations between selected potential predictive factors and probability of regulatory success of orphan drug and non-orphan drugs. Univariate Associations (nonparametric chi-square test of association) was conducted considering individual factors in isolation. Only three variables had statistically significant associations with probability of regulatory success. No all variables needed to hold up as useful predictors in a multivariate context. Table XI. above lists these variables and the cutoffs used for groupings of the four continuous variables. Three of the variables

have high significant association with probability of regulatory success of orphan drugs. These results suggest that clinical trials duration, clinical trial participation and the rare disease prevalence are inversely associated with probability of regulatory success of orphan drugs. Other factors analyzed but not show in this table were: pharmaceutical form (oral compound. v injections) *p.* 0.263 and company size (small v. large) *p.* 0.173

Summary PART I: Exploratory Research

Table XII. Summary of Part I: Exploratory Research (Florent, 2018)

Research Question	Hypothesis	Outcome
Is it possible to identify the relevant factors associated with regulatory approval of orphan drugs (OD)?	**H1:** Yes, it is possible to identify the relevant factors associated with regulatory approval of Orphan Drugs (OD) **$H1_o$**: No, it is not possible to identify the relevant factors associated with regulatory approval of Orphan Drugs (OD)	Fail to reject the hypothesis H1
RQ2: Is it possible to compare the relevant factors associated with regulatory approval of orphan drugs (OD)?	**H2**: Yes, it is possible to compare the relevant factors associated with regulatory approval for Orphan Drugs (OD) **$H2_o$:** No, it is not possible to compare the relevant factors associated with regulatory approval of Orphan Drugs (OD)	Fail to reject the null hypothesis $H2_o$
RQ3: Is it possible to evaluate the relevant factors associated with regulatory approval of Orphan Drugs (OD)?	**H3:** Yes, it is possible to evaluate the relevant factors associated with regulatory approval of Orphan Drugs (OD) **$H3_o$:** No, it is not possible to evaluate the relevant factors associated with regulatory approval of orphan Drugs (OD)	Fail to reject the hypothesis H3

PART II: Building an Algorithm of Approved Orphan Drug Index (AODI)

In this second part of the study, the objective is to develop and test an algorithm for predicting probability of regulatory success of orphan drugs with the objective of providing a tool to improve orphan drugs portfolio decision-making.

1. Construction of approved orphan drug index (AODI)

Given the results obtained from the univariate associations (factors evaluated in isolation) between selected potential predictive factors and probability of regulatory success of orphan drugs using a nonparametric chi-square test of association. An AODI index was formulated as the sum of the scores for three predictive factors: clinical trials duration, clinical participation and rare disease prevalence.

Table XIII. Approved Orphan Drugs Index (AODI) (Florent, 2018).

	SCORES		
FACTORS	**0**	**1**	**2**
Clinical Trial participation	> 500 subjects	500-250 subjects	< 250 subjects
Clinical Trial duration	> 36 months	36-18 months	< 36 months
Rare Disease prevalence	>500,000 patients	200,000-500,000 patients	< 200,000 patients

The cut off points were assigned by the literature review and over 10 years of regulatory experience. Higher scores of AODI are meant to be associated with higher probabilities of regulatory success of orphan drugs.

The data suggest that there is an inverse association between clinical trial duration, clinical trial participation and rare disease prevalence, meaning regulatory success of orphan drugs is associated with short clinical trial duration, low clinical trial participation and low rare disease prevalence. AODI was constructed based on results from meta-regression and data available in the public domain for 100 of the drugs approved by the FDA. For AODI to be a valuable tool and to be use in portfolio decision-making, the higher values of the index must have greater predictive power.

2. Validation and Standardization of Approved Orphan Drug Index (AODI)

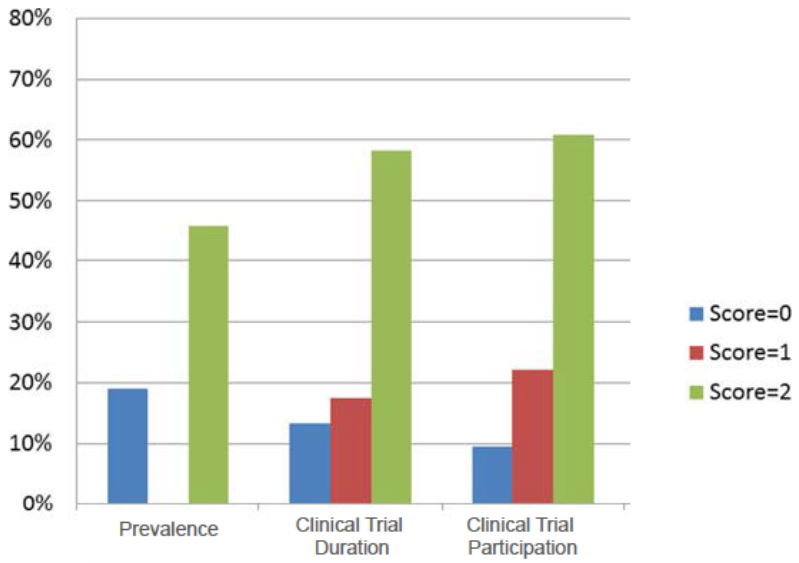

Figure 17. AODI Validation & Standardization (Florent, 2018)

As explained before, the Approved Orphan Drug Index (AODI) can be used as a diagnostic tool, where the condition diagnosed is probability of regulatory success of orphan drugs. A false positive in this scenario would be an AODI score indicating eventual marketing approval for a compound that will ultimately fail. A false negative would be an AODI score indicating failure for a drug that would ultimately succeed.

Figure above demonstrates the extent to which higher scores for individual factors are associated with probability of regulatory success of orphan drug. For AODI to be valid, it had to be tested using the FDA database of clinical trial from 1999-2017 with a total of (n=100) trials in phase II. For AODI to be a valuable tool in portfolio decision-making, higher values of the index must have greater predictive power. Clinical trial participation and clinical trial duration were both dominant factors. Prevalence scored low in association with probability of regulatory success of orphan drugs. Clinical trial participation is associated with probability of regulatory success of orphan drugs, as 61% of the drugs tested had a score of 2. Clinical trial duration was associated with probability of regulatory success of orphan drugs as 58% of the drugs tested had a score of 2. Rare disease prevalence also showed to be an associated with probability of regulatory success of orphan drugs as 45% of the drugs tested scored 2. AODI proves valid and can be used as a diagnostic tool.

Summary PART II: Building an algorithm of (AODI)

Table XIV. Summary of Part II: Building an Algorithm (Florent, 2018)

Research question	**Hypothesis**	**Outcome**
RQ4.1: Do shorter clinical trials increase the probability of regulatory success (PRS) of orphan drugs (OD)?	**H4.1:** Shorter clinical trials increase the probability of regulatory success (PRS) of orphan drugs (OD) **H4.1$_o$:** Shorter clinical trials decrease the probability of regulatory success (PRS) of orphan drugs (OD)	Fail to reject the hypothesis H4.1
RQ4.2: Do smaller clinical trials increase the probability of regulatory success of orphan drugs (OD)?	**H4.2:** Smaller clinical trials increase the probability of regulatory success (PRS) of orphan drugs (OD) **H4.2$_o$:** Smaller clinical trials decrease the probability of regulatory success (PRS) of orphan drugs (OD)	Fail to reject the hypothesis H4.2
RQ4.4: Does a lower rare disease prevalence increase the probability of regulatory success of orphan drugs (OD)?	**H4.4:** Lower prevalence increase the probability of regulatory success (PRS) of orphan drugs (OD) **H4.4$_o$:** Lower prevalence decrease the probability of regulatory success (PRS) of orphan drugs (OD)	Fail to reject the hypothesis H4.2

CHAPTER V

DISCUSSION

PART 1: Exploratory Research

When identifying factors associated with probability of regulatory success of orphan drugs in the systematic review; Orphan Drug Business Model (ODBM) 20.45%, Research and Development cost (35.60%) and Orphan Drug policy (23.48%) were the most common theories used and applied in orphan drug regulatory risk assessment. These results are consistent with literature review. Before the orphan drug act came into effect, academic research began to show rising of drug development costs (Hutt & Merrill, 1991). In the 1970s, the total cost of bringing a new drug to market was $182 million (in 2012 dollars), and by the 1980s, that number had risen to $205 million (in 2012 dollars) (Meekings, Williams & Arrowsmith, 2012). Current estimates of the total cost to bring a new drug to market are $1.5 billion (in 2012 dollars) (Meekings, 2012). The total cost of bringing a new drug to market includes: out-of-pocket costs, the cost of failures and the cost of capital (Sharma, et al., 2010) and only after a drug receives market approval, the pharmaceutical company can begin to recover the financial (Sharma, et al., 2010). For orphan drugs, the opportunity is diminished due to the limited pool of potential patients, which is one reason many pharmaceutical companies find it difficult to justify the investment required to develop treatments for rare diseases (Sharma, et al., 2010).

When looking at sub-category research and development of orphan drugs (R&D), competition (55%) and orphan drug development cost (35%) scored very high. This is also consistent with the literature as there is an association between orphan drug development and orphan drug regulatory approval. Orphan drug development is a risky venture. The small number of patients, despite the premium price, may not lead to high revenues and there is a significant risk of failure to reach and once this has been achieved, the probability of getting to market is likely to be much the same as the development of a non-orphan drug. Finch et al., 2015 addressed why both pharmaceutical and biotech companies want to develop drugs for rare diseases and whether orphan drug development is commercially viable mainly for the lack of competition.

When looking at sub-category orphan drug policy; rare disease prevalence (59%) and market exclusivity (25%) scored very high. These results are supported not only by the literature review that states that rare diseases are life-threatening or chronically debilitating disease that affects less than 200,000 people in the US but also by previous research of scholars in the field. It requires $1.5 Billion (in 2012 dollars) to research, develop and put through regulatory path a new orphan drug. Given the low prevalence of rare diseases there is a very low probability that two pharmaceutical companies would venture in a similar treatment for the same rare disease.

When looking at sub-category Orphan Drug Business Model (ODBM); clinical trial duration (43%) and clinical trial participation (27%) scored very high leaving company size (19%) and regulatory approval timeliness (11%) in 3rd and 4th place respectively. Small

patient population does not allow multiple parallel studies, so clinical study designs for orphan drugs have to be right first time. Pharmaceutical companies received protocol assistance for clinical trials as part of the Orphan Drug Act (ODA) incentive enrolling patients via patient advocacy groups such as: Global Genes, National Organization for Rare Disorders (NORD), OrphaNet and RareConnect. Clinical trial enrollment process is clearly different for orphan drugs than for non-orphan. In addition, these results also align with data found in FDA clinical trial database. Clinical trials for orphan drugs show small number of participants as demonstrated by Graboski in 1999. For example, when comparing number of participants enrolled in clinical trials for a new cardiovascular agent versus an orphan drug approved for hemo indication, the actual numbers are 230,000 versus 5 patients. The results of this study are supported by data found in public domain (Graboski, 1999). Explaining these results when we look in the orphan drug business model approach it seems like investing in research and development of orphan drugs for the treatment of rare diseases is an orphan business as of nobody wants to do it. The results obtain here explain a tangible problem pharma executive face every day when making portfolio go/no go decisions.

When comparing all three variables together in a multivariate context, clinical trial duration, clinical trial participation and rare disease prevalence, the results do not hold up meaning the result of this test was not statistically significant. See table XIV below:

Table XV. Univariate Association (together) between Potential Predictive Factors and the Probability of Regulatory Success (PRS) of Orphan Drugs (OD) (Florent, 2018)

Variable	**Coefficient**	**SE**	***p*. value**	**Odds Ratio**
Intercept	-1.0382	0.6616	0.1166	
Number of patients enrolled in Clinical Trials	-0.6413	0.5386	0.2338	13.606
Prevalence of Rare disease	-0.8858	0.5159	0.0860	0.170
Duration of Clinical Trials	-0.07349	0.5431	0.1760	3.230

Coefficient negative values represent possible inverse association

Odds ratio highlighted represent possible high association

p. <0.005 value for statistical significance

Statistical inference (logistic regressions) linked 3 variables to the probability of regulatory success of orphan drugs. In this logistic regression, three of factors taken together were clinical trial duration, clinical trial participation and rare disease prevalence because they have previously been identified in the quantitative meta-analysis and have shown significant statistical results in association with probability of regulatory approval of orphan drugs. However, a meta-regression provides a more useful and significant foundation for predictive purposes. The meta-regression analysis showed an inverse association between probability of regulatory approval and the independent variables with

an intercept value of -1.0382 and a *p. value* of 0.1166 meaning no statistical significance in these results.

Nevertheless, this test proves to be extremely helpful as it guided in terms of directionality of the three variables mentioned above. There seems to be an inverse association between the probability of regulatory success of orphan drugs and clinical trial duration, clinical participation and rare disease prevalence. Results about odds ratio also provided additional information about which factor, again when evaluated together, had higher association with probability of regulatory success of orphan drugs. Clinical trial participation scored high at 13.606 and as explain earlier, these results are consistent with information found in the literature review "low prevalence disease means less patients available to enroll in clinical trial" (Grabowski, 1999).

When evaluating the same factors now in isolation using a univariate association all three factors clinical trial duration, clinical trial participation and rare disease prevalence showed statistical significance results in association with probability of regulatory success of orphan drugs. An additional factor, research and development cost was included in the test as it showed predominance in meta-analysis but no statistical significance in the univariate association.

Table XVI. Univariate Association (in isolation) between potential predictive factors and Probability of Regulatory Success (PRS) of Orphan Drugs (OD) (Florent, 2018).

Factor	**Factor value**	**Percentage Approved (%)**	***p.* value**
Clinical trial duration	<18 months	46.7	0.0015
	18-36 months	14.8	
	>36 months	8	
Rare disease prevalence	<50,000	39.1	0.0020
	50,000-200,000	23.8	
	> 200,000	8.3	
Orphan drug development cost	<25,000MM	16.3	0.0401
	>25,000MM	36.7	
Clinical trial participation	<500 subjects	45.7	0.0010
	> 500 subjects	16.1	

p. <0.005 (value for statistical significance)

These results suggest that clinical trial duration, clinical trial participation and rare disease prevalence (number of patients with a rare condition) are highly associated with probability of regulatory success of orphan drugs. In addition to have statistically significant results in the univariate association test, it also corroborates the directionality (inverse association) of the independent variables as they associated with probability of regulatory approval of orphan drugs. Low clinical trial participation, low prevalence and short clinical trials are associated with higher probability of regulatory success of orphan drugs. These results are consistent with the literature review. For example, in 1999 Grabowski demonstrated that seven orphan drugs in phase III clinical trials had a mean of

588 patients with a range between 152 and 1281 total patients compared to an average of more than 5,000 subjects for a non-orphan drug (Grabowski, 1999).

PART 2: Building an Algorithm of Approved Orphan Drug Index (AODI)

In this second part of the discussion focus on the development and test process of an algorithm for predicting probability of regulatory approval of orphan drugs in order to provide a tool to improve orphan drugs portfolio decision-making.

First, an algorithm of Approved Orphan Drug Index also known as AODI was constructed. Given the results obtained from the univariate associations (factors evaluated in isolation) between clinical trial duration, clinical trial participation and prevalence of rare disease and probability of regulatory approval of orphan drug using a nonparametric chi-square test of association. AODI index was formulated as the sum of the scores for the three predictive factors as they showed in previous test to be statistically significant and also identified in the literature review.

Table XVII. Approved Orphan Drugs Index (AODI) (Florent, 2018).

	SCORES		
FACTORS	**0**	**1**	**2**
Clinical Trial participation	> 500 subjects	500-250 subjects	< 250 subjects
Clinical Trial duration	> 36 months	36-18 months	< 36 months
Rare Disease prevalence	>500,000 patients	200,000-500,000 patients	< 200,000 patients

The results for previous test suggest that there is an inverse association between clinical trial duration, clinical trial participation and rare disease prevalence, meaning probability of regulatory success of orphan drugs is associated with short clinical trial (duration), low clinical trial participation and low rare disease prevalence. AODI was constructed based on results from meta-regression and data available in the public domain for 100 drugs registered and approved by the FDA since 1999. For AODI to be a valuable tool and to be use in portfolio decision-making, the higher values of the index must have greater predictive power.

Table XVIII. FDA Clinical Trials (phase II interventional studies) 1999-2017 (FDA Database, 2017).

Sponsor	**Clinical Trial Title**	**Disease**	**Prevalence**	**Participation**	**Duration**
Allergan	A study of 2 dose of *MAP0010* in asthmatics adults.	Asthma (Common disease).	26,000,000	560 adults	74 months
Afferent Pharmaceuticals, Inc.	A study to assess the tolerability of a single dose of *Gefapixant (AF-219/MK-7264)* in subjects with Idiopathic Pulmonary Fibrosis (IPF).	Idiopathic pulmonary fibrosis (IPF) (Rare disease).	20,000	6 adults	20 months

Source: clinialtrial.gov results from 02/21/2018

FDA database of clinical trial under phase 2 interventional trials from 1999-2017 was used. AODI scores were calculated for *MAP0010* a new drug developed by Allergan for the treatment of asthma in adults. 26 million adult Americans currently suffer from this pathology. A total of 560 adults participated in this clinical trial phase two randomized test that lasted 74 months (FDA database, 2018). This new drug *MAP0010* developed for the treatment of asthma scored zero (0) in the AODI index which is logical and expected. Asthma is not a rare disease; it is a serious public health issue in the US that affects more that 200,000 Americans and there are multiple treatment and therapies available in the US market for it diagnose and treatment. However, the example of *Gefapixant (AF-219/MK-7264),* an orphan drug developed by Afferent Pharmaceuticals, Inc. for the treatment of idiopathic pulmonary fibrosis (IPF) a well-known rare condition (FDA database, 2018). IPF is a serious and debilitating rare disease that produce scaring of the lungs tissue. In the US only 20,000 adults suffer from this life-threating disease. *Gefapixant (AF-219/MK-7264)* scored two (2) in the AODI index. AODI was tested over 20 times using similar examples in 2018. Data from orphan drugs versus non-orphans (within the same therapeutic class) was tested and the results were very consistent (see Chapter IV validation and standardization of Approved Orphan Drug Index). AODI proves valid and can be used as a diagnostic tool in portfolio decision making of orphan drug regulatory approval.

Pharmaceutical companies have long used estimates of probability of regulatory success for orphan drugs in general and by therapeutic class as inputs in their decision-making regarding the formulation of their portfolios of investigational drugs and whether at various critical points during the development process to abandon or proceed. An easy-

to-apply algorithm was created to assist those decisions for orphan drugs registration. The AODI (Algorithm Orphan Drug Index) scoring metric was shown to be strongly associated with probability of regulatory success. The algorithm depends on only three factors, with its scale running from 0 to 2. The three factors were inversely related with probability of regulatory success of orphan drugs and the underlying rationales for their effects are less straightforward. The speed with which phase II testing was conducted may be an indicator of operational excellence and it could be an indication that the treatment community recognizes that the orphan drug has the potential to make a significant contribution to patient care. Finally, an inverse relationship between prevalence and approval success rates may indicate the lack of a recognized standard of care, more accurately defined patient populations, a lower hurdle for regulatory approval, or some combination of these conditions. An advantage of the AODI metric is that it will help pharmaceutical companies to assign more appropriate probabilities of regulatory success to good drugs.

Revised conceptual framework

After evaluating results, the conceptual framework for orphan drug regulatory approval looks as follow:

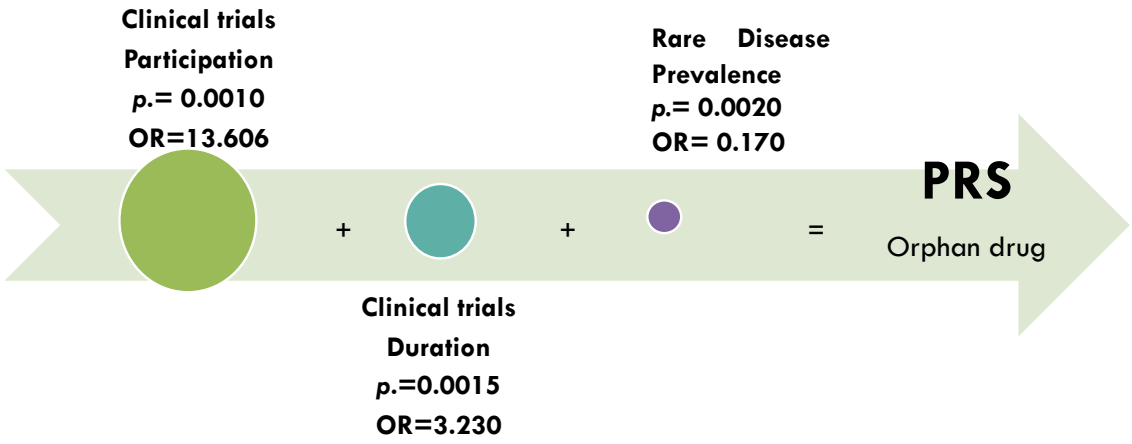

Figure 18. Revised conceptual framework for Probability of Regulatory Success of Orphan Drugs (Florent, 2018).

In chapter II, it was mentioned that all factors extracted from the literature review such as development cost, clinical trial duration, clinical trial participation and orphan drug tax credit contributed equally to the probability of regulatory success of orphan drugs. Today however, after conducting a systematic review of all the studies published and data available in the public domain. It is possible to confidently suggest that clinical trial participation, clinical trial duration and rare disease prevalence are the only factors that play a key role in association to the probability of regulatory success of orphan drugs. Figure 18. above shows study weight (odds ratio) to each factor that showed statistically significant association (in isolation) with probability of regulatory success however these

results do not mean that one factor weights more than the other when assessing the probability of regulatory success of orphan drugs. Clinical trial participation reported a high odds ratio as it intimately linked to rare disease prevalence. The low the rare disease prevalence the lower the clinical trial participation. It is also noteworthy to mention that reporting weights (odd ratio) is a very important requirement for the validity and reliability of a meta-regression.

Revised algorithm for orphan drugs regulatory risk assessment

Based on results obtained from the quantitative Meta-analysis, the original proposed algorithm was adjusted as follow:

Current for Non-Orphan Drugs

$$PRS\ (NOD) = \frac{\text{Competition (n)} + \text{R\&D cost (\$)}}{\text{Disease Prevalence (n)} + \text{ME (t)} + \text{company sales (\$)}}$$

Proposed for Orphan Drugs

$$PRS\ (OD) = \frac{\text{CT size (n)} + \text{CT duration (t)} + \text{R\&D cost (\$)}}{\text{Rare Disease Prevalence (n)} + \text{ME (t)} + \text{company size (ODTC) (\$)}}$$

Revised for Orphan Drugs

$$PRS\ (OD) = \frac{1}{\text{CT participation (n)} + \text{RD prevalence (N)} + \text{CT duration (t)}}$$

Figure 19. Revised Algorithm for Probability of Regulatory Assessment of Orphan Drugs (Florent, 2018)

Absent of validation datasets, and cognizant of the need to address generalizability, cross-validation was performed. While this technique does not eliminate the chance that selection bias influenced the results, the convergence of many repetitions on the same conclusions provides some assurance that the results are not overfit to the sample size used in this study.

$$\text{PRS } (MAP0010\ ) = \frac{1}{560\ (n) + 26{,}000{,}000\ (N) + 74\ (t)} \times 1000 = 0{,}0003846^{*}$$

$$\text{PRS } (AF\text{-}219/MK\text{-}7264\ ) = \frac{1}{6\ (n) + 20{,}000\ (N) + 20\ (t)} \times 1000 = 0.049$$

Figure 21. Calculations of Probability of Regulatory Success for Orphan and Non-Orphan Drugs (Florent, 2018)

In Figure 20. Using the same information of drugs found in FDA clinical trial database, a comparison was conducted between a non-orphan drug developed for the treatment of asthma *versus* an orphan drug developed for the treatment of idiopathic pulmonary fibrosis (IPF) .The first result from the non-orphan drug is null as this formula has been validated to be used only for orphan drug regulatory assessment meaning it is not

specific for non-orphan drugs. Factors associated with regulatory approval of non-orphan drugs are different in nature to orphan drugs as stated in the literature review. It is key to evaluate and consider other factors such as competition and company size which are not integrated in this formula hence it is not appropriate. The second result, however, is more appropriate and mathematical acceptable as it shows in Figure 21. It is not only appropriate to use the algorithm that has been validated for the assessment of regulatory approval of orphan drugs, but the results derived from this mathematical formula is absolute and correct. In the AODI index high scores are associated with high probability of regulatory success whereas in this mathematical formula (algorithm), values closer to one (1) is an good indicator of high probability of regulatory success of orphan drugs.

At the moment, it is not suggested that the scoring algorithm be used in a robotic fashion to make go/no-go decisions for orphan drugs in development, but rather that it be considered along with traditional success rate metrics and considerations specific to the drug in question. Using an algorithm to assign probability of regulatory success is not meant to preclude failure, nor is it meant to limit risk taking. Instead, assessing probability of regulatory success using an algorithm-based method might help to push resources into drugs for which support is logical and to limit ill-conceived risk taking of the sort that consumes considerable research and development resources.

Study Limitations

1) Personal bias: Empirical and practical knowledge of the regulatory process of drug approval specifically of orphan drugs. This limitation was mitigated by following Cochrane protocol for data gathering and a modified Delphi process with advisor (Hasson, 2000) to make sure the inclusion and exclusion criteria were applied appropriately without bias.

2) Generalization: In this case, because the lead researcher was conducting a quantitative meta-analysis the assumption is that the results are representative of all literature. This study limitation was mitigated by following Cochrane protocol.

3) Software availability: Specialized software CMA® and IBM™SPSS® regression was needed to conduct a quantitative meta-analysis. Lead researcher took advance statistical classes and used special meta-analysis software to ensure the results reflected are indeed correct.

4) Time and resources: this research was an intensive and thoughtful process that must be engaged for years, therefore time and financial investment is necessary to make proper connections and reasonable results outcomes. As lead researcher I mastered time–management as well as developed a personal tool to organize and classify studies.

5) Finally, having an excellent relationship with chair and committee. Makes all the difference. Being able to communicate honestly and effectively with the chair is essential including knowledge about the problem being sought to be analyzed. This level of support was critical to complete this study.

CHAPTER VI

CONCLUSION

Many factors were identified, compared and evaluated. Clinical trial duration, clinical trial participation and rare disease prevalence showed significant results as predicting factors in orphan drug approval as a result a revised algorithm specific for assessment of orphan drug risks was created.

The AODI metric and the results obtained can be viewed as part of the effort to improve drug portfolio decision-making. It would be helpful to obtain more complete data on orphan drugs than the one currently from the public domain. This is particularly true for clinical trial outcomes, especially safety characteristics. Additional information about characteristics of the drugs themselves and how those characteristics relate to targets and genetics could potentially also be very useful.

Pharmaceutical companies will now have a standardized tool that can be used to predict regulatory success. This academic incentive will encourage pharmaceutical companies to invest confidently in orphan drugs research and development. This model can now be tested and validated using the FDA drug approval database since the factors associated are link directly to the data available in the FDA approval database.

Future Research

It has been established that the next step of this research is to use data available in public domain about clinical trials for orphan drugs during phase III and use it to test the proposed algorithm as it was not tested for sensitivity and specificity. In addition, it would be a good idea to liaise with FDA office of Orphan Product Development to obtain specific data and calibrate proposed algorithm. It is the intention of this study to offer the proposed algorithm to senior leaders in the pharmaceutical industry who are looking to expand their orphan drug portfolio and study the real-life applicability.

Finally, it is the ultimate goal of this study to learn as much as possible about the tool and evaluate future pharmaceutical trends for example to create similar tool for ultra-rare diseases (<50,000) and rare cancers (identified industry trend).

Dissertation Significance and Conclusion

This study provides an objective means by which any pharmaceutical company can do a reasonable and reliable calculated risk analysis for orphan drug regulatory assessment and consequently increase orphan drug designation (ODD) in the US. By doing so, the industry will be increasing orphan drug access to patients.

Meta-analysis is an excellent tool to identify and evaluate factors associated with orphan drug approval in order to ascertain a reasonable and relevant algorithm that could be used in the industry.

Meta-analysis is valuable as a research methodology when prospective studies are not possible due to, for example, proprietary information not being allowed to be used for research purposes.

Meta-analysis provided a standardized approach for examining the existing literature on Orphan drug regulatory approval and its results refuted expert opinion and misconceptions.

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APPENDIX A

Letter to Institutional Review Board (IRB)

Milky C Florent
[redacted]

Mary F. Ruzicka, Ph.D.
Professor
Director, Institutional Review Board
Presidents Hall
400 South Orange Avenue
South Orange, New Jersey 07079

Re: **Milky C Florent Dissertation Study:** Seton Hall University Pre-IRB application submission.

November 10, 2017

Dr. Dr. Ruzicka,

Please find attached my IRB application for my dissertation study titled "Meta-analysis to identify and evaluate factors associated with regulatory approval of Orphan Drugs (ODx) to develop an algorithm for predicting regulatory approval (success) and to develop a standardized tool to improve orphan drug portfolio decision –making", for the Seton Hall's IRB's consideration and review.

Accompanying my application, please find attached appendices detailing additional information about the methodology I will be following, since I'm conducting a quantitative systematic literature review (published literature) and meta-analysis with no human subjects.

I appreciate your consideration of my IRB application and look forward to a hopefully favorable response. If you need anything further, please contact me at [redacted] or via email at [redacted]

Sincerely,

Milky C Florent, PhD Student, IHSA Department

Cc Dr. Deborah DeLuca (Dissertation Chair)

Joanne Deberto

APPENDIX B

First Letter from Institutional Review Board (IRB)

SETON HALL UNIVERSITY
1 8 5 6

December 6, 2017

Milky Florent
[redacted]

Dear Ms. Florent,

The Institutional Review Board at Seton Hall University has received the Application for your study entitled "Regulatory Approval of orphan Drugs (Odx) to develop and Algorithm for Predicting Regulatory Approval (Success) and the Develop a Standardized Tool to Improve Orphan Drug Portfolio Decision-Making."

However, it cannot be reviewed because documents submitted for Dissertation Proposal Approval and for approval from Pfizer, Inc. are both dated from 2015.

Please submit a statement from yourself and your mentor that what was approved in 2015 is still the same research submitted to the IRB in November, 2017.

Sincerely,
Mary F. Ruzicka, Ph.D.
Mary F. Ruzicka, Ph.D.
Professor
Director, Institutional Review Board

cc: Dr. Deborah DeLuca

APPENDIX C

Second Letter from Letter to Institutional Review Board (IRB)

SETON HALL UNIVERSITY
1 8 5 6

April 16, 2018

Milky Florent
[redacted]

Dear Ms. Florent,

The IRB is in receipt of the application for your research entitled "Regulatory Approval of orphan Drugs (Odx) to develop and Algorithm for Predicting Regulatory Approval (Success) and the Develop a Standardized Tool to Improve Orphan Drug Portfolio Decision-Making."

Your Application does not fall under the purview of the IRB, not even in exempt status, because your study does not involve human subjects. A systematic literature review and meta-analysis of data found in published studies is not human subjects research.

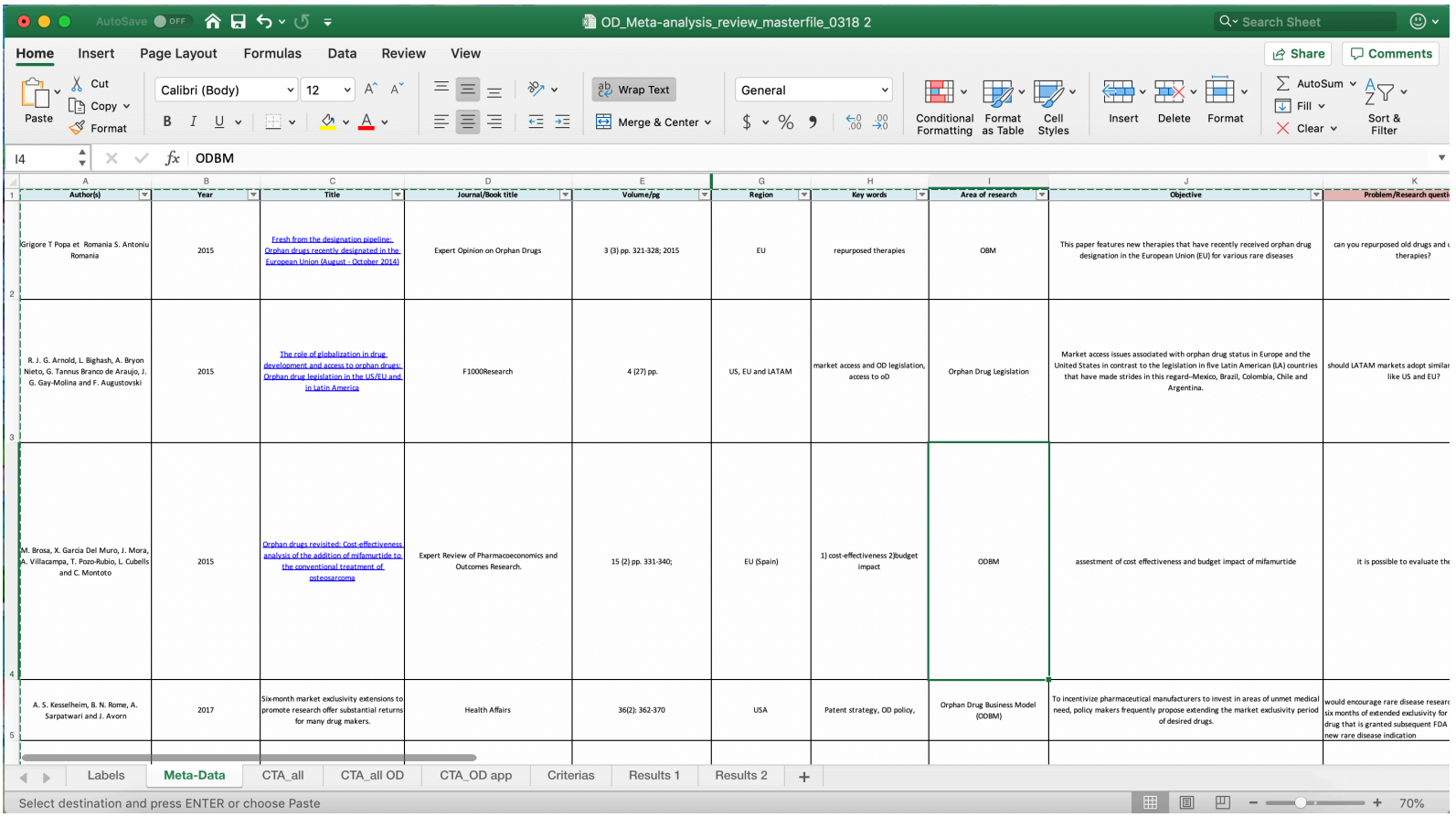
Sincerely,

Mary F. Ruzicka, Ph.D.
Professor
Director, Institutional Review Board

cc: Dr. Deborah DeLuca
cc: Dr. Terrence Cahill

APPENDIX D

Meta-Analysis (raw data) File



OD_Meta-analysis_review_masterfile_0318 2

Author(s)	Year	Title	Journal/Book title	Volume/pg	Region	Key words	Area of research	Objective	Problem/Research questi
Grigore T Popa et Romania S. Antoniu Romania	2015	Fresh from the designation pipeline: Orphan drugs recently designated in the European Union (August - October 2014)	Expert Opinion on Orphan Drugs	3 (3) pp. 321-328; 2015	EU	repurposed therapies	OBM	This paper features new therapies that have recently received orphan drug designation in the European Union (EU) for various rare diseases	can you repurposed old drugs and t therapies?
R. J. G. Arnold, L. Bighash, A. Bryon Nieto, G. Tannus Branco de Araujo, J. G. Gay-Molina and F. Augustovski	2015	The role of globalization in drug development and access to orphan drugs: Orphan drug legislation in the US/EU and in Latin America	F1000Research	4 (27) pp.	US, EU and LATAM	market access and OD legislation, access to oD	Orphan Drug Legislation	Market access issues associated with orphan drug status in Europe and the United States in contrast to the legislation in five Latin American (LA) countries that have made strides in this regard–Mexico, Brazil, Colombia, Chile and Argentina.	should LATAM markets adopt similar like US and EU?
M. Brosa, X. Garcia Del Muro, J. Mora, A. Villacampa, T. Pozo-Rubio, L. Cubells and C. Montoto	2015	Orphan drugs revisited: Cost-effectiveness analysis of the addition of mifamurtide to the conventional treatment of osteosarcoma	Expert Review of Pharmacoeconomics and Outcomes Research.	15 (2) pp. 331-340;	EU (Spain)	1) cost-effectiveness 2)budget impact	ODBM	assestment of cost effectiveness and budget impact of mifamurtide	it is possible to evaluate the
A. S. Kesselheim, B. N. Rome, A. Sarpatwari and J. Avorn	2017	Six-month market exclusivity extensions to promote research offer substantial returns for many drug makers.	Health Affairs	36(2): 362-370	USA	Patent strategy, OD policy,	Orphan Drug Business Model (ODBM)	To incentivize pharmaceutical manufacturers to invest in areas of unmet medical need, policy makers frequently propose extending the market exclusivity period of desired drugs.	would encourage rare disease researc six months of extended exclusivity for drug that is granted subsequent FDA new rare disease indication

Labels | Meta-Data | CTA_all | CTA_all OD | CTA_OD app | Criterias | Results 1 | Results 2

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