



a Case Study on the Decision-Making Behind the Development of Linezolid, Daptomycin, and Lysobactin.

Citation

Hunt, Avery. 2020. a Case Study on the Decision-Making Behind the Development of Linezolid, Daptomycin, and Lysobactin.. Master's thesis, Harvard Extension School.

Permanent link

<https://nrs.harvard.edu/URN-3:HUL.INSTREPOS:37365024>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available. Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

A Case Study on the Decision-Making Behind the Development of
Linezolid, Daptomycin, and Lysobactin.

Avery Hunt

A Thesis in the Field of Biotechnology Management Principles
for the Degree of Master of Liberal Arts in Extension Studies

Harvard University

May 2020

Abstract

There is a mounting crisis in treatment of bacterial diseases. The appearance of nosocomial infections produced by multi-drug resistant bacteria is rapidly increasing and at the same time the pharmaceutical industry has been exiting new antibiotic discovery. To help understand why, we investigated the decision making processes behind three novel antibiotics that were initially discovered in the late 1980's and early 1990's: daptomycin, linezolid and lysobactin. Each antibiotic was investigated by two highly qualified scientific organizations, each of which came to opposing opinions regarding the clinical utility and commercial potential of the drug. After reviewing the literature and interviewing key scientific staff members working on each of these molecules, we have identified factors needed to generate positive development decisions. Technical factors included investment in the optimization of dosing for improved drug exposure, toxicological evaluation and the failure to develop an effective research formulation. Organizational factors included decision timing, therapeutic area focus, organizational support for risk taking, and the presence of a project champion.

Acknowledgments

This thesis would not have been possible without the help of Donald Kirsch: my teacher, mentor, thesis advisor, and friend. His knowledge and enthusiasm for drug discovery, combined with his personal experiences and quirky stories during his tenure in the pharmaceutical industry inspired me to write this thesis examining the side of drug discovery that we don't read in journals or hear in the news. Thank you for your unwavering support throughout my professional journey.

Table of Contents

| | |
|-------------------------------------------------------------|-----|
| Acknowledgments..... | iv |
| List of Figures..... | vii |
| I. Introduction..... | 1 |
| Antibiotic Drug Discovery..... | 1 |
| What is an Antibiotic?..... | 3 |
| The Rise and Fall of the Antibiotic Era..... | 5 |
| Challenges and Opportunities in Antibiotic Development..... | 8 |
| Case Studies..... | 11 |
| II. Background..... | 12 |
| Daptomycin..... | 12 |
| Linezolid..... | 14 |
| Lysobactin..... | 16 |
| III. Results..... | 18 |
| Daptomycin..... | 18 |
| Linezolid..... | 20 |
| Lysobactin..... | 24 |
| IV. Discussion..... | 29 |
| Project Termination..... | 29 |
| Project (Re)initiation..... | 31 |

| | |
|-----------------------------------------|----|
| Timing is Everything | 32 |
| Importance of a Champion..... | 35 |
| Risk Taking vs. Risk Aversion | 39 |
| Therapeutic Focus..... | 41 |
| How Can We Make Better Decisions? | 43 |
| V. Concluding Remarks..... | 45 |
| Future Directions | 45 |
| VI. References..... | 49 |

List of Figures

| | |
|----------------------------------------------------------------------------|----|
| Figure 1: Overview of major antibiotics and mechanisms | 5 |
| Figure 2: Timeline of antibiotic discovery..... | 6 |
| Figure 3: Number of antibiotics reaching FDA approval by decade | 8 |
| Figure 4. Companies researching antibiotics vs. antibiotic resistance..... | 11 |
| Figure 5: Structure of daptomycin | 13 |
| Figure 6: Proposed mechanism of action of daptomycin..... | 14 |
| Figure 7: Structure of linezolid..... | 15 |
| Figure 8. Proposed mechanism of action of linezolid..... | 15 |
| Figure 9. Structure of lysobactin..... | 16 |
| Figure 10. Proposed Mechanism of action of lysobactin..... | 17 |

I. Introduction

Antibiotic Drug Discovery

Over the last 50 years antibiotic drug discovery has undergone significant decline. This is often attributed to the failure of researchers to discover novel antibiotics coupled with the plethora of known antibiotics readily available. However, this decline has recently become a serious concern in the medical community due to the ever-rising antibiotic resistance and fear that we are losing the “arms race” against infectious pathogens. Many refer to the 1950 to 1960’s as the “golden age” of antibiotic drug discovery where more than half of the antibiotics still used today were discovered (Aminov, 2010). After this time only two truly new antibiotic drug classes were discovered and approved by the FDA. By the 1970’s the pharmaceutical industry largely shifted their focus to developing derivatives of known antibiotics rather than discovering antibiotics with new mechanisms. Many left the infectious disease research area altogether as diminishing returns made it no longer profitable. The 1980’s marked a pivotal shift for antibacterial development programs when companies faced the decision of continuing to pursue this increasingly commercially risky therapeutic area or dropping their antibacterial programs in pursuit of new, more lucrative therapeutic areas. In the early years of this decade, three new chemical classes of antibiotics with novel mechanisms were discovered: cyclic lipopeptides, cyclic desipeptides, and

oxazolidinones by scientists at Eli Lilly, Squibb, and DuPont, respectively. Despite encouraging data for all three drug classes, the programs were terminated by each company (Eisenstein et al., 2010; Brickner, 2007). The reasons behind the termination of these programs was largely unknown with little information disclosed to the general public.

Two pharmaceutical companies were paying attention to these programs and made the decision continue development when the founding companies backed out. The first, Cubist, took a keen interest in Eli Lilly's lipopeptide, daptomycin, and decided to license the program from them and continue analog development and clinical trials. Eventually their new drug delivery regimen led to success and FDA approval in 2003. The second company, Upjohn, had already begun initial structural studies of oxazolidinones when news of the program termination at DuPont came out. Although it was still not even an official program at Upjohn when this occurred, a few scientists persisted with their research and it eventually led to full development and FDA approval of the first oxazolidinone: linezolid in 2000.

Interestingly, cyclic depsipeptide antibiotics were not pursued by any other pharmaceutical companies despite data released by Squibb showing antibacterial properties twice as potent as its comparator, vancomycin, which is the golden standard for the treatment of multi-drug resistant gram-positive pathogens to this day (Bonner et al., 1988).

Examination of the key factors that led to the unexpected stories of these novel antibiotics has not been thoroughly investigated. Specifically, why did the founding companies abandon these breakthrough projects with the chance to have first-in-class

drug in a therapeutic area that had not developed a novel mechanism of action in decades? What roadblocks did these companies face that prevented them from developing these drugs? Did the companies who resumed research have information or technology that gave them a competitive advantage? There are many reasons to initiate or terminate drug development programs in order to survive in the competitive pharmaceutical industry and decision makers must do their best to evaluate every possible factor that could affect the success of their programs.

This paper will focus on the key decision-making factors by the various stakeholders in each company that led to the termination of the first programs developing oxazolidinones, cyclic desipeptides, and cyclic lipopeptides and the subsequent successful development of linezolid and daptomycin. Specifically, what internal and external forces played a role in these choices? For internal forces, this thesis will examine the scientific knowledge, drug pipeline and therapeutic focuses, financial status, and the key-decision makers at each company. For external forces, it will discuss the state of the antibiotic market within the pharmaceutical industry, antibiotics on the market and in development, limitations in research, and emerging antibiotic drug resistance.

What is an Antibiotic?

An antibiotic is a drug that is designed to selectively inhibit the growth or destroy pathogenic microorganisms without harming the host cells. This concept dates back to 1910 when Paul Ehrlich sought out to develop a “magic bullet” treatment after he noticed

that some dyes would selectively stain bacteria and not mammalian cells and thus were specifically binding to the bacteria (this dye effect also led to the classification of gram-positive/negative bacteria based on staining). He believed that by altering the side chains of these dyes he could selectively kill microbes (Williams, 2009). During his research, he also designed the first true screening method by developing hundreds of organo-arsenic compounds and testing them against rabbits infected with *Treponema pallidum* (the syphilis pathogen). He finally succeeded with compound 606 (salvarsan) which became the first antibiotic available on the market and sparked a revolution in medicine with treatment against the once incurable syphilis. Although Salvarsan, containing highly toxic arsenic, was not the safest “magic bullet” to administer to humans it showed the scientific community the public and that bacterial infections can be selectively targeted with medicine and paved the way for safer and more effective antibiotics. Today, antibiotic mechanisms fall into two main categories: bactericidal and bacteriostatic. Bactericidal antibiotics function by killing the bacteria while bacteriostatic antibiotics prevent growth (Pankey et al., 2004). Bactericidal antibiotics are often membrane or cell wall disruptors that cause the bacterial cell to rupture whereas bacteriostatic antibiotics usually block a key step in nucleic acid synthesis or protein translation (Figure 1). In practical use these definitions are largely arbitrary to their therapeutic usefulness since antibiotics are prescribed for infections based on empirical data gathered from clinical trials (Pankey et al., 2004).

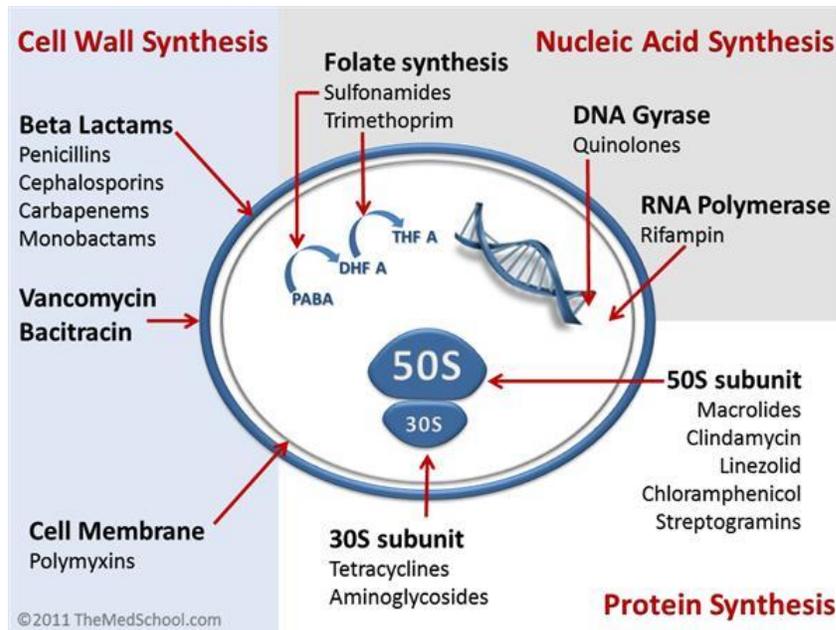


Figure 1: Overview of major antibiotics and mechanisms. (TheMedSchool.com, 2011).

The Rise and Fall of the Antibiotic Era

The success of the antibiotic era dates back to 1929 to the well-known discovery of penicillin by Alexander Flemming (Fleming, 1929). Fleming famously (and accidentally) discovered the antibacterial effects of *Penicillium* mold growing on his bacterial petri dishes. Despite his discovery of the penicillin substance and subsequent safety testing in both animals and humans, he was unable to isolate and purify the molecule to run true clinical testing on infected humans (Lax E, 2004). A decade later in 1940 an Oxford team led by Howard Florey and Abraham Chain devised a protocol to produce and isolate the molecule and showed its effectiveness in mice, yet yields were still too low to produce enough for human use. It wasn't until 1945, largely driven by the war effort, that a successful fermentation method was developed by Pfizer to mass-

produce and purify the drug for military and civilian use (Gwyn, 1975). After this breakthrough, research and development into new antibiotics exploded as other pharmaceutical leaders entered the race for novel antibiotics. Although Alexander Fleming ultimately failed to commercialize his discovery of penicillin, his famous method of visualizing the antibiotic activity of microorganisms against plates of pathogenic bacteria became the basis for antibiotic screening and led to the discovery of most of the major antibiotics (Aminov, 2010). The 1950-60's were rightly named "the golden age" of antibiotics when most antibiotic classes were discovered including about half of the most common drugs still used today (Davies, 2006). Figure 2 gives an overview of the different classes of antibiotics, introduction to the market, and first observed resistance. It should be noted that after the 1960's, no novel antibiotic mechanism was introduced until linezolid (oxazolidinone) and daptomycin (cyclic lipopeptide), more than 30 years later.

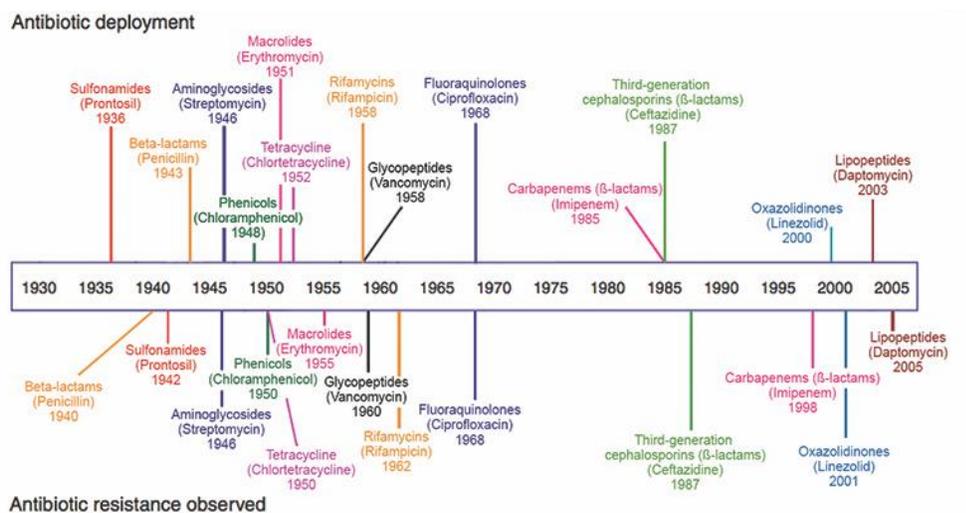


Figure 2: Timeline of antibiotic discovery: FDA approval (top) and observed resistance (bottom) (Clatworthy et al, 2007).

After the golden age of antibiotics, antibiotic discovery began to decline as major pharmaceutical companies began to exit the market in pursuit of more profitable therapeutic areas. This was driven both by the plethora of antibiotics already available and the lack of new antibiotic drug classes being discovered (Shlaes, 2015). Companies that still invested in antibiotics shifted their focus to modifying existing drug classes in the hopes of finding more potent derivatives, or derivatives that were active against resistant bacteria. This age of medical chemistry became the main strategy of most pharmaceutical antibacterial units after the golden age when it was clear that new antibiotics were not being found (Aminov, 2010). By the 1980's many pharmaceutical companies abandoned antibiotic development altogether as profitability in the area fell dramatically. This was caused by dwindling demand for new antibiotics as the best in class drugs seem to have been found and the rise of multi-drug resistant pathogens were not yet a major problem. Furthermore, highly profitable drugs in new therapeutic areas were entering the market that shifted the pharmaceutical industry to refocus efforts on more lucrative areas such as cardiology (ACE inhibitors, statins), immunology (vaccines, anti-inflammatories), and oncology (chemotherapies). By the 1990's many pharmaceutical companies once known for championing infectious disease programs such as Eli Lilly, Bristol-Myers Squibb, and Aventis began downsizing and exiting the area as well. The number of antibiotics approved in the 1990's compared to the 1980's was halved from 42 to 21 (Tomasi, 2018). This number continued to decline with only 15 new antibiotics approved between 2000 and 2018 (Figure 3)

Number of new antibiotics

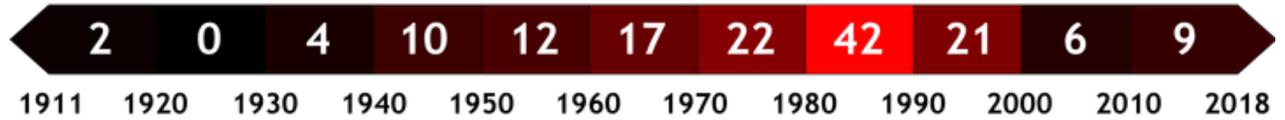


Figure 3: Number of antibiotics reaching FDA approval by decade. (Tomasi, 2018)

Challenges and Opportunities in Antibiotic Development

Although the lack of discovery of novel antibiotic drug classes led to the end of the golden age of antibiotics, it is ultimately the broken antibiotic market that has become the greatest deterrent for pharmaceutical companies willing to investment in antibiotic programs (Shlaes, 2018). The protocol for antibiotic prescription to treat infections by doctors advises the use of older antibiotics while withholding newer ones for only when a resistant bacterial infection is encountered. While this practice is appropriately employed to prevent the inevitable spread of drug resistant bacteria, it leaves pharmaceutical companies with an obvious disincentive to develop new drugs. Why would a company develop a drug that will not be frequently used and thus not generate profit? In the late 1970's the pharmaceutical industry saw the emergence of the first blockbuster drugs (\$1 billion dollars per year in sales): Tagamet (cimetidine) and Zantac (rantidine) for the treatment of stomach ulcers/acid reduction, and Capoten (captopril) for hypertension (Krecklel PA, 2018). These drugs were hugely profitable because they required once a day dosing, often for the rest of a patient's life. This achievement was eye-opening to the industry and drove many pharmaceutical companies to refocus their R&D efforts on

treatments for chronic diseases or lifestyle medicines that will require continual use. Although other factors are involved (population size, pricing, etc.), the sales difference between a daily-dose drug vs. a 7-10 day antibiotic regiment once in a patient's lifetime is clear-cut. This was further compounded by the fact that new antibiotics were restricted to reserve formulary. Even now, the few pharmaceutical companies still brave enough to risk developing new antibiotic therapies and successfully reach FDA approval often do not make back the cost of development. For example, Achaogen Inc., a pharmaceutical company focused on developing novel antibiotics to multi-drug resistant (MDR) bacteria, recently reached FDA approval of its first drug, Zemdri, (plazomicin) on June 18, 2018 after 15 years of development. Zemdri is the first antibiotic specifically designed to treat Carbapenem-resistant Enterobacteriaceae (CRE), a bacterium that kills around half of those it infects. It was hailed as a great achievement for the medical community in the fight against growing resistance but financially it was a complete failure. Its sales in the first 6 months on the market were less than \$1 million. Achaogen was forced to file bankruptcy less than a year after Zemdri's approval (Achoagen press Release, 2019). Zemdri was not the only antibiotic failure in recent years. Only 5 of the 16 antibiotics approved between 2000 and 2015 made more than \$100 million a year (Daniel GW, et al., 2017). The market for antibiotic has been struggling for decades.

Despite the difficulties facing the market, the emergence of new drug resistant bacteria has escalated in parallel with demand by the medical community for the need to develop new antibiotics to face the current danger as older antibiotics become obsolete. Vancomycin, discovered in the 1950's, was hailed as the golden standard gram-positive antibiotic that was impervious to bacteria resistance. Its mode of action (MOA) involves

binding to a conserved substrate of the bacterium's peptidoglycan cell wall rather than an enzyme prone to mutations that can evade small molecule inhibition (Hammes WP and Francis NC, 1977). However, after four decades of use the first vancomycin-resistant enterococci was reported in 1988 and resistant or tolerant strains continue to rise. (Leclercq R, et al., 1998). Meanwhile, methicillin-resistant *Staphylococcus aureus* (MRSA), once a rare occurrence isolated to hospital outbreaks, is now commonplace in the human population, identified in almost 50% of isolates from human samples (CDC, 2014). Despite the increase in resistant pathogens, Pharmaceutical companies have been steadily abandoning antibiotic drug discovery since the 1980's (Figure 10). Organizations such as the CDC and ISDA have tracked the movement and abundance of resistant strains and it is clear that the problem is getting worse every year. From the late 1980's into the 1990's specifically, resistance to the hallmark antibiotic erythromycin and vancomycin appeared to be on the rise and the need for new gram-positive antibiotics became evident. It was in this era that the three novel antibiotic classes that are the subject of this case study were discovered. However, what appeared to be a grand opportunity for the founding companies of these antibiotics turned into failure, only for two to be saved by different companies and turned into blockbuster drugs.

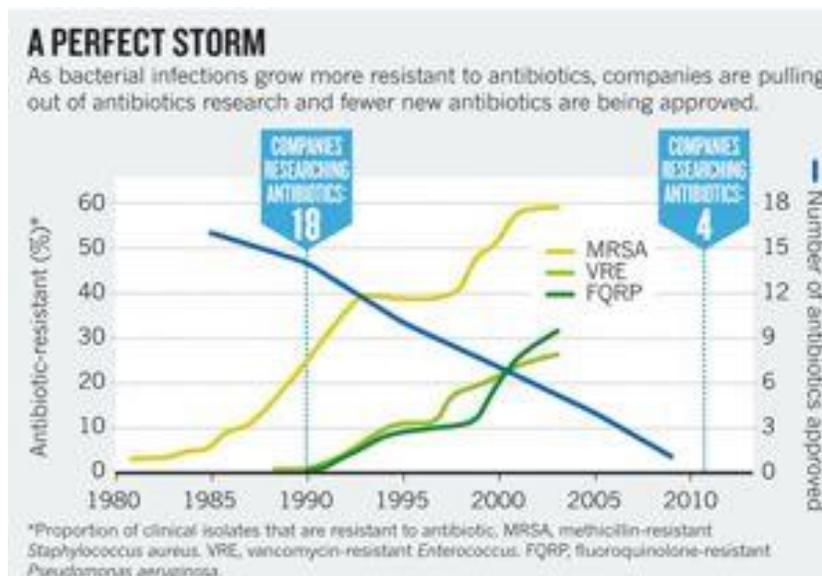


Figure 4. Companies researching antibiotics vs. antibiotic resistance. 1980-2010 (Cooper & Shlaes, 2011)

Case Studies

This thesis will analyze the decision making by stakeholders of the various companies involved in three different antibiotic programs: cyclic lipopeptides, oxazolidinones, and cyclic depsipeptides. Each program garnered significant attention and resources by the pharmaceutical industry in the 1980's and 1990's but were dropped by the companies who discovered them. However, the drugs continued to receive scientific interest and new companies initiated their own projects which led to the development of linezolid (oxazolidinone) and daptomycin (depsipeptide lipopeptide), which were approved by the FDA in 2000 and 2003, respectively. Interestingly, lysobactin (cyclic depsipeptide) has not been further developed by any pharmaceutical

companies despite promising efficacy data (Bonner et al. 1988) and a recently discovered novel mechanism of action (Lee et al, 2016).

II. Background

Daptomycin

Daptomycin is a 10 membered cyclic lipopeptide made up of 13 Amino acids (Figure 4). It is a natural product first isolated from *Streptomyces roseosporus* from a soil sample by Eli Lilly scientists (Tally and De Bruin, 2000). It was the first drug of its class discovered to have antibiotic properties against gram positive bacteria (Baltz et al, 2005). Although the exact mechanism of action has not been defined, it has been shown to disrupt the outer membrane in a calcium dependent fashion, causing rapid depolarization and cell death. Most hypotheses agree this is driven by insertion of the decanoic acid lipid tail in a phosphatidylglycerol fashion where it aggregates to cause leakage in the membrane (figure 5). Daptomycin is active against a broad spectrum of gram-positive bacteria and is well-known for its effectiveness against hard to treat or resistant infections such as MRSA, glycopeptide-intermediate *Staphylococcus aureus* (GISA), and vancomycin-resistant enterococci (VRE) (Vilhena and Bettencourt, 2012). Daptomycin is provided as an intravenous formulation for 900 mg/g for a 30 min dosage once per day. Due to this capability, it is used as a “last-resort” option when first line antibiotics have failed in order to help prevent resistant strains of bacteria from arising (WHO).

Daptomycin was first discovered and developed by Eli Lilly before being licensed by Cubist where development was completed, and the drug was brought to market in 2003 under the trade name Cubicin. Cubicin became a blockbuster drug for the company, steadily rising in sales each year from \$68.1 Million in 2003 to \$754 million in 2011. In 2014 sales surpassed \$1 billion under the new ownership of Merck (Merck sales report, 2014).

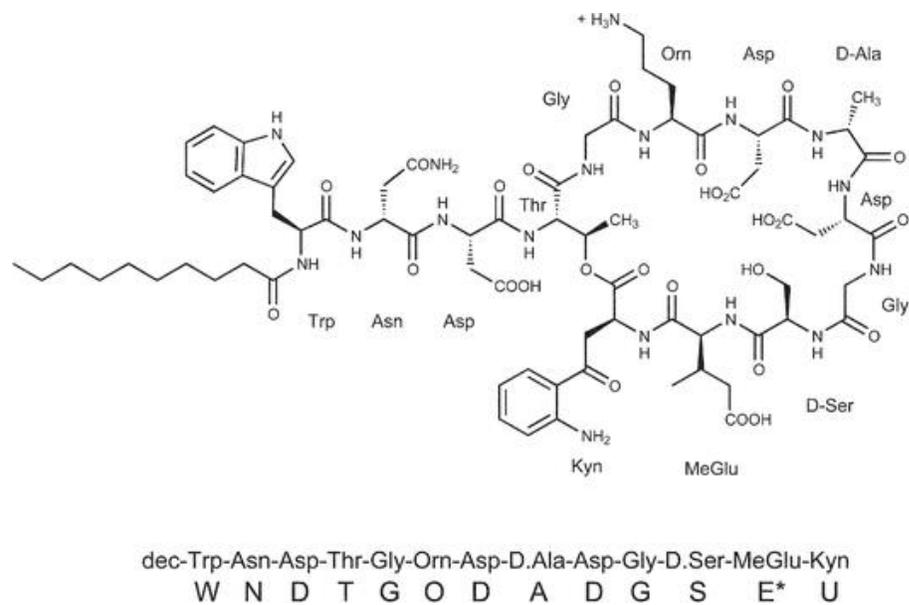


Figure 5: Structure of daptomycin. A cyclic lipopeptide and its amino acid core structure (Ball et al., 2002)

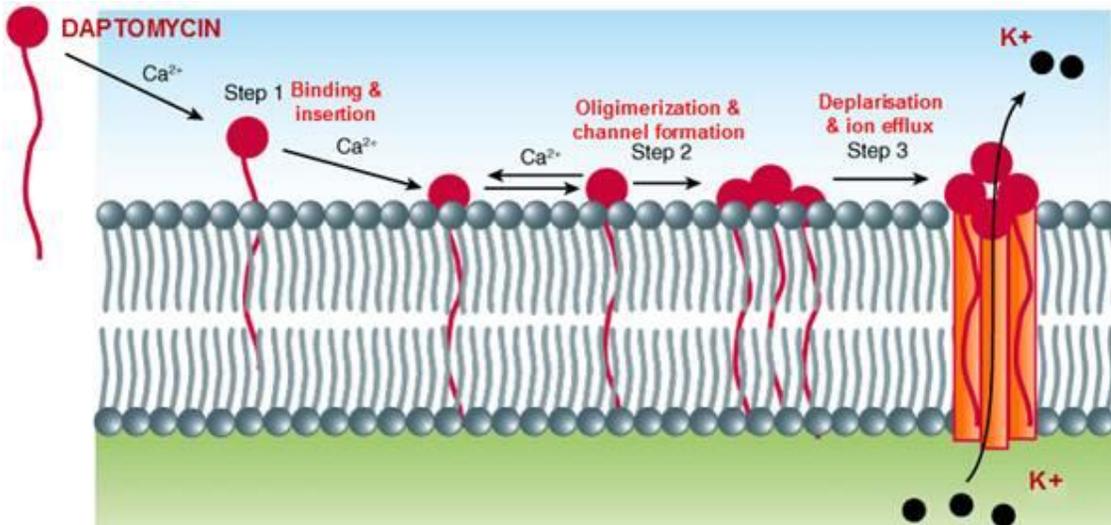


Figure 6: Proposed mechanism of action of daptomycin. The phosphatidylglycerol tail inserts itself into the cell wall where it aggregates and causes depolarization and a loss of membrane potential. (antibiotics-info.org, 2016)

Linezolid

Linezolid is a small molecule synthetic drug in the oxazolidinone class of compounds (Figure 6). Oxazolidinone antibacterial properties were discovered in a screening effort by DuPont for a plant anti-infective for the agricultural industry. DuPont discontinued development after preclinical experiments deemed them unsafe, but an independent effort at Upjohn led to the discovery and approval of linezolid in 2000 (then Upjohn & Pharmacia) under the trade name Zyvox. Linezolid is protein synthesis inhibitor with a unique MOA of blocking the formation of the initiation complex composed of the 30S and 50S ribosome rather than a downstream part of synthesis (Figure 7). Linezolid is used for the treatment of serious Gram-positive bacteria that are resistant to other antibiotics. It is used a last-resort antibiotic when alternatives have failed because of its unique MOA and broad spectrum. Linezolid has absolute oral

bioavailability, meaning 100% of the drug taken orally is absorbed by the bloodstream. This gives it an advantage over other gram-positive last resort antibiotics that must be taken intravenously. Linezolid sales were in the low hundreds of millions during its initial years but rose steadily to become a blockbuster drug by the turn of this decade reaching peak sales between \$1.5 and 2 billion dollars under the ownership of Pfizer (Shlaes, 2017).

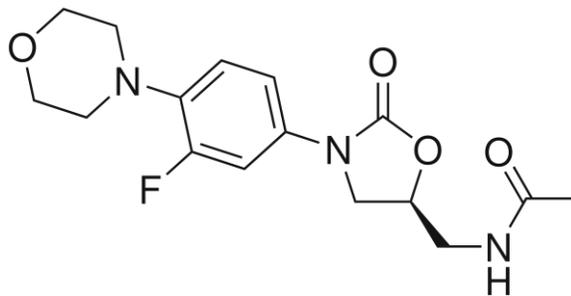


Figure 7: Structure of Linezolid. An oxazolidinone (Wikipedia.com, 2009).

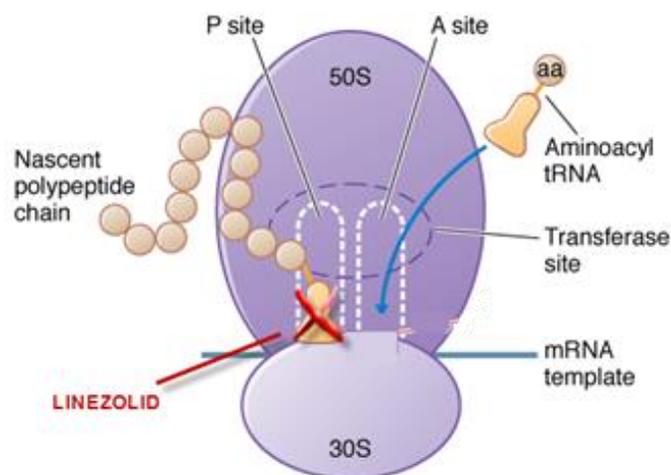


Figure 8. Proposed mechanism of action of linezolid. Binds to the P site of 50S ribosomal unit preventing binding of the 30S subunit which prevents protein synthesis (antibiotics-info.org, 2016)

Lysobactin

Lysobactin is an 11 amino acid cyclic depsipeptide isolated from *Lysobacter sp* (Figure 8). It was identified independently by groups at Shinogi Research Institute and Squibb in 1988. Researchers at Squibb filed a patent and conducted preclinical experiments showing 2-4 fold increase in potency vs vancomycin against aerobic and aenorbic Gram-positive bacteria. Additionally, they provided evidence of a different cell wall synthesis inhibition MOA than vancomycin-like antibiotics (O'Sullivan et al., 1988). In 2016, a group of Harvard researchers confirmed this (Figure 9). However, there was also evidence of higher acute toxicity vs vancomycin (Bonner et al., 1988). Lysobactin did not reach clinical development.

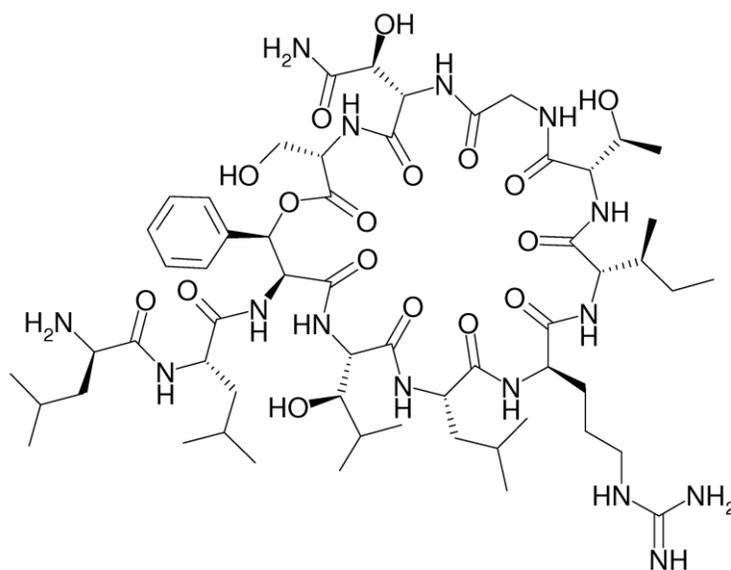


Figure 9. Structure of lysobactin. A cyclic depsipeptide (Wikipedia.org, 2007).

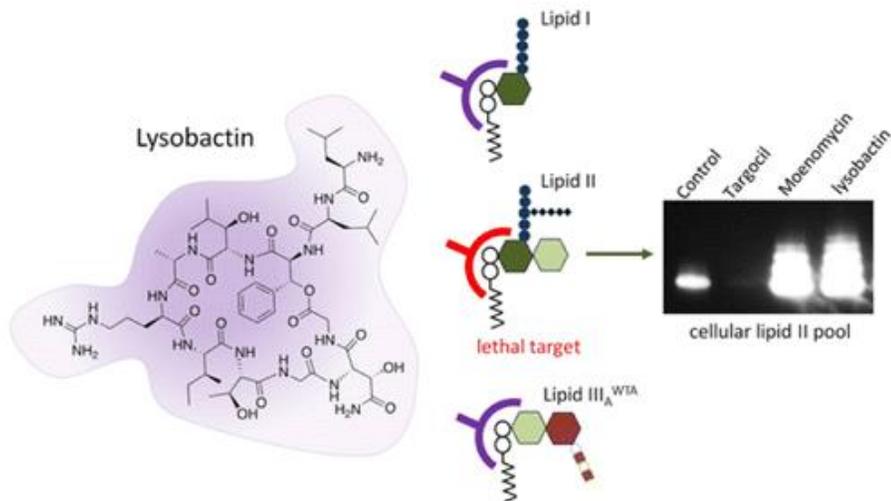


Figure 10. Proposed Mechanism of action of lysobactin. Binds to lipid I, lipid II and lipid III_A^{WTA} substrates of the peptidoglycan and wall teichoic acid biosynthetic pathways. The inhibition and buildup of lipid II ultimately causes lethality (lee et al., 2016).

III. Results

Daptomycin

Daptomycin was discovered by a team of Eli Lilly scientists screening a soil sample from Mount Ararat in Turkey for antibiotic producing microorganisms (Baltz et al, 2010). The isolated bacterium, *Streptomyces roseosporus*, produced a family of related lipopeptides with antibiotic properties (Baltz et al, 2005). Under the leadership of Richard Baltz, daptomycin was chosen as the ideal candidate for development because of its low toxicity and efficacy in initial animal models. Eli Lilly began clinical studies of intravenous daptomycin in the late 1980s. Initial phase I and II studies looked promising and didn't lead to any health problems in volunteers. However, the pharmacokinetic studies showed that the drug exhibited high protein binding and may only provide sufficient drug exposure for 6 hours (Woodworth et al, 1991). This led to new phase I and II trials using twice daily doses. During the phase II trial, a dosage of 6 mg/kg every 12 hours successfully treated *Staphylococcus aureus* bacteremia in patients, but the investigators believed a higher dosage would be needed to effectively treat a full range of infections, requiring additional studies. In the final phase I study at 8mg/kg every 12 hours, 2 out of the 5 volunteers developed muscular toxicity and increases in creatine phosphokinase kinase leading Eli Lilly to conclude that the therapeutic window may be too narrow to pursue in future trials. This led to the decision to suspend phase II trials,

revisit the genetic studies on *S. roseosporus* and explore new biosynthetic pathways to produce lipopeptide analogs (Eisenstein et al, 2010). They did this using genetic methodologies for cloning the biosynthetic genes of daptomycin to generate hybrid molecules. Eventually, lipopeptide research ended in 1996 when Eli Lilly abandoned its natural product antibiotics program altogether accompanying the downsizing of its Infectious Disease Discovery Division. This decision was driven both by the industry shift away from antibiotics as well as a new focus target-based drug discovery approaches which became popular with advances in genomic screening (Eisenstein et al, 2010).

Meanwhile, Cubist Pharmaceuticals was in search of a drug for its pipeline after its recent founding in 1992 with the singular focus of developing drugs against infectious disease. This was quite an anomaly during an era when larger pharmaceutical companies (such as Eli Lilly) were leaving the area. Cubist recruited Dr. Francis Tally as their CSO in 1995 and he soon set his sights on in-licensing daptomycin from Eli Lilly. This decision was made soon after hearing a short seminar on lipopeptide antibiotics from R.H. Baltz who was visiting Cubist for a job interview. (Eisenstein et al, 2010). R.H. Baltz recalls Tally saying: “Don’t be surprised to see me at Lilly, because I am going to license daptomycin for Cubist to develop” (R. H. Baltz, personal communication; Eisenstein et al, 2010). Cubist completed licensing of daptomycin a year later. Dr. Tally believed that a good therapeutic index existed and worked closely with Frederick Oleson to understand the pharmacokinetics of the antibiotic that led to the muscle toxicity issues that had troubled the Eli Lilly clinical trials. They built on Eli Lilly’s work to understand the systemic dosing effects and correlation of C_{max} (peak serum concentration of a drug)

or AUC (total bodily exposure to a drug) to toxicity. In 1998 Cubist started a crucial canine study to elucidate this problem. Through this diligence they found an unanticipated result in which a single high dosage of 75mg/kg every 24 hours had significantly fewer adverse effects vs 25 mg/kg every 8 hours while still providing equivalent amounts of daptomycin exposure to the canines in terms of AUC (Oleson et al, 2000). This led to the resumption of clinical trials using once daily dosing of daptomycin to treat gram-positive infections. Daptomycin was approved in 2003 under the trade name Cubicin for treatment of gram-positive skin and skin-structure infections. It is now also used to treat serious vancomycin and other drug resistant gram-positive infections and has become most profitable IV antibiotic ever. (Eisenstein et al, 2010).

Cubist took a chance to pursue antibiotics and license daptomycin while larger pharmaceutical companies were abandoning their research. Despite the external shifting paradigm, it is clear that internal forces at Cubist saw an opportunity and made the right decision.

Linezolid

Linezolid is an oxazolidinone derivative with development that dates back to the 1970's. Oxazolidinones as a structural class were first characterized as Monoamine Oxidase Inhibitors in the 1950's (Riain et al., 2010). DuPont discovered their effectiveness in treating bacterial and fungal plant infections in a wide scale screening exercise and patented a series of them in 1978 (Fugitt et al, 1982). This was followed by a further patent in 1984 for bacterial treatment in mammals. In 1987, Slee et al published

the first data on the in vitro and in vivo efficacy of two preclinical candidates, DuP-105 and DuP-704 along with their novel mechanism of action. Despite the hype and promising discovery of a new class of antibiotics, preclinical studies pointing to lethal bone marrow toxicity in rats led DuPont to abandon the project altogether (Jadhaver, 2015).

Although toxicological data was not publicly shared, word of mouth came out that acute toxicity in rats was discovered during preclinical development and DuPont decision makers concluded they could not achieve a viable therapeutic index. Toxicology of oxazolidinones was also investigated later by independent researchers, which supporting this finding (Renslo, 2014). Robert Taber Ph.D., Director of Pharmaceutical Research at DuPont during this period, recalls: “We found many active compounds but none that didn’t cause profound weight loss in rodents of repeat dosing which we determined was caused by liver toxicity. We made and tested a lot of oxazolidinones but never found any that met our safety criteria.” (Tabor, personal communication, 2019). DuPont abandoned further oxazolidinone research in early 1989 amid extensive strategic planning that resulted in dropping of the infectious disease area altogether.

It is important to understand the historical context of pharmaceutical business at Dupont to analyze why this seemingly promising project was abandoned. Historically DuPont was a chemical research company known for its production of various polymers and agricultural products. With the growing importance of pharmaceuticals worldwide, DuPont wanted to capitalize on their diverse chemical library and set up new screening operations for plant and human therapeutics. Their first FDA approved drug was Symmetrel in 1966, a prophylactic used to treat Influenza. Understanding that they lacked

real expertise in therapeutics, they acquired Endo pharmaceuticals in 1969 for their pharmaceutical experience, which helped them market the drug and expand their research capabilities. The combination of DuPont's chemical library and Endo's research platform formed their first drug discovery capabilities. At the time, they did not have a specific therapeutic focus and purposefully pursued a wide range of therapeutic targets to investigate the capabilities of their chemical matter to become useful drugs. Dupont still did not have extensive expertise in preclinical and clinical development while they were developing this pharmaceutical research platform. In the mid 1980's, the pharmaceutical arm of DuPont went through an extensive strategic planning that resulted in the dropping of the infections area to focus on other prospects (Tabor, personal communication, 2019).

Although DuPont abandoned the project, it did not stop other researchers from continuing to explore oxazolidinone derivatives. This chemical class represented a novel mechanism of action in antibiotics, which was not ignored by antibiotic researchers that hadn't seen a new one in over two decades. In particular, the Brickner lab at Upjohn took a keen interest upon DuPont's disclosure of their two leads Dup-105 and Dup-721 at the 1987 meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. They immediately began a small side project exploring their own oxazolidinone structures and antibacterial properties (Brickner et al., 2008). At the time, Upjohn had a policy that researchers could allocate 10% of their time to their own independent projects which allowed for this research to happen. Dr. Steven Brickner's lab, consisting of himself and two other researchers, generated a series of novel oxazolidinone structures and began to examine SAR antibacterial properties. Although they had some promising leads, it was still not a fully endorsed project by Pharmacia by

the time that DuPont announced the failure of their two clinical compounds. Despite the news, Dr. Brickner continued his research and recruited Dr. Richard Piper's pathology lab to help quickly study the toxicology of their lead compounds. Bricker explains that they sought to "(1) establish the existence of a structure-toxicity relationship (STR) within the oxazolidinone series and (2) identify a viable means of focusing, as earliest as possible, on those oxazolidinone subclasses having the most favorable safety profiles" (Brickner et al., 2008). To do this they employed a novel month long, animal sparing study, dosing mice at 10-fold the ED50 of the drug in a comparative study vs the Dup-721 (Piper et al, 1996). This provided a quickly robust, if not comprehensive, toxicity screen. Dr. Brickner describes: "This was quite a huge hurdle, and it allowed us to have a robust outcome that said, yes, our compound was not toxic, whereas the racemic Dup-721 tested under the same conditions in rats was toxic, and lethal in several animals. This was such a critical aspect for our continuation of the program" (Brickner, Personal communication, 2019). Two years later Uphon filed an IND on two clinical leads that maintained the efficacy of the DuPont compounds without the accompanying toxicity (Brickner, 1996). Phase I trials of the drug showed remarkable tolerability. Gastrointestinal events such as diarrhea or nausea were the only side effect observed (Hutchinson, 2003). Phase II and Phase III trials continued to show success in the treatment of multi-drug resistant strains of *Enterococcus*, *Staphylococcus*, and *Streptococcus*. Linezolid was approved by the FDA in 2000 under the tradename Zyvox as injection, tablets, and oral suspension. It soon became a top seller and one of the most important drug against antibiotic resistant gram positive bacteria. Sales topped at \$1.3

billion in 2014 under the ownership of Pfizer before its patent expired in 2015 (Pfizer 2014 financial report).

DuPont's termination of the oxazolidinone project sent red flags to all researchers investigating this new antibiotic class. From a managerial viewpoint, a project should be a "no go" if the original discoverers and patent holders of a drug ended preclinical trials without any further investigation or attempt to license to a new company. Without the background context it certainly seems counterintuitive that Upjohn continued research on oxazolidinones when it wasn't even an official project recognized by management. Ironically, the fact that it was *not* yet an official Upjohn project (still a 10% allotted time by Upjohn side research project) allowed Dr. Brickner to continue his work without push back from higher decision-makers. Through his tenacity and help of willing colleagues, the work of a few scientist were soon able to demonstrate that oxazolidinones could achieve a good therapeutic index, which launched the full scale development and approval of the first oxazolidinone antibiotic

Lysobactin

In the wake of growing vancomycin resistance and the search for an alternative, the researchers at Squibb devised an ingenious two-plate assay system to identify vancomycin-like compounds, by seeding agar plates with a complex cell wall preparation containing +/- diacetyl-lysyl-D-alanyl-D-alanine (the vancomycin substrate binding substrate). Agents of interest were selected by identifying smaller inhibition zones on the

site containing the substrate. Lysobactin was identified as the most promising candidate with a 2~4-fold increased potency over vancomycin against Gram-positive bacteria without any sign of rapid resistance development. However their paper reported one experiment of acute toxicity in mice with an LF50 of 77mg/kg iv and 132mg/kg ip compared to >400mg/kg iv and >1000mg/kg ip with vancomycin. However, the LD50 concentration was still more than 30 times higher than the ED50 calculated to treat systemic infections (Bonner et al., 1988). Coincidentally, a separate group of researchers at Shionogi Research laboratories described two new antibiotics isolated from *Cytophaga sp.*: katanosin A and katanosin B (lysobactin) in the same year (Shoji et al., 1988).

Despite the promising results and a discovery patent on Lysobactin, Squibb did not pursue any preclinical development (Donald Kirsch, personal communication, 2019). Internally, there was much pushback from decision-makers given their current strategical outlook. One factor was Squibb's recent success with captopril, the First ACE inhibitor to reach market in 1980. The success of the drug put in perspective the profitably that can be achieved with a pill-every-day vs a one and done treatment that antibiotics represent (Joe O'Sullivan, personal communication, 2019). There was also pushback against developing another antibiotic after the disappointment of their previous one, the monobactam aztreonem. Aztreonem was a narrow spectrum antibiotic representing a new class of beta lactam-derivatives to be brought to market. Despite its poor spectrum compared to other beta-lactams, Richard Sykes, the Director of Microbiology championed the project to get the drug to market. He succeeded in pushing the through development at Squibb despite its poor profile and unsure market outlook. The monobactam became a pharmaceutical flop with poor sales and little clinical significance.

A few years later lysobactin came on the scene but the key players in the monobactam program were heavily against supporting another questionable antibiotic and gave minimal resources to the initial development. After the initial screening and isolation of the molecule, Adrienne Tymiak Ph.D, a Principal Investigator in natural products isolation and structure elucidation, worked on lysobactin chemistry with the help of only one assistant. She used bioactivity guided isolation to purify the active component and determine the structure. The state of NMR mass spectrometry at this time made the task extremely difficult given the size and cyclical structure of the compound. It was eventually determined through a combination of spectroscopy, degradative studies, and single amino acid analyses. While initial structure characterization was difficult, producing and investigating a series of analogs was an even bigger hurdle. Adrienne explains: “I explored the structure/activity relationships for lysobactin analogs through semi-synthesis (through degradation and synthetic modification of the natural product and its degradants), however was unable to generate an active analog that lacked toxicity. I was unable to generate a sufficient quantity of a macrocyclic lactam analog of lysobactin to test whether a stabilized cyclic variant would be similarly potent and less toxic” (Adrienne Tymiak, personal communication, 2019).

Proper compound formulation and delivery were also poorly understood when toxicological studies were carried out. Bonner et al, 1989, provides data of only one toxicology experiment on rats with vancomycin as a comparator. Adrienne notes “to me, it was unclear whether the toxicity results were exaggerated by the crude mode of drug delivery in the toxicology testing. The toxicity was observed within minutes of injection, suggesting to me that the lysobactin could have precipitated out of solution almost

immediately.... I am not convinced that the in vivo toxicity testing actually evaluated the toxicity potential of the intact lactone. Once the lactone was opened, the linear peptide retained in vitro toxicity but no longer had antibiotic activity.... Today, the very insoluble and relatively unstable lysobactin could have been formulated by a pharmaceuticals expert in a variety of different ways to better test its potential for efficacy while minimizing toxicity". Unfortunately, both the chemistry and discovery teams' sentiments were outweighed by the toxicology data and the dissenters in management. Joe O' Sullivan, a scientist on the Lysobactin project, remembers "the organization/management was exhausted from the monobactam battles and there was no champion, even though the compound was more potent than vancomycin, the LD50s were still high... instead of celebrating a novel MOA, it was painted as a failure and Sykes turned against the project" (personal communication, 2019). The lack of chemical expertise to generate analogs with improved toxicology relative to vancomycin, coupled with the disappointment of aztreonem and subsequent loss in faith in profitability of antibiotics, quickly led to termination of the project without further research. Furthermore, the announcement of other competitors in the space with less toxic molecules (such as daptomycin) condemned lysobactin to be a non-viable lead at Squibb with no effort to out-license the compound (Tymiak, personal communication, 2019).

Lysobactin was largely forgotten by the industry in a few years and Squibb (Bristol-Myers Squibb after the 1989 merger) and closed its infectious disease division (Donald Kirsch, personal communication, 2019). There have only been handful of publications involving lysobactin since the 1988 breakthrough, but nothing

groundbreaking until a recent group of Harvard researchers discovered its novel mechanism of action 28 years later (Lee et al., 2016).

Squibb's decision to drop a novel antibiotic 2~4 times more potent than vancomycin with still seems questionable given their lack of understanding behind the toxicity. At the time, other researchers were pursuing vancomycin-like antibiotics. Bonner et al, 1988 acknowledged that lysobactin exhibited a similar microbiological profile to LY146032 (daptomycin) which was reported only a year earlier. However, Lilly decided to pursue Daptomycin into clinical trials before they ended clinical trials out of their own toxicity concerns in 1996. Squibb appeared to be in an analogous drug development position in 1988 and decided against moving forward.

IV. Discussion

Project Termination

Linezolid and lysobactin shared a similar story in which the projects never got past preclinical phase due to toxicity concerns that seemingly weren't properly investigated. Lysobactin, from the start, lacked a "champion" in management to advocate for the project following the economic failure of their recently approved monobactam aztreonem. The simple toxicology experiments in mice, as reported in Bonner et al, 1988, was the "definitive data" they used to terminate the project. However, the chemistry lead, Adrienne Tymiak, noted that the acute toxicity may have simply been due to insolubility of the formulation and, at the time, she lacked the resources and the technology to synthesize investigate safer analogs. Furthermore, soon after these findings Squibb underwent a merger to become Bristol-Myers Squibb in 1989, in which their natural products divisions were combined leading to reevaluation of drug priorities in which lysobactin was left behind. Squibb soon moved away from natural product antibiotics and infectious diseases altogether. Similarly, Oxazolidinones at DuPont lacked the resources and R&D expertise to thoroughly investigate the preclinical toxicity of their compounds efficiently and they were unable to show a good safety profile (Robert Tabor, personal communication, 2019). This is evidenced by the fact that the Brickner lab separately identified a compound they deemed safe which was to be their lead candidate before

discovering was already under the DuPont patent (Brickner. , 2008). DuPont eventually had a reevaluation of their pharmaceutical strategy in the mid 1980's. Due to the failure of their first two leads and better prospects elsewhere, similar to Squibb, the decision was eventually made to drop the infectious disease department all together (Robert Tabor, personal communication, 2019).

Daptomycin had a different termination story than Linezolid and Lysobactin, in which decisions did appear largely data driven. The lipopeptide class was discovered around the same time as lysobactin with a comparable spectrum of activity, but the compound underwent extensive semi-synthetic SAR work by Eli Lilly scientists to produce an analog with a good therapeutic index (Boeck et al, 1988). This is in contrast to lysobactin, which appeared to be much more difficult compound to characterize and synthesize stable analogs. Once Eli Lilly got past their toxicity concerns with a promising lead compound, the company appeared committed to see the project through.

Unfortunately, phase 2 clinical trials showing adverse muscle toxicity led decision makers to conclude that the therapeutic window was too small and the drug was shelved to continue research into other lipopeptides (Eisenstein et al., 2010). As it would turn out, the clinical scientists failed to devise a dosing scheme (as was later implemented in Cubist clinical trials) that would limit systemic exposure to the drug.

There is a saying in the pharmaceutical industry that is a good lens for this analysis: If a project is going to fail, fail well and fail early. In other words, figure out and analyze the definitive experimental data needed that will determine whether a project should move forward or be terminated, and figure it out quickly before development costs start to add up (Booth, 2013). Did these projects “fail well” given the resources and

knowledge they had at their disposal? This is a hard question to answer because the decisions were not singularly based on data alone. One can argue that the founding companies of oxazolidinones, cyclic lipopeptides and cyclic desipeptides had enough data to conclude that there was no clear path forward. However, it is clear that there were additional factors driving the decision to end these projects. These factors will be further examined.

Project (Re)initiation

The stories of the first cyclic lipopeptides and oxazolidinones failures were not lost to Cubist and Upjohn, respectively. However, each company had something in common in having key individuals in the right place and time who saw opportunity when others saw failure, and took the risk to continue research. Through their insight they were able to reexamine the projects and carry out the right experiments with the help of the right people to push their projects past the toxicity issues seen by their predecessors.

For daptomycin, this person was Dr. Francis Tally, the CSO at Cubist Pharmaceuticals. A career medical scientist in infectious diseases and antibiotics, he was recruited to Cubist in 1995 to jumpstart their vacant antibiotic pipeline, and as noted earlier, immediately worked to license daptomycin from Eli Lilly. Although he had not previously worked on lipopeptide antibiotics, he was familiar with the work through his correspondence with R.H. Baltz at Eli Lilly (for the full story refer to Eisenstein et al., 2010). Another vital factor to daptomycin's development was the recruitment of new

talent for the job. Frederick Oleson joined Cubist to work with Dr. Tally on developing new formulation and treatment options on the same day that the in-licensing of daptomycin was finalized. Together they examined the Eli Lilly clinical trial data, and seeing incongruities, decided that a solution may be possible with daptomycin rather than trying to produce a new lipopeptide. Despite the phase II failure at Eli Lilly, they took the risk to reinitiate the iv program with a new treatment regimen and to try to elucidate the muscle toxicity issues with the drug. Their intuition proved to be right and a safe dosing schedule was achieved that allowed daptomycin to eventually achieve FDA approval.

The oxazolidinone project at Upjohn, similarly, would not have occurred without Dr. Brickner. He began his own research in recognition of the potential of oxazolidinone antibiotics before it was endorsed by Upjohn management. Furthermore, he took the risk to continue his work after the demoralizing news that DuPont was unable to find a safe compound. Like Dr. Tally, his research would not have been able to progress without the recruitment of additional help. Pathologist Dr. Richard Piper volunteered to collaborate with him and designed the crucial toxicity studies that allowed them to quickly characterize their compounds, leading to the discovery that some of their lead compounds appeared safe at 10-fold their ED50 values.

Timing is Everything

An important factor to consider in the decision-making of these projects is the timing in terms of the both the state of the companies and the state of the antibiotics in

relation to the pharmaceutical industry as a whole. It is clear that all of the founding companies were shifting away from antibiotics and infectious disease programs (as was most of the pharmaceutical industry) to focus on more lucrative investments. This process was evident at Squibb where sales of captopril were booming to become its first blockbuster surpassing \$1 billion in sales the late 1980's (Congressional Record, 1992). At the same time their new monobactam was bringing in only \$50-60 million (New York Times, 1987). Similarly, Eli Lilly decided to end natural products as improvements in genomics made target-based drug discovery the new industry standard. This opened doors to new therapeutic areas which in turn led to the downsizing of their infectious disease research (Priest and Erdemli, 2014). DuPont was in a different position in which their pharmaceutical division was entirely new addition to the company. They used a broad strategy to develop their pipeline by utilizing their large chemical library and targeting several therapeutic areas without bias. A decade later, they reevaluated their strategy by looking at what was working well, and narrowed their focus on the most promising opportunities. Unfortunately, oxazolidinones and the infectious disease division did not make the cut.

While most pharmaceutical companies were exiting antibiotic research, others saw growing opportunity to develop novel agents to treat the growing number of resistant pathogens. (Shlaes, 2015). During the 1990s it was becoming increasingly apparent that vancomycin-resistant, and multi-drug resistant bacteria were on the rise correlated with the demand by the medical community for new treatments. Both Upjohn and Cubist were acutely aware of this while developing their oxazolidinone and cyclic lipopeptide programs, and it was factored in on whether profitability would be realized if their drugs

reached approval. It can be argued that the ~5-10 year gap between discovery of these classes and initiation of clinical trials at Upjohn and Cubist was a critical time period in persuading the strategic teams to move forward, given the concurrent rise of resistance and dearth of antibiotics being developed. It should be reiterated that the discovery of oxazolidinone and cyclic lipopeptide antibiotics were both disclosed in 1987 around the same time that the first vancomycin resistant infections were reported. However, it wasn't until the 1990's that the true dangers of VRE and multi-drug resistant pathogens became publicly accepted after communal outbreaks were reported in increasing numbers (Handwerger et al, 1993, Shlaes and Bradford, 2018). Indeed, after the oxazolidinone project was approved by senior discovery management at Upjohn, "...the team formulated a set of distinct goals and a strategy for identifying compounds having vancomycin-like activity and other attributes worthy of entering clinical trials.... focused on finding compounds with in vitro and in vivo activity vs MRSA that was comparable to or better than vancomycin" (Brickner, 2008). Similarly, at Cubist, when Tally and Oleson decided to reinstate IV clinical programs of daptomycin they factored in "increasing rates of vancomycin-resistant or intermediately susceptible gram-positive organisms in hospitals" (Eisenstein et al., 2014). This critical evaluation may have been the key decision for moving forward with daptomycin immediately rather than continuing research on new lipopeptides.

Timing is clearly an important factor in decision-making for any drug development project. For the antibiotics in this case study, the founding companies may not have seen the full profit potential of their drugs despite the increasing incidences of antibiotic resistance being reported every year. By the time Upjohn and Cubist evaluated

the antibiotic landscape years later, scientists in both companies were acutely aware of the pharmaceutical need these novel antibiotics could fulfill. This timing helped drive the decision to continue with development.

Importance of a Champion

Another important factor determined from this analysis is the importance of a key player to “champion” a disputed project and lead it through development. It appears that the discovering companies of the three drugs of this subject lacked a leader who saw potential in further developing the projects (Eli Lilly may be omitted as they put in a significant amount of research under the leadership of Richard Baltz). However, Dr. Brickner and Dr. Tally at Upjohn and Cubist, respectively, stepped up to become “champions” of these projects despite widespread doubt that the novel antibiotics could be developed into FDA approved drugs. Through the framework of key players, or lack thereof, we can see their influence on the decision-making at each company.

Dr. Brickner and Dr. Tally were both “champions” of their projects meaning that they stepped up to advocate, promote and lead the development of these projects. They took the risk of owning these projects, and through their scientific expertise paved a path forward to successful development. At Upjohn, Dr. Brickner was allowed to work independently on his oxazolidinone chemical and pharmacokinetic research as part of the company's 10% personal project time allocation. Since he had no oversight from managerial decision-makers, he was able to pursue research on oxazolidinones amidst the

growing doubt of the chemical's potential to be a drug. Dr. Tally, on the other hand, was the CSO of Cubist. He was hired to make the risky decisions and in which he had the ultimate choice (unless the CEO intervened). Cubist was also under pressure to get something in their stagnant pipeline and Dr. Tally saw opportunity to get a clinical stage drug into their portfolio. Additionally, both Dr. Brickner and Dr. Tally had additional scientific knowledge of the projects that DuPont and Eli Lilly lacked. At Upjohn, Dr. Brickner and his team had longstanding experience in medicinal chemistry and were able to efficiently synthesize, test, and characterize safe oxazolidinone antibiotics where DuPont's new pharmaceutical research group failed to do so. At Cubist, Dr. Tally and his team identified a disparity in the Eli Lilly clinical trials that prompted them to re-initiate the i.v. program of daptomycin using a new dosing scheme. These advantages led to more informed decision-making driven by Dr. Brickner and Dr. Tally to push the projects through development.

While Dr. Tally and Dr. Brickner were instrumental to the success of their projects, the key players at the discovering companies did not see a feasible path forward and thus did not speak up in support. As a result, the projects lacked a champion to advocate or influence decision-making to keep them running.

At DuPont, the oxazolidinone project did not have a clear champion due to the lack of scientific expertise or experience in antibiotic development. After the pharmaceutical division formed, Dr. Robert Tabor was recruited in 1982 to become director of Pharmaceutical Research and was responsible for heading research in CNS, Cardiovascular, Immuno-inflammatory, Cancer and Infectious Disease. Working below him was Martin Forbes, the head of Cancer and Infectious Disease Biology. It is evident

by the umbrella of therapeutic areas they oversaw that DuPont was agnostic to their research and was focusing on understanding their capabilities first. As Dr. Tabor explains, “the idea was to identify new therapeutic uses in the DuPont chemical library... my initial charge was to identify any promising leads or drug discovery opportunities that we might expeditiously convert to potential products” (Robert Tabor, personal communication 2019). They lacked specific expertise in any specific area so they cast a wide net to see what caught and could become profitable. They had very little personnel expertise in antibacterial research and the oxazolidinones were their first antibiotic screening program. After their failure to identify and leads that passed met their safety criteria, their evident lack of a champion with antibiotic expertise led to DuPont to drop the infectious disease area along with the oxazolidinones to pursue better prospects elsewhere.

Eli Lilly had a very different background in which they had a longstanding history in pharmaceuticals and antibiotic discovery in particular. They discovered some of the most important antibiotics still widely used today such as vancomycin and erythromycin in the 1950’s, to cephalexin in 1970. However, by the early 1990’s Eli Lilly was experiencing the same antibiotic R&D and sales losses that led to many of their competitors to exit the therapeutic area. At the same time, the daptomycin i.v. clinical study was struggling to reach their safety criteria and scientific leaders, such as Richard Baltz, were focusing on genetic studies to produce new cyclic lipopeptides rather than advocating for daptomycin as their best path forward. The new Vice President for Infectious Diseases Discovery at Eli Lilly, Barry Eisenstein, also advocated against continuation of the clinical trials. As a result, daptomycin had no champion to lead a path

forward amidst the clinical struggles. Eli Lilly shelved further clinical trials in hopes of a new candidate to emerge from Baltz's lipopeptide genetics work (Eisenstein et al., 2008).

At Squibb, decision-makers were still shaking off the frustration of the monobactam flop when the new antibiotic lysobactin was brought to their attention. The antibiotic activity was extremely promising, but the pharmacokinetic profile was poorly understood and the single safety profile raised red flags immediately. There is evidence by the speed at which the project was terminated that management was not willing to risk developing a potential failure. The new head of drug discovery, Bill Scott, was thoroughly against it, saying that "only an idiot would pursue the development of lysobactin" (Donald Kirsch personal communication, 2019). However, many scientists directly working on the project believed there may have been a path forward. Joe O'Sullivan, a biochemist on the project, recalls "a decade earlier, Lysobactin would have raced to the clinic. But times had changed: the organization/management was exhausted from the monobactam battles and there was no champion – I was too new to the industry to fight the right way" (personal communication, 2019). Adrienne Tymiak believed that the limited technology in working with the complex cyclic non-natural amino acid molecule led to an incomplete understanding of the chemistry and toxicology results. She ultimately conceded with the decision to drop the project due to the data they had in hand. "The biologists involved in toxicity evaluation had a strong voice in driving the decision to drop the project... given the limitations of technology and expertise at the time... I understood and accepted the decision to terminate the project" (personal communication, 2019).

It is clear that no one wanted, or was willing, to champion the project given the conditions at Squibb. It may be that the managerial decision-makers made the right decision and no safe formulation or analog would have been possible. Or maybe not. Without a champion, lysobactin development was never resumed. To date, it is unknown whether the novel antibiotic class has the right characteristics become a successful antibiotic alongside linezolid and daptomycin.

Risk Taking vs. Risk Aversion

Drug development is always a gamble and pharmaceutical companies' must hedge their bets to expect more failure than success. This is necessary given that on average, only about 1 in 10 drugs entering clinical trials will reach FDA approval (Hay et al., 2014). This high failure rate often leads decision-makers in pharmaceuticals to focus more risk aversion strategies to minimize development losses by only choosing very (perceived) promising drugs into clinical trials.

At Squibb it was evident that they were focusing on risk aversion and "high success" drugs after the monobactam flop and contrasting captopril blockbuster. Through this development, decision-makers had a new lens in R&D to focus on highly lucrative drugs to make up for their less profitable development pathways. In addition, the head of drug discovery, Bill Scott, was famously risk averse and was quick to find reasons to stop projects. For example, he was opposed to the development of the statin drug, pravastatin, on safety concerns. Pravastatin was pursued despite Bill's objections and went on to

become a billion dollar a year selling blockbuster drug. As a result of a culture of risk aversion Squibb saw a much smaller number of drugs entering their pipeline in the 1990's (Donald Kirsch personal communication, 2019). Once lysobactin showed signs of toxicity, it was quickly rejected by management without considering more pre-clinical research in what they perceived from past experiences was a risky therapeutic area.

Dupont and Eli Lilly took a more intermediate stance in their risk-taking towards antibiotics. They invested in further development of their projects despite some risk but got out appropriately once a more complete evaluation of their drugs was achieved. For DuPont, this occurred after extensive SAR investigation of oxazolidinones in which their chemists were unable to decouple toxicity with antibiotic activity. For Eli Lilly, termination occurred only after multiple clinical trials led them to believe a therapeutic index up to the FDA's standard could not be achieved.

Cubist and Upjohn, on the other hand, were extreme risk-takers by resuming projects that were determined to be unsuitable for development by the discovering companies. Cubist took this risk largely because they were running out of time to get a drug into development. Cubist was a new company focused solely developing novel antibiotics while other pharmaceutical companies were exiting the area. Four years after their found they still had little to show for their efforts with no lead compounds in development. With a therapeutic focus increasingly known for failure, Robert Tally recognized the need to take risks that big pharma wouldn't take and went ahead to license the lipopeptide research from Eli Lilly. For Cubist and daptomycin, it turned out to be worth the risk. Upjohn, similarly, took the risk to continue its oxazolidinone research despite news of failure out of DuPont. Dr. Brickner, specifically took personal risk by

owning the project and recruiting others to design and carry out toxicity studies rather than dropping his research and saving face at the high chance of failure. Like Cubist, this risk-taking led to success.

Perhaps champions are just risk takers who are willing to place a bet on doing something of potential great value at the risk of doing much damage to their careers. In the two cases where there were champions, things worked out handsomely for them because their bets paid off well. Perhaps we do not have a lot of counter examples where the champion was wrong because their careers were crushed, and their stories were never told.

Therapeutic Focus

It is clear that shifting therapeutic focuses played a large role in the decision-making by each of the companies. The pharmaceutical industry, as was mentioned in-depth already, was struggling to discover novel antibiotics and recoup high costs of development, pressuring them to exit the therapeutic area altogether. However, internally each company had its own therapeutic priorities to support their strategic pipelines.

Squibb, of course, felt enormous pressure to exit antibiotics after the challenging development of aztreonam was topped off with disappointing sales. They abandoned antibiotic research a few years later with greater focus on cardiovascular therapy and more lucrative areas. Again, this came when the success of captopril was fully realized with increasing annual sales. They strategically focused their efforts to find another such

blockbuster drug financial transformative potential (Bristol-Myers bought Squibb largely based on the profitability of captopril).

DuPont at the time was still trying to find its therapeutic identity for its fledgling pharmaceutical department. They had an agnostic stance towards their therapeutic focus, instead strategically casting a wide net against a plethora of targets to see if their large chemical library had certain strengths in specific areas. In the mid 1980's they evaluated the results of this strategy which led to ending the infectious disease research area to pursue better prospects elsewhere.

Eli Lilly has had a longstanding history and dedication to infectious disease therapeutics. They dedicated many years of research and several clinical trials trying to get their lipopeptide program through FDA approval, but it was all met with disappointment. During this time Eli Lilly was also embracing the genetic revolution and target-based discovery for developing new drugs and decided to end their other natural product antibiotics program altogether, seeing it as obsolete (Eisenstein et al., 2015). This shift away from natural products, the foundation for most historical antibiotics led to a major downsizing of their infectious disease program and a shift towards other therapeutic areas.

For Upjohn, their success with oxazolidinones was more serendipitous rather than having anything to do with therapeutic strategic planning. As mentioned previously, it was Dr. Brickner insight and independent research that led to the early success and eventual adoption of the program into Upjohn's official portfolio. Without this early success, Upjohn would likely not have pursued further antibiotic research. Cubist was quite the opposite with their sole therapeutic focus being antibiotics and having very little

success in their early in-house R&D efforts. Licensing of Daptomycin was a needed risk to get their pipeline going.

How can we make better decisions?

This thesis has examined the many factors that drive decision-making in pharmaceutical industry using three antibiotics as case studies. It is clear that the choices these companies made were not simply a matter of numbers or guessing and the analysis of their decision making requires an in-depth look behind the scenes at each organization. Internal politics and the influence of champions, timing of development, therapeutic focuses, and risk-taking were all evaluated in this analysis. After examining these case studies, the question remains: how can pharmaceutical companies make better drug development decisions? Once the decision to initiate a project is made, data gathered during research should be the main factor driving decisions on whether to pursue certain courses of action (Phil Needleman or similar reference). As we saw from these case studies, the founding companies all terminated their projects once they believed they had enough data to bar a path forward. It is up to managers to make decision given the data on hand. Amidst uncertainty, there is little decision-makers can do except gather more data. Of course, in the pharmaceutical industry we have learned that if you're going to fail, it is best to fail early, so this comes down to a decision again factoring in the amount of risk one is willing to take. As this paper has deduced, internal and external factors also

play a critical role when these points of uncertainty in the project are reached. It's rarely obvious in pharma to know when you have enough data.

An important factor that clearly affected decision-making in these case studies is the importance of a leader to champion the project. From these case studies, it is clear that ownership of a project can drive or drop a project in spite of good or bad data supporting a drug. For the founding companies, it seemed that lack of expertise and confidence by the leaders ultimately drove the decisions to terminate. In contrast, scientific insight and willingness to take risks by the leaders at Upjohn and Cubist led to initiation of the uncertain projects. Another factor to consider is that larger pharmaceutical companies may be more risk averse because they have the benefit of choosing the least risky projects from their large research portfolios or use their resources to begin new research. New or smaller companies (such as Cubist in this case) may be more inclined to risk-taking if they do not have another option in their portfolio or resources to begin a new project,

In conclusion, decision-makers in pharmaceutical drug development must use the data on hand and evaluation of the pharmaceutical landscape and decide what level of risk they are willing to take. The high level of risk-taking by Upjohn and Cubist led to monumental success but this is often not the case. It is impossible to foresee whether a drug will get past criteria of clinical trials or correctly forecast the sales of a drug upon FDA approval. It is up to key leaders with expertise in both science and management to champion promising projects despite uncertainty from their peers.

V. Concluding Remarks

Future Directions

Experts on all sides agree that the antibiotic development system is broken. The medical community has increasingly been warning the public that we are losing the arms race against bacteria and demanding new drugs, yet fewer antibiotics are reaching FDA approval, and those that do have a high chance of not recouping development costs. However, there has recently been a resurgence in antibiotic R&D as pharmaceutical companies appear to be listening to the medical communities call while the FDA has lessened the strictures in the development pathway with support of the government program GAIN.

As of June 2019, there were 42 new antibiotics in clinical development (PEW Charitable Trusts, 2019). This comes amidst the growing reality of multi-drug resistance bacteria while some of the most vital antibiotics are becoming less useful in fighting infections. The golden standard gram-positive antibiotic, vancomycin, was once thought to be impervious to antibiotic resistance since it targeted a conserved cell wall structure (rather than a highly mutable enzyme). Forty years later it began to lose its effectiveness and fully resistant genes encoding new cell wall substrates began to spread. As of 2013 30% of *Enterococcus* species isolates from the US are vancomycin resistant, while

infections from these super bugs cause 1,300 deaths each year. (CDC, 2013). It is clear that the crisis is on our doorstep, yet the broken antibiotic market continues to discourage pharmaceutical companies from investing in new programs.

Many non-profit organizations such as the IDSA, NIH, and the Bill and Melinda Gates foundation are raising awareness of this dilemma and have interceded through the issuing of grants for research and advocating for new legislature to streamline R&D and make the market profitable once again. In 1982, US congress recognized the need to incentivize pharmaceutical companies to pursue treatments for rare diseases since there was little market for these drugs. Their solution was the Orphan Drug Act which gave tax incentives and exclusivity rights to companies investing in drug development programs for rare diseases (Volmar et al. 2019). It was a huge success, helping patients and leading to the formation of profitable companies, such as renowned Genzyme, dedicated solely to developing therapeutics that met the legislature's criteria. However, antibiotic resistance continued to be ignored as a serious threat by congress despite the rising death toll. Many non-profit organizations such as the IDSA, NIH, and the Bill and Milanda Gates Foundation are at the forefront of this issue to make a change. Finally answering to the call, Congress passed the Generating Antibiotic Incentives Now (GAIN) Act in 2012. This law extends novel antibiotic patent exclusivity rights for an additional five years, along with fast-tracking the FDA approval process (Pewtrusts, 2013). However, the law calls for a high level of drug novelty to meet the criteria to gain these incentives and recent evaluations of the antibiotic pipeline has seen little improvement "GAINed" (Brennan 2018). Studies argue that the incentives are lacking "pull" incentives to

accelerate a new antibiotic development market illustrated by the lack of statistically significant change (Siemm et al., 2018).

Several other proposals have been laid out by researchers to offer new “pull” solutions to inventive pharmaceutical companies to decrease uncertainty and guarantee antibiotic sales by the time of FDA approval. David Shlaes defines these proposals as “de-linked” models which separate sales volume from revenue by guaranteeing return of investment (Shales et al., 2015). In a market entry reward model, companies would be guaranteed upfront payment for future sales. Buyers, such as hospitals, would be required to pre-purchase the drug at a set price determined upon approval. In an insurance model, the government agrees to buy a certain quantity of the drug upon approval and thus guarantees a market to antibiotic developers (Towse et al., 2017). A more audacious proposal calls for “Transferable exclusivity vouchers” (Outtersen et al, 2016). In this model, companies that gain approval for novel antibiotics against highly resistant pathogens would be allowed to gain an extended exclusivity on their patent of choice. For companies with blockbuster drugs, even a few months of extra exclusivity can lead to hundreds of millions in extra profit. This also specifically targets large pharmaceutical companies to get back into antibiotic R&D as a means to increase revenue from their most profitable drug programs. There may be some hope with the DISARM Act introduced by congress this year which follows the voucher model by requiring Medicare to reimburse hospitals for new and important antibiotics (Jacobs, 2019). Despite bipartisan support it hasn’t shown signs of advancement yet. Furthermore, in a medical system designed to rarely use new antibiotics these pull incentives still may not be enough. As the seriousness of bacterial infections rise both doctors and patients must

acknowledge the need to change the whole paradigm. Kevin Outterson, the director of the government funded non-profit CARB-X which provides antibiotic grants, points out: “You’d never tell a cancer patient, ‘Why don’t you try a 1950s drug first and if doesn’t work, we’ll move on to one from the 1980s,’” (Jacobs, 2019). A patient shouldn’t be forced to wait until they are on a deathbed to be given the best antibiotics available.

The market for antibiotic development remains broken while the propagation of antibiotic resistant pathogens continues to rise. The background and case studies in this paper illustrate that market demand and large profits are achievable if a novel antibiotic class is able to reach FDA approval. Pharmaceutical companies must be willing to take more risks in this therapeutic area and find the next novel antibiotic in order to fight the losing arms race against resistant pathogens.

VI. References

- Aminov, R. I. (2013). Biotic acts of antibiotics. *Frontiers in Microbiology*, 4.
- Ball, L.-J., Goult, C. M., Donarski, J. A., Micklefield, J., & Ramesh, V. (2004). NMR structure determination and calcium binding effects of lipopeptide antibiotic daptomycin. *Organic & Biomolecular Chemistry*, 2(13), 1872.
- Baltz, R. H., Miao, V., & Wrigley, S. K. (2006). Natural Products to Drugs: Daptomycin and Related Lipopeptide Antibiotics. *ChemInform*, 37(14).
- Barbachyn, M. R., & Ford, C. W. (2003). Oxazolidinone Structure—Activity Relationships Leading to Linezolid. *ChemInform*, 34(30).
- Booth, B. (2013, March 28). Phil Needleman's Ten Commandments of Drug R&D. Retrieved from <https://www.forbes.com/sites/brucebooth/2013/03/27/phil-needleman-ten-commandments-of-drug-rd/>.
- Brennan, Z. (2018, February). FDA to Congress: Consider Changes to GAIN Act. Retrieved from <https://www.raps.org/news-and-articles/news-articles/2018/2/fda-to-congress-consider-changes-to-gain-act>.
- Brickner, S. J. Zyvox (2007). *Comprehensive Medicinal Chemistry II*, 8, 157-171
- Brickner, S. J., Hutchinson, D. K., Barbachyn, M. R., Manninen, P. R., Ulanowicz, D. A., Garmon, S. A., . . . Zurenko, G. E. (1996). Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential

- Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections. *Journal of Medicinal Chemistry*, 39(3), 673-679.
- Carpenter, C., & Chambers, H. (2004). Daptomycin: Another Novel Agent for Treating Infections Due to Drug-Resistant Gram-Positive Pathogens. *Clinical Infectious Diseases*, 38(7), 994-1000.
- Clatworthy, A. E., Pierson, E., & Hung, D. T. (2007). Targeting virulence: a new paradigm for antimicrobial therapy. *Nature Chemical Biology*, 3(9), 541–548.
- Dimasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*, 47, 20–33.
- Dvorchik, B. H., Brazier, D., Debruin, M. F., & Arbeit, R. D. (2003). Daptomycin Pharmacokinetics and Safety following Administration of Escalating Doses Once Daily to Healthy Subjects. *Antimicrobial Agents and Chemotherapy*, 47(4), 1318-1323.
- Dvorchik, B., & Damphousse, D. (2004). Single-Dose Pharmacokinetics of Daptomycin in Young and Geriatric Volunteers. *The Journal of Clinical Pharmacology*, 44(6), 612-620.
- Eisenstein, B., Oleson, J. F., & Baltz, R. (2010). Daptomycin: From the Mountain to the Clinic, with Essential Help from Francis Tally, MD. *Clinical Infectious Diseases*, 50(S1).
- Fugitt, R., Luckenbaugh, R. (1982) 3-(p-alkylsulfonylphenyl)oxazolidinone derivatives as antibacterial agents. U.S. Patent 4,340,606
- Hutchinson, D. (2003). Oxazolidinone Antibacterial Agents: A Critical Review. *Current Topics in Medicinal Chemistry*, 3(9), 1021-1042.
- Huycke, M. (1998). Multiple-Drug Resistant Enterococci: The Nature of the Problem and an Agenda for the Future. *Emerging Infectious Diseases*, 4(2), 239–249.

- Jackson, N., Czaplewski, L., & Piddock, L. J. (2018). Discovery and development of new antibacterial drugs: Learning from experience? *Journal of Antimicrobial Chemotherapy*, 73(6), 1452-1459.
- Jacobs, A. (2019, December 25) Crisis Looms in Antibiotics as Drug Makers Go Bankrupt. *The New York Times*. Retrieved from <https://www.nytimes.com/2019/12/25/health/antibiotics-new-resistance.html?action=click&module=Top%20Stories&pgtype=Homepage>
- Jagusztyn-krynicka, A. K., Wyszynska, A. (2008) The Decline of Antibiotic Era : New Approaches for Antibacterial Drug Discovery. *Polish Journal of Microbiology*, 57(2), 91-98
- Jadhavar, P., Vaja, M., Dhameliya, T., & Chakraborti, A. (2015). Oxazolidinones as Anti-tubercular Agents: Discovery, Development and Future Perspectives. *Current Medicinal Chemistry*, 22(38), 4379-4397.
- Leclercq, R., Derlot, E., Duval, J., & Courvalin, P. (1988). Plasmid-Mediated Resistance to Vancomycin and Teicoplanin in *Enterococcus Faecium*. *New England Journal of Medicine*, 319(3), 157–161.
- Lee, W., Schaefer, K., Qiao, Y., Srisukinimit, V., Steinmetz, H., Muller, R., Kahne, D., Walker, S. (2016). The Mechanism of Action of Lysobactin. *J Am Chem Soc*, 138(1), 100-103
- Local Bacterium Makes Good. (1987, February 25). Retrieved from <https://www.nytimes.com/1987/02/25/business/business-technology-local-bacterium-makes-good.html?searchResultPosition=1>.

- MacFarlane, Gwyn. (1979). Howard Florey: the making of a great scientist. *Oxford: Oxford University Press*, 327–346.
- Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin, and gentamicin. (1994). *American Journal of Infection Control*, 22(5), 325.
- Oleson, F. B., Berman, C. L., Kirkpatrick, J. B., Regan, K. S., Lai, J., & Tally, F. P. (2000). Once-Daily Dosing in Dogs Optimizes Daptomycin Safety. *Antimicrobial Agents and Chemotherapy*, 44(11), 2948-2953.
- Outterson, K., & McDonnell, A. (2016). Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy. *Health Affairs*, 35(5), 784–790.
- Renslo, A. R. (2010). Antibacterial oxazolidinones: Emerging structure–toxicity relationships. *Expert Review of Anti-infective Therapy*, 8(5), 565-574.
- Slee, A. M., Wuonola, M. A., Mcriphey, R. J., Zajac, I., Zawada, M. J., Bartholomew, P. T., . . . Forbes, M. (1987). Oxazolidinones, a new class of synthetic antibacterial agents: In vitro and in vivo activities of DuP 105 and DuP 721. *Antimicrobial Agents and Chemotherapy*, 31(11), 1791-1797.
- Priest, B. T., & Erdemli, G. (2014). Phenotypic screening in the 21st century. *Frontiers in Pharmacology*, 5.
- Rhee, K. Y., & Gardiner, D. F. (2004). Clinical Relevance of Bacteriostatic versus Bactericidal Activity in the Treatment of Gram-Positive Bacterial Infections. *Clinical Infectious Diseases*, 39(5), 755–756.
- Sfeir, M. M. (2018). The GAIN Act legislation to combat antimicrobial resistance: Where do we stand? *Infection Control & Hospital Epidemiology*, 39(12), 1499–1500.

- Tally F.P., De Bruin M.F. (2000) Development of daptomycin for Gram-positive infections. *Journal Antimicrobial Chemotherapy*. 46(523) 6.
- Tally F.P., Zeckel M., Wasilewski M.M, Carini C., Berman C.L., Drusano G.L., Oleson F.B. (1999) Daptomycin: a novel agent for Gram-positive infections, *Expert Opinion on Investigational Drugs*. 8(8) 1223-1238
- Shoji, J., Hinoo, H., Matsumoto, K., Hattori, T., Yoshida, T., Matsuura, S., Kondo, E. (1988). Isolation and Characterization of Katanosins A and B. *The Journal of Antibiotics*. 41(6) 713-718.
- Towse, A., Hoyle, C. K., Goodall, J., Hirsch, M., Mestre-Ferrandiz, J., & Rex, J. H. (2017). Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy*, 121(10), 1025–1030.
- Tran, T., Munita, M., Arias, C. (2015). Mechanisms of Drug Resistance: Daptomycin Resistance. *Ann N Y Acad Sci*. 1354 32-54.
- Woodworth J.R., Nyhart E.H., Brier G.L., Wolny J.D., Black H.R. (1992) Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob. Agents Chemother*, 36, 318–325.
- Zhanel, G. G., Schroeder, C., Vercaigne, L., Gin, A. S., Embil, J., & Hoban, D. J. (2001). A Critical Review of Oxazolidinones: An Alternative or Replacement for Glycopeptides and Streptogramins? *Canadian Journal of Infectious Diseases*, 12(6), 379-390.

