Spring 2023

Cultivating Health, Not Wealth in the United States' Healthcare System: Comprehensive Revisions for the Orphan Drug Act of 1983

Kayla Smith
Regis University

CULTIVATING HEALTH, NOT WEALTH IN THE UNITED STATES' HEALTHCARE SYSTEM: COMPREHENSIVE REVISIONS FOR THE ORPHAN DRUG ACT OF 1983

A thesis submitted to
Regis College
The Honors Program
in partial fulfillment of the requirements
for Graduation with Honors

by

Kayla Smith

April 2023

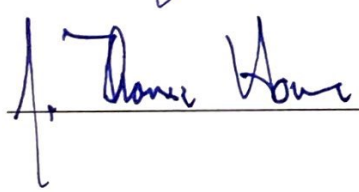
APPROVAL PAGE

Thesis written by

Kayla Smith

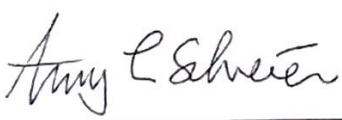
Approved by

Thesis Advisor



Thesis Reader

Accepted by



Director, Regis College Honors Program

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Acknowledgements

Special thanks to Dr. Stacy Chamberlin for her guidance and advice throughout the scientific and writing processes, and to Dr. Thomas Howe for providing commentary on the ethical aspects of the thesis. Thanks also to Dr. Kateri Ahrendt for introducing me to the Orphan Drug Act of 1983, and for her special insight into the drug development industry.

Abstract

Name: Kayla Smith Majors: B.S. in Biochemistry & B.S. in Mathematics

CULTIVATING HEALTH, NOT WEALTH IN THE UNITED STATES' HEALTHCARE SYSTEM: COMPREHENSIVE REVISIONS FOR THE ORPHAN DRUG ACT OF 1983

Advisor: Dr. Stacy Chamberlin

Reader: Dr. Thomas Howe

This thesis explores the way in which the Orphan Drug Act of 1983, originally instituted in response to a lack of treatments for rare diseases in the United States of America, has failed to achieve its initial objectives in the 40 years since its implementation. In evaluating various successful examples of government subsidization programs designed to intervene in private industry, this thesis composes the criterion required for funding-based legislation which maximize market outcomes while minimizing tax-payer burden. An analysis of the synthetic organic chemistry industry – and a case study into the production of a particular orphan treatment for a rare form of T-cell lymphoma – outlines the ways in which the ODA has resulted in declines in the developments in the field of medicinal chemistry, struggles which are not experienced in areas like the budding work of environmental chemistry. Additionally, a cultural and ethical review of the ODA's societal impact reveals the detrimental effects on patients due to severe price gouging and lack of innovation in pharmaceutical products, outgrowths of the loopholes pharmaceutical companies utilize to maximize profitability through the legislation. Ultimately, this thesis suggests that 1) "orphan" must be defined more stringently, 2) market exclusivity must be granted on the basis of molecule (not the entire disease), and 3) in the event that a treatment turn profitable, the company receiving funds should be reevaluated for funds mishandling.

Introducing Remarks

I was 19 when I was diagnosed with systemic lupus erythematosus (SLE). Actually, I remember my doctor's reticence; my score on the SLEDAI was low enough that I barely qualified for a diagnosis, but after knowing me a total of 2 weeks, she prescribed me 200 mg of hydroxychloroquine daily in hopes to prevent the progression of my disease.

That was over three years ago, now; I was pulled off of hydroxychloroquine one year ago after developing acquired long QT syndrome, a potentially fatal adverse side-effect of which I was symptomatic within the first three months of using the treatment (though it was realized in my chart 26 months into taking the prescription). In searching for a new medication, my insurance denied my application for Benlysta, the cutting-edge, first ever biologic drug designed for treating SLE (and recently shown to basically stop disease development altogether) – I simply wasn't sick enough at the time for my insurance to be willing to pay close to $5,000 a month for my treatment. Instead, I was instructed to try a different, far less effective treatment; if I could prove that my disease state persisted for 6 months while on a different medication, I would be eligible to reapply for Benlysta. I subsequently started azathioprine, a conventional immunosuppressant, 3 months ago and my white blood cell count has dropped to dangerously low levels, only adding to my SLEDAI score, which has almost doubled since the time of diagnosis. Should my next round of blood work come back to show still reduced white blood cell counts, I intend to again apply for what seems to be the only treatment on the market which has any promise of helping me get my disease under control.

I think one would be crazy to go through the trials and tribulations of fighting with doctors and health insurance companies and the pharmacy and one's own body to not once ask "what did *I* do wrong to get here?" Though I understand that desperate cry (quite, quite

personally), I think that the framing of the question is fundamentally insufficient. There are certainly instances in which one's personal choices lead to impending medical crises, but most often those of us frequent in the halls of hospitals and the seats of specialists' waiting rooms and the lists of patients on red-alert watch, are not responsible for what begot our sicknesses. Instead, there are two primary sources for our time being consumed with scans and tests and trials – nature and an industry compulsively dictating to nature how it *should* work. More specifically, that which we cannot control and those who wish deeply to control us.

The fact of the matter is that life is finite, and life is not without pain. Some of us enjoy a life of great health but experience strife elsewhere in our lives; others of us field health challenges but are surrounded with great support in the periphery; still others of us live somewhere in between those lines. Regardless, no one will make it out of this life without encountering pain; how else would we be certain that we are alive at all? Societally, however, we have divorced the physical from the metaphysical, attempting to nullify all diseases with a monolithic, infallible answer: medication. To the pleasure of the medical industry, this infatuation with the desire to control, mitigate, and eliminate pain altogether, has developed into an insatiable obsession, ultimately aiming to prolong life indefinitely.

Now, that claim might sound particularly hearty just out the gate, but is it wrong to notice the West's pill-dependent approach to medicine? And to that extent, to whom do the benefits of medication-reliant medical practices belong? It certainly doesn't seem to benefit the patients receiving medication after medication; how many of us have struggled with a treatment or developed adverse symptoms worse than the issue the drug was meant to address in the first place? It doesn't seem to benefit the doctors either, as it seems that their job has been reduced to marking check boxes and signing prescription forms for the medicine "best fit" for the situation

in front of them. If doctors are merely puppets for pharmaceutical companies to get their product marketed to patients, it certainly doesn't feel necessary to require more than a kindergarten education to sign *Your Doctor, M.D.* on the dotted line. What then, of the pharmaceutical companies? Do they reap the benefits of hooking patients onto greatly detrimental, unaffordable treatments that persist for years, if not a lifetime? It would certainly seem so.

There is no question that pharmaceutical treatments have their place in the theater of providing medical care to the sick of our communities, but it would seem that our society has grown overly dependent on that half of health care. Doing so has American medical practices vulnerable to the predations of pharmaceutical companies looking to sway doctors into selling particular prescriptions. Naturally, doctors are incentivized to prescribe particular prescriptions and doing so can lead to inaccurate or ineffective diagnosing of a patient's symptoms, a mistake which can lead to detrimental treatment outcomes. Over the course of time, patients grow exasperated, feeling that instead of being treated holistically, they are simply receiving pharmaceutical medicines with no intention of ever being treated for the root cause of the illness. Moreover, as this procedure continues ad infinitum, health in the United States continues to decline and the lining of the pharmaceutical companies' pocketbooks thicken, and thicken, and thicken.

So, it seems that the more rhetorically appropriate questions to ask here are, "What did *we* do wrong to get here? *How* did we end up this way?" Though it would be incredibly difficult to trace our developing and eventual dependence on pharmaceutical treatments back to its inception, we can certainly address the "how," the mechanism by which the United States has grown medication-frenzied. This thesis argues that the Orphan Drug Act of 1983 (ODA) is at fault for the disconnection between the promise that big pharma products will assist medical

practices in helping their patients and the disheveled, heart-wrenching reality we face today. Furthermore, this essay evaluates the extent to which the United States Federal Government has made no qualms about aiding and abetting this travesty that the pharmaceutical companies consistently exact on sick, dying Americans searching desperately for help. Finally, this project offers a comprehensive guide of reform not only for the letter of the legislation itself, but for the tone with which the West approaches medicine.

While the ODA primarily affects patients with rare diseases, the legislation has countless indirect consequences. As aforementioned, the Act, yes, imposes stipulations and subsidizes the development of medications for rare diseases, but how do those benefits for the pharmaceutical companies manifest throughout our culture? Our approach to medicine? It is unfortunate, yet true, that the term "health care" has lost its meaning because in reality, the "health care" industry stopped caring for its patients a long time ago. In complete honesty, an on-looker into the state of the practice of medicine throughout the United States would more likely describe our situation as the pharmaceutical companies' promise of health but actual cultivation of wealth on their own behalf. The time for checks and balances for the ODA is *well* overdue, so let's get started.

Chapter One
An Introduction to the Orphan Drug Act of 1983

Central to the premise of this thesis is both the letter of the Orphan Drug Act of 1983 itself, as well as the contextual circumstance which led to its eventual proposition and implementation. In the years preceding the writing and passing of the ODA by Congress, advocates for patients with rare diseases – to include, but not limited to, Gaucher's disease, Tourette's syndrome, Huntington's disease, and severe combined immunodeficiency (SCID) – formed the National Organization for Rare Disorders (NORD).[1] This coalition was foundational in the demand for orphan drug development and their persistence led to the eventual enactment of the order.[2]

Specifically, the ODA was designed to foster the development and production of drugs for "rare diseases or conditions," a term which the United States Congress defines as "any disease or condition which (a) affects less than 200,000 persons in the United States, or (b) 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."[3] The bill, though primarily geared toward the development of drugs for rare diseases, grants subsidization to treatments for rare diseases at large, to include pharmaceuticals, medical devices, or "medical

[1] Swann, J. (2018). The story behind the orphan drug act. *United States Food and Drug Administration*, retrieved from https://www.fda.gov/industry/orphan-products-development-events/story-behind-orphan-drug-act.

[2] (Swann 2018)

[3] U.S.C. (2013). Orphan drug act – relevant excerpts. *Orphan Drug Act of 1983*, retrieved from https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts.

foods"[4] which all satisfy the criterion stated above.[5] In response to the issues raised by NORD, the ODA was designed to supplement government-funded subsidization for the development of treatments and therapies for small populations which were not otherwise on the market and hence anticipated to remain highly unprofitable. Explicit benefits include "7-year marketing exclusivity to sponsors of approved orphan products, a tax credit of 50 percent of the cost of conducting human clinical testing, and research grants for clinical testing of new therapies to treat orphan diseases" in order to grant pharmaceutical companies sufficient provisions.[6]

The "exclusive marketing rights" granted these companies by the Act allows that no other institution can take the same medicinal treatment to market "unless they can prove clinical superiority" until the 7-year period expires.[7] Smaller offices within the United States Food and Drug Administration (FDA) include the Office of Orphan Products Development, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research, all of which are participatory in the designation of "orphan" status, writing of grants to companies, and review for market approval.[8] A revision of the bill in 2013 authorized the allotment of $30,000,000 for "each of the fiscal years 2013 through 2017" for these grants and contracts for a total of $1.2 billion over the course of only four years.

Special exceptions for clinical trials (both domestic and outside of United States borders, an atypical provision) are also granted to programs for the design of orphan drugs.[9] Specifically,

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[4] Interestingly, this provision writes that food which is "formulated to be consumed or administered eternally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements…are established by medical evaluation" are considered to sufficiently fulfill the requirements to receive subsidization per the bill (U.S.C. 2013).

[5] (U.S.C. 2013)

[6] Gottlober, P. A. (2001). The orphan drug act: implementation and impact. *Department of Health and Human Services: Office of Inspector General*.

[7] (Gottlober 2001)

[8] (Gottlober 2001)

[9] (U.S.C. 2013)

the ODA writes that treatments for rare diseases or conditions are granted two extensive exceptions for clinical testing. First, as stated previously, the bill credits pharmaceutical companies developing these treatments "an amount equal to 50 percent of the qualified clinical testing expenses for the taxable year" where qualified clinical testing expenses are defined as "the amounts which are paid or incurred by the taxpayer during the taxable year…[though] shall not include any amount to the extent such amount is funded by any grant, contract, or otherwise by another person (or any other government entity)."[10]

Second, the bill provides specifications with regard to the timing and methodology of clinical testing. In terms of chronology, the ODA writes that clinical trials must occur "before the date on which an application with respect to such drug is approved under section 505(b) of such Act or, if the drug is a biological product, before the date on which a license for such drug is issued under section 351 of the Public Health Service Act."[11] With regard to practical conventions, the Act requires that the trials are conducted "only to the extent such testing is related to the use of a drug for the rare disease or condition for which it was designated"[12] which is typical for all new pharmaceutical treatments. However, the Act allows further, less conventional provisions for treatments for rare diseases in that testing outside of the United States is acceptable in circumstances where "there is an insufficient testing population in the United States, and such testing is conducted by a United States person or by any other person who is not related to the tax payer to whom the designation under section 526 of the Federal Food, Drug, and Cosmetic Act applies."[13] While treatments which are to be prescribed to

[10] (U.S.C. 2013)
[11] (U.S.C. 2013)
[12] (U.S.C. 2013)
[13] Please note that section 526 of the Federal Food, Drug, and Cosmetic Act is better known as the Orphan Drug Act of 1983, but is mentioned here as Title 21, Section 526. (U.S.C. 2013)

patients in the American health care system are generally expected to be well-tested amongst the target population, this provision coincides with the argument that for drugs receiving the rare designation due to minimal patient population (less than 200,000 affected in the United States), effective clinicals must be allowed to reach beyond the borders of the United States.

In the original signing of the Act into federal legislation, Congress indicated that they found remotely no likelihood that these orphan drugs would be produced without some form of government intervention, and thus found that changes in federal law were necessary in order to "reduce the costs of developing such drugs and to provide financial incentives to develop such drugs."[14] In a review of the Act following the first 17 years of its institution, Gottlober, then Regional Inspector General of the Office of Evaluation and Inspections (Sacramento Chapter), demonstrated that the Act not only resulted in an increase in the number of orphan drugs being produced and sent to market, but that there was noticeable growth within the industry itself, marking a roughly 20% growth in the biotechnology industry (*Figure 1*, Gottlober 2001).[15]

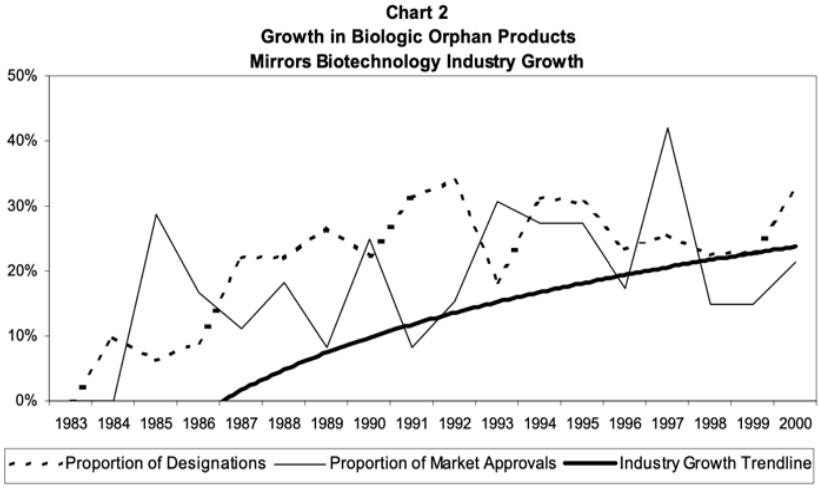

Figure 1 Trends of biologic orphan product designations and approvals since passing of ODA, 1983-2000 (Gottlober 2001).

[14] (U.S.C. 2013)
[15] (Gottlober 2001)

Gottlober's report continued, writing that the "Orphan Drug Act's incentives and the Office of Orphan Products Development's clinical superiority criteria motivate drug companies to develop orphan products… [and] provides a valuable service to both companies and patients."[16] Continuing to provide support for the Act and its seemingly positive ramifications, Gottlober reported that the Office of Orphan Product Development also found that "although the average patient population for designated orphan products [had] climbed since 1983…the average prevalence was approximately 73,000 patients at the time of designation" when evaluating the treatments which applied for rare disease classification for the year 2000 (the year Gottlober compiled the report).[17] Throughout the analysis, Gottlober's report makes no clear suggestions that any revisions to the bill were glaringly necessary at the time.

While the 2001 report on the ODA manages to present a rosy depiction of the Act and its benefits, Gottlober briefly mentions some rather harrowing insights into the perspective of the pharmaceutical companies working under the guise of rare disease classifications. First, pharmaceutical companies allegedly "complained that [the] FDA's reviewing divisions…took too long to complete the safety and efficacy reviews" and that for various, especially rare conditions, companies were unable to complete the clinical trials required by the FDA.[18] Furthermore, and perhaps more interesting, is the inclusion of one pharmaceutical company's confession to Gottlober, which writes:

> The Office [of Orphan Products Development] maintains a database of product information on the Internet that patients use to identify new treatments under development and products that have been approved for their disease. The NORD uses the

[16] (Gottlober 2001)
[17] (Gottlober 2001)
[18] (Gottlober 2001)

> information to refer patients to drug companies researching treatments for rare conditions. One company told use that by publicizing the efforts of orphan sponsors, the Office of Orphan Products Development has created yet another incentive – the potential for positive relations with patients and investors.[19]

Not only does Gottlober illuminate pharmaceutical companies arguing that the approval process was too long and extensive – an admission which "most acknowledged, however, that applying a different standard for the health and safety of orphan products could compromise public health and safety"[20] – he furthermore demonstrates that these companies were beginning to exploit the developing market for orphan drugs as early as 2001.

This brazen mention of the state of perspective within the industry, though short-winded, indicates that the ODA, though not specifically advised to be revised at the publishing of Gottlober's review, was already in need of clarification and restriction within the first 20 years of its implementation. Pharmaceutical companies were quick to exploit this most simple functional aspect of the ODA, and the following chapters will identify and analyze the ways in which this industry has manipulated the poor wording and execution of this legislation to benefit their profit margin indefinitely more than the patients the ODA was written to assist.

[19] (Gottlober 2001)
[20] (Gottlober 2001)

Chapter Two

Government Involvement in the Market Place: Stagnation Versus Explosion of Development

In order to provide a fair assessment of the Orphan Drug Act of 1983 as a government subsidization program, it is important to evaluate the successes and failures of similar legislation in other areas of the sciences. Doing so will not only demonstrate that government programs *can* work (granting some hope that the Act could be reformed and ultimately function better while in action) but will furthermore clarify how unsuccessful and damaging this bill has been on the United States economy, the medicinal chemistry industry, and the healthcare system at large. From this analysis, we will also gain a greater understanding of what makes a piece of funding-bound legislation functional, and what scaffolding has been instituted in the past which might supplement the proposal for changes which this thesis ultimately provides.

There is no question that since its inception, the United States of America has been on the forefront of most every innovation in recent history. The infrastructural and technological development of the Western world (and the world at large) has, in many senses, rested almost entirely on the shoulders of unique American thinkers willing to make sacrifices to find discoveries which continue to lead our societies to a greater quality of life. One could easily argue that an itch for investigation and invention is intrinsic to the fabric of the American nation. Though there are countless of these developments throughout American history which are well-worth discussing, two of these endeavors are of particular interest for this analysis: the Space Race and the Human Genome Project. Both of these outstanding demonstrations of ingenuity and scientific excellence were funded by the United States' Federal Government and have each yielded incredible outgrowths for the rest of Western society. It is pertinent and imperative, then,

to evaluate these instances of government involvement in the scientific marketplace to understand exactly how ill-founded and poorly functioning the ODA is today.

Following the end of World War II, the United States was, for lack of better terminology, high on its own supply. Graced by geography, the continental 48 went unharmed by the devastating events of war which ripped through Europe, and the economic state of the United States was seemingly unscathed in comparison to the rest of the nations on the global front. After deploying the first (and, thus far, only) nuclear bombs in Japan and effectively asserting military dominance on the world stage, the United States enjoyed the perks of supremacy in every aspect of the word in the years shortly after the war ended. Feeling confident and secure in these facts, the United States experienced a period of relaxation, particularly characterized by the movement to demilitarize the United States defense strategies and allow for a greater focus on developing and maintaining technological superiority.[21] Due to the comfort which the United States took in the war-borne desolation felt by its competitors on the world stage, this new attention to building innovations in technology was allowed to assume a largely free-market, not necessarily commercially bound approach.[22]

To achieve this new trek of technological development, funding for research in the natural sciences was allocated to universities across the country, such that 83% of these research projects were funded by the federal government as early as 1945 in the immediate aftermath of the war.[23] Some government officials, however, felt that this funding was insufficient; Vannevar Bush, the director of the wartime Office of Scientific Research and Development, argued that scientific research could only *really* occur without the pressure of "recognized commercial

[21] Douglass, J. A. (1999). The cold war, technology and the American university. Research and Occasional Paper Series: University of California, Berkley, 2(99).

[22] (Douglass 1999)

[23] (Douglass 1999)

application."[24] That is, it was Bush's perspective that if America truly wanted to excel on the scientific front, folks in research institutions needed to be completely free of all expectation to generate profit. Because of this, Bush pushed for the founding of a federal agency with the sole responsibility "to set science policy and distribute funding;" eventually, this rhetoric led to the establishment of the National Science Foundation in 1950, which quickly ushered the proliferation of agencies designed to oversee and finance scientific research of all varieties.[25] Interestingly, upon the conception of these agencies, $150 million was allocated to higher education institutions to fund research, but a select 13 universities collected 85% of those funds through "federal research contracts."[26] Rather rapidly, the United States of America grew to associate national security and economic growth with work performed in universities and academies across the nation.

In fact, this understanding that the United States' dependence on the university system to provide new innovations was fostered further by the gradually increasing budget extended to these universities. Though there was disagreement about how federal funding was to be allocated to institutions of higher education – seeing as the Department of Education had yet to be implemented as the separation between the federal government and schooling was still upheld – "basic research" never got a cut in capital.[27] Douglass comments on this phenomenon in his evaluation of the relationship between university level research and the Space Race, writing:

> In 1955, federally funded organized research at American universities and a select number of colleges had climbed to $169 million. Another $180 million went to university managed laboratories, such as Los Alamos. By early 1957, federal contracts for research

[24] (Douglass 1999)
[25] (Douglass 1999)
[26] (Douglass 1999)
[27] (Douglass 1999)

> had climbed to $229 million, with university managed laboratories consuming an additional $240 million. …In 1939, organized research consumed only 4.8 percent of all expenditures in American higher education, both public and private. By 1945, that number increased to 9.4 percent, and by 1955 to 15 percent.[28]

These monies supported the transition from primarily agriculture-focused research (which preoccupied minds prior to the Second World War due to events like the Great Depression) toward more cutting-edge technologies like electronic devices, pharmaceutical treatments, and engineering developments geared toward traditional national defense.[29] Clearly, the United States federal government was deeply invested in scientific research following the end of World War II.

This cultural dependence on and admiration of higher education quickly faltered, however, on an eerie October night of 1957, just 12 years after the end of World War II. As individuals and families all across the United States of America looked upward in horror, they watched the USSR's Sputnik slowly rotate about the earth, an event which struck panic through the halls of the United States federal government. Despite all the funding of research through academic institutions for over a decade, nothing came out of these universities which could even hold a candle to the Soviet Union's aircraft in orbit around the globe.[30] Almost immediately, the perspective that America retained an omnipotent strong hold over the world shriveled – clearly they were no longer the technological tyrants on the world stage, so what was the likelihood that the Soviets had gained the miliary upper hand, too?

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[28] (Douglass 1999)
[29] (Douglass 1999)
[30] (Douglass 1999)

Unprepared upon the USSR's successful launching of Sputnik, the United States was struck with the harsh realization that the West was without any form of a tangible space program, resulting in a "perceived 'missile gap'… [and an] 'educational and technology gap'" as well.[31] Despite obvious calls to reinvest in the American military, President Dwight D. Eisenhower resisted. Instead, he addressed the citizens of his nation, saying that "the American people could make no more tragic mistake then merely to concentrate on military strength."[32] In the immediate aftermath of Sputnik's launch, Eisenhower met with the Science Advisory Committee on Defense Mobilization, a meeting which rendered two consequences: first, Eisenhower agreed to a "full-time science advisor" who would be positioned in the executive branch and would be responsible for allocating federal funds to research and development as well as establish the greatly needed NASA program, a force which would concertedly focus to develop the West's first ever space program.[33]

Second, the former president agreed that the federal government would need to flush the education setting with a substantial amount of funding, "from the elementary school to the research university, to expand the number of scientists and engineers, and to substantially increase America's research prowess," a move onto education which had never been undertaken by the federal end of government in the United States.[34] In the immediate aftermath of the Sputnik launch, it was obvious that the United States was greatly lacking on the educational front, and Eisenhower's administration was tightly focused on not only flushing the university system with more students, but increasing the quality and grade of education from the ground up.

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[31] (Douglass 1999)
[32] (Douglass 1999)
[33] (Douglass 1999)
[34] (Douglass 1999)

The pressure was on to raise the next generation of scientists, which seemed to be the only way to fight the Soviets in this Cold War.

The urgency to answer the Soviets ultimately resulted in writing the National Defense Education Act into legislation in 1958. This law explicitly outlined that an "educational emergency exists and requires action by the federal government. Assistance will come from Washington to help develop as rapidly as possible those skills essential to the national security."[35] The passing of this bill resulted in the immediate doubling of federal expenditures on education, demonstrated by an increase in loan programs for students, the development of graduate programs which focused on the sciences and engineering, money for the improvement of curricula covering the hard sciences, mathematics, and foreign languages – only to name a few.[36]

Various institutions – new and old – grew entangled with university research in the wake of this new funding, including the Department of Defense (DOD), the Atomic Energy Commission (AEC), the National Science Foundation (NSF), and, of course, the National Aeronautics and Space Administration (NASA).[37] Between the years of 1955 and 1965, "federal expenditures for R&D swelled from $2.7 billion to more than $15 billion," as research in the scientific industries expanded to range from directly defense related (like the computer) to more general "scientific endeavors."[38] While adjusting for inflation, this increase in funding is on the order of 200%,[39] the steepest and most aggressive increase in federal funding following the launch of Sputnik. In fact, it was noted that "since Sputnik, an estimated 75 percent of all

[35] (Douglass 1999)
[36] (Douglass 1999)
[37] (Douglass 1999)
[38] (Douglass 1999)
[39] (Douglass 1999)

engineers and scientists who entered the field of scientific research had gone into federally subsidized undertakings in both public and private sectors. Fortune magazine stated the obvious,

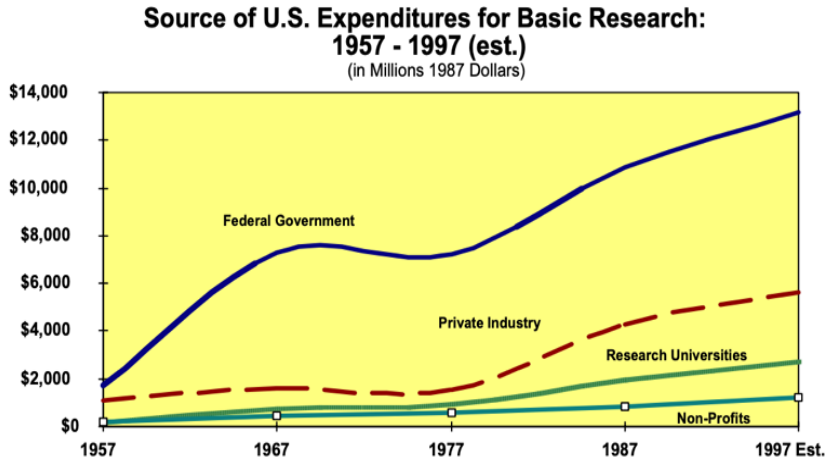

Figure 2 Federal expenditures on basic research between 1957-1997 (Douglass 1999).

'science and technology have become the wards of the federal government.'"[40] Figure 2 very clearly demonstrates this incredible expansion in expenditure, and it's clear that the funding never really dropped off, even after Neil Armstrong walked across the surface of the moon.

As demonstrated in Figure 2, comparing the spending estimated for the year 1997 on basic research – just forty years since the federal funding bomb that the United States government dropped on the university research setting –increased seven-fold. Looking even closer, we find that between 1955 and 1965, federal investment for basic research alone increased by 320% which is visualized in Figure 3.[41] In terms of the delineation of spending by federal program, in the year 1965 alone, NASA funded $790 million worth of basic research, followed by $268 million by the Atomic Energy Commission, $237 million by the Department of Health, Education, and Welfare, $220 million by the Department of Defense, and $143 million

[40] (Douglass 1999)
[41] (Douglass 1999)

by the National Science Foundation.[42] Due to this trend in spending, 28% of the United States' federal government research and development expenditures were devoted to basic research alone.[43]

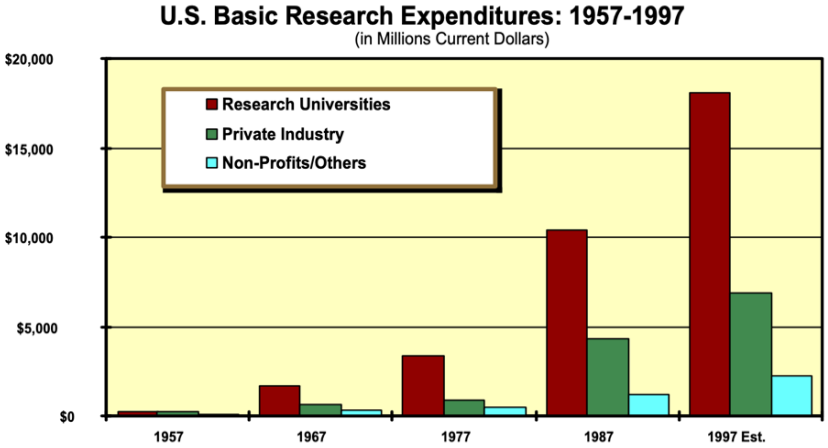

Figure 3 Distribution of federal basic research expenditures across institutions between 1957-1997 (Douglass 1999).

This evaluation of the Space Race does not claim that this funding was not important. It is easily arguable that the landing of men on the moon and the various successful manned-explorations of space which followed set the tone for the remainder of the Cold War, one which ultimately led to success on the behalf of the United States. That being said, the obsessive focus of Bush's "proclaimed paradigm government role in promoting and sustaining basic research"[44] inevitably led to the lack of funding for private industry which was purportedly supposed to utilize the research conducted at the university-level to generate products. In Figure 3, we see that funding for basic research at universities was greater than that for private industry by a ratio of 3 to 1, and this trend continued all through the remainder of the twentieth century.[45]

Again, this research was incredibly fundamental in providing the grounds to win the Space Race with the Soviet Union, an invaluable byproduct of this immense spending. It is worth

[42] (Douglass 1999)
[43] (Douglass 1999)
[44] (Douglass 1999)
[45] (Douglass 1999)

questioning, however, why this trend of significant expenditure on behalf of the American taxpayer continued following the moon-landing in 1969. Bush's insatiable pursuit to secure consequence-less research seems to invalidate the demand for funding for these universities. Not all Americans continued into higher education, and yet a significant amount of the money which was due to the United States federal government from their own pockets was vanishing to the vat of so-called 'quintessential' research at colleges across the United States, and yet they rarely (if ever) got to see what came of that funding. The reality of the matter is that Americans had skin in the game when it came to developing NASA and the supplementary research which went into the United States' domination of the space-front of the Cold War. Afterwards, however, it seemed as though this funding of universities was simply a transfer of wealth between the working and upper classes, a relocation which never presented benefit to the former again.

Despite this questionable continuation of funding following the United States' incredible success over the Space Race, it is well-worth noting that the United States would never have come upon these incredible discoveries and astronomical achievements were it not for the great sense of competition felt between the United States and the Soviet Union throughout the Cold War. In many senses, this seemingly untenable task remained exactly that *until* there was a race toward its completion. In this sense, it seems that competition is not only necessary but intangibly crucial to the process of great discovery. Furthermore, it is obvious that no single company or individual could have accomplished these feats in isolation; only the entirety of our country, *united* on this front, was able to develop a wildly successful space program in less than a decade and a half.

Overall, it's obvious that this implementation of government spending was important and successful. In a greatly strenuous time, the United States collected its greatest minds and the

Americans at home were more than willing to fund this great assemblage of intelligence with the promise that the nation would prevail. Looking backward now, it would be ridiculous – nearly on the order of Eisenhower's demilitarization stunt – to reduce our nation's insistent hunger for research. As such, Americans must be willing to continue to buy in to the budding fields of research, *so long as* that research commits to pursuing discoveries which will benefit those at home.

Though the Space Race was most definitely a feat which no individual could surmise, the issue of healthcare and health-related research is arguably more monstrous than successfully launching men into space from the surface of the earth. Toward the end of the twentieth century, biologists and practicing doctors alike found themselves surrounded by an exhausted system. The technology available to geneticists in the 1980s hemmed in the researcher's ability to provide the practitioner valuable information with which doctors might treat their patients, especially those with rare disorders and aggressive forms of cancer.[46] Somewhat naturally, the underlying, unquenchable desire of the American spirit piqued again as a group of revolutionary biologists presented a radical idea: to map the human genome.

In 1984, Renato Dulbecco, the first public advocate for the Human Genome Project (HGP), published his argument for this absurdly progressive development in the field of biology: only through an understanding of the human genome would we begin to understand and effectively address the issue of cancer.[47] The following spring, then Chancellor of University of California, Santa Cruz, Robert Sinsheimer, assembled twelve of experts on the issues of genetics

[46] Rood, J. E. & Regev, A. (2021). The legacy of the Human Genome Project. *Science, 373*(6562), 1442-1443.

[47] Hood, L. & Rowen, L. (2013). The human genome project: big science transforms biology and medicine. Genome Medicine, 5(79).

and biologic research to discuss the constraints and ramifications such an endeavor would face.[48] Ultimately, the committee determined that the project would first be nearly impossible to achieve, and second rather morally questionable; at the end of the conference, six experts endorsed the initiative and six strongly opposed.[49] Of those who did not support the mapping of the human genome, their primary arguments were that "big science is bad science because it diverts resources form the 'real' small science" and that the field of biology, as it stood, was not prepared to undertake that kind of development.[50]

As advocates continued attempts to drum up support for this strenuous research venture, as much as 80% of biologists were expressly against the idea, including the government-funded National Institutes of Health (NIH).[51] Surprisingly, no agency of the United States federal government which was directly linked to health was calling for this project to proceed. Instead, the Department of Energy (DOE) initialized the HGP under the guise of needing to increase the understanding of radiation effects on the human genome, a worthwhile endeavor in the aftermath of the nuclear bombs dropped in the final months of World War II.[52] Perhaps even more grandiose was the fact that members of Congress were more supportive of the effort than many biologists. Aware of the numerous life-saving applications of this research which would greatly increase the United States' standing in the incredibly competitive field of medicinal developments worldwide, the legislative branch was ready to fund the HGP.[53] After an endorsement by the National Academy of Science in 1988, the program began in 1990.[54]

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[48] (Hood & Rowen 2013)
[49] (Hood & Rowen 2013)
[50] (Hood & Rowen 2013)
[51] (Hood & Rowen 2013)
[52] (Hood & Rowen 2013)
[53] (Hood & Rowen 2013)
[54] (Hood & Rowen 2013)

Despite the fact that naysayers projected that the HGP would be incalculably costly and time consuming, the project was complete in 15 years, publishing the finished sequence in 2004, for a total of $3 billion spent, notably "ahead of schedule and under budget."[55] While the HGP most certainly delivered invaluable information in the form of a fully mapped human genome, unforeseen challenges in the process of building the map led to an even greater developmental footprint left by the project in its entirety. In the early 1990s, as the HGP was just beginning, it was assumed that the existing technology – now referred to as "first generation sequencing," a gel electrophoresis-based method to synthesize sequencing ladders and labeling processes – was "too cumbersome and low throughput for efficient genomic sequencing."[56] In fact, in the first iteration of this research, the initial reference sequence was "deciphered using a 96-capillary (highly parallelized) version of first-generation technology" which over the course of time was optimized due to efforts of biotechnology companies.[57]As these optimization efforts continued, the goal of the HGP rapidly shifted from attempting to ascertain a complete physical map of the human genome to instead generate the reference sequence itself.[58] In his plans to create a company, Celera, which would decipher the entirety of a sequence at once instead of piece by piece, Craig Venter's revolutionary thinking ultimately led to "government funding agencies to endorse production of a clone-based draft sequence for each chromosome," an innovation which accelerated the timescale of the project at large.[59]

Additionally, the investigatory process employed by the researchers involved with the HGP were wisely innovative and well-planned. Prior to attacking the entirety of the human

[55] (Hood & Rowen 2013)
[56] (Hood & Rowen 2013)
[57] (Hood & Rowen 2013)
[58] (Hood & Rowen 2013)
[59] (Hood & Rowen 2013)

genome – much larger than that of other species – preliminary rounds were performed whereby smaller sequences of model organisms (yeast, worm, fruit fly, small flowering plants) were successfully mapped.[60] In doing so, researchers developed clear techniques and methodologies with which the project as a whole could approach the mapping of the large, unwieldy human genome synergistically. This proved to be a rather lucrative effort as the 20 chapters of the international consortium working on the project were then able to participate in "culture of cooperation."[61] Of these, five mapping centers in particular – Wellcome Trust Sanger Institute, Broad Institute of MIT and Harvard, The Genome Institute of Washington University (St. Louis), Joint Genome Institute, and Whole Genome Laboratory at Baylor College of Medicine – continued after the preliminary efforts, ultimately providing the reference sequence which the HGP intended to find.[62]

By the end of the decade and a half devoted to this project, biologists not only "produced a curated and accurate reference sequence for each human chromosome," notably with only a few gaps, but also provided an extensive contribution to the budding interdisciplinary field of biotechnology.[63] One paper outlines five of these specific developments: first, the HGP provided a catalogue of the parts which compose most human proteins, and subsequently "non-coding regulatory RNAs."[64] This knowledge provided the foundation for what has been referred to as the "emergence of 'systems biology,'" which has positively influenced the way in which biologists approach medicine.[65] Second was the novel field of proteomics, a study dedicated to "identifying and quantifying the proteins present in discrete biological compartments."[66]

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[60] (Hood & Rowen 2013)
[61] (Hood & Rowen 2013)
[62] (Hood & Rowen 2013)
[63] (Hood & Rowen 2013)
[64] (Hood & Rowen 2013)
[65] (Hood & Rowen 2013)
[66] (Hood & Rowen 2013)

Understanding the functionality of proteins is fundamental to modulating their behavior (specifically with regard to healthcare), and this outgrowth of the HGP has allowed biologists and practitioners alike to best approach protein-based issues, especially with sophisticated analytical tools like mass spectrometry.[67] Third, the HGP offered substantial insight toward the working theory of evolution; discovery of Neanderthal sequence within that of humans indicates that there was a time during which *Homo sapiens* and *Homo neanderthalensis* genomically diverged.[68] Fourth, the scope of the HGP required a collaborative effort between the data and natural sciences. As such, the process of determining the reference sequence forced the development of "sophisticated computational and mathematical approaches" to biology, a "cross-disciplinary" effort which remains consistent and growing today.[69] Lastly, the HGP was the first demonstration of "big science" in the field of biology (a concern which naysayer biologists originally outlined as a reason against its completion).[70] This effort, beyond successful in achieving its nominal task, provided invaluable data which were otherwise inaccessible; clearly, this would have been untenable for any single institution, a point which supporters of the HGP express strongly.

Looking with an even broader perspective, it was calculated that for a $3.5 billion investment, the HGP's return was roughly $800 billion, approximately 230 times what was originally spent.[71] The copious amounts of data, technology, and knowledge which were provided to biology research labs, firms, and doctors' offices were beyond what could have been imagined prior to the start of the HGP. Since the completion of the reference genome, various

[67] (Hood & Rowen 2013)
[68] (Hood & Rowen 2013)
[69] (Hood & Rowen 2013)
[70] (Hood & Rowen 2013)
[71] (Hood & Rowen 2013)

projects have been designated to gain a better understanding of classes of genetic disorder. Some of these include the HapMap Project (intended to identify haplotype blocks in frequently occurring single nucleotide polymorphisms), the 1000 Genomes Project (devoted to produce a more holistic inventory of single nucleotide variations across various populations), and multiple smaller Genome-Wide Association Studies (GWAS, focused on labeling which genetic variations are endemic to specific groups). [72]

All of this research in symphony has allowed the science of medicine a great leap forward; diagnostic panels identify dangerous diseases which accelerate rapidly before it's too late (hepatitis, lung cancer), genetic testing grants patients a deeper understanding of familial health, and the ability to treat the progression of diseases has improved drastically.[73] A particularly interesting outgrowth of this project is the ease with which patients can complete genetic testing; it is even popular now to submit genetic data to better understand one's genealogy, a valuable yet unforeseen societal benefit to the mapping of the reference genome.[74] Interestingly, research in this regard has revealed an evolutionarily shocking truth: there exists "no race-specific genes in humans;" proponents of the HGP argue that this fact is especially important on the societal front.[75]

While the benefits of the HGP are seemingly obvious, modern biologists are now acknowledging the issues the project completely failed to address. One paper argues that the project which greatly influenced the fields of "scientific and clinical research, drug development, and medical practice" remains "incomplete 20 years later."[76] Though by Congress' standards the

[72] (Hood & Rowen 2013)
[73] (Hood & Rowen 2013)
[74] (Hood & Rowen 2013)
[75] (Hood & Rowen 2013)
[76] (Rood & Regev 2021)

HGP was considered finished on its publication in 2003, biologists now argue that two questions remain unanswered by the project: what is considered a 'complete' reference in the field of biology, and how would that reference be effectively utilized to benefit the health of humans?[77]

As it stands, these researchers assert that the original HGP was insufficient, arguing that the reference genome which was released in 2003 was only a "draft," and an incomplete one at that (see Figure 4). Due to the methodology employed throughout the course of the project, the HGP primarily mapped common "and then increasingly rare" variants, whereas the remaining 8% of "repetitive heterochromatin sequence" was not discovered and added to the sequence until 2021.[78] Additionally, a more comprehensive evaluation of the reference sequence which was published in 2003 presents a rather fundamental issue: the published genome was "inherently biased" due to the lack of representation for non-European individuals.[79]

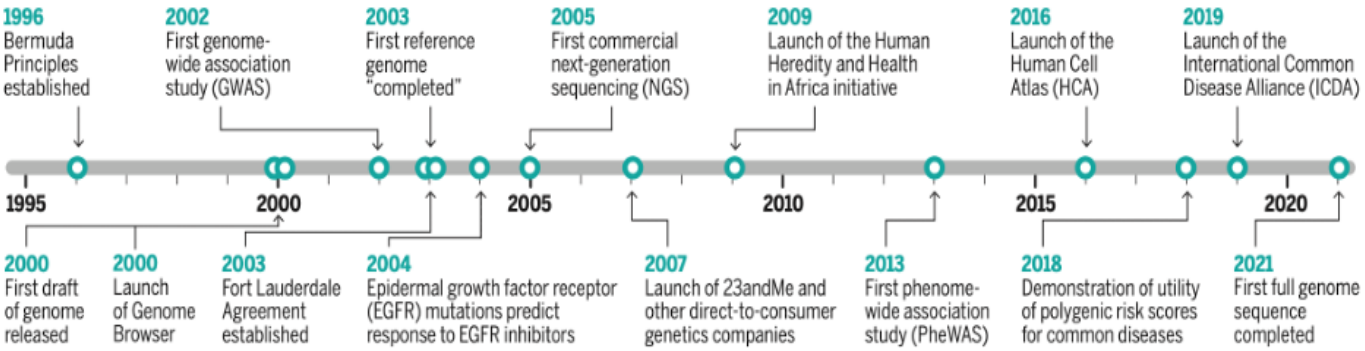

Figure 4 Chronology of the Human Genome Project and its byproducts from 1995-modern discoveries (Rood & Regev 2021).

Despite these worthy criticisms of the HGP – areas for growth which are being actively addressed through programs like the Human Heredity and Health in Africa (H3Africa) and the Global Alliance for Genomics and Health (GA4GH) initiatives[80] – this analysis nonetheless finds that this instance of government involvement in the marketplace of scientific research was

[77] (Rood & Regev 2021)
[78] (Rood & Regev 2021)
[79] (Rood & Regev 2021)
[80] (Rood & Regev 2021)

successful. The benefits outlined which were byproduct of this research are quite literally priceless, both in improving our understanding of evolution and how to continually revise and better our approaches to healthcare. Though the fight against cancer and incurable diseases continues, it is obvious that the field of medicine would be significantly further from offering successful treatment options were it not for this exceptional episode of big science.

In the evaluation of both the Space Race and the Human Genome Project, this analysis has established that in two greatly differing situations, 'big science' – that is, a large research forum funded by an even larger consortium – *can* be successful in light of government spending. Naturally, this fact lends hope to the failing institution of the existing ODA. However, this analysis has furthermore identified various factors which must be inherent to the situation which necessitates government involvement in the theater of scientific research. There, of course, must be clear and obvious reasons for taxpayer spending. Unlike the situations for development of a space exploration program and the mapping of the human genome, the ODA currently fails to clearly identify how government spending allotted to pharmaceutical companies will be utilized for the benefit of the patient. Shoddy wording – especially in defining 'rare' and 'orphan' – allows for mishandling of resources, leading to the benefit of companies and the detriment to their constituents.

Moreover, both the Space Race and the Human Genome Project were laced with a sense of urgency. For the Space Race, the fate and safety of the Western world depended on the development of space exploration equipment; this strenuous, overbearing competition with other world powers ultimately led to the greatest boom in the history of engineering in the United States. With regard to the Human Genome Project, exasperated practitioners and biologic researchers were in desperate need for a greater understanding of the human body at the

molecular level – without it, patients were left without treatments for lethal cancer and rare diseases. As such, the task of mapping the human chromosomes was so imperative that what was considered impossible was achieved in only 15 years. Unfortunately, it's rather apparent that these pharmaceutical companies feel no such pressure to find new treatments for patients with rare illnesses, nor make them financially accessible. Extensive periods of market exclusivity allow companies with rare drug designations to sit on their patents, essentially stonewalling the progression of products for extremely unwell patients.

For these reasons, this analysis argues that the ODA must be fundamentally reframed. In order that this be a successful act of legislation – both financially and morally – the ODA requires significant revision. We must redefine the intentions of this act such that the primary benefactors of this research are our patients with rare illnesses, not the fiduciaries which conduct the investigatory process.

Chapter Three
An Evaluation of Methodological Innovation in the Organic Synthesis Research and Development Industry

It would be incorrect to state that synthesis at large has remained essentially stagnant since the implementation of the Orphan Drug Act of 1983, but only by technicality. The field of organic synthesis is ostensibly divided into two categories: medicinal development and other research. The former endeavors to discover and target illnesses at the molecular level, and then design and produce drugs to be prescribed for treatment; this, of course, is the field to which this legislation applies. The latter, however, is synthetic chemistry research pursued for any other purpose. In the modern era, this has been largely devoted to environmental research. Where staggering amounts of environment-focused development have occurred within the last few decades, the same simply cannot be said with regard to medicinal research.

Referring back to the letter of the legislation, the need for the ODA was warranted for two reasons: first, patients with a disease which affected at or less than 200,000 people in the United States had no treatment options.[81] Second, some treatments on the drug market were simply too expensive/dangerous to synthesize (even if they were for illnesses which affected more than 200,000 patients in the United States), and pharmaceutical companies thus held "no reasonable expectation that the cost of developing and [producing]…will [be] recovered from [the] sales…of such drug."[82] Clearly, by this excerpt – directly from the legislation's definition of "orphan" drug – one would assume that the funding provided to pharmaceutical companies for the developments of these medications would be used as such, to design and optimize the

[81] (U.S.C. 2013)
[82] (U.S.C. 2013)

synthesis of small molecules which are otherwise inaccessible to a company by the funding of its own private investors.

We find, however, that few (if any) of these pioneering discoveries have come due to the funding and market protection provided by the ODA. While it is difficult to know exactly what goes on behind the closed doors of the orphan drug development processes – due to market exclusivity, a more stringent and privileged kind of patent granted and endorsed by the ODA – we nonetheless have a slight insight into these companies. At both lower-level research institutions (universities, etc.) and competing pharmaceutical companies, professionals often analyze a given small molecule and devote substantial time, effort, and money to rework the mechanism for synthesis hidden within the patent. As such, these works published by institutions 'reworking' the synthesis of small molecules allow an onlooker to estimate what kinds of mechanisms are being designed and used at the commercial level. This, of course, is an incredibly valuable insight; how else are we to evaluate the degree of progress achieved by these companies receiving ODA funding?

Eli Lilly and Company, a pharmaceutical business which currently makes and sells 44 medications primarily intended for diabetes, cancer, and most recently, COVID-19,[83] provides an excellent example of this phenomena. Targretin – or by its generic name, bexarotene – was invented by synthetic chemists working in the Departments of Medicinal Chemistry, Cell Biology, Pharmacology, and New Leads Discovery under Ligand Pharmaceuticals Incorporated in the summer of 1994.[84] In November of 1997, Eli Lilly entered a contractual agreement in which Ligand would invest in the design, production, and sales of Targretin and its prospective

[83] Lilly. (2022). Current Medicines. *Lilly*. [Accessed Fall 2022]. Retrieved from https://www.lilly.com/our-medicines/current-medicines.

[84] Boehm, M. F. et al. (1994). Synthesis and structure – activity relationships of novel retinoid X receptor-selective retinoids. *Journal of Medicinal Chemistry, 37,* 2930-2941.

analogues.[85] This "collaborative agreement" was initially focused on developing a "novel series of potent RXR agonists for treatment of non-insulin dependent (type II) diabetes mellitus."[86] After Phase II clinical trials, however, it was determined that while the first-generation medication increased insulin-sensitivity in patients as desired, "the studies also revealed an unwanted tendency to alter lipid profiles in diabetic patients."[87] This trend indicated that Targretin alone would not be completely successful in application, and would thus need to be paired with some form of "lipid-lowerer."[88]

Based off of the data collected in the Phase II trials, Eli Lilly and Ligand ultimately decided to cease the development of first-generation Targretin for type II diabetes.[89] Subsequently, Ligand "regained the rights of the oral form of Targretin from Lilly," a repossession which would allow the company to "accelerate development in its other applications," like breast cancer and psoriasis, which were not covered under the original agreement with Eli Lilly.[90] However, in a separate partnership between the pharmaceutical companies, it was determined that Eli Lilly could continue to develop Targretin in conjunction with a "selective estrogen receptor modulator" like Lilly's osteoporosis drug Evista (raloxifene) for the ultimate goal of treating cancer.[91]

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[85] Securities and Exchange Commission. (1998). Schedule 13D, Cusip Number 53220K207. U.S. Securities and Exchange Commission. Retrieved from https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwjwtPD5xfT7AhV_AjQIHUloCBsQFnoECA8QAQ&url=https%3A%2F%2Finvestor.lilly.com%2Fstatic-files%2Fd004af2c-415e-479b-b323-a822e161b045&usg=AOvVaw3aj498mlf1jX2678zobv85.

[86] Faul, M. M., Ratz, A. M., Sullivan, K. A., Trankle, W. G., & Winneroski, L. L. (2001). Synthesis of novel retinoid X receptor-selective retinoids. *Journal of Organic Chemistry, 66*, 5772-5782.

[87] Marketletter. (1999). Lilly scraps Targretin development agreement with Ligand. *Business Insights: Global*. Retrieved from http://bi.gale.com.dml.regis.edu/global/article/GALE|A54159001/7a9b117155ea37e28df5805e92c3be8c?u=regis.

[88] (Marketletter 1999)

[89] (Marketletter 1999)

[90] (Marketletter 1999)

[91] (Marketletter 1999)

Ultimately, Ligand elected to file for "the use of Targretin gel and capsules in the treatment of cutaneous T-cell lymphoma," an illness with orphan status, in the first half of 1999.[92] In June of the same year, Ligand Pharmaceuticals received an approved orphan designation for the production of Targretin with market exclusivity slated to expire at the end of December, 2006.[93] As such, Lilly Research Laboratories, an extension of Eli Lilly and Company, pursued and published an extensive report on the synthesis of bexarotene analogues in efforts to provide synthesis procedures for similar small molecules which were suspected to demonstrate better effects in patients with diabetes.[94]

Throughout this thorough investigation of small molecules like bexarotene, the team lead by Faul at Eli Lilly Labs furthermore endeavored to develop the existing synthesis mechanism for bexarotene originally invented and published in 1994. In the original five-step synthesis mechanism, 2,5-dichloro-2,5-dimethylhexane was synthesized by bubbling dry hydrogen chloride gas over 2,5-dimethyl-2,5-hexanediol with a 56% yield.[95] Faul instead streamlined the formation of 2,5-dichloro-2,5-dimethylhexane by using reagent grade hydrochloric acid and then immediately proceeded to the formation of the tetrahydronaphthalene compound used in the following mechanistic step, a "one-pot" solution which presented a 99% yield (a substantial increase!).[96] Additionally, Friedel-Crafts acylation was originally assisted by ~2.0 equivalence

[92] (Marketletter 1999)

[93] It is worth noting here that due to the selling of the Targretin patent to Eisai in 2006, the FDA records show that Eisai was awarded the orphan designation; however, Ligand Pharmaceuticals was the original owner of the designation and didn't sign the approval over until the patent for Targretin was sold to Eisai. (Food and Drug Administration. (1999). Search Orphan Drug Designations and Approvals: Targretin (Bexarotene). *U.S. Department of Health and Human Services.* Retrieved from https://www.accessdata.fda.gov/scripts/opdlisting/oopd /listResult.cfm.)

[94] (Faul et al. 2001)

[95] (Boehm et al. 1994)

[96] (Faul et al. 2001)

aluminum chloride catalyst ($AlCl_3$),[97] a process which was optimized in the Faul paper by using 15% equivalence ferric chloride catalyst ($FeCl_3$), increasing overall yield by nearly ten percent.[98]

Moreover, in the first iteration of bexarotene synthesis, olefination proceeded by methyltriphenylphosphonium bromide catalyst (Ph_3PCH_3Br) in the presence of sodium amide base ($NaNH_2$) via the Wittig reaction.[99] Though this mechanism was effective (87% yield),[100] the reduction reagents used are both dangerous to the chemist at the bench and extremely harmful ecologically. Sodium amide base, when in contact with water, "releases flammable gases which may ignite spontaneously," and lab technicians are furthermore instructed to wash all skin exposed to the reagent vigorously, as the base is extremely corrosive to biological material.[101] Due to the substantially increased likelihood of unwanted ignition, Boehm's procedure necessitated a nitrogenous environment.[102] Furthermore, methyltriphenylphosphonium bromide exudes hazardous fumes and is toxic to aquatic life with "long lasting effects,"[103] making the disposal particularly difficult. To address this issue, Faul's team reversed the order the of Boehm's final mechanistic steps, electing to first perform ester hydrolysis (establishing the carboxylic acid), then to reduce the ketone to a tertiary alcohol, and finally to execute olefination by the Dean-Stark apparatus.[104] Though this new pathway added an additional step to the

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[97] (Boehm et al. 1994)

[98] (Faul et al. 2001)

[99] (Boehm et al. 1994)

[100] (Boehm et al. 1994)

[101] ThermoFisher Scientific. (2021). Sodium amide safety data sheet. *ThermoFisher Scientific*. Retrieved from https://www.fishersci.com/store/msds?partNumber=AC339240250&productDescription=SODIUM +AMIDE%2C+99%25+25GR&vendorId=VN00032119&countryCode=US&language=en.

[102] (Boehm et al. 1994)

[103] ThermoFisher Scientific. (2021). Methyltriphenylphosphonium bromide safety data sheet. *ThermoFisher Scientific*. Retrieved from https://www.fishersci.com/store/msds?partNumber=AC156955000&productDescription= METHYLTRIPHENYLPHOSPHONI+500GR&vendorId=VN00032119&countryCode=US&language=en.

[104] (Faul et al. 2001)

synthesis mechanism, it required less-harsh reagents (organometallic Grignards),[105] which ultimately resulted in more ethically-disposable byproducts.

While the extensive report published by Faul and her team at Eli Lilly Labs was enlightening and managed to add a significant number of small molecules to the canon of bexarotene-like compounds, many avenues of investigation were not examined to the same degree. Faul's mechanistic pathway to synthesize bexarotene presented an overall yield of 51%, a reasonable increase from Boehm's 41% overall yield, especially considering Faul's choice to add an additional synthetic step to the pathway.[106,107] Though this increase was impressive, the desire for optimization certainly wasn't satisfied by a yield of roughly half; in fact, the Grignard-Dean Stark methodology presented a 66% yield,[108] which was actually less successful than the Wittig mechanism utilized by Boehm. Faul mentions the potential for the Suzuki-Miyaura cross-coupling method, a synthesis pathway which utilizes custom boronic acids and the strong base n-butyl lithium.[109] Though this coupling mechanism flashes impressive yields which were far better than the Grignard-Dean Stark method (88%),[110] n-butyl lithium is even more dangerous than sodium amide, the base used in Boehm's original pathway. In fact, a research assistant at UCLA died due to the spontaneous ignition of n-butyl lithium in 2009.[111]

In separate papers published after Faul's, the Suzuki-Miyaura cross-coupling of complex aryl groups was investigated further as an alternative to Wittig olefination or ketone reduction

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[105] (Faul et al. 2001)
[106] (Faul et al. 2001)
[107] (Boehm et al. 1994)
[108] (Faul et al. 2001)
[109] (Faul et al. 2001)
[110] (Faul et al. 2001)
[111] Kemsley, J. (2009). Researcher dies after lab fire. *Chemical and Engineering News, American Chemical Society*. Retrieved from https://cen.acs.org/articles/87/web/2009/01/ Researcher-Dies-Lab-Fire.html.

and subsequent dehydration.[112] Though this research was not necessarily in relation to the synthesis of bexarotene explicitly, the paper nonetheless explored and determined methods of Suzuki coupling which were safer than those outlined in Faul's paper. McDaniel and his research team at the University of Montana determined in 2011 that the use of "bulky electron-rich Buchwald phosphine ligands," palladium (II) acetate catalyst ($Pd(OAc)_2$), and cesium carbonate base (Cs_2CO_3) were optimal conditions for the Suzuki-Miyaura coupling reaction, consistently presenting 50% yields.[113] This research also utilized microwave conditions (instead of traditional heating), as it was found that the reaction was better monitored in this fashion.[114] Unfortunately, these findings present yields less than the Wittig, the Grignard-Dean Stark, or the n-butyl lithium activated Suzuki-Miyaura procedures outlined in Faul's paper, despite the fact that this procedure is substantially safer than those aforementioned.

Following these publications, few research institutions have come out with any new findings about the synthesis of bexarotene. One paper published in 2014 detailed the optimization of the custom boronic acid synthesis pertinent to the proposed Suzuki-Miyaura synthetic pathway of bexarotene but did not detail any data with regard to increasing the experimental yield of the compound itself.[115] A handful of papers exist exploring the synthesis of

[112] McDaniel, S. W., Keyari, C. M., Rider, K. C., Natale, N. R., & Diaz, P. (2011). Suzuki-Miyaura Cross-Coupling of Benzylic Bromides Under Microwave Conditions. Tetrahedron Letters, 52(43), 5656-5658.

[113] (McDaniel 2011)

[114] (McDaniel 2011)

[115] Takemoto, Y., Takakia, K., & Yoshida, H. (2014). A masked diboron in Cu-catalyzed borylation reaction: highly regioselective formal hydroboration of alkenes for synthesis of branched alkenylborons. *Chemical Communications, 50*(61), 8299-8302.

disila-bexarotene analogues,[116,117] but scientific searches about the compound prescribed to patients are few and far between, the most extensive being that published by Faul.

Though it may simply be the case that the synthesis of bexarotene can be no further optimized, this analysis finds that jumping to such a conclusion might be naïve. As stated previously, the orphan designation awarded to Ligand Pharmaceuticals by the FDA in 1999 was slated to end in December of 2006. Interestingly, we find that in October of 2006, Ligand sold the rights of Targretin to the United States extension of the Tokyo-based pharmaceutical company Eisai, Eisai Incorporated.[118] In 2012, Eisai granted another Japanese pharmaceutical business, Minophagen Pharmaceutical Company, the "exclusive rights to develop and commercialize bexarotene in Asia, Oceania, the Middle East and Eastern Europe, amongst other regions," though Eisai retained the rights over the medication in the United States.[119]

Shortly thereafter, Eisai, Inc. "transferred the New Drug Application (NDA) for Targretin" to United States-based Valeant Pharmaceuticals International Incorporated in February of 2013 for $65 million.[120] In May of the same year, Valeant purchased Bausch and Lomb for $8.7 billion, conglomerating the pharmaceutical companies.[121] A few years later,

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[116] Buttner, M. W., Natscher, J. B., Burschka, C., & Tacke, R. (2007). Development of a new building block for the synthesis of silicon-based drugs and odorants-alternative synthesis of the retinoid agonist disila-bexarotene. Organometallics, 26, 4835-4838.

[117] Daiss, J. O., et al. (2005). Synthesis, crystal structure analysis, and pharmacological characterization of disila-bexarotene, a disila-analogue of the RXR-selective retinoid agonist bexarotene. *Organometallics, 24*, 3192-3199.

[118] Eisai Co., Ltd. & Minophagen Pharmaceutical Co., Ltd. (2012). Eisai and Minophagen Pharmaceutical conclude license agreement concerning the development and commercialization of cutaneous T-cell lymphoma treatment bexarotene in Asia, Oceania, the Middle East and Eastern Europe, etc. *Eisai Global*. Retrieved from https://www.eisai.com/news/news201212.html.

[119] (Eisai Co., Ltd. & Minophagen Pharmaceutical Co., Ltd. 2012)

[120] Valeant Pharmaceuticals International, Inc. (2013). Valeant Pharmaceuticals acquires U.S. rights to Targretin form Eisai Inc. *Bausch Health*. Retrieved from https://ir.bauschhealth.com/tools/viewpdf.aspx?page=%7B4CEC537C-783A-4CF2-88F3-D0C22A53FD76%7D.

[121] Perriello, B. (2013). Valeant confirms $9B acquisition of Bausch & Lomb. *WTWH Media LLC*.

Valeant Pharmaceuticals was rebranded to Bausch Health Companies Incorporated, which is the company which holds the rights over Targretin in the United States to this day.[122]

The sheer number of times which this medication has been transferred between pharmaceutical companies certainly raises some eyebrows. Not only have there been virtually no new findings on the synthesis of bexarotene since Eli Lilly Labs produced their exploratory paper, but the exchanging of rights over the drug happened at very specific times. Ligand's sell to Eisai, Inc. is the most obvious, of course, as the transfer occurred only two months prior to the expiration of Ligand's market exclusivity. By the time that Eisai, Inc. was in possession of Targretin's rights, its market exclusivity would end in 2013, the same year that the company sold the medication to Valeant, and in fact sold it as an NDA.[123] Naturally, this would indicate that Valeant would hold market exclusivity of the orphan designation until 2020, though it conveniently rebranded in 2018.

The fact of the matter is that the transfer of this orphan designation and the concurrent privileges therein occurred with market exclusivity expirations synonymously. This signals to the onlooker not that these companies were selling Targretin to optimize synthesis, nor for the sake of mechanistic research. Clearly, the trading of this medication was dependent on exacting perpetual aid from the United States Federal Government under the guise of the ODA, a clear abuse of the system in place. We furthermore suspect this is the case, as each transfer of the orphan designation required that the former owner of the patent receive compensation for whatever profit was made by the new proprietor.[124,125] Naturally, this example would indicate

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[122] Valeant Pharmaceuticals International, Inc. (2018). Valeant will become Bausch Health Companies Inc. *Bausch Health*. Retrieved from https://ir.bauschhealth.com/news-releases/2018/05-08-2018-120255538.

[123] (Valeant Pharmaceuticals International, Inc. 2013)

[124] (Eisai Co., Ltd. & Minophagen Pharmaceutical Co., Ltd. 2012)

[125] (Valeant Pharmaceuticals International, Inc. 2013)

that the field of medicinal chemistry is greatly suffering at the hand of the ODA. Unfortunately, however, we can be certain that this is not an isolated event. The incentives to pass around an orphan indication without improving its synthesis – an enhancement which would reduce the cost for patients – and to continually receive exorbitant amounts of government funding are simply too great.

It is laughable, then, to compare the innovations in environmental-based synthetic research to that of recent medicinal chemistry. While there are many new and exciting discoveries occurring in this area of environmental research, one particularly interesting developmental projection is the synthesis of Blatter radicals. The benzo[*e*][1,2,4]triazin-4-yl family – more commonly referred to as "Blatter" – is a class of heterocyclic aromatics carrying a radical within the triazinyl framework. First mentioned in works like *Stable Radicals: Fundamentals and Applied Aspects of Odd-Electron Compounds* (see Chapter 7, "Verdazyls and Related Radicals Containing the Hydrazyl [R_2N-NR] Group")[126] and Volume 19 of the journal Advances in Heterocyclic Chemistry: Heterocyclic chemistry in the 21st century (see Chapter 7, "Stable N- and N/S-Rich Heterocyclic Radicals: Synthesis and Applications"),[127] benzo[*e*][1,2,4]triazin-4-yl derivatives have been a topic of deep and broad study for the last decade.

The Blatter radical, with its long-term stability and ease of functionalization, has presented a wide growth in the understanding of molecular packing, molecular magnetism, and the process of crystal engineering. As the breadth of the Blatter radical family continues to

[126] Hicks, R. G. (2010). Stable Radicals: Fundamentals and Applied Aspects of Odd-Electron Compounds. *Wiley*, 270-273.

[127] Constantinides, C. P. & Koutentis, P. A. (2016). Stable N- and N/S-Rich Heterocyclic Radicals: Synthesis and Applications. *Advances in heterocyclic chemistry: heterocyclic chemistry in the 21st century, 199*, 173-207.

broaden, detailed studies with regard to antiferro- and ferromagnetism present in the Blatter radical framework have donated additional information to the wealth of knowledge the molecule has to offer. Specifically, due to the characteristic rigidity and stability of the Blatter radical, ferromagnetic exchange interactions have been induced upon annulation[128] and even more studies have begun investigating how magnetism depends on the zwitterionic ground state of di-Blatter radicals.[129] These focused investigations into molecular magnetics helps inform paths for innovation, including various medicinal applications (MRI),[130] industrial developments (thin films),[131,132] and environmental projects (organic batteries).[133,134] Recently, redox-flow battery applications are of the greatest interest and import.[135]

As one of the leading investigators in this new class of compounds, Dr. Piotr Kaszynski has devoted many of the last years to concerted research of the benzo[*e*][1,2,4]triazin-4-yl and its planar derivatives. Publishing countless papers on its synthesis, structure, crystalline packing, and magnetic behavior, Kaszynski and his teams across the world have contributed an invaluable amount of information to the canon of organic radical literature. In one particular study, Kaszynski discovered the planar Blatter radical derivative, 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yl, and published and extensive account of this derivative's synthesis, structure, and magnetic

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[128] Bajaj, A., Khurana, R., & Ali, M. E. (2021). Auxiliary atomic relay center facilitates enhanced magnetic couplings in Blatter's radical. *The Journal of Physical Chemistry, 125*, 4133-4142.

[129] Khurana, R., Bajaj, A., & Ali, M. E. (2022). Tuning the magnetic properties of a diamagnetic di-Blatter's zwitterion to antiferro-and ferromagnetically coupled diradicals. *Physical Chemistry Chemical Physics, 24(*4), 2543-2553.

[130] Saenz, F., et al. (2022). Blatter-type radicals as polarizing agents for electrochemical overhauser dynamic nuclear polarization. *Chemical Communications, 58*, 689-692.

[131] Rogers, F. J. M., et al. (2020). Recent advances in the chemistry of benzo[e][1,2,4]triazinyl radicals. *Organic and Biomolecular Chemistry*, *18*, 8255-8277.

[132] Hande, A. A., et al. (2020). UV-photoelectron spectroscopy of stable radicals: the electron structure of planar Blatter radicals as materials for organic electronics. *Physical Chemistry Chemical Physics, 22*, 23637-23644.

[133] (Hande et al. 2020)

[134] Steen, J. S., et al. (2022). Blatter radicals as bipolar materials for symmetrical redox-flow batteries. *Journal of the American Chemical Society, 144*, 5051-5058.

[135] (Steen et al. 2022)

behavior (see Figure 5).[136] Following this discovery, Kaszynski's investigation into the family of planar Blatter radicals spans across the Western nations, especially concentrated in the United States and Poland. Under his research operation in Łódź, Poland, his research team pioneered a synthetic mechanism for the concerted and efficient "radical chain cyclization of aryl iodides" and the ultimate formation of planar Blatter radicals of various derivations utilizing.[137] Unlike in previous iterations which employed arduous and low-yield mechanisms, this paper utilized Bu3SnH- and TMS3SiH-assisted cyclization methods, drastically improving yields and providing the avenue through which new planar derivatives could be synthesized.[138]

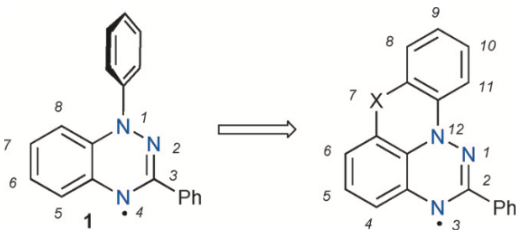

Figure 5 Left, 1,3-diphenyl-dihydrobenzo[e][1,2,4]triazin-4-yl; right, benzo[e][1,2,4]triazin-4-yl derivative with 2-phenyl substituent, planar Blatter radical discovered by Kaszynski et al. circa 2016 (Kaszynski, Constantinides, & Young Jr. 2016).

Following the optimization of the planar Blatter radical synthetic mechanism, Kaszynski's most recent investigation transpired in conjunction between the Łódź research team and an exploratory unit at Middle Tennessee State University, Murfreesboro, Tennessee. Utilizing the mechanistic pathways optimized by his research team in Poland, Kaszynski's research sought to functionalize the planar Blatter radical by installing a basic, electron-donating

[136] Kaszynski, P., Constantinides, C. P., & Young Jr., V. G. (2016). The planar Blatter radical: structural chemistry of 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yls. *Angewandte Chemie International Edition, 55*, 11149-11152.

[137] Bartos, P., Celeda, M., Pietrzak, A., & Kaszynski, P. (2022). Planar Blatter radicals through Bu3SnH- and TMS3SiH-assisted cyclization of aryl iodides: azaphilic radical addition. *Organic Chemistry Frontiers, 9*, 929-938.

[138] (Bartos et al. 2022)

substituent, pyridine, proximal to the lone electron.[139] In doing so, it was predicted that the resultant compound would participate in acid-base complexation and co-crystallization with various poly-carboxylic acids, an area of Blatter radical chemistry yet to be fully investigated.[140]

Installing a pyridinyl ring proximal to the triazinyl framework of the Blatter radical infrastructure suggested an increased likelihood of molecular magnetism and subsequent magnetic packing, a phenomenon not yet observed.[141] This most recent iteration of Kaszynski's research expanded on the existing 2-phenyl planar Blatter radical (the first planar derivative published, Figure 6), as the lack of hetero atoms on the phenyl substituent provided no influence on the overall magnetic behavior of the molecule.[142] However, at high temperatures, the 2-phenyl derivative demonstrated essentially ideal paramagnetic behavior where at low temperatures the molecule showed weakly increasing antiferromagnetic behavior.[143] As such, it was predicted that the formation of the 2-pyridinal derivative would ultimately induce detectable ferromagnetic behavior, greatly informing the science of molecular and crystal engineering.[144]

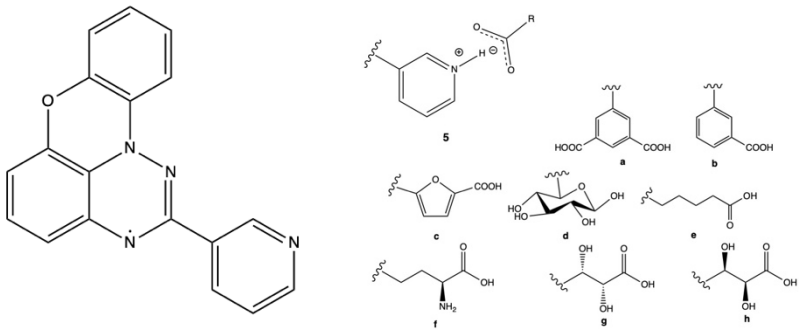

Figure 6 Left, 2-pyridinal derivative; right, poly-carboxylic acid complexations (Smith et al. Est. 2023).

[139] Smith, K., Hietsoi, O., Friedli, A., & Kaszynski, P. (Est. 2023). Synthesis, characterization, and acid co-crystallization of a pyridinal Blatter radical derivative. *Not yet published; National Science Foundation Summer 2022 Research Experience for Undergraduates, Middle Tennessee State University.*

[140] (Smith et al. Est. 2023)

[141] (Smith et al. Est. 2023)

[142] (Kaszynski, Constantinides, & Young Jr. 2016)

[143] (Kaszynski, Constantinides, & Young Jr. 2016)

[144] (Smith et al. Est. 2023)

The 2-pyridinal planar Blatter radical derivative chapter of Kaszynski's research is actively approaching both completion and publication, and already provides incredibly promising data. In a fashion much unlike the situation apparent with the development of optimal synthesis procedures for bexarotene, the research into the phenomena of complex organic radicals has exploded in the last decade, with an incredible number of compounds being added to the Blatter radical family within the last year alone.[145,146]

Kaszynski and his research present an especially interesting case. Due to the promise his research holds – new discoveries of molecular packing which will help inform the engineering of safe, renewable, entirely organic redox-flow batteries – there seems to be a general consensus that this research is deeply important, and moreover needs to be completed with haste. This is emphasized by the fact that his research receives funding from various institutions from multiple countries,[147,148,149] making it clear that these compounds are of international interest. Additionally, the field of Blatter radical research is not monopolized; as the years go on, more research institutions are dipping their cups into the seemingly overflowing font of Blatter radical chemistry.[150] This indicates that the rapid discovery and development in this small region of synthetic chemistry is furthermore propelled by institutional competition, a phenomenon necessary for innovation discussed at length in Chapter 2.

Though one might claim at first that Blatter radical chemistry is more urgent due to the impending threat of climate change, it would seem unwise to argue that environmental research that is far from being applied is of greater value than making treatments to aid actively suffering

[145] (Bartos et al. 2022)
[146] (Smith et al. Est. 2023)
[147] (Kaszynski, Constantinides, & Young Jr. 2016)
[148] (Bartos et al. 2022)
[149] (Smith et al. Est. 2023)
[150] (Rogers et al. 2020)

humans more accessible. This thesis intends to assert no such claims that climate change and its supplementary research are not important. Instead, it would seem that as important as it may be to heal our environment, it is equally – if not more – important to prioritize the health and well-being of humans on earth *at this moment*. The reality is that if we as a society are more eager for the rapid development of ergonomic batteries than effective, safe treatments for cancers and incurable diseases, we are a society in need of profound realignment. If anything, we must instill the drive to pursue both endeavors, though this analysis would argue that the latter has been neglected for far too long.

It seems obvious, then, that the medicinal chemistry industry has a lot to learn from the booming environmental side of synthesis. First, pharmaceutical companies have grown much too comfortable in the lax framework of the ODA, and enough is enough. It is catastrophic that not one, *but multiple*, pharmaceutical companies be able to pass around the same orphan designation without making any significant change, continuing to reap the profiting benefits on the dime of the United States federal government (and in turn, the unknowing taxpayer). Second, this cushy culture of 'pharmaceutical development' has resulted in a complete lack of competition within the industry of medicinal design of orphan drugs. Countless examples of intra-industry competition have proven to proffer rapid and long-lasting innovation, and that of the growth of the Blatter radical field is no different; in fact, it offers a blueprint for the pharmaceutical industry to follow. The ODA has, put simply, allowed our pharmaceutical companies to grow stagnant, simply rebranding old material for the security of government funding and market exclusivity; it's time that we reframe this system.

Chapter Four

Case Study: Bexarotene, the Life-Saving Treatment for End-Stage Cutaneous T-Cell Lymphoma

Introduction

Treatments for cancer can be both incredibly complicated and astronomically expensive, especially in the cases of rare cancers. As stated previously, Targretin (generic name bexarotene), is a pharmaceutical treatment prescribed as a pill to patients with "cutaneous T-cell lymphoma,"[151] or in an alternative gel form for those with "cutaneous lesions."[152] To be eligible for bexarotene, however, patients must have tried at least one conventional systemic therapy which failed to treat said lymphoma effectively.[153] Whether ingested or applied topically, bexarotene is a retinoid which "selectively binds and activates retinoid X receptor subtypes,"[154] a functionally different pathway from traditional treatments, providing further warranting for bexarotene only being prescribed after other treatments have failed. Unlike many other cancer therapies, bexarotene activates these receptors which subsequently regulate genes responsible for "cellular differentiation and proliferation," a core issue with the occurrence, manifestation, and spreading of tumors and cancer cells.[155] It is suspected that this mechanism additionally prevents drug resistance (as it models an existing pathway), which ultimately induces the apoptosis of cutaneous T-cells participant in the active lymphoma, though the exact pharmacologic mechanism of bexarotene is unknown.[156]

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[151] Food and Drug Administration. (2015). Highlights of Prescribing Information: Targretin. *U.S. Department of Health and Human Services.* Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021055s010lbl.pdf.

[152] Food and Drug Administration. (2009). Drug Label: 1% Targretin Gel. *Department of Health and Human Services.* Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021056s003lbl.pdf.

[153] (F.D.A. 2015)

[154] (F.D.A. 2015)

[155] (F.D.A. 2015)

[156] (F.D.A. 2015)

As mentioned above, Targretin was designated as an orphan drug in June of 1999.[157] More specifically, in 1999 Ligand Pharmaceuticals received the United States patent number 5,780,676 for the "drug product" and "method of use" of bexarotene 75 mg capsules and was guaranteed seven years of market exclusivity.[158] Additionally, the inventors of the bexarotene molecule, Boehm et al. (1994), received United States patent number 5,962,731 in October 1999 for bexarotene and all related molecules, despite originally filing for patent in the year immediately after their publication (1995).[159] In August of 2014, however, the Center for Drug Evaluation and Research (CDER) awarded Banner Pharmacaps Incorporated the rights to produce the generic form of bexarotene.[160] Due to patent 5,780,676 expiring in July of 2015 and patent 5,962,731 expiring in October of 2016, the CDER determined that Banner was authorized to produce and sell generic 75 mg bexarotene capsules prior to the end of the aforementioned patents, and furthermore granted 180 days of generic drug exclusivity upon the start of production.[161]

At present, Targretin can be purchased in pill form for $26,202.45 for 100 capsules,[162] or in 1% gel form for $30,713.99 for 60 grams.[163] Some financial relief can be found in the generic form of bexarotene where the pill form can be purchased for $6,012.20–$7,523.22 for 100

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[157] (F.D.A. 1999)

[158] Center for Drug Evaluation and Research. (1999). NDA 21055 Administrative Documents. *Food and Drug Administration, Department of Health and Human Services.* Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21055_Targretin_admindocs.pdf.

[159] United States Patent and Trademark Office. (1999). Patent Number 5,962,731. *Department of Commerce.* Retrieved from https://patentimages.storage.googleapis.com/6b/1b/4f/a0fd9d556a79ac/US5962731.pdf

[160] Center for Drug Evaluation and Research. (2014). ANDA 203174 Approval Package. *Food and Drug Administration, Department of Health and Human Services.* Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/203174Orig1s000.pdf.

[161] (C.D.E.R. 2014)

[162] Drugs.com. (2022). Targretin Prices, Coupons and Patient Assistance Programs. *Drugs.com*. [Accessed December 2022]. Retrieved from https://www.drugs.com/price-guide/targretin.

[163] Drugs.com. (2022). Targretin Gel Prices, Coupons and Patient Assistance Programs. *Drugs.com*. [Accessed December 2022]. Retrieved from https://www.drugs.com/price-guide/targretin-gel.

capsules, at roughly 25% the cost of the name brand treatment.[164] Within the last year, a generic version of the 1% topical bexarotene gel has also come on to the market, and can be purchased for $26,747.77–$28.264.63 for 60 grams.[165] Although the generic form of the bexarotene gel is not priced substantially lower than the brand name equivalent, the addition of the generic version is nonetheless exciting for patients seeking this medication.

Though it may be that bexarotene is incredibly difficult to synthesize, the area of cutaneous cancer therapies, however, has shown to be a 'cash-cow' for the pharmaceutical industry. One paper writes that "targeting research and development investment in oncology drugs may be a strategic business decision: owing to the versatility of their use for multiple cancer types, orphan oncology drugs can offer a higher profit potential than can noncancer orphan therapies."[166] The purpose of this synthetic case study is to investigate both the mechanism of producing bexarotene and subsequently the validity of the extremely high patient cost for the treatment. Doing so will thus allow a determination of whether the cost of life-saving treatments like bexarotene are unjustified or appropriate to the level of difficulty of synthesis.

Reaction Mechanism and Synthesis Overview

Below is the outline of the mechanistic pathway for the synthesis of bexarotene (Figure 7). Step One is a two-part mechanism in which the diol starting material **1** is first chlorinated via an S_N1 nucleophilic substitution to yield compound **2** (not isolated), which then undergoes Friedel-Crafts Alkylation after addition to toluene in an electrophilic aromatic substitution resulting in compound **3**. In Step Two, compound **3** undergoes Friedel-Crafts Acylation (again,

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[164] Drugs.com. (2022). Bexarotene Prices, Coupons and Patient Assistance Programs. *Drugs.com*. [Accessed December 2022]. Retrieved from https://www.drugs.com/price-guide/bexarotene#oral-capsule-75-mg.

[165] Drugs.com. (2022). Bexarotene topical Prices, Coupons and Assistance Programs. *Drugs.com*. [Accessed December 2022]. Retrieved from https://www.drugs.com/price-guide/bexarotene-topical#topical-gel-1.

[166] Karas, L., Lu, C. Y., Agrawal, P. B., & Asgari, M. M. (2019). The impact of the orphan drug act on food and drug administration-approved therapies for rare skin diseases and skin-related cancers. Journal of American Academy of Dermatology, 81(3), 867-877.

electrophilic aromatic substitution) to yield compound **4**. Step Three performs basic ester hydrolysis on compound **4** to yield compound **5**. Step Four uses the organometallic Grignard mechanism to reduce the ketone on compound **5** to a tertiary alcohol, resulting in compound **6**. Finally, Step Five performs condensation on compound **6** via Dean-Stark trap to yield the final product, bexarotene **7**. Procedures and characterization methods are modified from Faul's publication on the synthesis of retinoid X receptor molecules like bexarotene.[167] In the following sections, experimental findings of Steps One through Five are discussed.

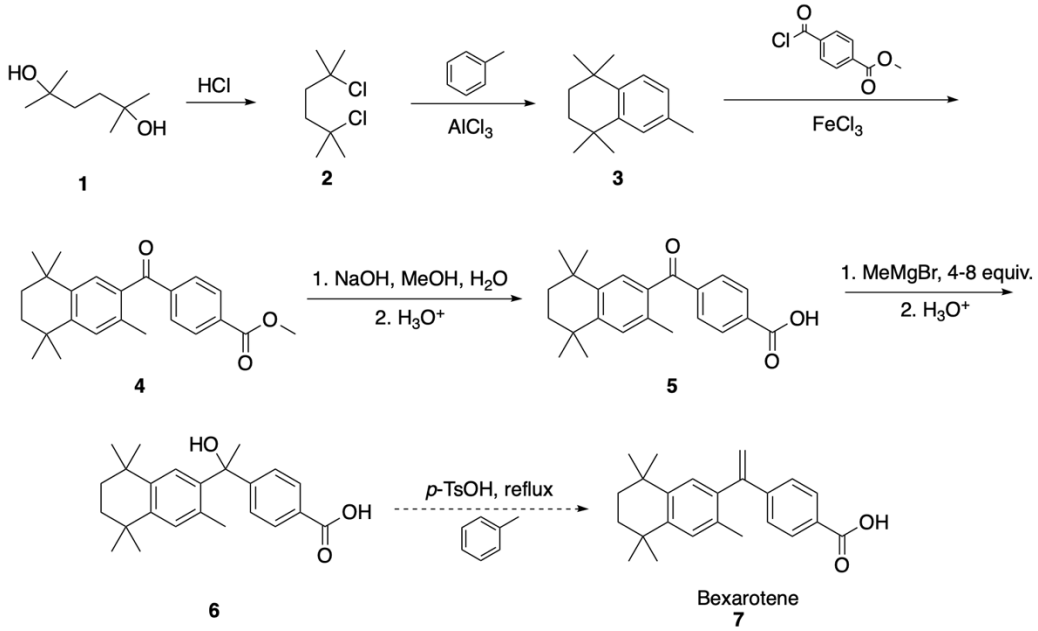

Figure 7. Complete synthetic mechanism of Targretin (bexarotene). Note the following names of the above labeled compounds: **1** – 2,5-dimethyl-2,5-hexanediol; **2** – 2,5-dichloro-2,5-dimethylhexane; **3** – 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene; **4** – 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalene) carbonyl]-methyl ester-benzoic acid; **5** – 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalene) carbonyl]-benzoic acid; **6** – 4[1-hydroxy-1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalene) ethyl]-benzoic acid; **7** – 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl]-benzoic acid (bexarotene).

[167] (Faul et al. 2001)

Experimental Section

*Preparation of Hydronaphthalene Compound **3***

20 g of **1** (136.86 mmol) was combined with 130 mL of reagent grade HCl (4.24 mol), and the solution was stirred at ambient temperature for three hours. For the duration of stirring, the flask remained in a water bath to prevent overheating. After three hours, 207 mL of water and CH_2Cl_2 each were added to dissolve any existing solids in solution (this solution contained compound **2**). Organic-aqueous extraction was performed to isolate the organic layer and the aqueous solution was back extracted with 50 mL of CH_2Cl_2. The combined organic layers were then dried with $MgSO_4$ and isolated again by vacuum filtration. The dried organic layer was combined with 22.5 mL of toluene (205.29 mmol) and was set to stir. Over the course of 30 minutes, three 0.05 equivalence of $AlCl_3$ (6.84 mmol) were added in titration fashion for a total of 2.738 g of $AlCl_3$ (roughly 0.15 equivalence, 20.533 mmol).[168] Once the solution changed to a dark orange-red color, reaction progress was checked via aliquot ^{1}HNMR, which verified that the reaction was complete. The flask was placed in a water bath to ensure that temperature remain <25ºC, in which 200 mL of water was added to the solution to quench the reaction. 200 mL of hexanes were then added to the solution and the organic layer were extracted, and the aqueous layer was back-extracted with an additional 50 mL of hexanes. The combined organic layers were then washed with 200 mL of water, 100 mL of saturated brine, and dried with Na_2SO_4. The organic solution was isolated from drying reagent via vacuum filtering and was then concentrated via vacuo to yield 24.1 g of colorless oil, compound **3** (87% yield compared to 99%

[168] Procedure in literature suggests that 5% equivalence $AlCl_3$ is sufficient to push Friedel-Crafts Alkylation, but in previous iterations of this mechanism, we found that 5% was not enough. In this iteration, we added 5% portions until reaction was as described in the literature (dark red solution), which was ultimately 15% equivalence (Faul et al. 2001).

yield in literature[169]). Product was characterized by ^{1}HNMR: 1.44 (q, 12H), 1.8 (t, 4H), 2.4 (s, 3H), 7.3 (s, 3H). See Appendix A-C for ^{1}HNMR data for compounds **1**-**3**.

*Formation of Methyl-ester Compound **4***

6.60 g of intermediate **3** (32.62 mmol) and 6.954 g of 4-(chlorocarbonyl)-methyl ester-benzoic acid (35.015 mmol) were dissolved in 10 ml of dichloroethane, and as the solution was stirring, 0.528 g of $FeCl_3$ was added (3.26 mmol). A reflux condenser was secured to the top of the flask and the reaction was stirred and heated to 75ºC for 16 hours (due to the long heating period, condenser was seated without water). Reaction progress was monitored by TLC in 15% EtOAc/hexanes (which was considered complete once the TLC indicated clear separation of starting material and product). The reaction was then cooled and quenched with 19.8 mL of methanol, resulting in a light green, opaque slurry which was then stirred at ambient temperature for 8 hours. The slurry was then vacuum filtered in triplicate, in which each portion of mass collected was rinsed with minimal cold methanol.[170] Each mass collection from filtrate was of decreasing purity; the first (most pure) collection yielded 5.298g, the second collection yielded 1.523 g, and the final (least pure) collection yielded 1.460 g for a total mass collection of 8.281 g. In total, yield of compound **4** was 69.6% as compared to 81% reported in literature.[171] The product of acylation was lightly tan, fine powdery solid and was characterized by ^{1}HNMR: 1.44 (q, 12H), 1.8 (t, 4H), 2.4 (s, 3H), 4.0 (s, 3H), 7.6 (s, 2H), 7.9 (d, 2H), 8.1 (d, 2H). See Appendix D for ^{1}HNMR data for compound **4**.

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[169] (Faul et.al 2001)

[170] Procedure outlined in the literature only suggests one iteration of vacuum filtering, but upon our first extraction, we noticed a significant portion of precipitate falling through with the filtrate; as such, we chose to do three full extractions of the filtrate to maximize total mass recovery (Faul et.al 2001).

[171] (Faul et.al 2001)

*Formation of Benzoic Acid Compound **5***

5.0 g of **4** (13.72 mmol) was combined with 50 mL of methanol. This suspension was then treated with 2.18 mL of 50 w/w NaOH (81.44 mmol), heated to 60ºC reflux, seated with a reflux condenser (without water) and stirred for two hours. Reaction progress was monitored by TLC in 15% EtOAc/hexanes (once TLC was clean, reaction was considered complete). The solution was then cooled to about 55ºC, and the flask was set in an ice bath; 6.85 mL of concentrated HCl was then added dropwise through the condenser (so as not to lose any yield should the reaction become exothermic). The resultant slurry was stirred for one hour. Reaction progress was monitored by TLC in 15% EtOAc/hexanes. After reaction completion, 100 mL of CH_2Cl_2 and water each were added to the slurry and the organic layer was extracted. The aqueous layer was furthermore back extracted with 50 mL of CH_2Cl_2. The combined organic layers were then dried with $MgSO_4$ and isolated via vacuum filtration; the resultant solution was then concentrated via vacuo.[172] A total of 4.326 g of white chalky powder compound **5** was collected for a yield of 90% versus the 97% published in the literature.[173] Compound 5 was characterized by ^{1}HNMR and was found to be slightly impure: 1.44 (q, 12H), 1.8 (t, 4H), 2.4 (s, 3H), 4.0 (s, 0.5) (methyl ester impurity), 7.6 (s, 2H), 7.9 (d, 2H), 8.1 (d, 2H), 11.0 (s, 1H); COOH peak outside of range of ^{1}HNMR (60 MHz instrument). See Appendix E for ^{1}HNMR data for compound **5**.

[172] Extraction practice was adjusted from procedure suggested in literature; previous iterations of this step demonstrated that product would not crash out of methanol successfully which elicited an organic-aqueous extraction (Faul et al. 2001).

[173] (Faul et al. 2001)

*Formation of Tertiary Alcohol Compound **6***

For the process of reduction, two separate procedures were run side by side to test the effectiveness of each; Reaction A performed the Grignard reduction per the procedure suggested in the literature (where organometallic reagent is placed in flask and compound **5** was titrated into reaction solution) and Reaction B performed the reverse of the same procedure (such that compound **5** was placed in the flask and organometallic reagent was titrated into reaction solution).[174] As such, reaction preparation and set up for Reactions A and B differed, but subsequent workup was equivalent.

Prior to reaction set up, compound **5** was dried via azeotrope with toluene three times to remove any remaining water from the material. For Reaction A, 3.0 mL of 3M MeMgCl diluted in 6.0 mL THF (40.51 mmol, 73.97 mmol) was cooled to -10ºC under nitrogen and then added to a round bottom flask with a stir bar and sealed with a septum via needled syringe. The flask was then placed in a salted ice bath and set to stir. 0.399 g of compound **5** (1.139 mmol) was diluted in 4 mL of anhydrous THF (49.31 mmol) and was then added to the Grignard reagent dropwise (again via a needled syringe through septum). Once all of **5** was added to flask, the reaction mixture was mixed for four hours. Upon complete addition of **5**, reaction solution turned to a dark green color and retained color change until quenching. For Reaction B, 0.397 g of compound **5** (1.133 mmol) was diluted in 4 mL of anhydrous THF (49.31 mmol) and was then added to a round bottom flask with a stir bar and sealed with a septum via needled syringe. The flask was then placed in a salted ice bath and set to stir. 3.0 mL of 3M MeMgCl diluted in 6.0 mL THF (40.51 mmol, 73.97 mmol) was cooled to -10ºC under nitrogen and was then added the

[174] Though Lilly Research Laboratories are known for their procedural chemistry, it is uncommon for organometallic reagents to be placed on underneath starting material (usually, Grignard reagent is titrated on top of starting material). As such, we intended investigate if the published procedure could be optimized by reversing the order of operations (Faul et al. 2001).

reaction flask dropwise (again via a needled syringe through septum). Once all organometallic reagent was added to flask, the reaction mixture was mixed for four hours. Upon the complete addition of **5**, reaction solution turned to a dark green color but returned to clear color after one hour of mixing.

Reaction progress was monitored via TLC in 5% MeOH: CH_2Cl_2 mobile phase. Once TLC demonstrated reaction completion, both flasks were quenched with 15 mL of 1M HCl (493.7 mmol), and 50 mL of toluene and water each were added to both reaction flasks. The organic layers were then extracted separately, and each aqueous layer was back extracted with 25 mL of toluene. The combined organic layers for Reaction A and Reaction B, respectively, were each washed with 50 mL of water and then 25 mL of saturated brine; solutions were dried further with Na_2SO_4. Solutions were isolated via vacuum filtration and then concentrated via vacuo. Both Reactions A and B resulted in chalky white precipitates; mass collected from Reaction A was 0.215 g and mass collected from Reaction B was 0.134 g; neither of these came to yield any product, though the literature reported a 66% yield.[175] Upon ^{1}HNMR characterization, it was furthermore determined that Grignard reduction did not take place; competitive byproducts and impurities from incomplete basic ester hydrolysis were carried through into Grignard reaction, and ultimately prevented the successful ketone reduction; it was thus concluded that intermediate **6** was not produced. Labeled characterization by ^{1}HNMR for both Reactions A and B of the incomplete formation of compound **6** is found in Appendix F.

Projected Formation of Bexarotene Compound 7

Due to the discovery of competitive byproducts and impurities and the resulting conclusion that the Grignard reduction did not take place, the final step of condensation via

[175] Note that 66% yield reported was yield after Grignard reduction, Dean-Stark condensation, and column chromatography purification (Faul et al. 2001).

Dean-Stark trap has yet to be performed. Following the purification of compound **5**, the Grignard reduction can be repeated to yield intermediate **6** which can then be reduced further to the final product, **7**. Purification of compound **5** by silica column chromatography was performed to attain increased, though imperfect purity; this ^{1}HNMR data is included in Appendix G.

Conclusion

In our investigation of the synthetic mechanism of the pharmaceutical drug bexarotene, we experienced the challenges of production outlined in Faul's exploratory paper, all of which attested to the overall difficulty of the production of this molecule. Though bexarotene is egregiously priced – both the brand name and generic versions – it seems that the degree of difficulty of its production somewhat justifies the subsequent pricing. That is, our inability to optimize this synthesis process with great success is indicative that bexarotene is an expensive molecule, both in production costs and the labor required. However, this is investigation is one performed by undergraduate students with limited access to industry-level equipment and practices. The lack of recent publications regarding the mechanistic approach to the production of bexarotene from more sophisticated institutions leaves one to question what procedures are utilized at the industrial level, and how (or if) they have improved since Boehm's invention of the molecule and Faul's extensive exploratory report. The chemical hinderances experienced in this iteration of synthesis seem not to be isolated, as Faul frequently mentions the difficulties which the team at Eli Lilly Labs experienced in the improvement of this synthetic procedure,[176] and yet no other papers provide evidence that innovative development has occurred.

This seemingly unchanged circumstance brings the bexarotene orphan indication into question. If the molecule is simply difficult to synthesize, federal funding under the ODA would

[176] (Faul et al. 2001)

be appropriate, as the production of bexarotene would simply require monetary supplementation. Originally, the design of the ODA was intended to provide relief in this exact way, supplying supplementary funding for the making of exorbitantly costly medicines. It is interesting to note, then, that in the most recent financial reports published by Bausch Health (the pharmaceutical company which currently owns Targretin) demonstrate that Targretin grossed $31 million revenue in fiscal year 2020[177] and $28 million revenue in fiscal year 2021.[178] Bausch furthermore notes in this report that Targretin was the fourth and fifth top-selling ortho-dermatologic products for the years 2020[179] and 2021,[180] respectively.

The fact of the matter is that there are only 16,000-20,000 Americans with cutaneous T-cell lymphoma, and there are only 1,000 new cases every year in the United States.[181] These data can be used to furthermore estimate that there is one diagnosis of the most typical form of cutaneous T-cell lymphoma per 1,000,000 Americans.[182] Though the expenditures required to manufacture this product are not public knowledge, it would be difficult for one to assume that Bausch Health is losing substantial amounts of money in the production of this drug, and more so to convince oneself that Bausch seems to need federal funding for this kind of production, especially considering the patient price as mentioned above. That is, if this product is so difficult to make and is marketed to so few patients in the United States, how is it such a profitable

[177] Bausch Health. (2021). Financial Results: 4Q & FY 2020. *Bausch Health Companies Incorporated.* Retrieved from https://ir.bauschhealth.com/~/media/Files/V/Valeant-IR/reports-and-presentations/4q20-bausch-health-earnings-presentation.pdf.

[178] Bausch Health. (2022). Financial Results: 4Q & FY 2021. *Bausch Health Companies Incorporated.* Retrieved from https://ir.bauschhealth.com/~/media/Files/V/Valeant-IR/reports-and-presentations/bausch-health-fourth-quarter-and-full-year-2021-earnings-presentation.pdf.

[179] (Bausch Health 2021)

[180] (Bausch Health 2022)

[181] National Organization for Rare Disorders. (2021). Cutaneous T-Cell Lymphomas. *Rare Disease Database, National Organization for Rare Disorders, Inc.* Retrieved from https://rarediseases.org/rare-diseases/cutaneous-t-cell-lymphomas/.

[182] (N.O.R.D. 2021)

medicine? It would seem that some level of abuse is being exacted on the orphan designation gifted Targretin, and subsequently Bausch Health.

Overall, the experimental process of synthesizing bexarotene has proven to be rather difficult, and one which we plan to continue to investigate and eventually optimize in future research. Regardless, the industrial production of Targretin and incredible profit therein certainly sounds alarm bells, only strengthening our resolve to demonstrate that bexarotene can be synthesized in cost-effective manner.

Acknowledgements

This research team would like to thank Will Oprisu, Kristian Hooker, and Brian Martinez, for their joint work on this endeavor, as well as Dr. Ahrendt, Dr. Kallan, and Dr. Stevens for guidance and helping find materials. Additionally, we thank the Regis University Chemistry Department for providing materials and equipment. Finally, we thank Tanden, Collin, and Kassidy for providing information and procedures from previous research.

Chapter Five
Societal Costs and Ethical Discomfort: When Patients Get the Brunt of the Orphan Drug Act

Thus far in our evaluation of the Orphan Drug Act of 1983, we have discussed a myriad of areas where the legislation has fallen short of its promise. We determined that, foundationally, the characteristics of the ODA prevent the bill from being functional in practice, due to a profound lack of features necessary for a successful government-private industry relationship. We explored the ways in which the development within the synthetic chemistry industry has stalled in medicine and exploded in environmental research due to incentives within the ODA. We looked closely at a case study, examining synthetic procedures, and strived to decipher the difference between medicines that are difficult to synthesize and those that are simply too profitable to give up government funding. Though all of these topics greatly inform the ways in which the ODA desperately needs reform, one stone remains unturned: how this legislation actively favors pharmaceutical companies and subsequently commits abuse against the patients to which these businesses are called to serve.

In 2016, a completely unconventional – and, quite frankly, courageous – display of concern was published in an editorial composed by a coalition of 106 doctors regarding the likely price increase of the treatment for the rare disease Lambert-Eaton myasthenic syndrome (LEMS).[183] LEMS is an exceedingly "rare autoimmune disorder of the neuromuscular junction" leading to the gradual loss of muscle function, affecting only 400 patients in the United States

[183] Burns, T. M., et al. (2016). Editorial by concerned physicians: unintended effect of the orphan drug act on the potential cost of 3,4-diaminopyridine. *Muscle & Nerve, 53*, 165-168.

and approximately 2.8 individuals per million worldwide.[184] Gathered from medical practices across the United States and the United Kingdom, the authors of this letter appealed to the United States legislative branch to address the impending reclassification of the medication amifampridine (3,4-diaminopyridine or 3,4-DAP), the drug used to treat LEMS, as an orphan drug.[185]

In February of 2016, the time at which this letter was published, amifampridine recently underwent "randomized, controlled trials pursuant to submission for United States FDA approval under the ODA" by firms Jacobus Pharmaceutical Company Incorporated and Catalyst Pharmaceuticals Incorporated.[186] Where it would seem that most orphan designation applications are for newly discovered medications, amifampridine was an existing drug which was widely accepted as the preferred treatment method of LEMS since it was published as such in 1983.[187] The authors furthermore mention that the production of amifampridine is quite simple and inexpensive;[188] in fact, students at Regis University in Denver, Colorado complete the second half of this synthetic mechanism in undergraduate organic chemistry labs.[189] In the more than 30 years that amifampridine was prescribed, four trials demonstrated the efficacy of the treatment and physicians in the United States were granted IND cards – Investigational New Drug – under Jacobus Pharmaceuticals which allowed providers to administer the therapy at no cost to patients.[190]

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[184] National Organization for Rare Disorders. (2021). Lambert-Eaton Myasthenic Syndrome. *Rare Disease Database, National Organization for Rare Disorders, Inc.* Retrieved from https://rarediseases.org/rare-diseases/lambert-eaton-myasthenic-syndrome/.

[185] (Burns et al. 2016)

[186] (Burns et al. 2016)

[187] Lundh, H., Nilsson, O., & Rosén, I. (1983). Novel drug of choice in Eaton-Lambert syndrome. *Journal of Neurology, Neurosurgery, & Psychiatry, 46*(7), 684-685.

[188] (Burns et al. 2016)

[189] Ahrendt, K. (2022). Synthesis of Amifampridine (3,4-Diaminopyridine). *Organic Chemistry II Laboratory, Department of Chemistry, Regis University.*

[190] (Burns et al. 2016)

Though the running of trials for ODA approval may have seemed randomly timed to some, these doctors were not so surprised. In 2010, a United States pharmaceutical company under the name BioMarin acquired the rights of Firdapse (3,4-diaminopyridine phosphate), the phosphate salt of amifampridine.[191] Upon obtaining these licenses, Firdapse was immediately authorized for sale by the European Orphan Drug legislation for the treatment of LEMS, basing the prospective efficacy on evidence presented in the trials performed on the base form of the medication (3,4-diaminopyridine).[192] Where the base form was sold for approximately $1,600 USD per year, Firdapse was peddled to patients for a drastic $60,000 USD per year.[193] The East Midlands Specialized Commissioning Group of the National Health Service in the UK concluded that since Firdapse was accepted as bioequivalent to the far more inexpensive amifampridine, the agency could not condone paying for Firdapse, leaving UK patients "with the option to pay for Firdapse out of pocket or find alternative sources."[194]

In the following year, BioMarin and Catalyst Pharmaceuticals began running clinical trials for Firdapse in the United States and Jacobus Pharmaceuticals followed shortly thereafter, performing clinical trials for amifampridine.[195] As some of the investigators participating in these trials, the authors of the editorial letter wrote that they feared an orphan designation of both Firdapse and amifampridine would subsequently result in the loss of patient access to treatment. The physicians furthermore noted that their patients, who had received treatment at no cost for thirty plus years would now be expected to pay a year's salary for life-saving medication, a moral qualm which they felt simply could not be overlooked.[196]

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[191] (Burns et al. 2016)
[192] (Burns et al 2016)
[193] (Burns et al. 2016)
[194] (Burns et al. 2016)
[195] (Burns et al. 2016)
[196] (Burns et al. 2016)

Despite their efforts, the fears of this physician coalition ultimately came true. In November of 2018, Catalyst Pharmaceuticals was granted market exclusivity for the sale of Firdapse for the LEMS orphan indication.[197] Shortly thereafter in 2019, Catalyst filed suit against the FDA, claiming that the presence of amifampridine marketed as Ruzurgi by Jacobus Pharmaceuticals violated the market exclusivity granted Catalyst's orphan approval.[198] Ruzurgi, the version of amifampridine administered to patients in the United States under IND per Jacobus, was originally given an orphan designation for LEMS in December of 1990.[199] As market exclusivity under the ODA ensures that the company with the orphan designation retains complete monopoly over the sale of a drug for a given designation remains unchallenged, Jacobus' product hence disputed this federally endorsed exclusivity for Catalyst.

While the case was under consideration, Jacobus voluntarily recalled Ruzurgi tablets on September 13, 2021, as the product was found to be "contaminated with yeast, mold, and aerobic bacteria" based on laboratory data performed by Jacobus' Canadian partner.[200] Only a few short months later on January 28, 2022, the United States Court of Appeals for the 11th Circuit "issued a mandate directing the District Court that heard Catalyst's claim against the FDA to enter summary judgement in favor of the Company."[201] Jacobus subsequently lost approval to

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[197] Food and Drug Administration. (2018). Search Orphan Drug Designations and Approvals: Firdapse (Amifampridine). *Department of Health and Human Services.* Retrieved from https://www.accessdata.fda.gov/ scripts/opdlisting/oopd/listResult.cfm.

[198] Park, B. PharmD. (2022). Ruzurgi Approved for LEMS No Longer Valid Following Court Decision. *MPR, Haymarket Media, Inc.* Retrieved from https://www.empr.com/home/ news/ ruzurgi-approval-for-lems-no-longer-valid-following-court-decision/.

[199] Food and Drug Administration. (1990). Search Orphan Drug Designations and Approvals: Amifampridine [Ruzurgi]. *Department of Health and Human Services.* Retrieved from https://www.accessdata. fda.gov/scripts/opdlisting/oopd/listResult.cfm.

[200] Jacobus Pharmaceutical Company, Inc. (2021). Jacobus Pharmaceutical Company Inc. Issues Voluntary Worldwide Recall of Ruzurgi (amifampridine) 10 mg Tablets Due to Yeast, Mold, and bacterial Contamination. *Food and Drug Administration, Department of Health and Human Services.* Retrieved from https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/jacobus-pharmaceutical-company-inc-issues-voluntary-worldwide-recall-ruzurgir-amifampridine-10-mg.

[201] (Park 2022)

distribute Ruzurgi in the United States[202] and furthermore lost its orphan indication which was originally approved in 1990.[203]

Following the removal of Ruzurgi from the market – the treatment which was given to patients for free in the United States by Jacobus – Catalyst now has market exclusivity for LEMS until November of 2025.[204] Per clinical trials as published on Catalyst's Firdapse website, an average of 60 mg daily was sufficient for successful treatment of LEMS.[205] Firdapse is sold for $218.10 per 10 mg pill, packaged as 120 tablets for $26,171.75.[206] Using these data, an individual with LEMS prescribed the average dosage (60 mg) should expect to ingest 2190 tablets a year for an annual market price of $477,639.00 before assistance programs. As the concerned physician coalition predicted in 2016, the reclassification of amifampridine as an orphan drug resulted in an incomprehensible price increase for what might be described as an invaluable life-saving treatment. Perhaps even more infuriating, amifampridine, *again*, is known to be both simple and inexpensive to manufacture; Catalyst's Firdapse, then, is a blatant exploitation of the ODA.

Unfortunately, the reality is that violations of this caliber are not uncommon. As mentioned multiple times thus far, the letter of the law is not expressly clear, and this fact allows for egregious loopholes, three in particular.[207] First, termed "salami-slicing," drug companies can

[202] Catalyst Pharmaceuticals, Inc. (2022). Catalyst Pharmaceuticals Announces Settlement of U.S. Patent Litigation and Resolution of Litigation Challenging Ruzurgi Approval with Jacobus Pharmaceutical. *Catalyst Pharmaceuticals, Inc.* Retrieved from https://ir.catalystpharma.com/news-releases/news-release-details/catalyst-pharmaceuticals-announces-settlement-us-patent.

[203] (FDA 1990)

[204] (FDA 2018)

[205] Catalyst Pathways. (2022). Taking Firdapse. *Catalyst Pharmaceuticals, Inc.* Retrieved from https://www.firdapse.com/starting-firdapse/taking-firdapse/.

[206] Drugs.com. (2022). Firdapse Prices, Coupons, and Patient Assistance Programs. *Drugs.com*. [Accessed December 2022]. Retrieved from https://www.drugs.com/price-guide/firdapse.

[207] (Karas et al. 2019)

"seek orphan designation and approval for narrow subsets of more common diseases."[208] That is, for some disease which affects a large population but contains a subgroup with a particularly rare manifestation, drug companies can apply for orphan designation for that particular specification, referred to here as "narrow subsets."[209] This can be a flagrantly profitable specification, as doing so allows one company to obtain orphan designations for 'diseases within diseases' (thus achieving the 'at or less than 200,000 affected' requirement), and this application process can be done for various illnesses. Ultimately, this allows pharmaceutical companies to stack multiple orphan indications – and all the benefits therein – for a single drug, a sort of 'double-dipping.' The "orphan" designation dictated by the ODA is specific to the *illness*, not the *medication* prescribed for treatment.

In one particular example, pembrolizumab, an immunotherapy "approved to treat 11 different types of cancer, including melanoma," has various orphan and nonorphan classifications.[210] One report wrote that "as of December 31, 2018, pembrolizumab had 3 approved dermatologic orphan indications and 4 additional orphan indications for nondermatologic cancers."[211] Those seven orphan designations, held by Merck & Company – the progenitor of pembrolizumab – are the following: hepatocellular carcinoma (HCC), small cell lung cancer, stages IIB-IV malignant melanoma, Hodgkin lymphoma, Merkel cell carcinoma, esophageal carcinoma, gastric cancer (including gastroesophageal junction adenocarcinoma), and primary mediastinal B cell lymphoma.[212] As such, Merck effectively retains market monopolies for these seven rare diseases, all for the same medication. Naturally, this means that Merck

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[208] (Karas et al. 2019)
[209] (Karas et al. 2019)
[210] (Karas et al. 2019)
[211] (Karas et al. 2019)
[212] Food and Drug Administration. (2022). Search Orphan Drug Designations and Approvals: Keytruda (Pembrolizumab). *Department of Health and Human Services*. Retrieved from https://www.accessdata.fda.gov /scripts/opdlisting/oopd/listResult.cfm.

compounds all of the funding *seven times* – market exclusivity, 25% tax credit, exemption of FDA review and user fees – not to mention the additional profit made by selling pembrolizumab to patients with non-orphan indications.[213] Its unsurprising, then, that pembrolizumab proves to be wildly profitable for Merck, bringing in $2 billion in the final quarter of 2018 *alone*.[214]

Second, "mass-market drug repurposing" is the process by which a pharmaceutical company takes a medication originally on market for a "nonorphan condition" and later applies to "receive approval for an orphan indication."[215] As the ODA guarantees funding for the research and development of prospective medications for orphan designations, drug repurposing in this fashion can be extremely profitable. Receiving funds to 'develop' a medication which exists, has surpassed clinical trials, and has been safely prescribed for years is an obvious 'cash-cow' for pharmaceutical companies; all that these businesses need to do is receive ODA approval, and their profit margins can increase immediately.

An excellent example of this repurposing is adalimumab, the "top-selling pharmaceutical drug worldwide," originally approved for rheumatoid arthritis.[216] In 2015, adalimumab received approval as an orphan treatment for moderate to severe hidradenitis suppurativa (HS),[217] an "inflammatory, chronic, and recurrent skin condition" which manifests as lesions and boils, affecting approximately 0.10% of the American population.[218] Beyond moderate to severe HS, adalimumab also possesses orphan indications for pediatric Chron's disease, non-infectious intermediate/posterior/panuveitis/chronic non-infectious anterior uveitis, pediatric ulcerative

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[213] (Karas et al. 2019)
[214] (Karas et al. 2019)
[215] (Karas et al. 2019)
[216] (Karas et al. 2019)
[217] Food and Drug Administration. (2015). Search Orphan Drug Designations and Approvals: Humira (Adalimumab). *Department of Health and Human Services*. Retrieved from https://www.accessdata.fda.gov /scripts/opdlisting/oopd/index.cfm.
[218] Jfri, A. MD, MSc, et al. (2021). Prevalence of Hidradenitis Suppurativa. *Journal of the American Medical Association Dermatology, 157*(8), 1-8.

colitis, and juvenile rheumatoid arthritis.[219] In 2016, adalimumab netted $13.6 billion in total sales revenue, approximately 4% of which was supplemented by orphan drug sales, roughly $544 million.[220] Repurposing, as shown in the case of adalimumab, allows pharmaceutical companies to make profit on both orphan and nonorphan sales for the same treatment.

In one evaluation of all the orphan indications approved since the year the ODA was passed, the paper reported the following:

> Among all drugs approved for treating rare diseases between 1983 and 2016, a total of 22% (98 of 449) also have a non–rare-disease indication. The rare-disease indication was obtained before or concurrently with the other indication for 45% of these drugs. Concurrent or subsequent approval for a non–rare-disease indication does not nullify incentives awarded under the Orphan Drug Act, which has led to questions about whether manufacturers have "sliced" indications to secure the statutory benefits.[221]

This study furthermore suggests that the stacking of orphan classifications occurs in both salami slicing and drug repurposing. The ODA not only allows retroactive orphan designation after a pharmaceutical company has proven efficacy in a non-orphan trial, but it seemingly encourages the behavior of simply reassigning existing medications to rare diseases for the sake of monetary gain on behalf of the producer. The circumstance between Ruzurgi and Firdapse seems to emulate the intersection between salami slicing and drug repurposing, as Catalyst was particularly cutthroat in ensuring that their exorbitantly pricey product was the only one available to patients.

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[219] (F.D.A. 2015)

[220] (Karas et al. 2019)

[221] Sarpatwari, A. & Kesselheim, A. S. (2019). Reforming the orphan drug act for the 21st century. *The New England Journal of Medicine, 381*(2).

Lastly is the issue of "market exclusivity prolongation,"[222] a tactic alluded to throughout this and other chapters (see the timeline of the bexarotene orphan designation in Chapter Four). Here, we see that an orphan drug "receives a new 7-year exclusivity period for each approved orphan indication," a trend which "could prolong market exclusivity beyond a drug's patent term."[223] This means that a singular contribution to the pharmaceutical market can "cost taxpayers significant sums by delaying generic entry beyond what legislators intended as a quid pro quo 'reward' for pharmaceutical innovation."[224] That is, due to the guarantee of the ODA, there is no economic pressure for the extremely high prices of orphan medications to reduce so long as a company retains market exclusivity. Patents are an important part of infrastructure to ensure the protection of intellectual property, but prolonging terms of market exclusivity effectively squanders competition within the marketplace. This installs what is equivalent to extensive, potentially eternal patents, preventing any sort of development of treatment options for patients suffering from that particular orphan indication.

These are obviously far-reaching issues endemic to both the structure and implementation of the ODA, and it is clear that these foundational errors only harm one party: patients. Interestingly, the ODA itself is not the only bill which acquiesces to this corrupt behavior by our pharmaceutical companies. The 340B Drug Pricing Program, designed to "help uninsured, indigent patients by giving qualifying health care facilities access to discounts for outpatient drugs," is federally facilitated and "imposes ceilings on prices drug manufacturers may charge for certain medications sold to qualifying health care facilities known as covered entities."[225] The

[222] (Karas et al. 2019)
[223] (Karas et al. 2019)
[224] (Karas et al. 2019)
[225] Fisher, N. C. (2019). The 340B Program: A federal program in desperate need of revision after two and a half decades of uncertainty. *Journal of Health Care Law and Policy, 22*(1).

Program does not, however, cover orphan drugs. Subsection 340B(e) titled *Exclusion of Orphan Drugs for Certain Covered Entities* writes that "the term 'covered outpatient drug' shall not include a drug designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act for a rare disease or condition," the ODA.[226] This indicates that yet another piece of federal legislation makes way for the catastrophic profiteering conducted by the pharmaceutical companies, yet again leaving the patient as the primary sufferer.

One paper argues that "Congress provided explicit protection of orphan drugs from drug discounting, and HHS, though clearly under pressure to undermine drug prices, showed no desire to place pressure on orphan indications."[227] These written provisions designed to allow pharmaceutical companies to continue price gouging patients with rare drug prices draws well-warranted scrutiny as whether to the formation of the 340B Program was intended to be or simply has become a vehicle to exacerbate the conditions of regulatory capture we see today. This outgrowth of regulatory legislation, seemingly calculated to weight the profitable standings of pharmaceutical manufacturers protected under the ODA, yet again leaves patients with rare indications completely defenseless and often without treatment.

Regardless of intention, it's clear that patients are not the priority of these pharmaceutical companies and are furthermore prevented from being the benefactor of supposedly protective actions. This notion, however, seems to be felt beyond patients burdened and struggling with financing their treatments. Within the last year, an interesting new development has cropped up on the pharmaceutical sales front. The Mark Cuban Cost Plus Drug Company (MCCPDC) claims

[226] (Fisher 2019)

[227] Stella, P. & Gold-von Simpson, G. (2014). Pharmaceutical pricing, cost containment and new treatments for rare diseases in children. *Orphanet Journal of Rare Diseases, 9*(152).

to offer the "lowest prices on 100 lifesaving prescriptions."[228] MCCPDC sets all treatment prices at manufacture prices "plus a flat 15% margin and pharmacist fee."[229] One example in particular is the medication Imatinib, prescribed for leukemia; retail price runs at $9,657 a month, costing "around $120 a month with a common voucher" but through MCCPDC, the drug is sold for $47 a month.[230] Cuban's devotion to selling drugs at only 15% above manufacture prices highlights that companies with orphan drug status are making *significant* price hikes. The CEO of MCCPDC pressed this issue, saying "The markup on potentially lifesaving drugs that people depend on is a problem that can't be ignored. It is imperative that we take action and help expand access to these medications for those who need them most."[231]

Where Cuban has centered his focus on making treatments more financially accessible, Brigham Buhler takes it a step further with his business, Ways2Well. After spending decades in the medical industry as a sales representative for pharmaceuticals and medical devices, Buhler left the traditional theater of medicine to create his own. Arguing that insurance companies – an entirely separate, and yet arguably equal contributor to the crisis faced by patients seeking treatment for rare diseases (and healthcare in general) not covered in depth here – are the primary barrier between patients and preventative medicine, Buhler made Ways2Well.[232] In his unconventional, never-tried-before model, Buhler focuses on blood testing and precautionary treatments, all financed by cash.[233] This system, he argues, allows that patients take control of

[228] Pasquini, M. (2022). Billionaire Mark Cuban's discounted pharmacy has launched. People Magazine, retrieved from https://people.com/human-interest/mark-cuban-discounted-pharmacy-has-launched/.

[229] (Pasquini 2022)

[230] (Pasquini 2022)

[231] (Pasquini 2022)

[232] Rogan, J. (Host). (2022, September 23). Brigham Buhler. (No. 1873) [Audio podcase episode]. In *The Joe Rogan Experience*. Spotify. Retrieved from https://open.spotify.com/episode/30NOm1ioG5mpmoQCNEjNgF?si=640c338e1fd549ec.

[233] (Rogan 2022)

their personal healthcare, and are not manipulated into dire situations of wellness by reprehensible insurance companies which prefer to only care for patients once they are ill.[234]

Though Buhler's company currently extends only to general wellness (as in, is not designed to assist in the specific treatment of rare diseases for some patients), his reconceptualization of health is a wise and necessary one, as is Cuban's design overhaul of pharmaceutical sales. The innovation in these businesses provide evidence that the orphan treatment issue could very well be quelled by the power of private investment. The success – and much needed relief on behalf of patients – of these companies highlights the lack of such development within the pharmaceutical industry, and calls into question the role of the federal government in funding synthesizing treatments. Companies like Cuban's demonstrate that treatments do not need to be marketed at such steep prices, *despite* the orphan or nonorphan status of the drug, and businesses like Buhler's indicate further that most institutions in the healthcare system of the United States are *not* designed for the benefit of the patient.

It is developments like these, then, which cause the greatest pondering over the ODA and how pharmaceuticals are designed and marketed in this country. Cuban and Buhler are not only demonstrative of the sheer power of private advancements but are clearly the moral better in this theater of health. Where pharmaceutical companies seek to maximize profit with minimal effort, these companies recenter the focus of healthcare on *people*, not the dollar sign attached to patients' illnesses. This not only offers a potential off-ramp for the seemingly endless ramifications of the ODA but provides hope that someday, healthcare for patients in the United States, with general and rare health concerns alike will be treated, not prescribed.

[234] (Rogan 2022)

Chapter Six

Cultivating a System for Health, not Wealth: Where Should We Go from Here?

While it is undeniable that money is an important piece of pharmaceutical design and development, funding from the federal government – an entity which can inflict oligarchical control over function – is not ethically nor morally correct, especially in the installation of the Orphan Drug Act of 1983. The art of science is a painstaking dedication to infinitesimal expansion of the canon of physical knowledge accrued about this universe, and yet laws like this allow the narcissistic curbing of that pursuit in the name of personal wealth, an action to the express detriment and suffering of those who these companies claim to serve and protect. The ODA gives these large pharmaceutical firms – who are not wanton for capital – various loopholes through which little research is conducted, few new drugs are put on the market, and therapy prices are made unaffordable as big pharma continues to accrue ungodly wealth.

Returning the drug market to private companies, while maintaining a degree of federal regulation (so as to prevent the unwanted deaths of patients due to poor pharmaceutical quality), might hold some tangible ethical benefits not proffered by the ODA. Regardless, in this industry, we have far greater ethical responsibilities than to the dollar, and we can no longer neglect this fact. The ODA is not performing as it was allegedly intended upon its passing through the legislature, and thus requires drastic revision. What, though, might those revisions look like?

Clearly, there are multiple areas of the legislation which are in desperate need of revision. First, the definition of "orphan" in the classification scheme needs to be far clearer. The version of the ODA to which this thesis has referred thus far is in fact an amended form of the bill. Originally, an orphan indication was defined as one which "occurs so infrequently in the United

States that 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 the sales in the United States of such drug,"[235] a definition largely similar to the second part of the existing description. Naturally, this required that pharmaceutical companies provide evidence of "commercial non-viability," a demand to which said companies were uncomfortable acquiescing.[236] Consequently, the ODA was amended in 1984 such that the definition of "orphan" included the prevalence based "less than 200,000 persons" affected in the United States; this provision allowed that pharmaceutical companies could exact all of the benefits of an orphan designation without proving that the development of a particular drug would be financially inadvisable.[237]

The second iteration of the definition – and in fact, the definition originally employed – indicates that companies can receive designation in the event that investment will not be returned in the research, design, and manufacturing of a particular small molecule. This specification, particularly in the event that supplementary financial diagnostic reports are required to evidence the need for orphan designation, suggests that the abuse of the ODA's loopholes might be mitigated. One paper suggests that,

> Elimination of the prevalence-based definition of orphan status and replacement with a definition based on commercial nonviability could reduce the ability of drug companies to profit excessively from orphan drug approvals by making orphan status contingent on adequate evidence that a drug is not expected to be commercially profitable. Measures to curb excessive profits are justifiable in light

[235] Herder, M. (2017). What is the purpose of the Orphan Drug Act? *Public Library of Science Medicine*, *14*(1).

[236] (Herder 2017)

[237] (Herder 2017)

> of the fact that a sizeable proportion of orphan drugs and scientifically ‘‘novel’’ drugs are discovered in a university setting, funded by taxpayer dollars.[238]

By restricting the definition of orphan in the literature of the legislation, and requiring specific evidence that a given company will not be able to make any return following manufacturing, large swaths of classifications obtained via the definition-based loophole will be eradicated. Furthermore, this redefinition would prevent companies from seeking narrow indications within diseases to classify as orphan disorders. Instead, this clarification would necessitate that federal funding via the ODA would be used for the express purpose of development for diseases which have little to no existing treatments whatsoever, the goal which the bill was originally installed to achieve.

Second is the issue of market exclusivity. Salami slicing and drug repurposing behaviors allow companies to obtain multiple designations for singular treatments, and furthermore grants that the terms of 7-year market monopoly be administered for each. This, of course, entitles one company to the exclusive rights over the treatment of an *entire rare disease* until exclusivity expires, permitting these firms to play with patients' lives in the most literal sense. Not only does this prevent patients from a foreseeable reduction in therapy pricing, but the innovation and intra-market competition between formulas is completely prohibited as well. One paper emphasizes this fact, writing,

> …although [market exclusivity] has been critical for the ODA's success, it has also allowed exorbitant prices for some FDA-approved orphan drugs. The intemperate pricing of many orphan drugs is also facilitated by US law that

[238] (Karas et al. 2019)

> prevents the FDA from considering cost in making decisions about regulatory approval of drugs.[239]

Explicit prevention of both slicing and market exclusivity compounding would prevent pharmaceutical companies from violating existing patent expectations in the United States and would subsequently allow for intradisciplinary development. Moreover, a strict limit on market exclusivity would increase the likelihood of patients seeing more options in the future, and reduced market prices overall.

Third is the issue of the tax credits afforded pharmaceutical companies in their efforts to create and manufacture orphan drugs. As it stands, companies are not required by the ODA to repay any form of subsidization provided by the federal government. One paper makes the following suggestion:

> A complementary reform would be to require certain manufacturers to repay the tax credits and research grants they received for developing a rare-disease drug. Such a policy could reframe the incentives provided under the Orphan Drug Act as a minimum guarantee. Were revenue from a drug to exceed a certain level (e.g., $500 million), its exclusivity would be terminated and the funds that manufacturers would be required to repay could be invested in rare disease research through the National Institutes of Health. For this provision to be enforced effectively, manufacturers could be required to report annual revenues for orphan-designated drugs to the government.[240]

The fact of the matter is that pharmaceutical companies are not *only* producing orphan treatments – the drug industry is obviously a wildly profitable one. Additionally, this thesis has outlined in

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[239] (Burns et al. 2016)
[240] (Sarpatwari & Kesselheim 2019)

great detail the extent to which these companies have abused the ODA benefits in order that orphan drugs become obscenely fruitful. It is henceforth ridiculous to protect these companies from repaying the loans provided them by the American taxpayer, especially considering the profits these companies stand to make on orphan designations per the current version of the bill. This revision would prevent pharmaceutical companies from taking federal funding for granted and billing the American people under the table.

The fact of the matter is that the majority of Americans today will never encounter the trials and tribulations of rare disease. At its very core, the United States has many incredible, fortuitous tenets which have withstood the test of time, one of these being: *no man should be left behind*. It is this principle, this thesis finds, instilled in the American people which seeks to make proper health care available to all, even those of us with overwhelming health challenges. Furthermore, the rationale behind the ODA in its inception, determined by the American public, asserts that research into the treatment of rare diseases is an invaluable effort despite the fact that most will never see its fruits. It is finally, then, this principle for which the ODA must be revised, as it is under its protection that pharmaceutical companies have stolen unfathomable amounts of money from the American taxpayer without ever upholding their end of the bargain.

As such, this thesis stands to make the following revisions. First and foremost, the definition of an orphan indication must be strictly based on the commercial viability of a product, and applications for such designations *must* require supplementary fiscal diagnostics. This definition prevents salami slicing and drug repurposing with the intention of price gouging and furthermore requires that government funding be allocated to the development of new products *only*. Second, market exclusivity must be restrained to the molecule itself, not the disease(s) it is used to treat. That is, market exclusivity will function much like a patent; companies will receive

rights over their molecule, not an entire rare disease, or multiple for that matter. Third, in the event that a particular orphan medication becomes profitable – and thus exceeds the fiscal projections presented to the federal government – ODA funding should cease immediately and the institution at hand should be reevaluated for funds mishandling to determine if federal loans should be repaid.

Government involvement in this industry should be used as an invisible force, increasing the number of products available for patients without any available treatments and refraining from squandering the natural energy of competition integral to the field of science and scientific development. The ODA was originally authored to offer treatments to patients, *not* to create a program through which pharmaceutical companies make egregious profit. The revision of this legislation requires us to ask of ourselves – as doctors, as medicinal chemists, as businessowners, as patients, as *people* – since when did healthcare become less focused on helping individuals achieve better health and more devoted to having the best profit margin? When did the genuine pursuit of science heed to the demands of business models and federal funding? Where, exactly, did our curiosity go? Our sense to help others, to help ourselves? This thesis finds that implementing these revisions is the first step to a long road ahead, answering each of these questions, one at a time.

Concluding Remarks

I would be lying to say that I have never wondered what my life would be like now if I had waited just a few months to begin treating my condition. I am not naïve to think that things would have been perfect; nature will always take nature's course. I am, however, willing to consider if things could have been better. Perhaps the progression of my disease state would have slowed, perhaps I could have avoided hours and hours of cardiac testing, lamenting over sudden and imminent death, praying that we could find a way to just make things better, or perhaps all that would have happened anyway. Even then, I am one of the lucky ones, a patient who has prevailed from her brushes with death at the pharmaceutical companies' hands. What of those who simply couldn't afford their medications, those who died due to complications unforeseen by shoddy clinical trials, those who died waiting for drugs that are supposed to be made under the guise of orphan exceptions, all at the hand of the ODA itself? Who do they have to call on? It seems that we have found our answer – thus far, no one, or at least not until these changes have been made.

And yet, I can't help but feel embittered still. As it stands, these pharmaceutical companies tend to apply for orphan designations for diseases affecting at or less than 200,000 patients in the United States. Roughly 1.5 million Americans have systemic lupus, which is only seven and half times the cutoff by the letter of the ODA, *but there only exists one medication designed for SLE*. One which was just recently FDA approved and is thus considered experimental and rarely covered by insurance. I am one of those patients, and as I wait to be eligible for this treatment, we are considering adding an additional medication to my regimen, the highly detrimental glucocoritcosteriod, prednisone. Unfortunately, repurposing medications for catch-all diseases like autoimmune disorders is a rather ineffective methodology, and I pray

every day that I might get the opportunity to start Benlysta and begin my slow journey to remission.

And let's be clear, I *am* one of the lucky ones, but two things can be true at once: I can be both blessed with relative health and be frustrated to see few treatments available to treat my rapidly progressing condition. This sentiment is true not only for SLE patients, either – the reality is that drug design needs to return to the pursuit of treating illnesses without existing options, not the current focus of turning over the greatest profit. Health and wellness of patients in the United States should not be treated like stocks on Wall Street, and yet our well-being seems to be no more than trade items for these pharmaceutical giants. In reality, it would seem that the ODA has transgressed against us all, and this thesis finds that we must rectify that error.

Out of all this research, rhetoric, and reason, one fact remains, *regardless*: there is no and never will be a cure for being human, a cure for which our pharmaceutical overlords crave. We are not machines, and neither should we be treated as such. Humans do not simply require medicinal "tune ups" as the engine in your vehicle does; we need contact, concentration, and care to instill, build, and maintain health in this life. Yes, there are some of us who need life-saving medication to help build that health – trust me, I would *never* want to take that away from someone – but *help* is the operative word, and that medication should not force patients into insufferable financial ruin or an even worse state of health in thanks to the industry building those treatments. It's time that we face the facts: health is so much more than what's in your medicine cabinet, so let's stop enriching the pharmaceutical companies like it isn't.

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Number=AC156955000&productDescription=METHYLTRIPHENYLPHOSPHONI+500GR&vendorId=VN00032119&countryCode=US&language=en.

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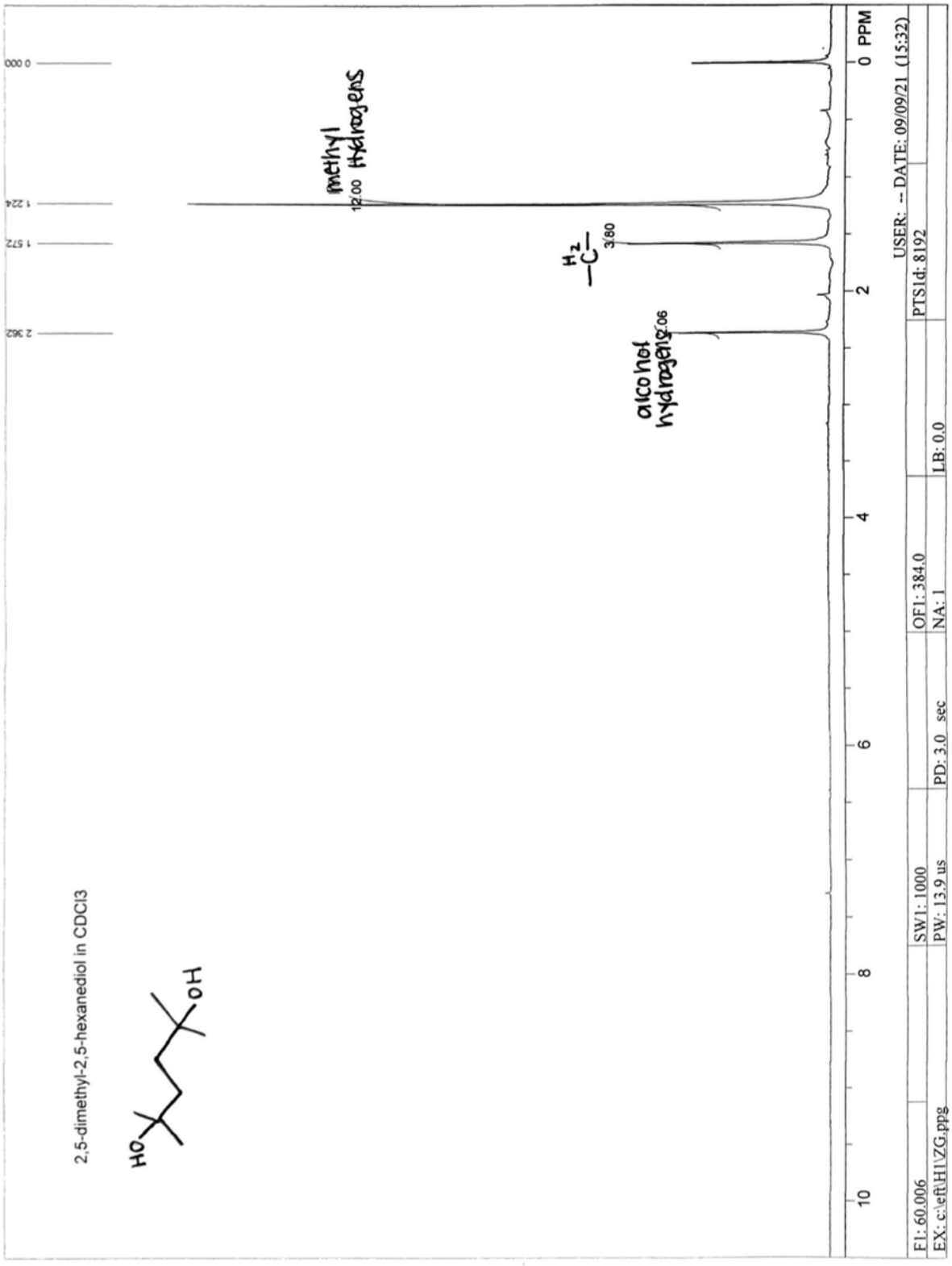
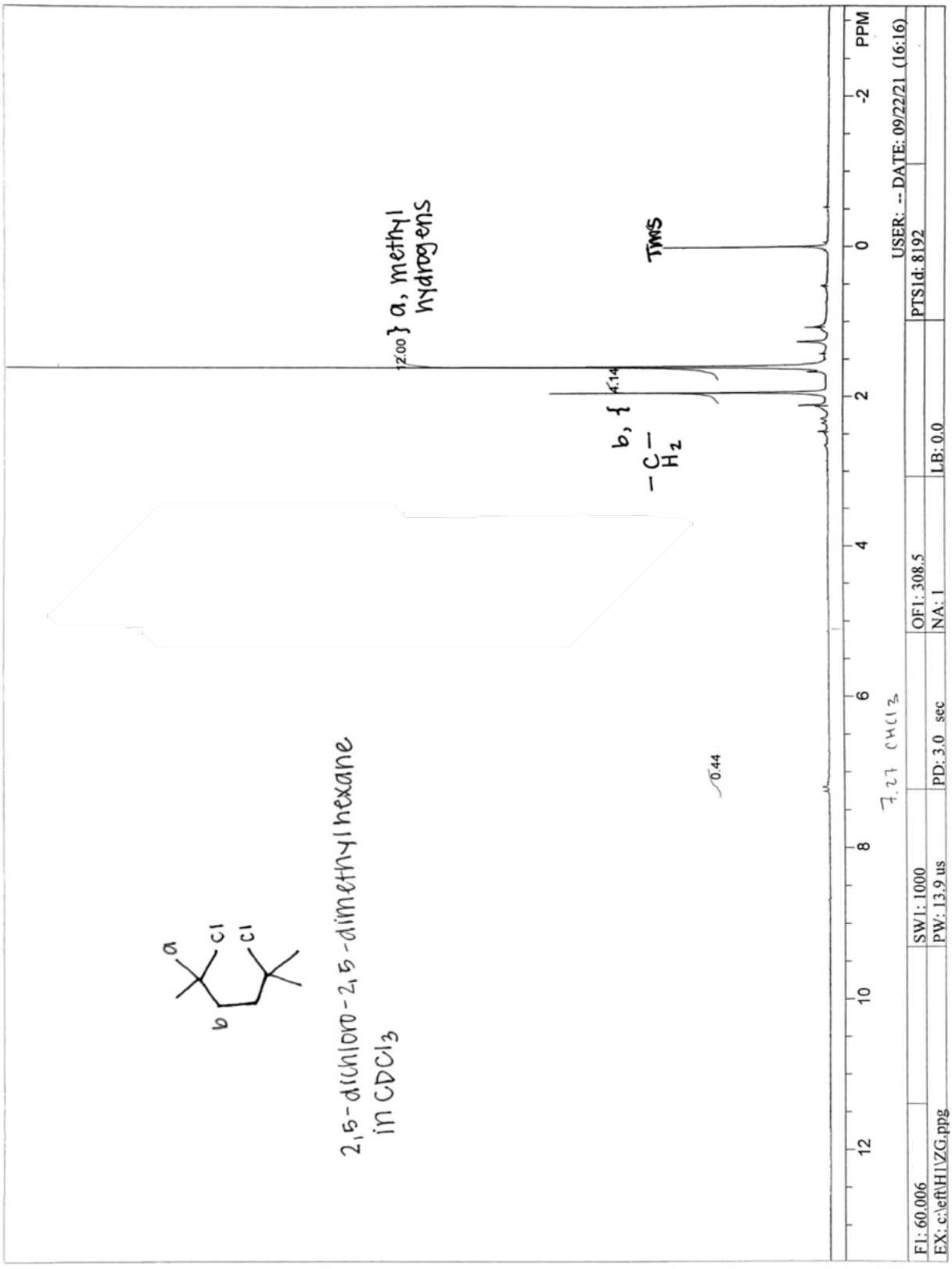
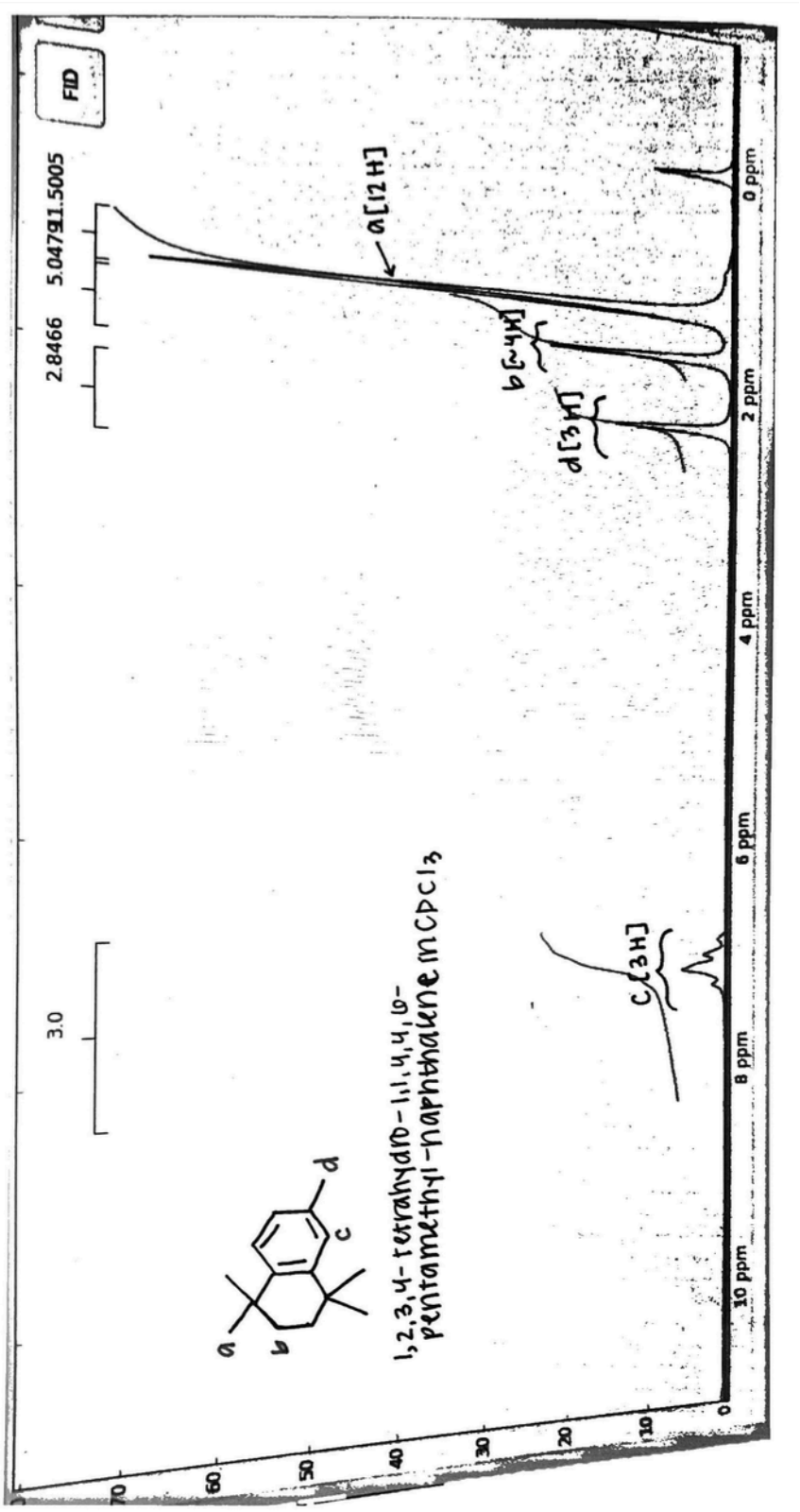
Appendix A: Labeled ^{1}HNMR Data of Compound 1



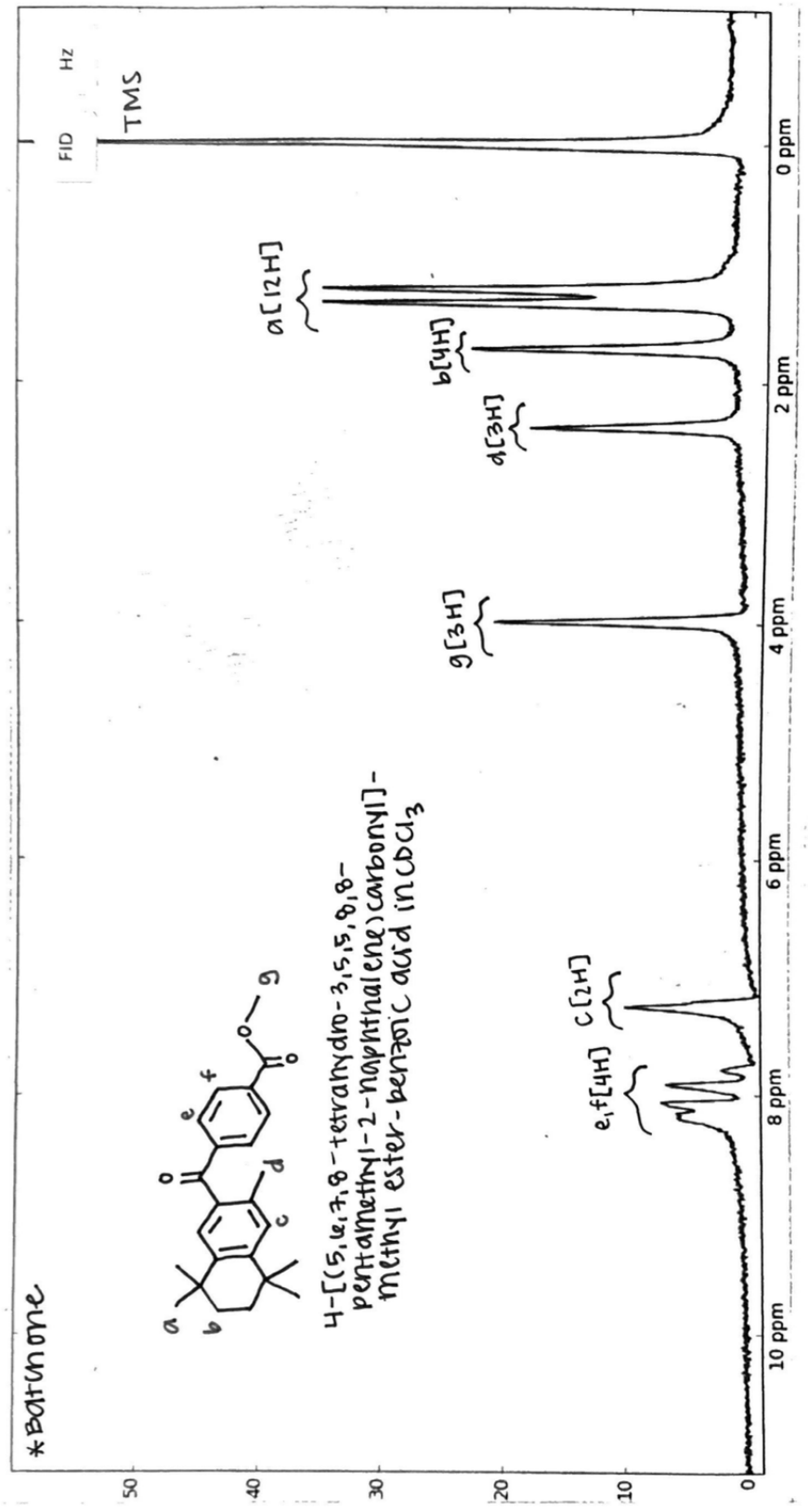
Appendix B: Labeled ^{1}HNMR Data of Compound 2



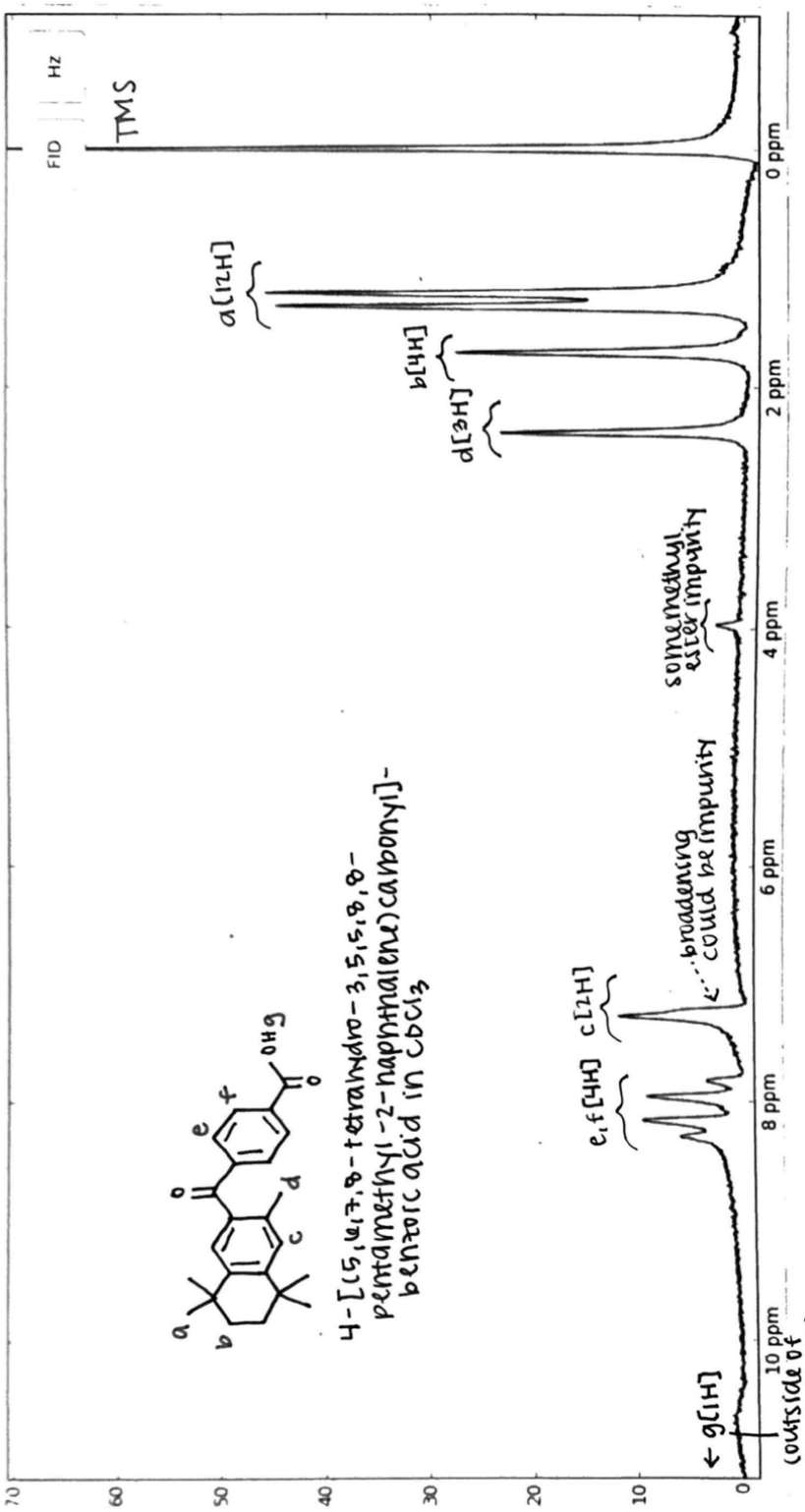
Appendix C: Labeled ^{1}HNMR Data of Compound 3



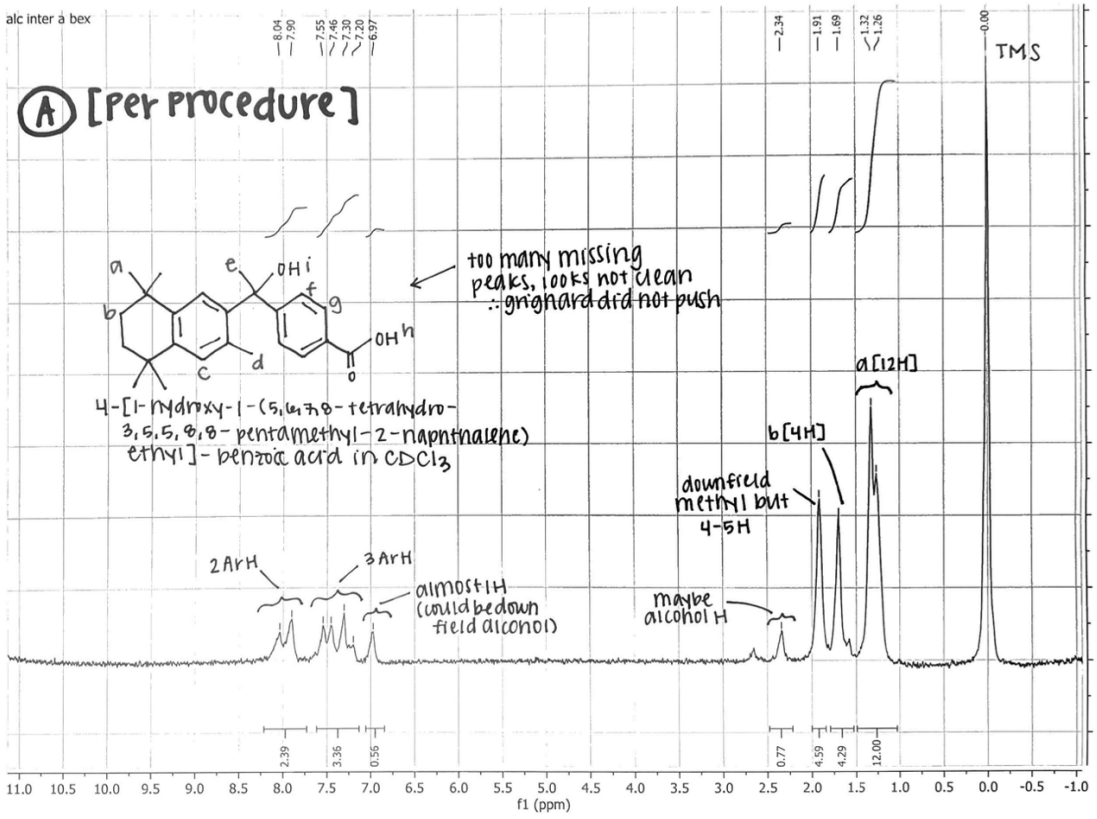
Appendix D: Labeled ^{1}HNMR Data of Compound 4

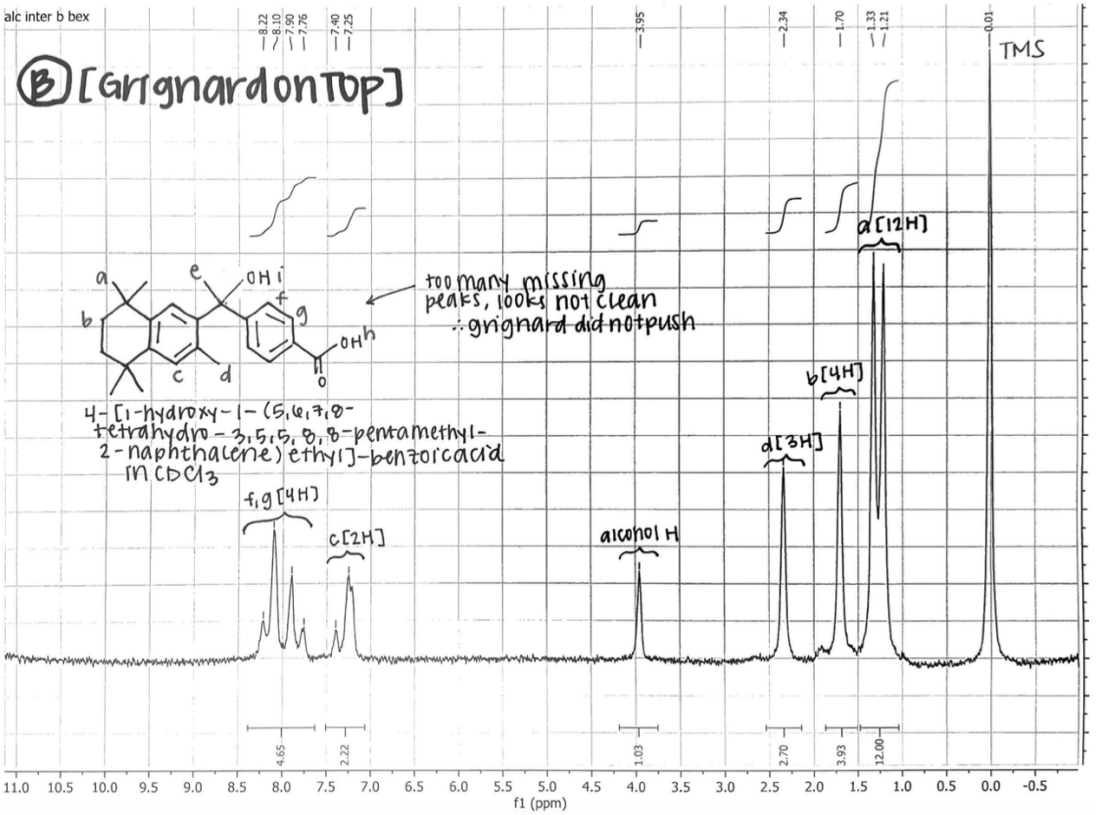


Appendix E: Labeled ^{1}HNMR Data of Compound *5*



Appendix F: Labeled ^{1}HNMR Data of Compound 6





Appendix G: Labeled ^{1}HNMR Data of *5* Cleaned via Column Chromatography —