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Feeling Evergreen: A Case Study of Humira's Patent Extension Strategies and Retroactive Assessment of Second-Line Patent Validity

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A Thesis in the Field of Biology
for the Degree of Master of Liberal Arts in Extension Studies

Harvard University
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Abstract

The United States pharmaceutical landscape has been shifting considerably throughout the 21st century, resulting in higher drug costs and smaller new product pipelines. One factor is the increased prevalence of patent evergreening and patent thickets. Patent evergreening occurs when a manufacturer files additional patents based on modifications to an existing product to extend patent protection period. Patient thickets occur when a manufacturer files multiple overlapping patents on different components of the same product. One of the first products to capitalize on this system was Humira, a rheumatoid arthritis drug. Humira's manufacturer, AbbVie, has been granted over 130 patents, resulting in a market exclusivity period stretching from launch in 2002 until 2023. The aim of this investigation is to determine the impact of Humira's evergreening strategy on the rheumatoid arthritis market, and to conduct a patent validity assessment to aid in determining the social cost and impact of the additional years of exclusivity. This study analyzed Humira's patents and available clinical trial data to assess evergreening strategy and quantify patient benefit and assessed financial metrics to determine the additional financial benefit to AbbVie per additional year of exclusivity. This investigation shows that Humira increased evergreening tactics in an attempt to prevent biosimilar competition and that subsequent formulations provided marginal patient benefit. Additionally, AbbVie was able to decrease research expenditures each year while increasing Humira's list price. Ultimately, though this strategy was successful for Humira, it may not be replicable in the future due to evolving antitrust litigation.

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Chapter I.

Introduction

The pharmaceutical landscape has shifted noticeably throughout the early 21st century. Drug prices have increased substantially while the number of new products approved and entering the market each year steadily decreases. Though manufacturers are allocating more resources towards research and development annually, the number of new innovations appears to be on the decline, with more resources being funneled to extant products.

The current US patent system ordinarily confers 20 years of market exclusivity to each new product. The goal of this exclusivity period is to allow the manufacturer a period of market dominance without competition that will allow for research and development costs to be recouped. However, in practice, the exclusivity period is interlocked with other factors and rarely results in a clean, 20-year grant.

Patent applications are typically filed during the early research phases of a drug molecule or innovation, often a decade before the product goes to market. The product then only has about half of the exclusivity period remaining before generic manufacturers can release products based on that original patent. A strategy that pharmaceutical manufacturers have developed to combat this dynamic is known as patent evergreening. Manufacturers can submit line extensions or secondary patents on their products that follow from the original patent. Typically, these secondary patents are based off a change made to the original drug, whether it be dosing, formulation, or mode of administration.

Whatever change is made, however, must prove to be beneficial to patients compared to the original formulation. Each of these secondary patents can confer another three years of exclusivity. Manufacturers often file large numbers of these secondary patents, at times as many as 100 different patents. These secondary patents can then lengthen the period of market exclusivity. A secondary practice, known as "patent thicketing," involves filing numerous patents on multiple components of a pharmaceutical product or medical device. The scope of these concurrent patents often overlap, so defeating one patent may leave the component in question protected under another patent in the thicket.

These practices are problematic for a few reasons. First, it can often be harmful to patients. Drug prices have risen rapidly in the past few decades, and during the period of market exclusivity in the U.S., a manufacturer is free to set their price at any benchmark they see fit. Many other countries also benchmark their drug prices to U.S. rates, resulting in global price increases. When generics are able to directly compete with a product, prices sharply drop as much as 75%. By delaying generic entry, prices remain high, often prohibitively so for many patients. Additionally, while insurance companies and benefit managers in the U.S. have tried to put up resistance to monopolistic pricing, these efforts are often unsuccessful, and the bottom-line ramifications tend to adversely affect patients more than they do pharmaceutical companies.

Second, more focus remains on extant products compared to pipeline products. The number of new products released annually has been steadily declining as companies devote increased resources to managing the lifecycle of their blockbuster products. Though the original goal of the patent system is to protect and reward innovation, it is much more lucrative to protect a product currently on market compared to one that has

yet to make it through late-stage clinical trials. Third, another concern is the validity of these line extension patents when viewed through the lens of patient benefit. Critics are skeptical of how much a change like a different pill color or altered packaging truly benefit patients and whether they are worthy of these second-line patents. The definition of "patient benefit" varies between patent offices and lacks a standardized definition.

One particular therapeutic area that encapsulates these dynamics is the rheumatoid arthritis market. Humira, the market leader, is currently the highest grossing product globally and has retained exclusivity since its launch in 2002. Abbvie, Humira's manufacturer, has filed over 200 line-extension patents on Humira and has successfully prevented generic competition until 2023. This market provides an interesting case study for patent dynamics as Humira really began to define and pioneer many of the strategies that have become more ubiquitous throughout the industry. This thesis aims to more fully understand and identify the impact these evergreening strategies have had on the rheumatoid arthritis market as a case study for larger industry ramifications.

Definition of Terms

Biosimilar- A biological medical product highly similar to another approved biological medication.

Blockbuster Product- A popular drug that accumulates an annual profit greater than $1 billion.

Evergreening- A legal strategy employed by any company with a proprietary patent by which they intend to extend the life of the original patent either through taking out new patents or by buying out or frustrating competitors.

Generic Product- A product sold under the general name of the molecule instead of a particular brand name.

Humira- The brand name of Adalimumab, a TNF blocker used for the treatment of rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.

Patent- A patent gives the owner legal right to exclude others from making, using, or selling an invention for a limited period of years. At the end of this term, the invention is publicly disclosed.

Patent Extension- A patent term extension is intended to extend the original term of a patent to make up for any time that was lost during the regulatory approval process.

Patent Thicket- A patent thicket is a term used to describe a series of overlapping patent rights on a single product.

Pipeline Product- A product still in the phases of development.

Rheumatoid Arthritis- An autoimmune disease that can cause joint pain, inflammation, and damage to the joints of the body. This is a chronic and degenerative condition typically managed by pharmaceutical therapy.

Second-line patent- Secondary patents, unlike primary patents, protect adjacent characteristics to the invention, thereby extending the protected term.

TNF- Tumor Necrosis Factor, an endogenous pyrogen responsible for apoptotic cell death, fever, and inflammation

Background of the Problem

The patent process is integral to the modern pharmaceutical industry for myriad reasons, ranging from protecting innovation to developing strategic market dominance. In America, the patent system has been often criticized for those selfsame reasons and more. However, patent law is inextricably linked with pharmaceuticals, and pharma companies focus substantial resources on how to structure their patents and the patent process writ large. To understand how patents became so integral to the pharmaceutical industry, a brief history of the American patent law system must be considered.

Pharmaceutical patents were considered highly unethical before the Civil War (Gabriel, 2014). The industry was split into two camps: one camp patented their medicines but kept the ingredients a secret and marketed wildly to the general public, while the other refused to keep ingredients a secret, did not patent, and only marketed to physicians. The former faction was considered unethical and were as a whole looked

down upon by the “ethical” segment of the industry. However, by World War I, patenting became recognized as a legitimate strategy, and companies cautiously embraced the pharmaceutical patent. This was in part due to the German embrace and domination of the patent system (Dutfield, 2009).

The American Pharmaceutical Association publicly denounced Germany’s approach to patents, as they felt German companies were establishing a monopoly in the pharmaceutical industry of America through manipulation of the patent system. The APA felt that this was occurring in two ways: first, important information integral to the manufacturing process was left out of the patent, so that even after expiration the process could not be replicated, and second, the name of the drug itself was indefinitely trademarked (Dutfield, 2009). Frustrated by German maneuvering, American pharmaceutical companies began to embrace the patent system and employ similar techniques and strategies. In the decades that followed, patenting pharmaceuticals became commonplace.

As patenting became more accepted, the associated laws and regulations evolved as well. In a series of landmark U.S. Supreme Court cases, the court denied the primacy of patents over antitrust laws and additionally asserted that patents did not grant manufacturers the right to fix minimum resale prices on their goods (Gabriel, 2014). In these cases, the court attempted to curtail the manufacturer’s ability to use patent laws to shape and control the market. Additionally, the Federal Trade Commission (FTC) was established to prevent “unfair” market practices and monopolization. In these formative years, the FTC was pivotal in defining and structuring the therapeutic goods market.

After World War II, US pharmaceutical companies began to invest seriously in in-house research and development, spurred by the need for better anti-infectives and the desire for greater pharmaceutical self-reliance (Dutfield, 2009). America experienced its first pharmaceutical revolution in the years that followed thanks to great advances in antibiotics, ultimately discovering about 60% of new pharmaceuticals on a global scale. In addition, direct-to-consumer marketing of pharmaceutical products began to rise in prominence. Initially, FDA regulations forbade advertising to consumers. However, by the 1960s, pharmaceutical companies became more clever about marketing and advertising, in part due to the creativity of Arthur Sackler, who developed ways to bypass FDA regulations (Keefe, 2021). For example, one campaign, for the anti-anxiety drug Librium, featured an article about a new tranquilizer for large cats and suggested it might soon become available for human consumption, generating substantial buzz without breaking regulations. Librium soon became the world's greatest commercial success in the history of drugs.

Pharmaceutical companies also began to explore ways to continue to capitalize on the success of older launches while still launching new products. For example, after the success of Librium, Roche wanted to launch Valium, another tranquilizer with nearly indistinguishable effects. Sackler and Roche's response to the issue was to market the products for different, yet similar, ailments, for example distinguishing between "anxiety" and "psychic tension." These anti-anxiety drugs and the concurrent marketing ushered in a new era of the pharmaceutical industry, where consumers became more informed and involved in choosing products for their own care as a result of direct-to-consumer advertising.

The last decade of the 20th century saw a large shift in the makeup of the pharmaceutical industry. Consolidation of many pharmaceutical companies occurred, allowing for market dominance by a much smaller number of entities. Additionally, the global market as a whole had become extremely competitive especially in select therapeutic classes. This has created an environment of ambiguous market dominance by any one single country and heightened the need for increased strategic business practices to maintain leadership on a global scale.

The development of business strategies specifically tailored to pharmaceutical patents has emerged and grown in recent decades in response to this dynamic landscape. Yet, critics say that the patent system is not living up to its original intent and instead is creating new and unfavorable dynamics for both patients and manufacturers. An understanding of these practices, and how they shape the market, is integral in piecing together what has gone wrong with the system in recent decades.

Generally, in order for a patent to be secured for a pharmaceutical product, the product must be new, involve an inventive step, be susceptible to industrial application, and be sufficiently supported by a description (Ahn, 2014). The application of these criteria varies from jurisdiction to jurisdiction, but on balance these are the fundamental requirements for a new pharmaceutical patent. If granted, the patent guarantees the new product 20 years of guaranteed market exclusivity (Komendant, 2020). This allows for the branded product to be priced and sold without competition from generics or biosimilars. Once the patent expires, generic manufacturers are able to produce the same product for decreased cost. At a high level, this appears to be an ideal system—drug manufacturers are given a period of exclusivity to recoup research and development costs

before competitors can enter the market. However, in practice there are additional complications and challenges.

To begin, patents are often filed early in the research and development process—not when the product goes to market—in order to protect the candidate molecule (Fachler, 2011). It typically takes place before the clinical trial testing required for FDA approval has occurred, which means that many products ultimately don't make it to market. A common figure cited is that for every five products that are selected for clinical testing, only one receives FDA approval (Fisher & Syed). Additionally, the period of patent pendency between filing and approval can take as long as two and a half years. Ultimately, when these factors are considered, the product only has about a decade of market exclusivity maximum, and at times, can have no exclusivity period at all due to the expiration of that original patent. The Hatch-Waxman Act attempted to offset some of this lost time, specifically half of the period devoted to clinical trials and all the time spent on the FDA approval process, by offering up to five years of patent extension. However, even with these adjustments, the patent is still more likely to expire before launch or shortly thereafter. The result is that the average product today is protected for roughly 12 years (Fisher & Syed).

Additionally, the prices surrounding research and development have markedly increased in recent years. Studies show costs of anywhere between $802 million and $5.3 billion for research and development costs of one drug (Fachler, 2011). This is up from a cost of $54 million in 1979. Of note is that over that same time period, the length of exclusivity of the patent protection period has not changed (Dutfield, 2009). Though one of the goals of the patent exclusivity period is to allow companies to offset the costs of

research and development, considered rewarding innovation, this often times is not feasible in the modern day. The product would have to perform exceptionally well to recoup those costs, which can be challenging if the product is developed in a therapeutic area with a smaller patient base or decreased demand. As a result, pharmaceutical companies have increasingly turned to techniques and tactics to lengthen this period of exclusivity in an attempt to increase the earning potential of their products.

Two primary strategies have emerged: "evergreening" and "patent thicketing." Evergreening involves developing second-line patents that extend the life of the original patent, or shift patients onto a very similar follow-along product produced by the same manufacturer (also called "product-hopping") (Dutfield, 2009). Focusing on the first type of evergreening, also referred to as a "line extension," these patents add exclusivities by adding "tweaks" to the existing product (Sanzenbacher, 2019). These "tweaks" can take several forms, from altered delivery regimens to reduced dosage requirements or reduced side effects (Dutfield, 2009). Each new patent confers an additional three years of exclusivity, so it behooves manufacturers to make these "tweaks" to retain market exclusivity for an increased period of time (Sanzenbacher, 2019). The number of line-extension patents has increased dramatically since the early 2000s, seemingly at the expense of truly new-to-market products and innovations.

"Patent thicketing" involves many patents being conferred at the same time, often on overlapping aspects of the innovation. Each component of the drug is protected separately, for example the coating, the delivery system, the formulation, and the composition would all be protected under separate patents. Some patents will even cover multiple aspects at once, perhaps covering both the composition and formulation of a

particular product. As a result, even if one patent expires, there are still many other concurrent patents, sometimes with substantially later expiration dates, that need to expire before generic manufacturers can enter the market.

Once the original patent expires, one might expect that generic manufacturers could begin producing that original formulation, leaving only the "tweaked" versions protected by the second-line patents. However, there are processes in place that prevent this from occurring as a practical matter.

The FDA maintains a list of Approved Drug Products with Therapeutic Equivalence Evaluations, also known as The Orange Book (Food and Drug Administration, 2021). This keeps track of all branded drugs with generic counterparts, as well as the use codes or cases for the branded products. In order to begin manufacturing a generic product, the manufacturer must submit an Abbreviated New Drug Application (ANDA) to the Orange Book before the patent on the branded product expires, certifying that the generic does not infringe on the current patent. However, when submitting this ANDA, the generic manufacturer must also certify for each unexpired patent in the Orange Book (United States Code, 2006 Edition, Supplement 4, Title 21 - FOOD AND DRUGS, 2010). Depending on the number of patents associated with a single product, this can create a substantial hurdle for generic entry, as it requires the generic manufacturer to go to the expense of assessing each patent to determine infringement potential. Having such an extensive number of patents simultaneously in place creates an effective strategy—even if generic manufacturers can contest one patent in court, there are many others that remain in place and each must be examined independently

(Hemphill, 2011). It is therefore often prohibitively expensive to contest these patents in court, and the only option is to wait for the expiry date.

A recent report revealed that the top 12 products on the market are protected by an average of 71 patents per drug, conferring an average of 38 years without generic competition (Komendant, 2020). Furthermore, the vast majority of new patents filed are on extant drugs—not on new therapies or innovations (Feldman, *'One-and-done' for new drugs could cut patent thickets and boost generic competition*, 2019). Between 2005 and 2015, 78% of "new" drugs associated with new patents were actually extended protection of products already on the market (Feldman, *May your drug price be evergreen*, 2018). This can be problematic for several reasons, relating to both price and innovation.

Another aspect of the patent exclusivity period that is frequently debated is the ability for a manufacturer in the U.S. to set prices unilaterally, without competition in place to drive prices lower. One study reveals that branded drug prices have increased by 68% since 2012, with some product prices increasing up to 168% in a six-year period (I-Mak, 2018). Such high prices can be harmful to patients, especially if there are not suitable alternatives on the market. Generic competition of branded products has been found to reduce prices by up to 60%, as generic products are typically priced much lower than the branded products they are modeled upon (IMS Institute for Healthcare Informatics, 2016). Since the generic manufacturers do not need to go through the process of research and development themselves, the production costs of the generic alternatives are substantially cheaper, which allows them to pass on a substantial price reduction to the consumer (Hill, Barber, & Gotham, 2017). Oral generics released between 2011 and 2013 were, on average, 74% cheaper than the pre-expiry branded

product. Therefore, the inability for generic products to enter a market due to excessive patenting can prevent drug costs from dropping. Additionally, in some instances, pharmaceutical companies will pay generic manufacturers to prevent them from entering the market, even if the patent has already expired (Dutfield, 2009). While this does allow the pharmaceutical companies to recoup research and development expenses, this can often be at the expense of patients affording necessary medication.

Another important factor to consider is whether patents truly spur innovation. The overall number of breakthrough medicines has been steadily decreasing, despite increased funding into research and development (Gurgula, 2020). This is due in part to the pharmaceutical industry funneling resources into "me-too" drugs, which are new products that feature modest improvements over existing products without introducing recognizeable new value. This allows for pharmaceutical companies to avoid the implicit risk in the research and discovery of a new drug. This is evolving into a common practice—between 1990 and 2004, 78% of all drugs licensed in that time period were considered "me-too" products (Fisher & Syed).

In addition to fewer new products being produced, there is also a nationwide drug shortage, resulting in a limited supply of products such as cancer drugs, anesthetics, and drugs for emergency medicine. This drug shortage has persisted for several years with little hope for resolution in sight (Fachler, 2011). The confluence of these conditions results in a narrow focus placed on existing drugs and away from the development of new products. Despite the original goal of the exclusivity period of patents being intended to protect and foster innovation, with the emphasis placed on lengthening the exclusivity

periods of blockbuster drugs already on the market, the result is reduced incentive for research and development for truly new, innovative products.

One of the primary criticisms of evergreening practices is that the line extension patents don't always seem meet the criteria for a truly new and innovative alteration to an extant product or marked patient benefit (CMAJ, 2013). In France, between 2005 and 2014, only 11% of new drugs were considered marked advances (Gøtzsche, 2018). A similar study has not yet been conducted in the U.S. landscape, though presumably the results would likely be similar. Though these line extension patents are supposed to confer substantial patient benefit, there is no consistent metric in place or benchmark to measure whether these secondary patents truly confer a marked advantage (Lehmann, 2016). Additionally, the definitions surrounding "novelty" vary across patent offices, creating further ambiguity around the requirements necessary for these second-line patents (Ahn, 2014). Again, this has negative ramifications throughout the pharmaceutical landscape. Not only are the legal definitions left ambiguous, but the prevention of generic competition results in the delay of price reduction and decreased incentive for innovation without substantial patient benefit to offset the costs.

Though this issue has become more prevalent at top manufacturers, Abbvie is considered one of the top offenders, particularly concerning its blockbuster product Humira (Liu, 2018). Humira, an anti-Tumor Necrosis factor α (TNFα) product primarily used to treat rheumatoid arthritis, is the top selling drug globally, grossing $18.4 billion in global sales. It first came onto the market in 2002 and surprisingly was not the first TNFα product to market. However, in addition to being an effective treatment for patients, Humira has become infamous for its carefully constructed patent thicket. Abbvie

has submitted a total of 247 patent applications in total for Humira (I-Mak, 2018). Humira currently has 132 patents filed that will block competition for 39 years (Komendant, 2020). Abbvie also aggressively protects its patents with extensive patent litigation and has successfully blocked any biosimilar entry in the US market until 2023 (Liu, 2018). Overall, 23 patent families have been identified, falling into five main classes: composition, combination, dosage, formulations, and new indications (Storz, 2016). However, analysis has not been conducted on the degree to which patient benefit is conferred by each successive patent.

Using Humira, and the rheumatoid arthritis market writ large, the aim of this thesis is to determine how patent evergreening and thicketing have shaped the market landscape and affected innovation and patient costs. Additionally, this thesis will devise and propose methodology by which patient benefit can be quantified and will use publicly available data to make determinations as to whether patient benefit was conferred by each of Humira's patents. These analyses will help measure and gauge the extent of the impact evergreening has had on the pharmaceutical landscape.

Question and Hypothesis

This thesis aims to more fully understand and identify the impact these evergreening strategies have had on the rheumatoid arthritis market as a case study for larger industry ramifications. I propose to answer the following questions:

1. What are the patent dynamics of the rheumatoid arthritis market and how have they evolved? What strategies have been developed and employed by manufacturers? Were they successful?

2. What were the justifications for Humira's secondary patents? What patterns have emerged? How was incremental patient benefit measured, if at all?

3. Is there a way to quantitatively measure patient benefit from original products to second-line patents?

4. What are the financial dynamics of Humira's second-line patents? Can there be an overall profitability determination made per additional year of exclusivity?

I hypothesize that the patent dynamics of the rheumatoid arthritis market have evolved markedly since Humira's launch. Prices for patients likely increased and innovative or breakthrough product launches likely decreased. I also hypothesize that the definition of patient benefit was in some instances loosely applied to Humira's secondary patents and that examination may not find appreciable differences. In order to assess these research questions, I will use a four-phased methodological approach.

Phase 1 will involve a high-level analysis of the patent dynamics of the rheumatoid arthritis market, focusing specifically on the timeline of product entry and any patent litigation that took place between manufacturers. Phase 2 will consist of an analysis of Humira's patents where I will categorize and analyze all patents based on the type of modification to the product. Phase 3 will consist of a focused study of published research papers focusing on Humira's different formulations and will aim to develop a methodological framework to assess patient benefit. Finally, Phase 4 will analyze the financial cost to society and financial benefit to Abbvie.

Implications of Research

This thesis will provide a deeper understanding of how patent evergreening affects pharmaceutical markets and will analyze the true differences and distinctions between secondary patents. It will also attempt to establish methodology for assessment of patient benefit that could be applied to other markets. Better understanding of these dynamics will provide insight into market ramifications and the pharmaceutical industry as a whole.

Chapter II.

Materials and Methods

Research and analysis will be conducted in four phases. The first phase will consist of an analysis of the greater dynamics and framework of the rheumatoid arthritis market. This will involve determining the timeline of product launches, how these products differ, what the various treatment paradigms are, and how costs have shifted. I will look at both new launches and reformulations of extant products. I will also examine any relevant patent litigation taking place between manufacturers, including recent biosimilar litigation. This will help me develop an overall understanding of the market dynamics at a high level and begin to unpack the various patent litigation strategies employed over time.

The second phase will involve pulling and categorizing Humira's patents from the USPTO database. I will pull the patents in chronological order starting with the original Humira patent and work through all approved and filed patents. This ultimate list will consist of 132 patents. I will then categorize all second-line or extension patents by mechanism or alteration, starting with the following categories: composition changes, formulation changes, dosage changes, new combinations, and new indications. I will also examine the text of each patent for justification as to why the second-line patent was filed. This will allow for insight into what strategies were successful for Humira and how these strategies evolved over time.

The third phase will involve developing a methodological framework for retroactive validation analysis. I will use published research papers to understand if altered formulations of Humira produced appreciable clinical benefit, and how said benefit was measured. I will then compare this to the original patent justification to assess whether there is indeed benefit to patients from any product changes made in these line-extension patents.

Finally, the fourth phase will involve an assessment of the financial impact and ramifications of the line-extension patents. I will assess financial data from Abbvie to compare the total cost of bringing Humira and its updated formulations to market, including research and development, to the overall gross revenue achieved through filing the line extension patents. I will also analyze the financial impact to patients with different types of insurance coverage.

Research Limitations

Research will be limited only to U.S. rheumatoid arthritis market dynamics and filed patents. No patents filed in other countries will be considered. Only approved and filed patents will be considered as well, which may not capture the full scope of attempted strategies and instead will only feature successful strategies and tactics. Additionally, as this is a focused case study in the rheumatoid arthritis market, primarily on Humira, the insights generated by this work may not be broadly applicable to other therapeutic areas due to differing treatment nuances.

The third phase will focus only on publicly available research papers and studies, which will likely limit the scope of the analysis. As there was not a new, published study

conducted after every additional patent was filed, Phase 3 will also be limited to certain modifications that were directly studied. Additionally, as I will be relying on published work and not conducting my own analyses, I will be accepting any and all research limitations posited in the studies' work as well.

The final phase will examine only publicly available financial data for AbbVie, which may not be fully representative.

Chapter III.

Results

Phase I: Market Overview and Dynamics

Rheumatoid arthritis is a progressive, inflammatory disease that causes the swelling and destruction of peripheral joints (Tada, Yamaji, & Tamura, 2020). The disease progresses steadily over time and continues to worsen unless inflammation is slowed or stopped (Stuart, 2020). Typically, this occurs through the use of medication, as it is rare for rheumatoid arthritis to go into remission without treatment (Stuart, 2020). There are several different classes of rheumatoid arthritis medications, many of which are powerful when used in combination.

Table 1. Rheumatoid Arthritis Medication Classes

Medication Class Name	**Description**	**Examples**
Disease Modifying Anti-Rheumatic Drugs (DMARDS)	Can slow the progression of RA and save joints and tissues from permanent damage	Methotrexate
Biologic Disease Modifying Anti-Rheumatic Drugs	A newer class of DMARDS. Most effective when paired with a conventional DMARD.	Humira, Enbrel, Remicade, Rituxan
Glucocorticoids	Reduce inflammation and pain and slow joint damage. Not for long term use.	Prednisone
Nonsteroidal anti-inflammatory medications (NSAIDS)	Pain relievers that can also reduce inflammation. Primarily over the counter products, although stronger NSAIDS are also available. Often used in combination with other drug classes.	Advil, Motrin, Aleve
Analgesics	Pain relivers	Codeine, Fentanyl

(Mayo Clinic, 2021)

Introduction to Biologics

Biologic DMARDs are the newest class of rheumatoid arthritis medications. Often called "biologics", these medications are protein-based and target inflammatory cytokines that cause joint destruction (Tada, Yamaji, & Tamura, 2020). Biologics are manufactured in living cells, which makes them costly and challenging to produce (Champion, Guha, & Salgado, 2013). There are three types of biologics used to treat rheumatoid arthritis: TNF inhibitors, IL-6 inhibitors, and JAK inhibitors. Early treatment with biologics is especially beneficial and biologics are most effective when taken in conjunction with Methotrexate (Movik, et al., 2011). However, due to their high cost, treatment paradigms typically require that patients start on a conventional DMARD alone, like Methotrexate, before beginning a more costly course of treatment with a biologic. Biologics are administered either by IV or by injection and are not a cure for rheumatoid arthritis (Stuart, 2020). Biologics need to be taken long term, which can compound cost-related issues over time. Due to their efficacy, biologics make up most of the overall rheumatoid arthritis market share (Fortune Business Insights, 2017). Biologics also represent over 40% of drugs in the research and development pipeline (Champion, Guha, & Salgado, 2013).

Table 2. Biologic DMARDs

Product Name	**Brand Name**	**Product Type**	**Manufacturer**	**FDA Approval Date**
Infliximab	Remicade	Anti TNF	Janssen	November 1999
Adalimumab	Humira	Anti TNF	Abbvie	December 2002
Etanercept	Enbrel	Anti TNF	Amgen	July 2003
Rituximab	Rituxin	Antineoplastic	Genentech/Biogen	January 2007
certolizumab pegol	Cimzia	Anti TNF	UCB	May 2009

tocilizumab	Actemra	IL-6 receptor agonist	Genentech	January 2010
anakinra	Kineret	IL-1 receptor antagonist	Sobi	November 2011
Golimumab	Simponi	Anti TNF	Janssen	May 2013
sarilumab	Kevzara	IL-6 receptor agonist	Sanofi/Regeneron	May 2017
Abatacept	Orencia	Immunomodulator	BMS	July 2017

There are few head-to-head studies comparing the effectiveness of the biologics against each other (Janke, et al., 2020). In a recent systemic review and meta-analysis of available clinical study reports assessing the efficacy of biologics in combination with methotrexate, minimal statistically significant differences in efficacy were observed (Janke, et al., 2020). Patients typically begin on a TNF inhibitor, like Humira, because they have been on the market the longest and are usually covered by commercial insurance (Watson, 2018). Taking a biologic in combination with methotrexate helps keep the body from having an immune reaction to the powerful medication because the immune system views the biologics as foreign (Watson, 2018). The patient often will switch to a different biologic therapy if they have an allergic reaction, or the medication doesn't work.

The Rheumatoid Arthritis Market in the U.S.

The U.S. rheumatoid arthritis market is large and is projected to continue to grow in the coming years as more individuals are diagnosed and are living longer lives with the condition. The CDC predicts that by 2040, 25.9% of the total adult population will have doctor-diagnosed arthritis (CDC, 2021). Due to the increasing size and continued prevalence, having and maintaining market share in the space is essential.

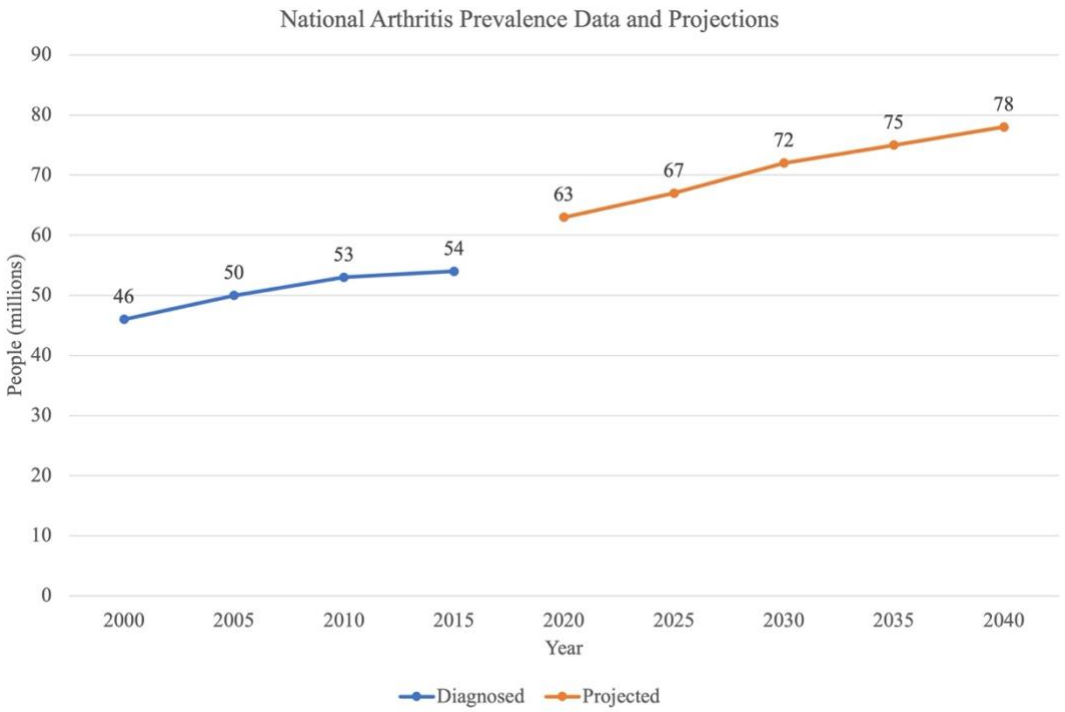


Figure 1. National Arthritis Prevalence Data and Projections

(CDC, 2021)

Humira has been the rheumatoid arthritis market leader and the world's best-selling drug for over five years, pulling in $19.83 billion in revenue in 2020 alone (Gibney & Figuracion, 2021). In addition to being approved for the treatment of rheumatoid arthritis, Humira is used to treat several other autoimmune conditions, including Crohn's disease and ulcerative colitis (Gibney & Figuracion, 2021). Humira brings in about 1/3 of the total immunology market value, which exceeds $34 billion (iData Research, 2018).

Surprisingly, there is scant direct competition between Humira and the other biologic products. There are several potential factors at play, including the varying

product types. Humira is an anti-TNF biologic, so it specifically targets tumor necrosis factor immune system molecules. The other major product types are JAK inhibitors, interleukin-6 inhibitors, or monoclonal antibodies, all of which target different immune system modulators and are tolerated differently on a patient-by-patient basis (Branning, 2016).

Additionally, Humira's payer management likely plays a large role, as most insurance companies require patients to first try an anti-TNF before attempting another biologic therapy (Watson, 2018). Humira's mode of administration likely also contributes to its tendency to be prescribed more often than other biologics. Humira is administered by auto-injector, which allows the patient to administer their own medication instead of visiting the prescriber's office for an infusion (Branning, 2016). Humira is the oldest auto-injector product, as Remicade is administered by infusion. Humira is also heavily marketed, and its longevity and brand exposure additionally contribute to its market dominance.

An unverified theory for the decreased competition between the biologics is collusion. An investigation by the U.S. House of Representatives Committee on Oversight and Reform alleged that AbbVie and Amgen, Enbrel's manufacturer and Humira's largest competitor, have engaged in shadow pricing tactics (Committee on Oversight and Reform, 2021). The two companies have consistently taken similar price increases instead of competitively pricing to gain market share. The graph below illustrates how the two products' market prices mirror each other almost exactly. Collusion between the biologics could contribute to consistently high prices and the lack of market movement.

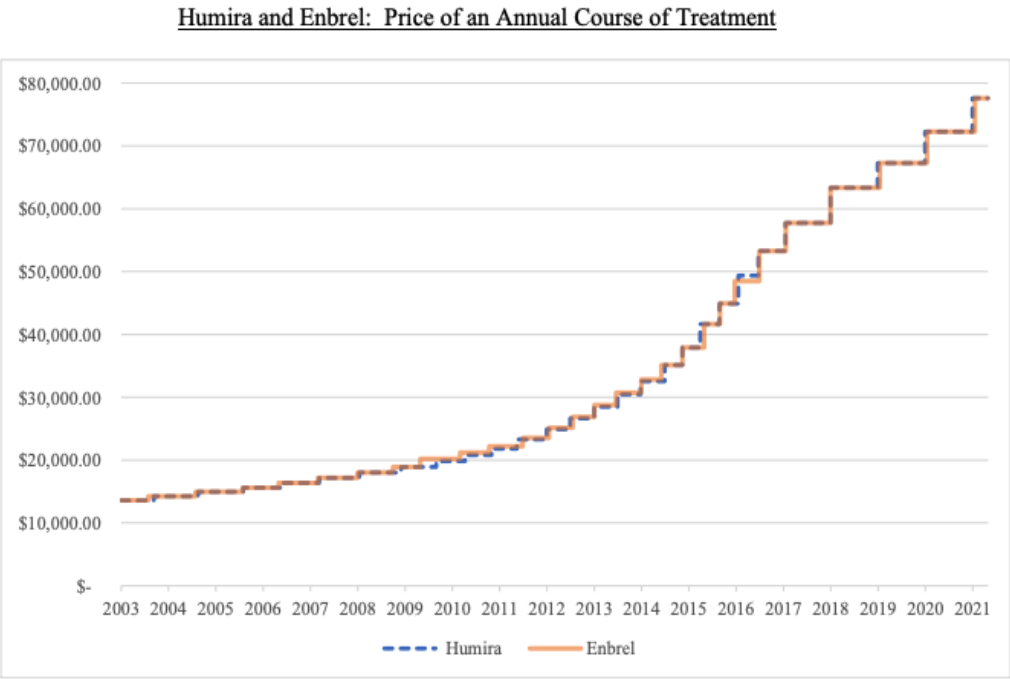


Figure 2. Humira and Enbrel Price Increases

(Committee on Oversight and Reform, 2021)

Introduction to Biosimilars

Humira's largest competitive concern is not only other biologics, but also biosimilars. Biosimilars are biological products that are highly similar to an FDA-approved biologic reference product and have no clinically meaningful differences (Fish & Richardson, 20020). Biosimilars have the same route of administration, strength, dosage, and potential side effects of the reference product, as well as the same potential treatment benefits (U.S. Food & Drug Administration, 2021). Biosimilars are rigorously evaluated for both safety and efficacy by the FDA before being approved (U.S. Food &

Drug Administration, 2021). However, the evaluative standards are different than for originator products. Though biosimilars need to be physically similar to the reference product, they do not need to be identical (Borenstein, 2019). Additionally, if a biosimilar is effective for one indication, like rheumatoid arthritis for example, it is automatically considered effective for all indications that the reference product was approved for (Borenstein, 2019).

Interchangeable biosimilars are biosimilar products that meet additional requirements that allow for them to be substituted for the biologic reference product without the intervention of a healthcare professional (U.S. Food & Drug Administration, 2021). This is similar to how some generic drugs are routinely substituted for small-molecule drugs at the pharmacy counter. The likelihood is that this type of substitution would happen frequently, and might even be required by some insurance companies, resulting in a potential drastic decrease in revenue for reference products.

Biosimilars in the U.S. Market

The biggest motivator for the adoption of biosimilar products is their potential cost saving benefits. Biosimilars are much cheaper to produce as there is substantially less research and development compared to an originator biologic. Additionally, there are often reduced manufacturing costs for biosimilars because of newer technology that can be used (Blackstone & Joseph, 2013). In the European Union, where adoption of biosimilars has happened more quickly, biosimilars are on average 30% less expensive for patients than their reference product (Blackstone & Joseph, 2013). This results in a savings of about $655 per prescription (Goldman & Philipson, 2021). Biosimilars also quickly amassed market share, taking about 50% of the volume of the reference product's

book of business on average (Goldman & Philipson, 2021). Though the U.S. market is markedly different, recent projections have estimated that biosimilars could lower prices on reference biologics by an average of 56% (Bisoimilars Forum, 2021).

However, biosimilars have been slow to take root in the U.S. despite the potential cost saving benefits (Laday, Doing the 'Patent Dance:' Untanging biosimilar litigation for physicians, 2020). In 2020, 26 biosimilars across therapeutic areas had been approved by the FDA, yet only 16 were sold in the U.S. market (Laday, *Doing the 'Patent Dance:' Untanging biosimilar litigation for physicians*, 2020). In 2021, the number of biosimilars approved by the FDA increased to 29, yet only 21 are currently on the market (Goldman & Philipson, 2021). There are several barriers to entry for biosimilars including the "natural monopoly" characteristics of biologic reference products, competition, brand awareness, and aggressive patent litigation between biosimilar manufacturers and the manufacturers of the biological reference products.

Biologics as "Natural Monopolies"

One factor for the delayed adoption of biosimilars is the fact that biologics are often considered "natural monopolies." Natural monopolies arise due to economies of scale. In natural monopolies, the average total cost decreases continually as output increases, creating the most efficiency when production is concentrated in a single firm. Because of substantial barriers to entry for biosimilars, both biologically and economically, continued dominance of biologics is the more efficient outcome.

Biologic drugs are much larger and more complex molecules than traditional pharmaceuticals, often referred to as small molecule drugs (Champion, Guha, & Salgado, 2013). Biologics are typically produced in cells following DNA insertion, which greatly

increases the complexity and cost of biosimilar production compared to generic production (Atteberry, Bach, Ohn, & Trisheim, 2019). There is also substantial difficulty in using analytical methods to verify that the resultant biosimilar has nearly identical characteristics to the originator product (Price II & Rai, 2016). As a result, biosimilars are not required to be chemically identical to the reference product, which suggests that competition will not happen solely on price, but also on quality (Champion, Guha, & Salgado, 2013). Though current studies and guidelines indicate that biosimilars are noninferior to the reference biologics, these assessments are based on post-manufacturing studies almost exclusively (Bonek, Roszkowski, Massalska, Maslinksi, & Ciechomska, 2021). Another challenging factor is the longevity of current biologic products on the market (Atteberry, Bach, Ohn, & Trisheim, 2019). This legacy supplier advantage, including extensive marketing campaigns and name recognition amongst patients, gives biologics an edge over newer biosimilars.

Additionally, biosimilars cannot be approved by the FDA until the reference biologic has been on the market for at least 12 years (Champion, Guha, & Salgado, 2013). This is different than in the small molecule drug space, where generics can enter a market after five years (Champion, Guha, & Salgado, 2013). As a result, biosimilars can only enter the market towards the end of the lifecycle of the reference biologic drug, which limits their overall potential earnings.

In addition, the reimbursement structure for biosimilars is not as favorable as generic reimbursement. In the small-molecule drug space, Medicare Part B reimbursement is 106% of the combined average sales price ("ASP") of both the branded and generic products. As a result, because branded products tend to be more costly,

providers have a wider profit margin if they prescribe a generic product compared to a branded product. For biosimilars, their reimbursement is set at 100% of the biosimilar's ASP and 6% of the reference product's ASP. For biologics, their reimbursement is 106% of the biologic's ASP. Because of this altered calculation, the profit margin of prescribing a biosimilar versus a biologic reference product is virtually the same, so there is no financial incentive for providers to prescribe biosimilars over biologics (Champion, Guha, & Salgado, 2013).

Biosimilar Competition

Another barrier for biosimilars is increased competition. As discussed above, biosimilars are less expensive to produce than originator biologics because of the decreased need for research and development. It can take between 7 and 8 years to develop a biologic and anywhere from $1-$4 million (Blackstone & Joseph, 2013). Manufacturing costs for biosimilars can be as much as 90% lower and can occur at a much faster pace (Blackstone & Joseph, 2013). Additionally, biosimilars are less risky to produce. Up to 95% of all drug projects never make it to market, and only 1 in 10 approved drugs become a commercial success (Blackstone & Joseph, 2013). For biosimilars, the market is already defined and few additional clinical trials need to be run, substantially reducing the risk of not making a return on investment. As a result, for manufacturers, creating a biosimilar is often more cost-effective than producing an originator biologic. This is potentially leading towards an oversaturation of the biosimilar market. Currently, companies are working on 21 different biosimilars for Rituxan (Blackstone & Joseph, 2013). If even a quarter of those biosimilars launch, it could result in slim market share for both the biologics and the biosimilars.

Biosimilar Litigation: The Patent Dance

Biosimilar manufacturers face several decisions when deciding to launch a biosimilar (Fish & Richardson, 20020). One option is to launch at risk. The other is to try to clear the patent rights of the reference product before launch in a mechanism known as the "patent dance". The patent dance typically involves multiple rounds of litigation, outlined in the Biologics Price Competition and Innovation Act. The biosimilar manufacturer must show that its product is similar to and has no clinically significant differences from the reference product (Fish & Richardson, 20020). There are additional requirements, including manufacturing facility standards and evidence that the route of administration, dosage form, and strength of the biosimilar are the same as those of the reference product (Biologics Price Competition and Innovation, 2009).

The first wave of litigation then involves identifying and narrowing the potential list of patents litigated. The biologic manufacturer provides a list to the biosimilar manufacturer, and the biosimilar manufacturer can provide a list of other patents it believes should be included in the litigation as well. If the biologic's patents haven't expired yet, the biosimilar manufacturer must either provide detailed statements with factual and legal bases for invalidity, unenforceability, or non-infringement, or a statement that it does not intent to go to market before the reference product's patents expire. This stage can continue if the parties cannot agree on the final list of patents. If they do agree on a patent list, the biologic manufacturer then has a defined time period to file a patent infringement complaint.

The second wave of litigation begins with biosimilar approval by the FDA. After that point, the biologic manufacturer can seek an injunction prohibiting sale of the

biosimilar and can assert any patent from the original list. If the reference products patents expire during this process, the result in *Amgen Inc. v. Hospira Inc.* suggests that the biosimilar manufacturer may still be liable for pre-launch infringing activities when the patents were still in force (Fish & Richardson, 20020). Resolution can either be through settlement or proceeding through litigation, resulting in either launch or launch delay of the biosimilar. The overall process is timely, often taking up to 8 months, and can be expensive for the biosimilar manufacturer to engage in. Over half of all biosimilars currently on the market launched "at risk" instead of completing the patent dance process (Hagen, 2021).

Humira Biosimilars and Associated Litigation

Humira was embroiled in litigation with biosimilar manufacturers seeking to capitalize on their 2016 loss of exclusivity. The FDA approved Amgen's Amjetiva (adalimumab-atto) as the first Humira biosimilar in September of 2016 (Laday, Market gears up for biosimilar boom in 2023 as Humira exclusivity draws to a close, 2021). Five more have followed, including Cyletzo, which the FDA approved as the first interchangeable biosimilar for Humira (Food and Drug Administration, 2021). However, a Humira biosimilar has yet to launch.

Table 3. Humira Biosimilars

Product Name	**Manufacturer**	**FDA Approval Date**	**Settlement-Enforced Launch Date**
Amjetiva	Amgen	September 2016	Jan 31, 2023
Cyletzo*	Boehringer Ingelheim	August 2017	Jul 1, 2023
Hyrimoz	Sandoz	October 2018	Sep 30, 2023

Hadlima	Samsung Bioepis	July 2019	Jun 30, 2023
Abrilada	Pfizer	November 2019	Nov 23, 2023
Hulio	Mylan	July 2020	July 31, 2023

**indicates interchangeable biosimilar. (Anderson, 2021)*

Humira's primary approach has been to delay biosimilar launch, first through litigation and the patent dance, and then through "pay-for-delay" settlements. AbbVie filed several patent infringement suits against biosimilar manufacturers, though most of these suits were unsuccessful (Silbersher, 2020). When they engaged in the patent dance, AbbVie submitted large numbers of patents, including some that were considered unrelated, like submitting formulation patents that were not being infringed upon by the biosimilars (Silbersher, 2020). Ultimately, both of those strategies were unsuccessful at delaying launch. Instead, AbbVie has settled with eight drug makers for all of them to delay launch of Humira biosimilars until at least 2023, known as a "pay-for-delay" settlement (Laday, *Market gears up for biosimilar boom in 2023 as Humira exclusivity draws to a close,* 2021). Some are considering this a "win" for patients, as some of Humira's patents aren't set to expire until 2037, so the settlements allow for biosimilars to enter the market 14 years earlier. AbbVie has also secured royalties from Boehringer Ingelheim in advance of the launch of Cyletzo.

However, pending litigation may alter this outcome. Alvotech filed a complaint against AbbVie in April 2021 seeking declaratory judgment that its biosimilar, AVT02, does not infringe on Humira's patents (Poulos, 2021). Alvotech also asserts that AbbVie was trying to "overwhelm Alvotech with 60-plus patent claims of questionable validity" during the patent dance (Laday, Market gears up for biosimilar boom in 2023 as Humira exclusivity draws to a close, 2021). Alvotech also accuses AbbVie of inflating its patent

portfolio by patenting inventions that it does not use in Humira's production, seeking multiple patents on the same invention to purposefully cause confusion, and acquiring patents through inequitable conduct (Poulos, 2021).

It is unclear what the outcome of Alvotech's suit against AbbVie will be, but it is unlikely to markedly affect Humira's patent portfolio. Many of Humira's patents have already been unsuccessfully challenged as the Patent Office has rejected prior validity attacks on some of the patents Alvotech questioned (Laday, *Market gears up for biosimilar boom in 2023 as Humira exclusivity draws to a close*, 2021). Additionally, in a similar suit between Amgen's Enbrel and Sandoz's biosimilar Erelzi, the U.S. Supreme Court denied a petition to review an earlier U.S. Court of Appeals ruling that Erelzi infringed on two of Enbrel's patents. This decision could indicate how similar litigation between biosimilars and reference product manufacturers might be handled. Though it won't prevent the biosimilars from launching, litigation could create enough of a delay to allow for reference product manufacturers will have time to launch newer products.

Additionally, though Humira's pay-for-delay settlements have been successful thus far, this strategy may not remain available to manufacturers in the future. In addition to private antitrust suits alleging that pay-for-delay schemes violate antitrust laws, the Federal Trade Commission may also bring lawsuits on behalf of consumers for violation of federal antitrust laws (Olivera, 2022). These pay-for-delay schemes have anticompetitive ramifications and result in higher prescription drug prices for consumers. Though the Supreme Court has held that pay-for-delay deals are not inherently illegal in a 2013 decision, the Biden administration has taken steps to prevent future pay-for-delay arrangements. President Biden's Executive Order titled "Promoting Competition in the

American Economy" encourages the FTC to outright ban pay-for-delay agreements, citing statistics that these agreements raise drug prices by nearly $3.5 billion per year (Olivera, 2022). Though it is unclear how the FTC will react or if Congress will decide to pass legislation, it appears that pay-for-delay deals might become disfavored as a strategy under the current administration.

Phase II: Patent Analysis

There have been 132 patents granted for Humira since 1998. Overall, AbbVie, and its predecessor Abbott, filed over 200 total patent applications (Silbersher, 2020). The granted patents cover the adalimumab molecule as well as other aspects of Humira, like the mode of administration, combinations with other products, dosages, and new indications (Table 4).

One of AbbVie's first patents was for antibody specification by target and broadly considered antibodies that bound human TNF alpha. This type of broad claim is typically only awarded to the person who has first identified and described a therapeutic target (Storz, 2016). However, TNF alpha was already a known target at the time this patent was filed as Genetech, Bayer, and Centocor had already filed patents relating to TNF alpha antagonists (Storz, 2016). As a result, AbbVie's patent needed to be more specific and therefore the scope of the patent did not restrict other anti-TNF biologics from being developed. Nevertheless, this pivotal patent, 6090382, was highly influential and has the highest number of associated second-line patents at 24. It has also been referenced in over 200 patents, including by biologic competitors and biosimilar manufacturers.

Since 1994, Humira's overall patent strategy has varied markedly over time. Throughout the 90s and 2000s, Humira filed a total of 12 patents. This figure is still

somewhat high, as 20 patents is typically considered a large number. However, in comparison to their later 100-plus patents, this period of time was not particularly active in comparison to later years. Comparing the years before and after 2002, when Humira was approved by the FDA, the bulk of their patents were filed after FDA approval. This is unusual for a product, as the majority of research and development that would require patenting occurs prior to product launch. However, this is emblematic of Humira's patenting strategy to continue to extend market exclusivity and prevent biosimilar competition.

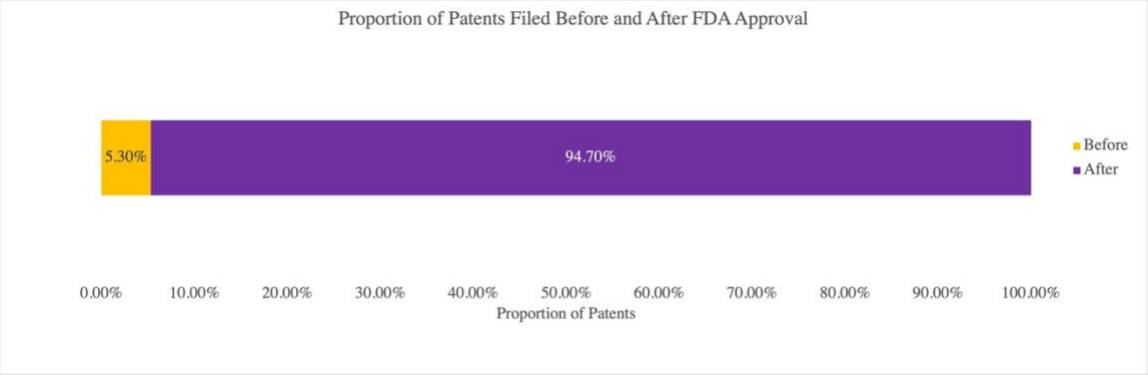


Figure 3. Proportion of Patents Filed Before and After FDA Approval.

Humira's major patent was set to expire in 2016 and as that year drew near, patenting activity began to increase substantially. From 2013 to 2016, Humira filed a total of 85 patents, the vast majority being second-line (Figure 4). This illustrates the growth of the patent thicket over time and how AbbVie launched their strategy in reaction to impending biosimilar entry.

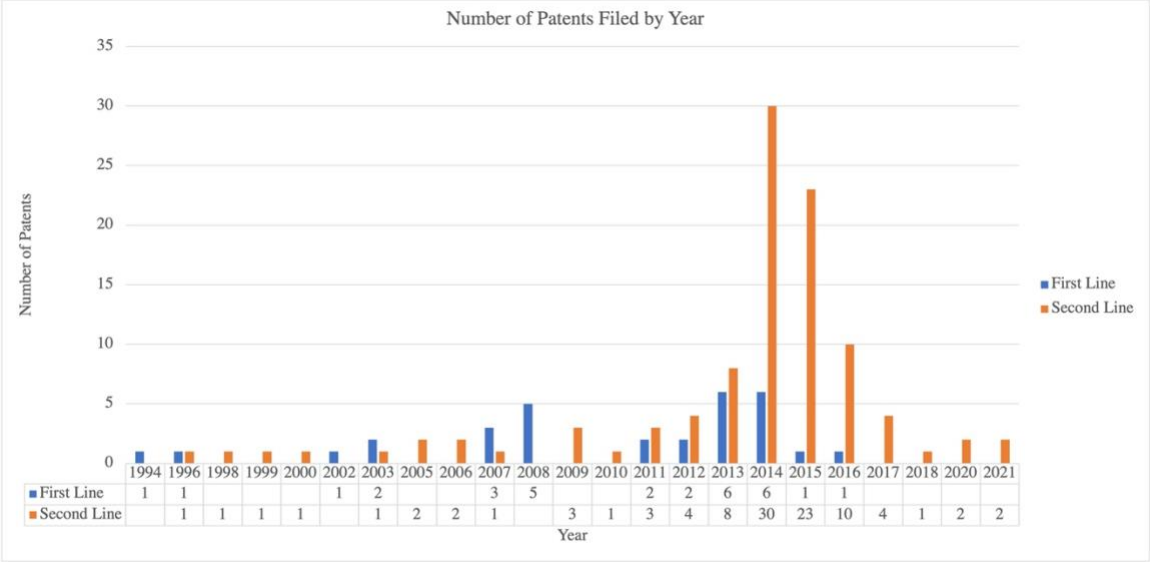


Figure 4. Number of Patents Filed by Year

As mentioned above, the majority of Humira's patents are second-line or extension patents. Of the 132 patents, only 31 are first-line, with the remaining 101 being second-line patents.

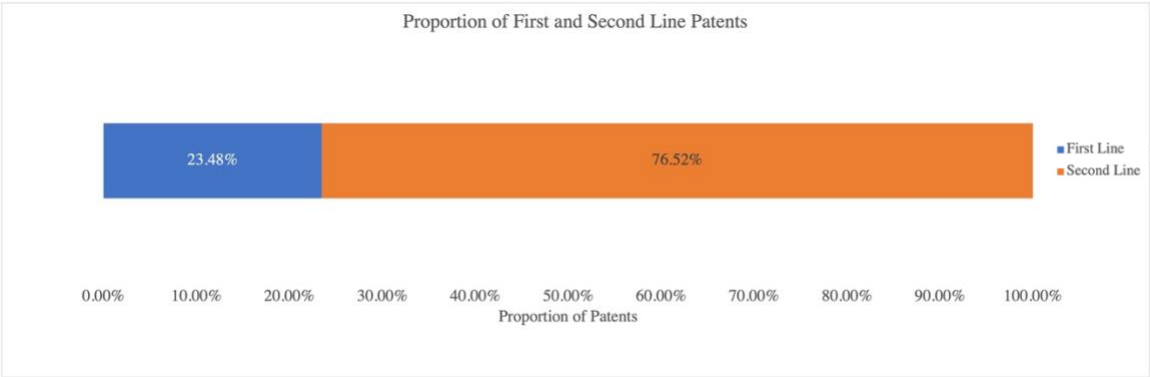


Figure 5. Proportion of First and Second-Line Patents.

There are three main first-line patents that result in the bulk of the second-line patents (Table 5). The first is patent 6000382, which is the patent for the TNF alpha target. Unsurprisingly, this patent is referenced often in the second-line patents that discuss the composition of Humira. The majority of these second-line patents are distinguished with differing antibody specifications. Some of these patents also discuss new indications or modes of administration as well. Additionally, some of the second-line patents refer to different dosages for new indications or the administration of Humira for diagnostic purposes.

The second is patent 8216583, which patents the formation of human antibodies for treating TNF-alpha associated disorders. The resultant second-line patents are very similar. The majority were filed in 2015, often on the same day, with minimal differences in the various claims. Most describe differing formulation specifications, like pH changes or the use of different sugar compounds. Overall, this group contains 22 patents that are remarkably similar to each other with minimal differences to formulation.

The third is patent 78632426 which describes the antibody purification process. The resultant second-line patents are also primarily related to the composition of Humira and detail differences in the process like differing mammalian host cells and different temperatures used. The remaining first-line patents did not result in substantial numbers of second-line patents themselves.

Table 5. First-line Patents and Associated Number of Second-line Patents

Patent Number	**Subject Matter**	**Number of Second-line Patents**
6090382	Human antibodies that bind human TNF alpha	24

8216583	Formation of human antibodies for treating TNF-alpha associated disorders	21
7863426	Antibody Purification	11
8093045	Fed-batch cell culture methods using non-animal-based hydrolysates	8
8889135	Methods of administering anti-TNF.alpha . Antibodies	6
9085618	Low acidic species composition and methods for producing and using the same	5
9062106	Methods for controlling the galactosylation profile of recombinanrly-expressed proteins	4
8420081	Antibody formulations and methods of making same	4
8708968	Removal of needle shields from syringes and automatic injection devices	3
8679061	Automatic injection device	2
9150645	Cell culture methods to reduce acidic species	2
8999337	Methods for treating juvenile idopathic arthritis by inhibition of TNF.alpha	2
5741488	Treatment of rheumatoid arthritis with anti-CD4 antibodies in conjunction with anti-TNF antibodies	1
9181337	Modulated lysine variant species compositions and methods for producing and using the same	1
9334319	Low acidic species compositions	1
9181572	Methods to modulate lysine variant distribution	1
9346879	Protein purification methods to reduce acidic species	1
8747854	Methods of treating moderate to severe hidradenitis suppurativa with anti-TNF-alpha antibodies	1
8969024	Compsotions and methods comprising binding proteins for adalimumab	1
8921526	Mutated anti-TNF.alpha antibodies and methods of their use	0
9624295	Uses and compositions for treatment of psoriatic arthritis	0
9505833	Human antibodies that bind human TNF alpha and methods of preparing the same	0
8821865	High concentration anti-TNF.alpha. Antibody liquid formulations	0
8911737	Methods of administering anti-TNF.alpha.antibodies	0

6805686	Autoinjector with extendable neefle protector shroud	0
9499614	Methods for modulating protein glycosylation profiles of recombinant protein therapeutics using monosaccharides and oligosaccharides	0
9193787	Human antibodies that bind human TNF alpha and methods of preparing the same	0
9550826	Glycoengineered binding protein compositions	0
9279015	Methods for treatment of ankylosing spondylitis using TNF alpha antibodies	0
8926975	Method of treating ankylosing spondylitis	0
9290568	Methods to control protein heterogeneity	0

The patent family dynamics have also shifted over time. Each family relates to a type of patent filed. Six main patent families were identified, relating to: New Indications, Mode of Administration, Formulations, Dosage, Composition, and Combination. The first patents, in the 90s and early 200s, were more varied in terms of the families identified (Figure 5). These patents involved the composition of Humira primarily, but also addressed combination usage, new indications, and modes of administrations. As time goes on and loss of exclusivity is approached, the dynamics shift towards primarily composition and formulation changes. There are still patents relating to new indications, dosage changes, and modes of administration, but the bulk of the patents are related to composition and formulation changes. These findings potentially point to the focus of AbbVie's research and development strategy regarding Humira. It is likely more cost-effective to make formulation and composition alterations, especially when the variations are minimal, compared to discovering new indications or changing dosages.

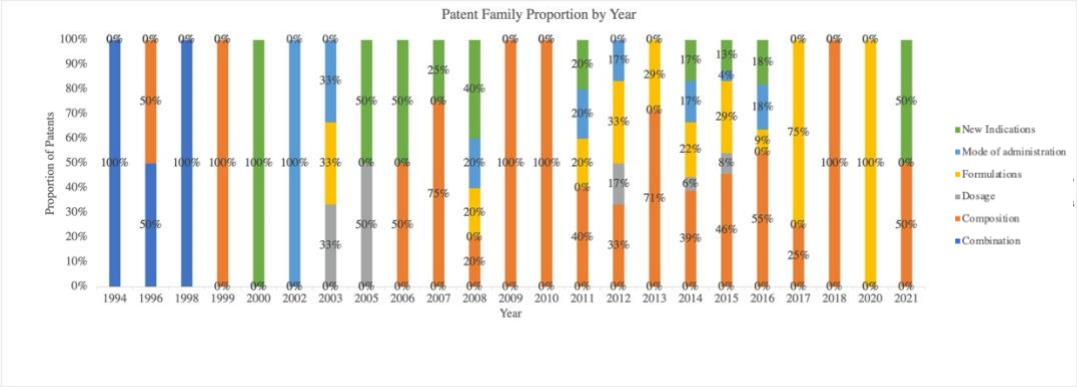


Figure 6. Patent Family Proportions by Year

Additionally, patents involving the composition of a molecule are often more challenging to litigate compared to manufacturing patents because manufacturing technology is less restrictive (Hagen, 2021). The patent data suggests that Humira's patent thicket was carefully crafted specifically to prevent biosimilar entry in advance of loss of exclusivity. The primary strategies focused on minimal composition and formulation changes, likely in order to create the most cost-efficient research and development strategy.

Phase III: Retroactive Validation Analysis

18 clinical trial reports and journal articles have been identified that directly compare Humira formulations, dosing schedules, or combination use. Of the 18 studies, 5 generated statistically significant results—a rate of 27.8 %. Due to the varying study designs and primary outcomes measured, each study will be discussed in turn and patient outcomes evaluated individually. Then, a high-level assessment will be made based on the aggregated results.

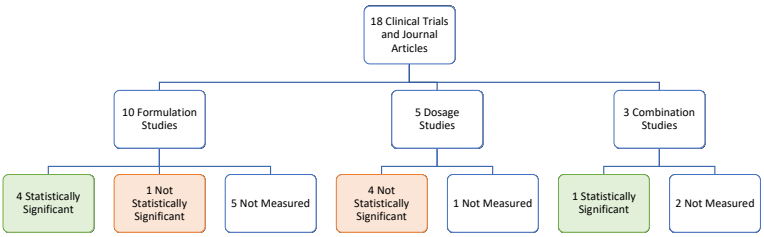


Figure 7. Clinical Trial and Journal Article Meta-Analysis

Formulation Studies

The greatest volume of studies involves the formulation family. Humira notably has two main formulations available—original formulation and citrate-free (D. Pilunni, 2021). The citrate-free formulation was introduced in 2016 with several key differences from the original formulation. Primarily, the citrate buffers were removed and the amount of liquid in the pre-filled syringe was decreased from .8 ml to .4 ml (AbbVIe, 2013). Additionally, the pre-filled syringe featured a thinner needle, a larger viewing window, and different colored packaging. The citrate-free formulation was touted to decrease injection-site pain as the primarily benefit, while retaining the same adalimumab strength.

The majority of the journal articles focus on the differences between the citrate-containing and citrate-free formulations regarding patient injection site pain. Of the 5

studies that compared these two formulations, 4 found a statistically significant reduction in injection site pain and one did not evaluate statistical significance.

The first study, *Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis*, used a visual analog scale ("VAS") to compare injection site pain immediately following administration of either citrate containing or citrate-free Humira (Peter Nash, 2016). A visual analog scale is a psychometric measuring instrument used to measure subjective characteristics or attitudes (Klimek, 2017). They are often presented as a continuum, for example, allowing patients to rate their pain on a scale from 1-10. They also often contain verbal descriptors (or word anchors) at each end to characterize the extremes of the feeling. This study asked patients to rate their injection site pain using a VAS immediately following administration of the original Humira formulation (40 mg/0.8 mL) or the new formulation (40 mg/0.4 mL) (Peter Nash, 2016). The study found a clinically and statistically significant decrease in injection site pain with the new formulation, with a mean difference on the VAS scale of -2.48 cm. Secondary outcome measures established that the tolerability and safety profiles were consistent with the original formulation.

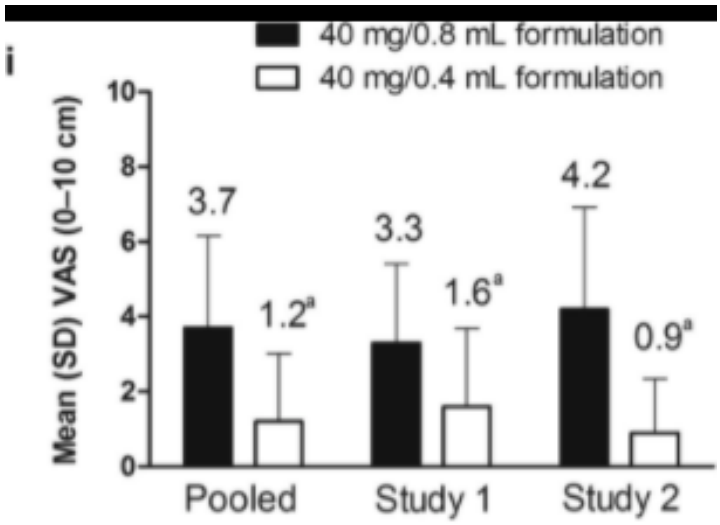


Figure 8. Mean VAS immediately after injection

(Peter Nash, 2016)

Three other studies also used a VAS to assess injection site pain after administration of original formulation Humira and citrate-free Humira. One, *New Adalimumab Formulation Associated With Less Injection Site Pain And Improved Motivation For Treatment*, also found a statistically significant decrease in injection site pain with the citrate-free formula (Tomohiko Yoshida, 2019). However, the difference in VAS measured was much larger than in the prior study, with a mean rating of 6.7 for the original formulation and 1.6 for the new formulation. This study also evaluated pain at injection and pain 10 minutes later and found both to be significantly lower regarding the new formulation. The study *Comparison of Injection Site Pain With Citrate-free and Original Formulation Adalimumab in Pediatric IBD Patients* found a similar VAS differential, but assessed a pediatric population with IBD instead of adults with

rheumatoid arthritis (Ashish S. Patel, 2019). This study also reported a statistically significant variance in injection site pain from 7.5 in the original formulation to 1 in the citrate-free formulation. Finally, *Patient-Reported Outcomes Regarding Adalimumab New Formulation* also reported statistically a statistically significant reduction in injection site related pain when comparing the citrate containing and citrate-free formulations, with 86.7% of their study population reporting much lower VAS values (P López Sánchez, 2018).

The fifth study in the formulation family that assessed injection site related pain between citrate containing and citrate-free formulations used a different methodology instead of a patient reported VAS score (D. Pilunni, 2021). Instead, this study conducted an analysis of reports of injection site reactions from 2016 until 2019. They found a substantial decrease in the reports of injection site reactions after the introduction of the citrate-free formula but did not conduct any statistical analyses.

Table 6. Number of Reports of Injection Site Reactions over Time

	2016	2017	2018	2019
Number of Reports	45	12	8	8

(D. Pilunni, 2021)

Based on the preceding studies, it is likely that the citrate-free formulation of Humira did result in appreciable patient benefit in decreased injection site related pain. Though the studies were conducted over different populations, all results point to a substantial decrease in pain. While it is likely that some of the reduction in pain is

attributable to the thinner needle, the formulation change could at least be in part responsible for the increased patient benefit. Additionally, another study measured patient adherence following a switch to the citrate-free formula and found a statistically significant decrease in discontinuation of 27% when comparing to the discontinuation rate of the original formulation (Martin Bergman, 2020). Taken in tandem, this collection of studies does point to significant increased benefit for patients taking the citrate-free formulation of Humira compared to the citrate containing formulation.

However, other formulations have not shown the same type of patient benefit. A cluster of four clinical trials, sponsored by AbbVie, all compared new and original formulations of Humira. All four studies took place in 2012, before the citrate-free version of Humira was released. None of the studies specify the "new formulation" being tested, but due to the timeline, it is unlikely that they are assessing the citrate-free version. Additionally, none of these studies assessed the statistical significance of their results and all use different primary outcome metrics. Instead, the percent change of the new formulation from the original formulation will be assessed across each metric.

The first study, NCT01712178, compared two formulations of adalimumab to assess pharmacokinetics, pharmacodynamics, and safety (AbbVie, 2013). The first assessment metric was serum concentrations of Adalimumab. Serum blood levels quantify the amount of a given medication present in the bloodstream at the time of testing. For treatment of rheumatoid arthritis, ideal adalimumab serum concentration levels should exceed 4.3 μg/mL (Rosas J, 2014). The study showed a percent decrease of 8% from the current formulation to the new formulation at 12 weeks, and then a percent

decrease of 4% at 24 weeks. Both new and current formulations exceeded the therapeutic 4.3 µg/mL serum concentration levels.

Table 7: Serum Concentrations of Adalimumab at Two Time Points

	Serum Concentrations of Adalimumab (ug/mL)		
	Current Formulation	New Formulation	% Change
12 Weeks	6.23	5.72	-8%
24 Weeks	6.17	5.95	-4%

(AbbVie, 2013)

The second primary outcome measure was a mean disease activity score. The mean disease activity score is a measure of disease activity and includes an assessment of tender and swollen joint counts as well as C-reactive protein levels and general health considerations. A score above 5.1 indicates high disease activity, a score under 3.2 indicates low disease activity, and a score under 2.6 indicates clinical remission. There was a smaller difference in disease activity scores of the current and new formulations, with a decrease of 1% at week 12 followed by an increase at 2% after week 24. Both current and new formulations show a disease activity between 3.2 and 5.1, indicating moderate disease activity.

Table 8: Mean Disease Activity Scores at Two Time Points

	Mean Disease Activity Scores		
	Current Formulation	New Formulation	% Change
12 Weeks	3.82	3.78	-1%
24 Weeks	3.46	3.54	2%

(AbbVie, 2013)

Though no definitive assessments can be made due to the lack of statistical analysis, the results of this study seem to indicate that this new formulation of adalimumab had minimal patient benefit over the current formulation. With decreased serum concentrations and relatively similar disease activity scores, it is difficult to assess what the benefit to this new formulation would be to patients without additional data points.

The next study, NCT01752855, is a continued assessment of the same patient population and new formulation as the prior study (Abbvie, 2013). The first primary outcome measure for this study is the mean change from the baseline disease activity scores. Comparing the change between the current and new formulations, ultimately there is a difference of -0.2, which, similarly to the conclusion drawn above, likely doesn't signify substantial patient benefit.

Table 9: Mean Change from Baseline Disease Activity Score

	Mean Change From Baseline in Disease Activity Score 28		
	Current Formulation for 24 weeks, new formulation for 24 weeks	New Formulation for 48 weeks	% Change
36 Weeks	-2.2	-2.4	9%
48 Weeks	-2.2	-2.4	9%

(Abbvie, 2013)

Additionally, the final patient outcome assessed was the mean change from baseline in a Health Assessment Questionnaire ("HAQ"). There was no change between the current and new formulations regarding the HAQ scores, again signifying that there was likely minimal appreciable patient benefit for this formulation (Abbvie, 2013).

The third study, NCT01561313, assessed the tolerability of two formulations of adalimumab, using a VAS (Abbvie, 2012). The results here are very similar to the *Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis* study, including similar VAS scores for current and new formulations as well as a similar decrease in injection site pain (Peter Nash, 2016). However, this study predates the Nash study by four years, and it is unlikely that the citrate-free formulation is being tested here. Though this study doesn't prove statistical analysis, due to the similar VAS scores and differential, it is likely that this new formulation provided a similar patient benefit as the citrate-free formulation.

Table 9: Injection Site Pain on a VAS

Injection Site Pain on a Visual Analog Scale (1-10)		
Current Formulation	New Formulation	% Change
3.3	1.6	-52%

(Abbvie, 2012)

The fourth study, NCT01502423, also measured injection site pain on a VAS of Adalimumab, comparing the current formulation to a new formulation (AbbVie, 2012). Similarly to the preceding trial, there is a marked differential in injection site pain between the current and new formulations. However, this trial shows a much larger differential between injection site pain for the current and new formulations. These two trials also take place over the same period of time, so they are likely testing two different formulations as the patient populations both consist of adults with RA. Like the above study, the formulation tested in this study likely does confer sufficient patient benefit when considering the reduction in injection site pain.

Table 10: Injection Site Pain on a VAS

Injection Site Pain on a Visual Analog Scale (1-10)		
Current Formulation	New Formulation	% Change
4.2	0.9	-79%

(Abbvie, 2012)

Regarding clinical trials and journal articles in the formulation family, there appear to be mixed results regarding the level of patient benefit attained. Because the clinical trials do not label the new formulations being tested, it is unclear if there is any overlap between these studies. There are likely at least 2, but no more than 3, different formulations being assessed in the clinical trials. Regarding the published journal articles, they all appear to be assessing the benefits of the citrate-free formula. Ultimately, it appears that the citrate-free formula does provide appreciable patient benefit regarding pain reduction in the injection site area. Two of the clinical trials that also use VAS as their primary outcome metric also seem to be testing formulations that provide similar patient benefit regarding injection site pain. The other formulations tested, however, do not appear to provide any additional patient benefit when comparing serum concentrations, disease activity scores, and health assessment questionnaires.

The patents covering the citrate-free formula, including those addressing the mechanical components of the auto-injector, like the thinner needle, do therefore appear to be justified in producing patient benefit. However, there have been 26 different second-line formulation patents filed for Humira. Though the meta-analysis of clinical trials was limited, the data suggests that only one (and at most three) formulations actually have measurable patient benefit, leaving over 20 patent formulas remaining with either no publicly available data for assessment or a low likelihood of producing substantial patient benefit. Additionally, the only metrics that showed patient benefit were related to injection site pain, which might have also been affected by the changed auto-injector design of Humira citrate-free.

Dosage Studies

There were five dosage studies identified among clinical trial and journal publications. None yielded statistically significant results—four of the five yielded results that were not statistically significant, and one study did not conduct a statistical analysis. The most common metric used for evaluation among these studies was clinical remission in patients with ulcerative colitis or Crohn's disease. In patients with ulcerative colitis, remission was evaluated using the Mayo Score, which is an endoscopic assessment to evaluate evidence of disease activity, like erythema, decreased vascular pattern, and friability (IG-IBD Scores, n.d.). For Crohn's disease, remission is defined by the Crohn's Disease Activity Index which assigns a score based on symptoms (Feagan, 2020). A score less than 150 would indicate clinical remission.

The first study assessed a high dose regimen (160 mg given each week for four weeks) compared to a standard dose regimen (160 mg followed by 80 mg) in both Crohn's disease and ulcerative colitis (Feagan, 2020). In the Crohn's disease patients, the rates of remission were 28.6% in the high dose arm and 26.2% in the standard dose arm. For ulcerative colitis, the results were similar in that there wasn't a sizeable difference in remission rates: 13.3% for the high dose arm compared to 10.9% for the standard dose arm. Both results were neither statistically nor clinically meaningful, indicating no appreciable patient benefit to taking a high dose regimen compared to a standard dose regimen.

The clinical trial results were similar in that none found a statistically significant difference in using a high dose regimen compared to a standard dosing regimen. One clinical study, NCT02065622, similarly assessed the impact of two different dosing

regimens in patients with ulcerative colitis (AbbVie, 2019). Upon analysis, it was found that there was no statistically significant difference in the percentage of patients who achieved remission between the higher dose and standard dose cohorts. Another clinical trial, NCT02065570, assessed the same dosing regimens but for patients with Crohn's disease (AbbVie, 2020). The results also showed no statistically significant difference in the proportion of patients who achieved remission between the standard and high dose cohorts.

Another clinical trial, NCT00647270, assessed high and standard dose regimens in people with rheumatoid arthritis (AbbVie, 2009). The evaluative metric here was the American College of Rheumatology 20 criteria ("ACR 20"). This assessment is a composite measured designed to evaluate both a 20% improvement in the number of tender and swollen joints as well as 20% improvement in at least three of the following five categories: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and C-reactive protein levels (eProvide, 2021). This study also did not find a statistically significant difference in ACR 20 responses between the high dose and standard dose regimens. This dosing regimen was also different and compared 40 mg every other week to an 80 mg monthly regimen.

The final clinical trial in this family, NCT02015793, assessed mean serum adalimumab concentration (AbbVie, 2015). This trial compared a low dose regimen (80 mg followed by 40 mg every other week) to the standard regimen (160 mg followed by 40 mg every other week). No statistical significance analysis was conducted on the data, but there was a 25% increase of serum concentration between the low and standard dose

regimens. Additionally, no secondary outcome metrics were measured to determine if there was measurable patient benefit or clinically significant outcomes.

Table 11: Mean Serum Adalimumab Concentration between Low and Standard Dose Regimens

Mean Serum Adalimumab Concentration at Week 8		
Low Dose (80mg at Week 0) followed by standard maintenance dose (40 mg eow)	Standard Dose (160mg at Week 0) followed by standard maintenance dose (40 mg eow)	% Change
7.99	10	25%

(AbbVie, 2015)

Overall, it does not appear that there is a clinically or statistically significant difference between dosing regimens across all of the studies. Of the four regimens tested, none appeared to produce a marked patient benefit over the standard regimen. AbbVie has seven patents, covering seven different dosing regimens, and the results from this data suggests that the various dosing schedules may not produce appreciable patient benefit.

Combination Studies

The three combination studies identified appear to yield the most appreciable patient benefit among a variety of assessment metrics. All three studies compare methotrexate and adalimumab combination therapy in comparison to adalimumab alone and methotrexate alone. In the first study, under the ACR response rate, there was a

statistically significant difference between combination therapy and monotherapy (Ferdinand C. Breedveld, 2006). In the two clinical trials, neither contained a statistical analysis, but there was a marked difference in joint disease activity scores and the proportion of patients who had low disease activity and no radiographic progression from baseline (AbbVie, 2010) (AbbVie, 2012).

This data indicates that combination therapy is more successful and has appreciable patient benefit in slowing disease progression compared to monotherapy. This family has also been the least patented by AbbVie. Of the two second-line patents, only one covers the combination use of Methotrexate and Humira together. Somewhat paradoxically, the family in which there is the fewest number of second-line patents is the most likely to have the greatest patient benefit and demonstrates true validity. Compared to the results in the formulation and dosage families, both of those families had much higher numbers of second-line patents, but less evidence showing patient benefit.

Phase IV: Financial Assessment

Drug Costs in Rheumatoid Arthritis

Branded drug costs have risen sharply over the past few years despite branded drugs making up an increasingly smaller proportion of market share compared to generics

(BlueCross BlueShield, 2018).

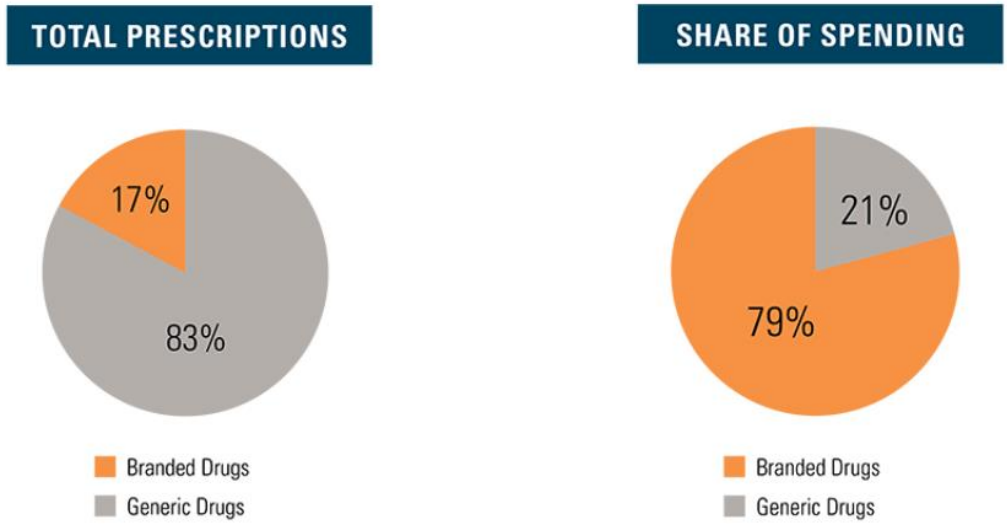


Figure 9. Proportion of Total Prescriptions and Share of Spending (2016)

(BlueCross BlueShield, 2018)

Humira has remained the world's best-selling drug, bringing in a global revenue of $20 billion (Rowland, 2020). AbbVie has also continued to increase the price of Humira since its launch in 2003. Since then, there have been 27 total price hikes and the price of a 40 mg syringe of Humira has increased by 470% (Brennan, 2021). The original price of a Humira syringe was $522 at launch—it has since risen to $2,984 per syringe, or $77,586 annually. Until biologics launch in 2023, Humira's price is expected to continue to rise (Rowland, 2020).

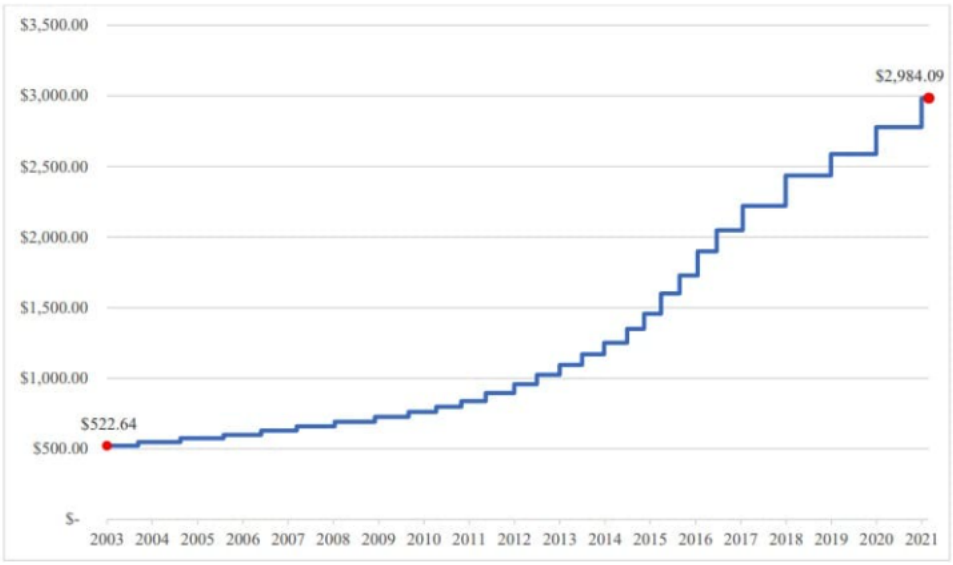


Figure 10. Humira Price per 40 mg syringe over time

(Brennan, 2021)

Patients and society-at-large are the ones who bear the brunt of Humira's hefty financial burden. There are three main insurance types: commercial or private insurance, Medicare, Medicaid. Additionally, there is also an uninsured population that takes Humira as well.

Patients with commercial or private insurance see the greatest potential variation in cost to patients. Humira is covered by most insurance plans (Marsh, 2018). However, most plans require that patients submit either a prior authorization form or complete step therapy. A prior authorization is a type of coverage approval from insurance companies. The insurance company requires that physician provide additional information before the insurance company decides whether or not the drug should be covered *(Marsh, Prior Authorizations: What You Need to Know*, 2019). If the prior authorization is denied, then

the patient has to pay the full out-of-pocket price of the drug. Step therapy is a process that insurance companies require where patients must first try a course of a different drug before they can receive the prescribed product. In the rheumatoid arthritis space, this drug is typically methotrexate. Patients need to show that they have tried the drug for a certain period of time, typically at least 30 days, and their physician is required to document that their condition did not adequately respond (Marsh, *What is Step Therapy? How to Get Insurance to Pay for Your "Non-Preferred" Drug*, 2018).

Once patients get past prior authorizations and step therapy, if required by their insurance company, the costs can vary based on each insurance plan's deductible amount and where patients are in terms of getting through their annual deductible (Stanford University, 2021). Because Humira is so expensive, patients can often hit their deductible within the first few prescriptions, and then face cost-sharing for the rest of the year, where they pay a percentage of the total cost, before the deductible resets in January.

AbbVie does offer a patient savings program, or a copay card, for patients with commercial insurance (AbbVie, 2013). This is a manufacturer-provided support program, so AbbVie pays the difference between the cost the patient is presented with at the pharmacy counter and the target copay, in this case, $5. These cards are only for patients with commercial insurance and often feature either monthly or annual caps. If the patient uses the card up to the cap, they then have to pay out of pocket for the remaining costs for that calendar year.

Insurance companies often cite that patient assistance programs act as an incentive for patients to use higher cost products despite lower cost alternatives being available (Ehrenberg, Adler, & Cox, 2020). Some insurance companies have therefore

implemented accumulator and maximizer plans to shift costs back onto manufacturers and patients. Accumulator benefit designs prevent manufacturer coupon buydowns from counting towards a patient's deductible (Ehrenberg, Adler, & Cox, 2020). As a result, instead of getting through their deductibles within a couple of months, patients are stuck in the deductible phase of their insurance plan, barring expenses outside of their Humira prescriptions. Once the patient then exhausts the maximum benefit of the patient assistance program, they are hit with the full cost of the drug to pay out-of-pocket. Maximizer programs are intended to use up the full cost of the patient assistance program by charging for more expensive therapies regardless of a patient's actual benefit design in order to get the highest possible buydown from manufacturer coupons (Ehrenberg, Adler, & Cox, 2020).

There is currently a rule in place, called the Notice of Benefit and Payment Parameter (NBPP) rule, that allows for insurance companies to implement accumulator plans. The U.S. House of Representatives introduced a bill to delay the NBPP rule until one year after the COVID-19 health emergency is lifted, temporarily blocking the spread of accumulator plans (Ehrenberg, Adler, & Cox, 2020). However, maximizer plan prevalence will likely continue to increase. These types of plans harm both manufacturers and patients and disincentivize the usage of patient support programs by manufacturers, which pushes costs back onto patients.

The high cost of Humira is thus primarily foisted onto patients and AbbVie itself, as well as onto society as a whole. Because commercial health insurance plans are based around risk pooling, healthy patients' premiums are used to cover the expenses of sick

enrollees, thus creating an increased societal cost as a result of increasing drug costs (Stanford University, 2021).

Medicare and Medicaid, both governmental insurance plans, operate very differently from commercial insurance in terms of cost-shifting. Additionally, patients on governmental insurance are not eligible to use patient support programs, so manufacturers are unable to meaningfully offset the drug costs.

Medicare Part D is the prescription drug benefit for patients with Medicare (Kaiser Family Foundation, 2021). Part D premiums can vary considerably based on the state where the patient lives and can range anywhere from $5.50 to $207.20 per month (Kaiser Family Foundation, 2021). In addition to the premiums, the Part D standard benefit structure has several phases that patients move through which affects their out-of-pocket cost over the course of the year.

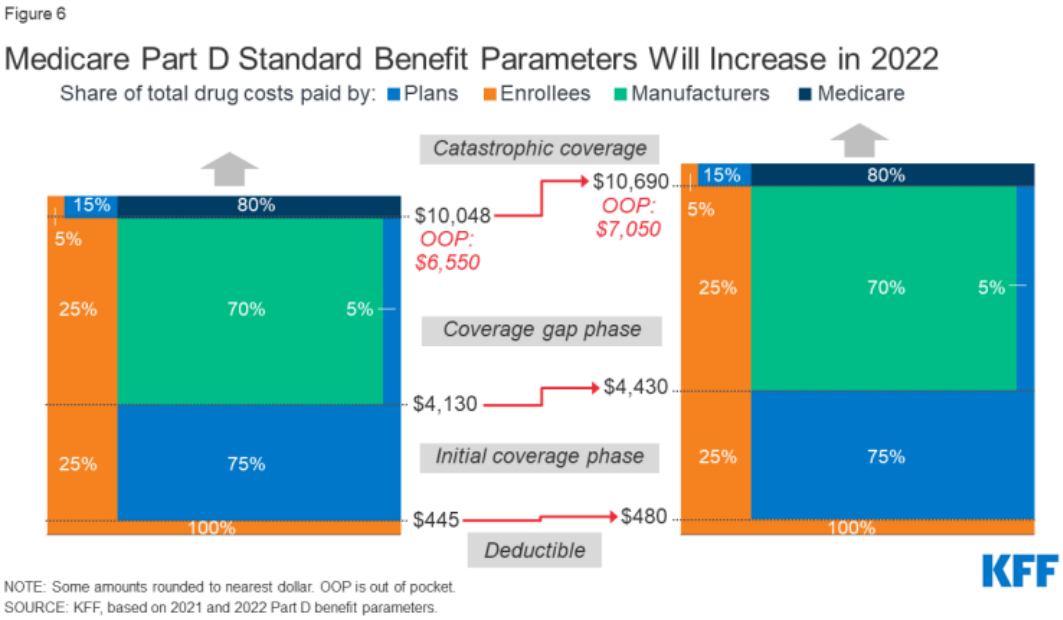


Figure 11. Medicare Part D Cost Sharing

(Kaiser Family Foundation, 2021)

Part D patients begin in the deductible phase, where they are completely responsible for all out-of-pocket costs up until $480. Then, patients move into a cost sharing phase where they pay 25% of the out-of-pocket costs, with the Part D plan covering the remainder. Patients then continue to pay 25% of the cost until they reach a cumulative out-of-pocket cost of $7,050. After that point, they shift into catastrophic coverage and continue to pay 5% of the total prescription cost through the end of the year (Kaiser Family Foundation, 2021). Because Humira has such a high monthly cost, most patients end up in catastrophic coverage within their first few months on the product and continue to pay at least $200 per month after that point.

Medicaid provides health coverage to eligible low-income adults, children, pregnant women, elderly adults, and people with disabilities (Medicaid, n.d.). Medicaid as a whole is funded by both states themselves and the federal government. Out-of-pocket costs for Medicaid patients vary among states, but typically patients do not pay more than $15 per prescription (Kaiser Family Foundation, 2018). Because Medicaid is partly funded through payroll taxes, society again bears much of the cost for these high-priced drugs.

Finally, uninsured patients face the full cost of the prescription on a monthly basis. However, AbbVie does provide assistance programs and scholarships to patients who are able to show sufficient financial burden and meet other criteria (AbbVie, 2013).

AbbVie's Research Expenditures

AbbVie executives have defended Humira's high drug costs as justified to fund research and development (Committee on Oversight and Reform, 2021). However, a recent report from the Committee on Oversight and Reform has shown that a large portion of AbbVie's research expenditures have instead been focused on defending Humira's market share through "enhancements" to Humira, resulting in more patents on the existing drug. AbbVie CEO Richard Gonzalez cited these "enhancements" as higher concentration formulations, smaller needle, new dispensing pens, and a monthly dosing regimen. However, the clinical trial results in Phase III have demonstrated that the only appreciable benefit of the formulation changes was a reduction in injection site pain, while the dosing changes resulted in no statistically significant differences in patient outcome. The more likely explanation is that the "enhancements" are instead focused on creating barriers for competition through patent evergreening and thicketing strategies. This theory was all but confirmed when an internal AbbVie presentation listed the creation of barriers as a key strategic component of the "enhancement" strategy.

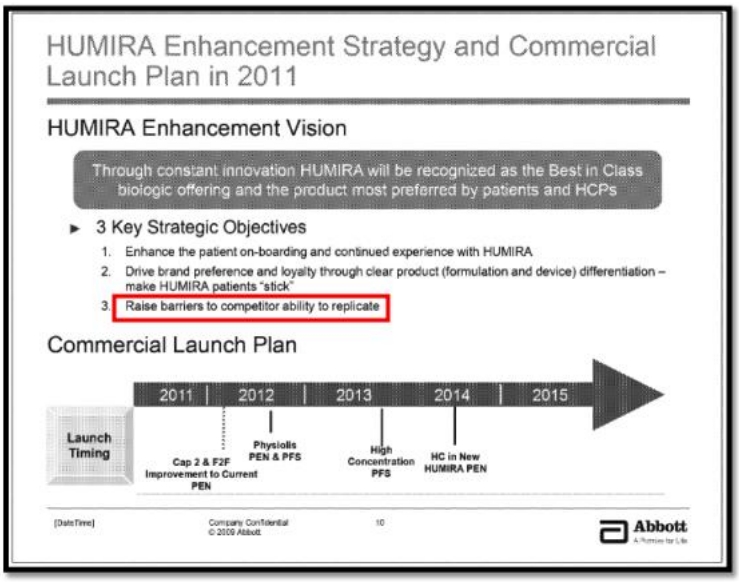


Figure 12. Internal Humira Presentation Slide

(Committee on Oversight and Reform, 2021)

Additionally, research expenditures overall were found to be a small fraction of overall revenue. Between 2009 and 2018, AbbVie spent $5.19 billion on research and development (Committee on Oversight and Reform, 2021). That amount made up only 7.4% of Humira's net revenue in the U.S. over the same period. Over that period of time as well, research and development costs have been slowly decreasing, while advertising expenditures have been rising.

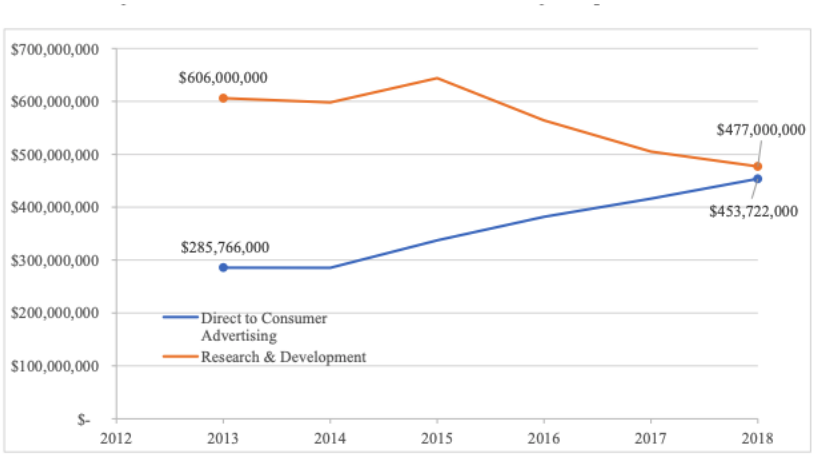


Figure 13. Humira Direct-to-Consumer Advertising Costs Compared to R&D Expenditure

(Committee on Oversight and Reform, 2021)

This data suggests that Humira's strategy of patenting "enhancements" to prevent competition has been very financially successful. By continuing to increase the price and

decrease research costs, each successive patent becomes less expensive to the overall book of business, creating a high profit margin for the overall strategic tactic.

Chapter IV.

Discussion

The results of this data suggest that AbbVie has developed a highly profitable strategy for maintaining market leader status and preventing biosimilar competition for Humira. By crafting their patent thicket, focusing research and development on minimal changes to the existing product, and continuing to raise prices, Humira's profit margins continue to increase. AbbVie has also been successful in litigation against biosimilars so far, preventing competition from entering the market until 2023. This strategy has allowed Humira over 20 years of market leadership and has, in large part, helped it become and maintain its status as the world's best-selling drug.

Turning to Humira's evergreening strategy, determining the retroactive validity of the second-line patents is as much a question of biology as one of social optimization. The patents themselves are distinguished from the original in terms of formulation, composition, and other changes that were deemed significant enough to earn a second-line patent. However, when considering the social utility of extending Humira's monopoly and domination of the rheumatoid arthritis space, a more delicate calculus is involved. Assuming the patent terms set forth in the Hatch-Waxman act are socially optimal and that around 20 years is an appropriate exclusivity period, the societal justifications for granting an extension become increasing nuanced. From a social cost perspective, because of the U.S. insurance system's penchant for risk pooling, "healthy" members of society bear the cost for less healthy members of society through the

payment of insurance premiums. Maintaining the monopoly of an expensive pharmaceutical product, like Humira, therefore can negatively impact the financial health of society writ large when lower cost biosimilar options are readily available and provide similar if not the same benefits to patients. To balance this cost on society, second-line patents would likely need to provide substantial and novel patient benefit above and beyond the level seen in many of the clinical trials evaluating the Humira formulations against each other, which overall showed little improvement in the management of rheumatoid arthritis symptoms and disease progression.

Regarding Humira's formulation changes, the data shows that the primary measurable benefit to formulation updates is reduced injection site pain for patients. Such a subjective outcome metric creates difficulty in quantifying the level of patient benefit observed. This therefore complicates the evaluation of whether the benefit shown justifies a longer term of patent exclusivity. There are two primary approaches that could aid in quantifying the patient benefit pain reduction provides. The first would be increased adherence. If a patient feels less pain when taking the product, they are likely to continue to take the product compared to another patient who experiences pain during every administration. One clinical study evaluated did in fact test adherence changes between the citrate and citrate-free formulations of Humira and found a statistically significant increase in adherence of 27% in the patient group taking the citrate-free, or less painful, version (Martin Bergman, 2020). An alternative metric to consider is the Quality Adjusted Life Year (QALY) (Prieto & Sacristan, 2003). The QALY measures the value of health outcomes by combining both the length of life and quality of life attained by a medical intervention. To calculate a product's QALY score, the change in utility value

induced by the treatment is multiplied by the duration of the treatment effective. This yields the number of QALYs gained by that treatment. In the comparison of citrate and citrate-free formulations, the clinical studies showed that the overall effect of the treatment of rheumatoid arthritis symptoms was roughly equal. Therefore, the duration of the treatment effective would be the same between both formulations. The marked change would then have to be between the change in utility value induced by the treatment. It is difficult to say if injection site pain reduction by a few points on a self-reported score would translate to a marked difference in utility value between the two products. As a result, it is unlikely that the QALY score would be substantially different between the two products, in that they yield about the same number of quality adjusted life years to patients regardless of formulation. To balance the social cost of maintaining an expensive monopoly, there would likely need to be substantial quantifiable patient benefit, and it is difficult to say if a reduction in injection site pain is enough.

Ultimately, Humira's strategy likely isn't replicable by other products. First, Humira was well positioned in launching in the early 2000s. The rheumatoid arthritis market only had one other product and Humira represented the first injectable product instead of an intravenous formulation. Additionally, Humira has shown itself to be effective in a wide variety of autoimmune indications. In other markets, this wide applicability likely won't be as feasible or yield the same type of market supremacy as in the autoimmune space. Since Humira was also one of the first products to develop and maintain such an extensive patent portfolio, there wasn't as much scrutiny or as much of an understanding as to how that behavior can stymie competition and lead to such large profit margins. This strategy likely cannot be implemented by a product towards the

beginning of their lifecycle, either. The development of the patent thicket is costly and requires a substantial investment of upfront capital. Most of Humira's patenting activity occurred over a decade after launch, after they already had substantial profit margins. A smaller company or a product earlier in its lifecycle likely wouldn't be able to make the same investment. As litigation around patent evergreening and patent thicketing increases, especially regarding antitrust matters, there may well be much greater scrutiny from the courts and regulatory bodies. It would also be unsurprising if the US Patent and Trademark Office were to apply the novelty test more forcefully to prevent similar activity. In addition, this strategy at whole is at best a delay tactic to allow for development of a more robust pipeline. At some point, the protections surrounding the product will expire, and to maintain financial health and long-term viability, the manufacturer will need to have other products in the pipeline and ready for launch to recoup lost profits.

Conclusion

Humira's evergreening strategy substantially impacted the development of the rheumatoid arthritis market by delaying biosimilar entry and continuing to raise prices. Additionally, there appears to be some patient benefit from second-line patented enhanced versions of Humira, but these benefits appear to be very limited and do not seem to justify the high numbers of second-line patents that have emerged. Ultimately, Humira's strategy is unlikely to be replicated by other products or in other markets primarily because of how litigation and perspectives around evergreening have shifted in recent years.

References

AbbVie. (2009, April). Study Number NCT00647270. *Study Comparing 80 mg of Adalimumab With Placebo, and Demonstrating the Non-inferiority of Monthly 80 mg Adalimumab Dosing Compared With 40 mg Adalimumab Every Other Week Dosing*. National Library of Medicine.

AbbVie. (2010, July). NCT00420927. *Study to Determine the Effects of Different Doses of Methotrexate (MTX) When Taken With Adalimumab in Subjects With Early Rheumatoid Arthritis (RA)*. National Library of Medicine.

AbbVie. (2012, September). NCT01185301. *Study to Determine the Effects of Different Doses of Methotrexate (MTX) When Taken With Adalimumab in Subjects With Early Rheumatoid Arthritis (RA)*. National Library of Medicine.

AbbVie. (2012, November). NCT01502423. *A Crossover Study of the Safety and Tolerability of Two Formulations of Adalimumab*. National Library of Medicine.

Abbvie. (2012, November). NCT01561313. *Crossover Study of Safety and Tolerability of Two Formulations of Adalimumab*. National Library of Medicine.

AbbVie. (2013). *Getting To Know Humira Citrate-free*. Humira. https://www.humira.com/citrate-free

AbbVie. (2013, May). NCT01712178. *A Study in Rheumatoid Arthritis (RA) Patients to Compare Two Formulations of Adalimumab for Pharmacokinetic, Pharmacodynamic and Safety*. U.S. National Library of Medicine.

Abbvie. (2013, October). NCT01752855. *Study in Rheumatoid Arthritis for Subjects Who Completed Preceding Study M13-390 With Adalimumab*. National Library of Medicine.

AbbVie. (2015, February). NCT02015793. *Study to Evaluate the Pharmacokinetics, Safety and Efficacy of Two Treatment Modules in Chinese Subjects With Moderate to Severe Crohn's Disease*. National Library of Medicine.

AbbVie. (2019, November). NCT02065622. *Study to Evaluate the Safety and Efficacy of Two Adalimumab Dosing Regimens in Subjects With Moderate to Severe Ulcerative Colitis*. National Library of Medicine.

AbbVie. (2020, January). NCT02065570. *Study to Evaluate Efficacy and Safety of Two Drug Regimens in Subjects With Moderate to Severe Crohn's Disease*. National Library of Medicine.

Ahn, H. (2014). *Second Generation Patents in Pharmaceutical Information.* Nomos.

Anderson, L. A. (2021, April 7). *Humira: One Drug, Many Uses, Billions of Dollars*. Drugs.com. https://www.drugs.com/slideshow/humira-one-drug-nine-uses-billions-of-dollars-1210

Atteberry, P., Bach, P., Ohn, J., & Trisheim, M. (2019, April 15). *Bioligics are Natural Monopolies (Part 1): Why Biosimilars Do Not Create Effective Competition*. Health Affairs Forefront. https://www.healthaffairs.org/do/10.1377/forefront.20190405.396631/full/

Bergman, M. (2020). Evaluation of Adherence and Persistence Differences Between Adalimumab Citrate-Free and Citrate Formulations for Patients with Immune-Mediated Diseases in the United States. *Rheumatology and Therapy, 8*(1), 109-118.

Biologics Price Competition and Innovation. (2009).

Bisoimilars Forum. (2021). *Biosimilars Have Significantly Lowered Prices of All Biologics.* Biosimilars Forum .

Blackstone, E. A., & Joseph, P. F. (2013). The Economics of Biosimilars. *Am Health Drug Benefits, 6*(8), 469-478.

BlueCross BlueShield. (2018). *Prescription drug costs trend update.* BlueCross BlueShield.

Bonek, K., Roszkowski, L., Massalska, M., Maslinksi, W., & Ciechomska, M. (2021). Biologic Drugs for Rheumatoid Arthritis in the Context of Biosimilars, Genetics, Epigenetics, and COVID-19 Treatment. *Cells, 10*(2), 323. https://doi.org/10.3390/cells10020323.

Borenstein, D. (2019, September). *Understanding Biosimilar Drugs; Are They as Good as They Say?* The Arthritis Connection. https://www.thearthritisconnection.com/ankylosing-spondylitis/understanding-biosimilar-drugs-are-they-as-good-as-they-say

Branning, G. (2016). Competition Heats Up in Rheumatoid Arthritis and Other Autoimmune Conditions. *Am Health Drug Benefits, 9*, 155-158.

Brennan, Z. (2021, May 18). House committee uncovers how Humira's price spiked by 470% as AbbVie execs cashed bonuses tied to the hike. *Endpoints News*.

CDC. (2021, October 12). *Arthritis Data and Statistics*. Centers for Disease Control and Prevention. https://www.cdc.gov/arthritis/data_statistics/national-statistics.html

Champion, S., Guha, R., & Salgado, M. (2013). Emerging Competition Issues in Biologics. *Antitrust Health Care Chronicle*.

CMAJ. (2013). *Drug patents: the evergreening problem.* Canadian Medical Association.

Committee on Oversight and Reform. (2021). *Drug Pricing Investigation.* Washington D.C.: U.S. House of Representatives.

D. Pilunni, C. S. (2021). Relationship between injection site reactions and different adalimumab formulations. Analysis of the adverse events reported in Italy in the period 2016-2019. *European Review for Medical and Pharmacological Sciences, 25*(8), 3300-3305. 10.26355/eurrev_202104_25468

Dutfield, G. (2009). *Intellectual Property Rights And The Life Science Industries :A Twentieth Century History.* World Scientific.

eProvide. (2021, March). *Amercian College of Rheumatology 20/50/70 criteria*. eProvide. https://eprovide.mapi-trust.org/instruments/american-college-of-rheumatology-20-50-70-criteria

Fachler, A. (2014). The Need for Reform in Pharmaceutical Protection: The Inapplicability of the Patent System to the Pharmacuetical System to the Pharmacutical Industry and the Reccomendation of a Shift Towards Regulatory Exclusivities. *Fordam Intellectual Property, Media & Entertainment Law Journal, 24*, 1059-1100.

Feagan, B. (2020). Clinical Implications of the Recent Dose-Ranging Studies of Adalimumab. *Gastroenterology & Hepatology, 16*(3), 139-141.

Feldman, R. (2018). May your drug price be evergreen. *Journal of Law and the Biosciences, 5*(3), 590-647. https://doi.org/10.1093/jlb/lsy022

Feldman, R. (2019, Feb 11). *'One-and-done' for new drugs could cut patent thickets and boost generic competition*. STAT. https://www.statnews.com/2019/02/11/drug-patent-protection-one-done/

Ferdinand C. B., M. H.-G. (2006). A Multicenter, Randomized, Double-Blind Clinical Trial of Combination Therapy With Adalimumab Plus Methotrexate Versus Methotrexate Alone or Adalimumab Alone in Patients With Early, Aggressive Rheumatoid Arthritis Who Had Not Had Previous Methotrexate Treatment. *Arthritis and Rheumatism, 54*(1), 26-37.

Fish & Richardson. (20020, August 13). *How Biosimilars Are Approved and Litigated: Patent Dance Timeline*. JD Supra. https://www.jdsupra.com/legalnews/how-biosimilars-are-approved-and-13217/

Fisher, W., Syed, T. (n.d.). *A War Not Easily Won: Curbing Infectious Diseases in Developing Countries.*

Food and Drug Administration. (2021, October 18). *FDA Approved Cyltezo, the First Interchangeable Biosimilar to Humira*. U.S. Food & Drug. https://www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira

Food and Drug Administration. (2021). *The Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.*

Fortune Business Insights. (2017). *Rheumatoid Arthritis Therapeutics Market Size, Share, and Industry Analysis By Product Type (Biologics, Non-Biologics), By Distribution Channels (Hospital Pharmacy, Retail Pharmacy, Online Pharmacy), and Regional Forecast 2018-2025.* Global: Fortune Business Insights.

Gøtzsche, P. C. (2018). Patients not patents: Drug research and development as a public enterprise. *European Journal of Clinical Investigation, 48*(2).

Gabriel, J. M. (2014). *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry.* Chicago: The University of Chicago Press.

Gibney, M., & Figuracion, K. (2021, March 22). *S&P Global Market Intelligence* . S&P Global. https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/cancer-drugs-show-big-sales-rise-in-2020-abbvie-s-humira-again-tops-list-63249898

Goldman, D. P., & Philipson, T. J. (2021, October 8). *Biosimilars competition helps patients more than generic competition*. STAT. https://www.statnews.com/2021/10/08/biosimilars-competition-helps-patients-more-than-generic-competition/

Gurgula, O. (2020). Strategic Patenting by Pharmaceutical Companies – Should Competition Law Intervene? *IIC - International Review of Intellectual Property and Competition Law, 51*(9), 1062–1085.

Hagen, T. (2021, September 9). *Strength of Patent Protection Varies by Patent Type*. AJMC: The Center for Biosimilars. https://www.centerforbiosimilars.com/view/strength-of-patent-protection-varies-by-patent-type

Hemphill, C. S. (2011). Evergreening, patent challenges, and effective market life in pharmaceuticals. *Journal of Health Economics, 31*(2), 327-339.

Hill, A. M., Barber, M. J., Gotham, D. (2017). Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health.*

iData Research. (2018, 06 18). *Will Humira Competitors Take Over the Immunology Drugs Market?* . iData Research. https://idataresearch.com/will-humira-competitors-take-over-the-immunology-drugs-market/

IG-IBD Scores. (n.d.). *Mayo Endoscopic*. Calculators in Gastroenterology. https://www.igibdscores.it/en/info-mayo-endoscopic.html

I-Mak. (2018). *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices.*

IMS Institute for Healthcare Informatics. (2016). *Price Declines after Branded Medicines Lose Exclusivity in the U.S.*

Janke, K., Biester, K., Krause, D., Richter, B., Schürmann, C., Hirsch, K., Hörn, H.. Kerekes, M. F., Kohlepp, P., Wieseler, B. (2020). Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. *BMJ, 370*, 2288.

Keefe, P. R. (2021). *Empire of Pain: The Secret History of the Sackler Dynasty*. New York: Doubleday.

Klimek, L. B. (2017). Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care. *Allergo journal international, 26*(1), 16-24.

Komendant, E. (2020). *Pharmaceutical Patent Abuse: To Infinity and Beyond!* Association for Accessible Medicines . https://accessiblemeds.org/resources/blog/pharmaceutical-patent-abuse-infinity-and-beyond

Laday, J. (2020, March 20). *Doing the 'Patent Dance:' Untanging biosimilar litigation for physicians*. Healio. https://www.healio.com/news/rheumatology/20200319/doing-the-patent-dance-untangling-biosimilar-litigation-for-physicians

Laday, J. (2021, June 18). *Market gears up for biosimilar boom in 2023 as Humira exclusivity draws to a close*. Healio. https://www.healio.com/news/rheumatology/20210617/market-gears-up-for-biosimilar-boom-in-2023-as-humira-exclusivity-draws-to-a-close

Lehmann, D. F. (2016). The Evergreening of Biopharmaceuticals: Time to Defoliate. *The Journal of Clinical Pharmacology*, *56*(4), 383-389.

Liu, A. (2018, August 6). *AbbVie, Roche and Pfizer the worst patent 'offenders,' says nonprofit.* Fierce Pharma. https://www.fiercepharma.com/pharma/drugmakers-game-patent-system-to-increase-drug-prices-says-nonprofit

Mayo Clinic. (2021, May 18). *Rheumatoid Arthritis*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/diagnosis-treatment/drc-20353653

Movik, E., Linnestad, K. K., Hagen, G., Kornør, H., Harboe, I., & Klemp, M. (2011). *Biologics for Early Rheumatoid Arthritis: Review of Health Economic Studies.* Norwegian Knowledge Centre for the Health Services.

Nash,P. (2016). Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis. *Rheumatology and Therapy, 3*(2), 257-270.

Olivera, Chelsea. (2022). *Is the End Near for Pharmaceutical Pay-for-Delay Deals?* University of Miami Law Review. https://lawreview.law.miami.edu/pharmaceutical-pay-for-delay-deals/#:~:text=%E2%80%9CPay%2Dfor%2Ddelay%E2%80%9D%20deals%20are%20agreements%20between%20generic,expiration%20of%20the%20drug's%20patent.

Patel, A.S. (2019). Comparison of Injection Site Pain With Citrate-free and Original Formulation Adalimumab in Pediatric IBD Patients. *American Journal of Gastroenterology, 114*, 835-855. doi: 10.14309/01.ajg.0000592952.86880.18.

Poulos, S. (2021, May 13). *Alvotech Files Suit Against AbbVie to Invalidate Humira Patent Portfolio*. JD Supra. https://www.jdsupra.com/legalnews/alvotech-files-suit-against-abbvie-to-2274806/

Price II, W. N., & Rai, A. K. (2016). Manufacturing Barriers to Biologics Competition and Innovation. *Iowa Law Review, 101*(3), 1023-1063.

Rosas J. (2014). Clinical relevance of monitoring serum levels of adalimumab in patients with rheumatoid arthritis in daily practice. *Clinical and Experimental Rheumatology, 32*(6), 942-948.

Rowland, C. (2020, January 8). Why price of Humira keeps rising despite FDA approval of generic competition. *The Washington Post*.

Sánchez, P.L. (2018). Patient-reported outcomes regarding adalimumab new formulation. *European Journal of Hospital Pharmacy, 25,* A236-A236.

Sanzenbacher, G. T. (2020). Drug insurance and the strategic behavior of drug manufacturers: Evergreening and generic entry after Medicare Part D. *Journal of Health Economics, 72*. 102332-102332.

Silbersher, Z. (2020, June 10). *Why was the Humira "patent thicket" antitrust case against AbbVie dismissed?* Markman Advisors. https://www.markmanadvisors.com/blog/2020/6/10/why-was-the-humira-patent-thicket-antitrust-case-against-abbvie-dismissed

Storz, U. (2017). Of patents and patent disputes: The TNFα patent files. Part 1: Humira. *Human Antibodies, 25*(1-2), 1-16.

Stuart, A. (2020, October 16). *Rheumatoid Arthritis Drug Guide*. WebMD. https://www.webmd.com/rheumatoid-arthritis/rheumatoid-arthritis-medications

Tada, K., Yamaji, K., Tamura, N. (2020). New Therapy in Rheumatoid Arthritis: Biological DMARDs and JAK Inhibitors. *Juntendo Medical Journal, 66*(1), 34-37.

Tomohiko, Y. (2019). New adalimumab formulation associated with less injection site pain and improved motivation for treatment. *Modern Rheumatology, 29*(6), 949-953.

U.S. Food & Drug Administration. (2021, October 12). *Biosimilar and Interchangeable Biologics: More Treatment Choices*. FDA. https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices

United States Code, 2006 Edition, Supplement 4, Title 21 - FOOD AND DRUGS. (2010).

Watson, S. (2018, June 29). *How to Work With Your RA Doctor to Switch Your Meds*. WebMD. https://www.webmd.com/rheumatoid-arthritis/features/ra-change-meds-biologic

Appendix

Table 4. Humira Patents

Patent Number	Date Filed	Date Granted	First Inventor	First or Second-line	Family (Composition, combination, dosage, formulations, new indications, mode of administration)	Subject Matter	Parent Patents	Justification	How many second-line?
5741488	4/28/94	4/21/98	Feldman, Marc	First-line	Combination	Treatment of rheumatoid arthritis with anti-CD4 antibodies in conjunction with anti-TNF antibodies	N/A	N/A	1
6090382	2/9/96	7/18/00	Salfeld, Jochen	First-line	Composition	Human antibodies that bind human TNF alpha	N/A	N/A	24
6258562	8/14/99	7/10/01	Salfeld, Jochen	Second-line	Composition	Human antibodies that bind human TNF alpha	6090382	Differing antibody specifications	N/A
6270766	8/1/96	8/7/01	Feldman, Marc	Second-line	Combination	Anti-TNF antibodies and methotrexate in the treatment of arthritis and Crohn's disease	5741488	Uses methotrexate with anti-TNF	N/A

6509015	3/31/00	1/21/03	Salfeld, Jochen	Second-line	New Indications	Human antibodies that bind human TNF alpha	6090382	Includes new indications	N/A
6770279	6/8/98	8/3/04	Feldmann, Marc	Second-line	Combination	TNF.alpha. Antagonists and cyclosporin in therapy of rheumatoid arthritis	5741488	Use of cyclosporin	N/A
6805686	5/6/03	#######	Fathallah, Marwan	First-line	Mode of administration	Autoinjector with extendable neefle protector shroud	N/A	N/A	0
7223394	3/7/21	5/29/07	Salfeld, Jochen	Second-line	Composition	Human antibodies that bind human TNF alpha	6258562, 6090382	Differing antibody specifications	N/A
7541031	4/17/07	6/2/09	Salfeld, Jochen	Second-line	Composition	Methods for treating rheumatoid arthritis using human antibodies that bind human TNFa	7223394, 6090382, 6258562	Differing antibody specifications	N/A
7588761	9/21/05	9/15/09	Salfeld, Jochen	Second-line	New Indications	Human antibodies that bind human TNF alpha	6090382	Includes new indications	N/A
7863426	4/4/07	1/4/11	Wan, Min	First-line	Composition	Antibody Purification	N/A	N/A	11
7919264	#######	4/5/11	Maksymowych, Walter	Second-line	Composition	Methods and compositions for determining the efficacy of a treatment for ankylosing spondylitis using biomarkers	6090382, 6258562, 6509015	Involves diagnostic use of anti-TNF.alpha. Antibody	N/A
8093045	9/13/07	1/10/12	Pla, Itzcoatl	First-line	Composition	Fed-batch cell culture methods using non-animal-based hydrolysates	N/A	N/A	8

8197813	3/10/09	6/12/12	Salfeld, Jochen	Second-line	Composition	Human antibodies that bind human TNF alpha	6090382, 650015	Differing antibody specifications	N/A
8206714	2/11/09	6/26/12	Salfeld, Jochen	Second-line	Composition	Methods for treating rheumatoid arthritis using human antibodies that bind human TNFa	7223394, 7541031, 6090382, 6258562	Differing antibody specifications	N/A
8216583	8/15/03	7/10/12	Kruase, Hans-Jurgen	First-line	Formulations	Formation of human antibodies for treating TNF-alpha associated disorders	N/A	N/A	21
8231876	9/15/10	7/31/12	Wan, Min	Second-line	Composition	Purified antibody composition	7863426	Differing antibody specifications	N/A
8372400	#######	2/12/13	Salfeld, Jochen	Second-line	Composition	Methods of treating disorders using human antibodies that bind human TNF.alpha	7223394, 7541031, 6090382, 6258562, 8206714, 7588761	Differing antibody specifications	N/A
8372401	5/8/12	#######	Salfeld, Jochen	Second-line	Composition	Human antibodies that bind human TNF alpha	7223394, 7541031, 6090382, 6258562, 8206714, 7588761, 8197813	Differing antibody specifications	N/A
8414894	#######	4/9/13	Salfeld, Jochen	Second-line	Composition	Human antibodies that bind human TNF alpha	6090382, 650015, 8197813	Differing antibody specifications	N/A
8420081	#######	4/16/13	Fraunhofer, Wolfgang	First-line	Formulations	Antibody formulations and methods of making same	N/A	N/A	4

8663945	#######	3/4/14	Pla, Itzcoatl	Second-line	Composition	Methods of producing anti-TNF-alpha antibodies in mammalian cell culture	8093045	Differing medium temperatures	N/A
8679061	3/5/08	3/25/14	Julian, Joseph	First-line	Mode of administration	Automatic injection device	N/A	N/A	2
8708968	1/24/12	4/29/14	Julian, Joseph	First-line	Mode of administration	Removal of needle shields from syringes and automatic injection devices	N/A	N/A	3
8715664	5/16/06	5/6/14	Hoffman, Rebecca	Second-line	New Indications	Use of human TNF.alpha. Antibodies for treatment of erosive polyarthritis	7223394, 6090382, 6258562	New indication for erosive polyarthritis	N/A
8747854	6/3/11	6/10/14	Okun, Martin	First-line	New Indications	Methods of treating moderate to severe hidradenitis suppurativa with anti-TNF-alpha antibodies	N/A	N/A	1
8753633	6/15/12	6/17/14	Salfeld, Jochen	Second-line	Composition	Human antibodies that bind human TNF alpha	7223394, 7541031, 6090382, 6258562, 8206714	Differing indications	N/A
8795670	#######	8/5/14	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8216583	Differing formulation specifications	N/A
8802100	#######	8/12/14	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8216583	Differing formulation specifications	N/A

8802101	#######	8/12/14	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8216583	Differing formulation specifications	N/A
8802102	1/3/14	8/12/14	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8216583	Differing formulation specifications	N/A
8808700	3/28/14	8/19/14	Hoffman, Rebecca	Second-line	New Indications	Use of TNF alpha inhibitor for treatment of erosive polyarthritis	6090382, 6258562, 6509015	New indication for erosive polyarthritis	N/A
8821865	#######	9/2/14	Neu, Michael	First-line	Formulations	High concentration anti-TNF.alpha. Antibody liquid formulations	N/A	N/A	0
8846046	#######	9/30/14	Kaymakcalan, Zehra	Second-line	Dosage	Low dose methods for treating disorders in which TNF.alpha. Activity is detrimental	6090382, 6258562, 6509015	Involves low doses	N/A
8883146	2/22/13	#######	Fraunhofer, Wolfgang	Second-line	Formulations	Protein formulations and methods of making same	8420081	Differing antibody specifications	N/A
8883156	6/26/13	#######	Wan, Min	Second-line	Composition	Purified antibody composition	8231876, 7863426	Differing antibody specifications and including differing modes of administration	N/A
8889135	6/5/02	#######	Fischkoff, Steven	First-line	Mode of administration	Methods of administering anti-TNF.alpha . Antibodies	N/A	N/A	6

8889136	4/11/05	#######	Hoffman, Rebecca	Second-line	Dosage	Multiple-variable dose regimen for treating TNF.alpha.-related disorders	6090382, 6258562, 6509015	New dosage for Crohn's disease	N/A
8895009	8/1/13	#######	Wan, Min	Second-line	Composition	Purified antibody composition	8231876, 7863426	Differing antibody specifications and including differing modes of administration	N/A
8906372	8/2/13	12/9/14	Wan, Min	Second-line	Composition	Purified antibody composition	8231876, 7863426	Differing antibody specifications including different indications	N/A
8906373	4/30/14	12/9/14	Banerjee, Subhashis	Second-line	New Indications	Use of TNF-alpha inhibitor for treatment of psoriasis	6090382, 6258562, 6509015	New indication for psoriasis	N/A
8906646	02/36/14	12/9/14	Pla, Itzcoatl	Second-line	Composition	Fed-batch method of making human anti-TNF-alpha antibody	8663995, 8093045	Differing method of antibody production	N/A
8911737	4/18/14	#######	Fischkoff, Steven	First-line	Mode of administration	Methods of administering anti-TNF.alpha.antibodies	N/A	N/A	0
8911741	7/2/14	#######	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8795670, 8216583	Differing formulation specifications	N/A
8911964	3/26/14	#######	Pla, Itzcoatl	Second-line	Composition	Fed-batch method of making human anti-TNF-alpha antibody	8663995, 8093045	Differing method of antibody production	N/A

8916153	6/26/13	#######	Wan, Min	Second-line	Composition	Purified antibody composition	8231876, 7863426	Differing antibody specifications	N/A
8916157	8/6/14	#######	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8795670, 8216583	Differing formulation specifications	N/A
8916158	8/6/14	#######	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8795670, 8216583	Differing formulation specifications	N/A
8921526	3/12/14	#######	Chumsae, Christopher	First-line	Composition	Mutated anti-TNF.alpha antibodies and methods of their use	N/A	N/A	0
8926975	6/17/14	1/6/15	Wong, Robert	First-line	New Indications	Method of treating ankylosing spondylitis	N/A	N/A	0
8932591	5/15/12	1/13/15	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8216583	Differing formulation specifications	N/A
8940305	7/2/14	1/27/15	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8795670, 8216583	Differing formulation specifications	N/A
8961973	3/28/14	2/24/15	Hoffman, Rebecca	Second-line	Dosage	Multiple-variable dose regimen for treating TNF.alpha.-related disorders	6090382, 6258562, 6509015	New dosage for Crohn's disease and psoriasis	N/A
8961974	3/28/14	2/24/15	Hoffman, Rebecca	Second-line	Dosage	Multiple-variable dose regimen for treating TNF.alpha.-related disorders	6090382, 6258562, 6509015	New dosage for Crohn's disease and psoriasis	N/A

8969024	8/27/08	3/3/15	Kaymakcalan, Zehra	First-line	Composition	Compsotions and methods comprising binding proteins for adalimumab	N/A	N/A	1
8974790	5/30/14	3/10/15	Fischkoff, Steven	Second-line	Mode of administration	Methods of administering anti-TNF.alpha.antibodies	8889135	Differing dosage schedule	N/A
8986693	10/9/14	3/24/15	Hoffman, Rebecca	Second-line	New Indications	Use of TNF-alpha inhibitor for treatment of psoriasis	6090382, 6258562, 6509015	New indication for psoriasis	N/A
8992926	9/26/14	3/31/15	Fischkoff, Steven	Second-line	Mode of administration	Methods of administering anti-TNF.alpha.antibodies	8889135	Differing dosage schedule	N/A
8999337	6/10/08	4/7/15	Medich, John	First-line	New Indications	Methods for treating juvenile idopathic arthritis by inhibition of TNF.alpha	N/A	N/A	2
9017680	#######	4/28/15	Fischkoff, Steven	Second-line	Mode of administration	Methods of administering anti-TNF.alpha . Antibodies	8889135	Altered dosage schedule	N/A
9061005	3/28/12	6/23/15	Hoffman, Rebecca	Second-line	Dosage	Multiple-variable dose regiment for treating idiopathic inflammatory bowel disease	8889136	Differing methods of administration and antibody specifications	N/A
9062106	4/26/12	6/23/15	Bengea, Cornelia	First-line	Formulations	Methods for controlling the galactosylation profile of recombinanrly-expressed proteins	N/A	N/A	4
9067992	12/8/14	6/30/15	Hoffman, Rebecca	Second-line	New Indications	Use of TNF-alpha inhibitor for treatment of psoriatic arthritis	6090382, 6258562, 6509015	New indication for psoriatic arthritis	N/A

9073987	5/30/14	7/7/15	Fischkoff, Steven	Second-line	Mode of administration	Methods of administering anti-TNF.alpha . Antibodies	8889135	Differing dosage schedule	N/A
9073988	12/8/14	7/7/15	Pla, Itzcoatl	Second-line	Composition	Fed-batch method of making human anti-TNF-alpha antibodies	8906646, 8663945, 8093045	Differing pH specifications	N/A
9085618	#######	7/21/15	Ramasubramanyan, Nataragan	First-line	Composition	Low acidic species composition and methods for producing and using the same	N/A	N/A	5
9085619	10/3/14	7/21/15	Fraunhofer, Wolfgang	Second-line	Formulations	Anti-TNF antibody formulations	8420081	Differing formulation specifications	N/A
9085620	4/8/15	7/21/15	Hoffman, Rebecca	Second-line	New Indications	Use of TNF-alpha inhibitor for treatment of psoriatic arthritis	6090382, 6258562, 6509015	New indication for psoriatic arthritis	N/A
9086418	2/25/21	7/21/15	Maksymowych, Walter	Second-line	New Indications	Methods and compositions for diagnosing ankylosing spondylitis using biomarkets	7919264, 6090382, 6258562, 6509015	Involves administering adalimumab for diagnostic purposes	N/A
9090688	9/22/14	7/28/15	Bengea, Cornelia	Second-line	Formulations	Methods for controlling the galactosylation profile of recombinanrly-expressed proteins	9062106	Differing media specifications	N/A
9090689	4/8/15	7/28/15	Hoffman, Rebecca	Second-line	New Indications	Use of TNF-alpha inhibitor for treatment of psoriasis	6090382, 6258562, 6509015	New indication for psoriasis	N/A

9090867	#######	7/28/15	Pla, Itzcoatl	Second-line	Composition	Fed-batch method of making human anti-TNF-alpha antibody	8911964, 8663945, 8093045	Differing methods of making antibody composition	N/A
9096666	#######	8/4/15	Pla, Itzcoatl	Second-line	Composition	Purified antibody composition	8213876, 7863426	Differing antibody specifications	N/A
9102723	#######	8/11/15	Wan, Min	Second-line	Composition	Purified antibody composition	8213876, 7863426	Differing antibody specifications and including differing modes of administration	N/A
9114166	12/2/14	8/25/15	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9150645	3/14/13	10/6/15	Subramanian, Kartik	First-line	Composition	Cell culture methods to reduce acidic species	N/A	N/A	2
9181337	#######	#######	Subramanian, Kartik	First-line	Composition	Modulated lysine variant species compositions and methods for producing and using the same	N/A	N/A	1
9181572	3/14/13	#######	Subramanian, Kartik	First-line	Composition	Methods to modulate lysine variant distribution	N/A	N/A	1

9187559	2/20/15	#######	Hoffman, Rebecca	Second-line	Dosage	Multiple- variable dose regiment for treating idiopathic inflammatory bowel disease	8889136, 6090382, 6258562, 6509015	Altered dosages for IBD and differing methods of adminstration	N/A
9193787	#######	#######	Chumsae, Christopher	First-line	Composition	Human antibodies that bind human TNF alpha and methods of preparing the same	N/A	N/A	0
9200069	2/4/15	12/1/15	Ramasubramanyan, Nataragan	Second-line	Composition	Low acidic species composition and methods for producing and using the same	9085618	Differing methods of administration	N/A
9200070	5/15/15	12/1/15	Ramasubramanyan, Nataragan	Second-line	Composition	Low acidic species composition and methods for producing and using the same	9085618	Differing mammalian host cells	N/A
9220781	7/14/15	#######	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9234032	1/16/14	1/12/16	Pla, Itzcoatl	Second-line	Composition	Fed-batch methods for producing adalimumab	8663995, 8093045	Differing pH and temperature specifications	N/A
9255143	2/11/15	2/9/16	Bengea, Cornelia	Second-line	Composition	Methods for controlling the galactosylation profile of recombinantly expressed proteins	9090688, 9062106		N/A

9266949	#######	2/23/16	Ramasubramanyan, Nataragan	Second-line	Composition	Low acidic species composition and methods for producing and using the same	9085618	Differing media specifications	N/A
9272041	8/14/15	3/1/16	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9272042	8/14/15	3/1/16	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9273132	7/10/15	3/1/16	Wan, Min	Second-line	Composition	Purified antibody composition	8916153, 8231876, 7864426	Differing antibody specifications including different indications	N/A
9279015	2/4/08	3/8/16	Wong, Robert	First-line	New Indications	Methods for treatment of ankylosing spondylitis using TNF alpha antibodies	N/A	N/A	0
9284370	4/6/15	3/15/16	Medich, John	Second-line	New Indications	Methods for treating juvenile idiopathic arthritis	8999337	Differing dosages for different ages and weights	N/A
9284371	#######	3/15/16	Pla, Itzcoatl	Second-line	Composition	Methods for producing adalimumab	8093045	Differing medium specifications	N/A

9289497	8/14/15	3/22/16	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9290568	2/26/15	3/22/16	Rives, Lisa	First-line	Composition	Methods to control protein heterogeneity	N/A	N/A	0
9295725	8/14/15	3/29/16	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9302011	#######	4/5/16	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216586, 9220781	Differing formulation specifications	N/A
9315574	#######	4/19/16	Ramasubramanyan, Nataragan	Second-line	Composition	Low acidic species composition and methods for producing and using the same	9085618	Differing method of antibody production	N/A
9321846	2/24/15	4/26/16	Kaymakcalan, Zehra	Second-line	Composition	Compositions and methods comrpising binding proteins for adalimumab	8969024	Differing antibody specifications	N/A
9327032	8/14/15	5/3/16	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A

9328165	8/31/15	5/3/16	Wan, Min	Second-line	Composition	Purified antibody composition	9096666, 8916153, 7863426	Differing compositions	N/A
9334319	3/14/13	5/10/16	Ramasubramanyan, Nataragan	First-line	Composition	Low acidic species compositions	N/A	N/A	1
9334320	5/28/14	5/10/16	Okun, Martin	Second-line	New Indications	Methods of treating moderate to severe hidradenitis suppurativa with anti-TNF-alpha antibodies	8747854	Differing endpoint treatment measures	N/A
9339610	4/15/14	5/17/16	Julian, Joseph	Second-line	Mode of administration	Removal of needle shields from syringes and automatic injection devices	8708968	Differing syringe specifications	N/A
9346879	#######	5/24/16	Ramasubramanyan, Nataragan	First-line	Composition	Protein purification methods to reduce acidic species	N/A	N/A	1
9359434	9/2/15	6/7/16	Subramanian, Kartik	Second-line	Composition	Cell culture methods to reduce acidic species	9150645	Differing amino acid and media specifications	N/A
9365645	2/3/16	6/14/16	Bengea, Cornelia	Second-line	Composition	Methods for controlling the galactosylation profile of recombinanrly-expressed proteins	9255143, 9090688, 9062106	Differing antibody specifications	N/A
9486584	11/6/15	11/8/16	Julian, Joseph	Second-line	Mode of administration	Automatic injection device	8679061	Differing injector specifications	N/A

9499614	3/13/14	#######	Hossler, Patrick	First-line	Composition	Methods for modulating protein glycosylation profiles of recombinant protein therapeutics using monosaccharides and oligosaccharides	N/A	N/A	0
9499615	7/20/15	7/20/15	Hoffman, Rebecca	Second-line	Dosage	Multiple- variable dose regiment for treating idiopathic inflammatory bowel disease	9187559, 8961973, 8889136	Differing dosages for different indications and using different modes of administration	N/A
9499616	#######	#######	Subramanian, Kartik	Second-line	Composition	Modulated lysine variant species compositions and methods for producing and using the same	9181337	Differing media specifications	N/A
9505833	#######	#######	Chumsae, Christopher	First-line	Composition	Human antibodies that bind human TNF alpha and methods of preparing the same	N/A	N/A	0
9505834	3/31/16	#######	Bengea, Cornelia	Second-line	Composition	Methods for controlling the galactosylation profile of recombinanrly-expressed proteins	9255143, 9090688, 9062106	Differing media specifications	N/A
9512214	2/28/14	12/6/16	Rives, Lisa	Second-line	Composition	Methods to control protein heterogeneity	9206390	Differing media specifications	N/A

9512216	6/3/16	12/6/16	Hoffman, Rebecca	Second-line	New Indications	Use of TNF.alpha.inhibitor	6090382, 6258562, 6509015	New indication for erosive polyarthritis	N/A
9522953	1/28/16	#######	Ramasubramanyan, Nataragan	Second-line	Composition	Low acidic species composition and methods for producing and using the same	9085618, 9315574	Differing composition specifications	N/A
9546212	6/10/16	1/17/17	Fischkoff, Steven	Second-line	Mode of administration	Methods of administering anti-TNF.alpha.antibodies	9017680, 8889135	Includes combinations with methotrexate	N/A
9550826	6/30/16	1/24/17	Labkovsky, Boris	First-line	Composition	Glycoengineered binding protein compositions	N/A	N/A	0
9572938	10/6/11	2/21/17	Julian, Joseph	Second-line	Mode of administration	Automatic injection device	8679061	Differing injector specifications	N/A
9624295	4/10/07	4/18/17	Medich, John	First-line	New Indications	Uses and compositions for treatment of psoriatic arthritis	N/A	N/A	0
9669093	2/12/16	6/6/17	Medich, John	Second-line	New Indications	Methods for treating juvenile idiopathic arthritis	9284370, 8999337	Differing ages and modes of administration	N/A
9683033	1/28/16	6/20/17	Subramanian, Kartik	Second-line	Composition	Cell culture methods to reduce acidic species	9359434, 9150645	Differing composition specifications	N/A
9708400	#######	7/18/17	Subramanian, Kartik	Second-line	Composition	Methods to modulate lysine variant distribution	9181572	Differing composition specifications	N/A

9732152	1/27/17	8/15/17	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9327032, 9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9738714	1/27/17	8/22/17	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9327032, 9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9750808	1/27/17	9/5/17	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9327032, 9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A
9913902	9/28/17	3/13/18	Wan, Min	Second-line	Composition	Purified antibody composition	9096666, 9273132, 8231876, 7863426	Differing antibody specifications and including differing modes of administration	N/A
9950066	4/11/16	4/24/18	Krause, Hans-Jurgen	Second-line	Formulations	Formulation of human antibodies for treating TNF-alpha associated disorders	9327032, 9114166, 8916158, 8911741, 8795670, 8932591, 8216583	Differing formulation specifications	N/A

1E+07	4/8/16	7/17/18	Julian, Joseph	Second-line	Mode of administration	Removal of needle shields from syringes and automatic injection devices	9339610, 8708968	Differing syringe specifications	N/A
1E+07	6/20/16	11/6/18	Pla, Itzcoatl	Second-line	Composition	Modified serum-free cell culture medium	9284371, 9234032, 8663945, 8093045	Differing media specifications	N/A
#######	11/8/18	8/10/21	Wan, Min	Second-line	Composition	Purified antibody composition	9273132, 909666, 8231876, 7863426	Differing modes of administration	N/A
#######	#######	11/9/21	Fraunhofer, Wolfgang	Second-line	Formulations	Protein formulations and methods of making same	9085619, 8883146, 8420081	Differing formulation specifications	N/A
1.1E+07	#######	12/7/21	Fraunhofer, Wolfgang	Second-line	Formulations	Protein formulations and methods of making same	9085619, 8883146, 8420081	Differing formulation specifications	N/A