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The Patent Dance



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Contents

Tables and figures	2
Introduction	3
1. Competitive Analysis.....	4
1.1. Biologics	4
1.2. Market Study.....	5
2. Strategic Management.....	12
2.1. SWOT Analysis.....	12
2.2. Porter's Forces Analysis	15
3. Innovation Patterns and Life Cycle stages of Technology, Product and Organization	18
3.1. Defining Innovative Patterns of Pharmaceutical industry	18
3.2. Technology Life Cycle of Drugs and Value of Pharmaceutical Patents	18
3.3. Discussion on the current Life cycle stage of Pharmaceutical Companies	21
3.4. Technology Lifecycle of Monoclonal Antibodies (mAbs)	23
3.5. Patterns of technological innovations in monoclonal Antibodies (mAbs) and mAbs patents	25
4. Patent Portfolio Analysis.....	27
4.1. Data Collection and Identification of Relevant Patent	27
4.2. Analysis of the Patent Portfolio by Technology and Function	28
4.3. Summary of Patent Portfolio	46
5. Technology Trajectory	47
5.1. Patent Count Trend.....	47
5.2. The evolution pattern of adalimumab technology	48
5.3. The evolution of each technology.....	49
6. IP Valuation.....	53
6.1. Income Approach (DCF Method)	53
6.2. Market Approach	57
7. Litigation	60
7.1 Litigation against Abbvie: How does Abbvie defend itself?.....	60
7.2. Inter Partes Review challenge on Humira patents	62
7.3 The First Humira Patent Dance: Abbvie v Amgen	65
8. Discussion and Conclusions	75

Tables and figures

Figure 1 Humira- From Disease to drug	4
Figure 2: Global Market Growth of Biologics and Biosimilars	5
Figure 3: Treatment Days of Anti-TNF from Year 2006 to 2015	6
Figure 4:Anti-TNF Biologics Share in Biologics Market	7
Figure 5:Sales of Humira and Competing mAbs for RA Diseases	9
Figure 6: Typical Drug development timelines and success rates.....	19
Figure 7:Pharmaceutical patent evaluation and licensing using a stochastic model and Monte Carlo simulations Liangchuan Wu & Lianghong Wu	20
Figure 8: Publications of monoclonal antibody research	23
Figure 9: Technology Fishbone Diagram	29
Figure 10: Function Fishbone Diagram	29
Figure 11: Technology Segmentation landscape of Humira	33
Figure 12: Main IPC trend (Base Composition)	35
Figure 13: Main IPC trend (Manufacturing Technology).....	38
Figure 14: Patent Count trend (Product Formulation).....	40
Figure 15: Patent Count trend (Administration Devices)	42
Figure 16 :Patent Count Trend (Method)	45
Figure 17: Patent Count Trend.....	48
Figure 18:Evolution of technologies used in developing Adalimumab	48
Figure 19:Application Trend of Base Composition.....	50
Figure 20: Humira Patent Portfolio Expiry dates.....	54
Figure 21: Application Date of the 61 patents (Source: IP tech)	67
Figure 22: Legal and Technological Connectivity of the 10 chosen patents	70
Figure 23Patent Scope Comparison of ‘157 family	71
Figure 24:Comparison between ‘945 and ‘964	72
Figure 25 : Opportunities in IP Strategy	75
Table 1: Estimated Market Value of TNF related diseases.....	7
Table 2: Indications of Humira and Other Competing Drugs in Anti-TNF Market.....	8
Table 3: Humira Biosimilars’ Development Status.....	10
Table 4: List of Recent Pharmaceutical Mergers and Acquisitions in terms of Values.....	22
Table 5: Adalimumab Patent Landscape.....	28
Table 6: Adalimumab Tech-Function Matrix.....	30
Table 7: Key Patents (Base Composition)	34
Table 8: Key Patents by legal interest (Manufacturing Technology).....	36
Table 9: Key Patents by Citation Strength (Manufacturing Technology)	37
Table 10: Main IPC classifications	37
Table 11: Key Patents by legal interest (Product Formulation)	39
Table 12: Key Patents by citation strength (Production Formulation).....	40
Table 13: Key Patent by citation strength (Administration Devices)	41
Table 14: Key Patents by citation strength (Assessment Devices).....	43
Table 15: Key Patents by legal interest (Method)	44
Table 16: Key Patents by Citation Strength (Method)	44
Table 17: Calculation of NPV based on DCF method	56
Table 18: Valuations of Humira	59
Table 19:Patents in first-round litigation categorized by the relevant technology.....	68
Table 20: Comparison of the procedural rights under Hatch-Waxman Act and BPCIA.....	74

Introduction

In 1982, Eli Lilly had its recombinant human insulin, Humulin approved for therapeutic use and it was the first biologic drug to be approved. Since then, the development of biologics has steadily grown into a global market valued at US\$209Bn in 2016.

Developing biologics is as extremely resource-intensive task, where huge amount of money, time, technical knowledge and etc. are needed in its development with but no guarantee that the investment will bear fruit.

Given the resources that have been poured into the development of its products, IP strategy is essential to protect the right of the biologics innovator from its infringers or competitors. Moreover, in the biopharmaceutical industry, patents are virtually equal the products.

It is estimated that US\$80bn of value will be eliminated from the biologics market between 2016-2021. However, with effective IP strategy, a biologics innovator is able to extend its right protection.

On 4th of August 2016, Abbvie Inc has filed a lawsuit against Amgen to block Amgen from getting into Adalimumab's market with its biosimilar.

In our case study, we will be focusing on how Abbvie's can fully optimize its IP portfolio and strategy to protect its right against Amgen and other biosimilar companies.

1. Competitive Analysis

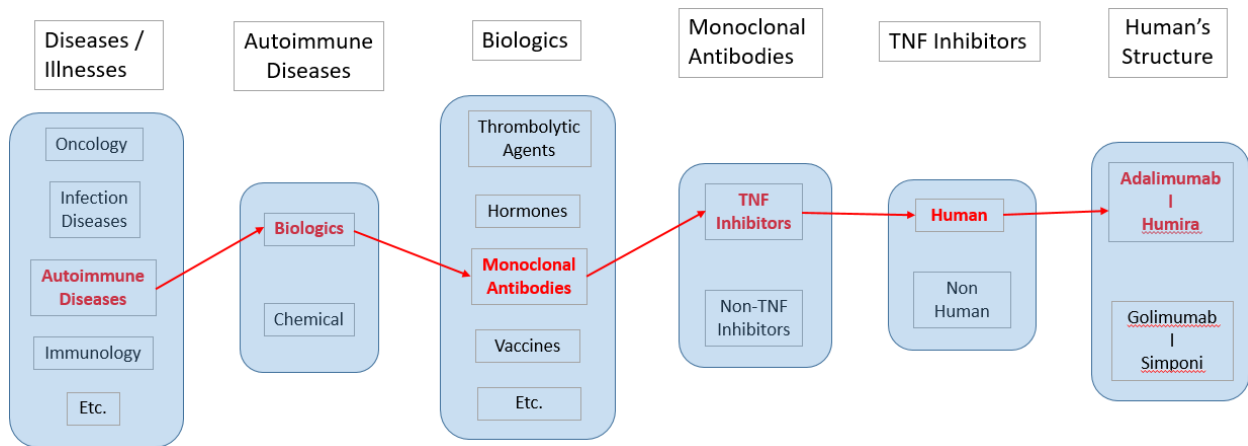


Figure 1 Humira- From Disease to drug

The main subject of this report is **Humira**. Humira is the trade name of adalimumab which currently belongs to Abbvie.

1.1. Biologics

Biologics are biopharmaceutical products derived from living things. Biologics are in the form of proteins, sugars, nucleic acid, tissues & cells or combination thereof.

Generally, the word “biologics” refers to a wide range of biological products in the field of medicine.

However, restrictively, it is used for medications which are produced by recombinant DNA technology.

The medications are generally classified into three types:

1. Monoclonal antibody
2. Substances which are similar to body's key signaling proteins
3. Receptor constructs

This report will only be focusing on a particular component of 1.

Monoclonal Antibodies (mAbs)

Antibodies which are made from identical immune cells that are all clones of a unique parent cell are known as **mAbs**. Generally, mAbs help to (1) flag cancer cells, (2) trigger cell-membrane destruction, (3) block cell growth, (4) prevent blood vessel growth, (5) block immune system inhibitors, (6) attack cancer cells, (7) deliver radiation treatment, (8) deliver chemotherapy, (9) bind cancer and immune cell and etc.

The structure of mAbs can be human, humanized or chimeric. Basically, the mAbs target specific proteins or antibodies in the body which cause diseases or illnesses. Some of the widely used mAbs are products like Adalimumab, Rituximab and Infliximab.

1.2. Market Study

According to prnewswire.com, global biologics market will expand at 10.9% CAGR from 2016 to 2024. In 2016, the value of biologics market is estimated to be US\$209.78Bn and it is expected that in 2024, it will rise to US\$479.75Bn.

Based on IMS's report dated September 2013, the biologics market share was 11% of the total pharmaceutical market which is equivalent to US\$46Bn and will grow to 19-20% of total pharmaceutical market which is equivalent to US\$205Bn - US\$235Bn.

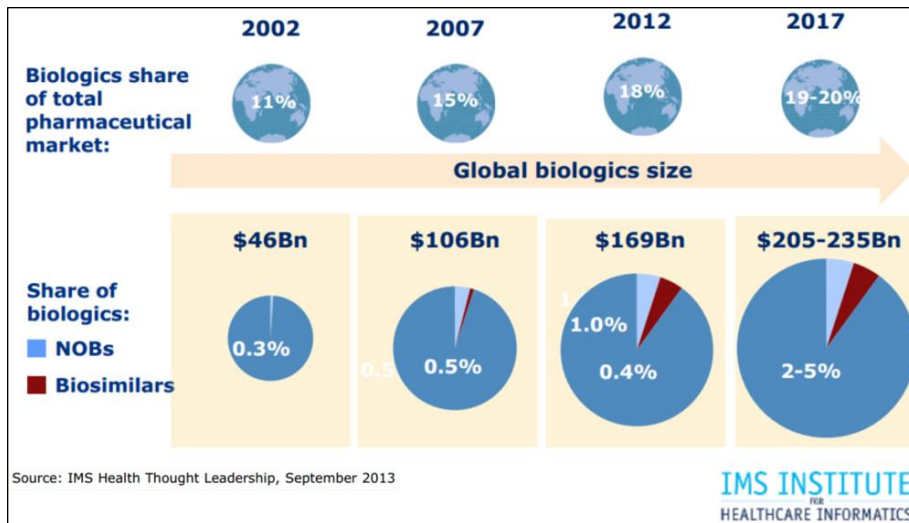


Figure 2: Global Market Growth of Biologics and Biosimilars

Very high capital is required to develop biologics. Besides, the regulatory approval process is also very complex. However, compared to traditional drug, biologics have relatively higher success rate of approval. Due to stringent manufacturing processes, regulatory processes and product parameters, clinical trials and approval often required longer time. Ultimately, these lead to higher cost of capital needed for R&D and marketing.

Biologics market can be classified by product and by application. Biologics products are monoclonal antibodies, vaccines, recombinant hormones / proteins, cell therapy, gene therapy and etc. While the field of biologics application are like oncology, infection diseases, immunology, autoimmune diseases and etc.

1.2.1. Market of TNF Inhibitors

TNF inhibitors are used to treat diseases which caused by TNF produced in the body. It is to reduce the effect of inflammatory response of autoimmune diseases. However, it may increase the risk of infection because TNF α helps to protect the body from infection. Among the well-known TNF related disease are rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis arthritis and etc.

There are a few brands of mAbs TNF inhibitors in the market namely, Adalimumab, Infliximab, Golimumab and Certolizumab.

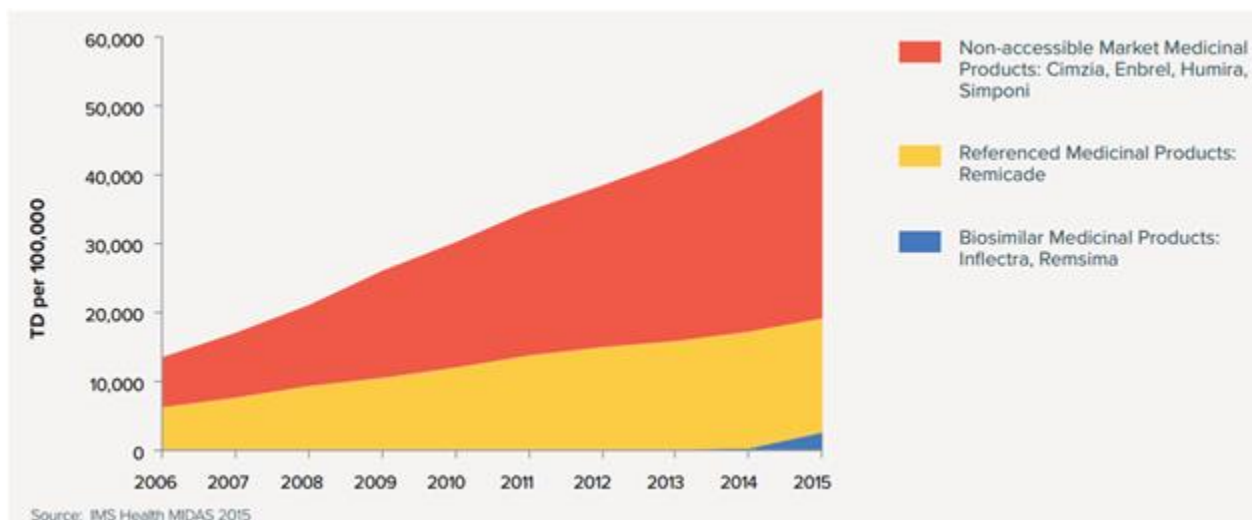


Figure 3: Treatment Days of Anti-TNF from Year 2006 to 2015

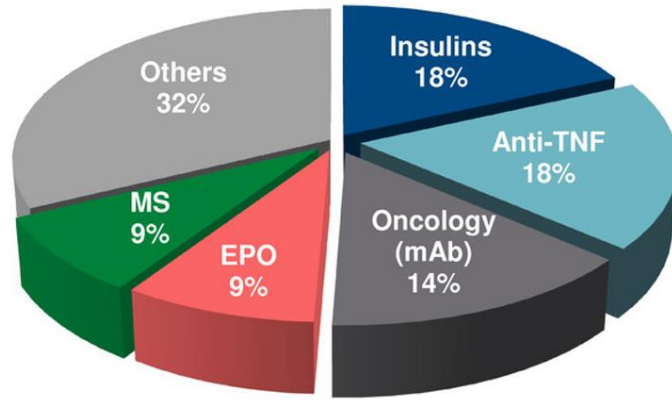
In 2015, IMS Health's Studies shows that demand of TNF Inhibitors which calculated in treatment days has grown steadily from 2006 to 2015. With some of the biologics patents coming close to expiration, we can see the emerging of biosimilar in market. By observing the trend, it can be told that the demand of TNF Inhibitors will keep growing unless there are better drug in the market in terms of cost, efficacy, side effect and etc.

According to Westpharma's report dated May 2014, the TNF Inhibitors accounted 18% of the biologics marker.

Growing Share of Medicines are Biologic



Key Therapy Areas account for 70% of total Biologics Market



Market Intelligence

Figure 4: Anti-TNF Biologics Share in Biologics Market

Disease	Value	Source
Rheumatoid Arthritis	\$80.7 B (2020)	linkedin.com
Crohn's Disease	\$4.2 B (2022)	fiercepharma.com
Psoriatic Arthritis	\$3.7 B (2022)	pharmatimes.com
Ulcerative Colitis	\$4.2 B (2022)	statista.com
Ankylosing Spondylitis	\$661 M (2016)	prnewswire.com

Table 1: Estimated Market Value of TNF related diseases

1.2.2. Adalimumab – Humira

Adalimumab is monoclonal antibody, TNF inhibitor which is widely used for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa, and juvenile idiopathic arthritis.

Humira is a trade name of Adalimumab which is marketed by Abbvie. It is discovered by a collaboration between BASF Bioresearch Corporation and Cambridge Antibody Technology and it is the first monoclonal antibody approved by FDA in 2005 to treat rheumatoid arthritis.

There are many TNF related disease, however no one product which can be used to treat all the disease. Humira has the upper hand where it can be used to treat most of the TNF related diseases. It is reported in July 2016 that Humira generated \$14B of sales for Abbvie which is equivalent to 64% of Abbvie's net revenue in the quarter.

Summary of EMA information for approved indications of Anti-TNF products							
	Humira	Remicade	Remsima	Inflectra	Enbrel	Simponi	Cimzia
Rheumatoid Arthritis	●	●	●	●	●	●	●
Juvenile idiopathic Arthritis	●				●		
Psoriatic Arthritis	●	●	●	●	●	●	●
Axial Spondyloarthritis, comprising: Ankylosing Spondylitis (AS) Axial Spondyloarthritis without radiographic evidence of AS	● ●	●	●	●	● ●	● ●	● ●
Crohn Disease	●	●	●	●			
Paediatric Crohn Disease	●	●	●	●			
Ulcerative Colitis	●	●	●	●		●	
Paediatric Ulcerative Colitis		●	●	●			
Psoriasis	●	●	●	●	●		
Paediatric Plaque Psoriasis	●				●		
Hidradenitis suppurativa	●						

Table 2: Indications of Humira and Other Competing Drugs in Anti-TNF Market

1.2.3. Humira's Competition

Humira's total global sales in 2015 was US\$14 billion and it is projected to be US\$20 billion in 2020¹. Humira's sales perform better compared to other TNF inhibitors like Remicade and Enbrel which are targeting rheumatoid diseases. In 2015 Remicade and Enbrel accounted about US\$8 billion and US\$5 billion each.

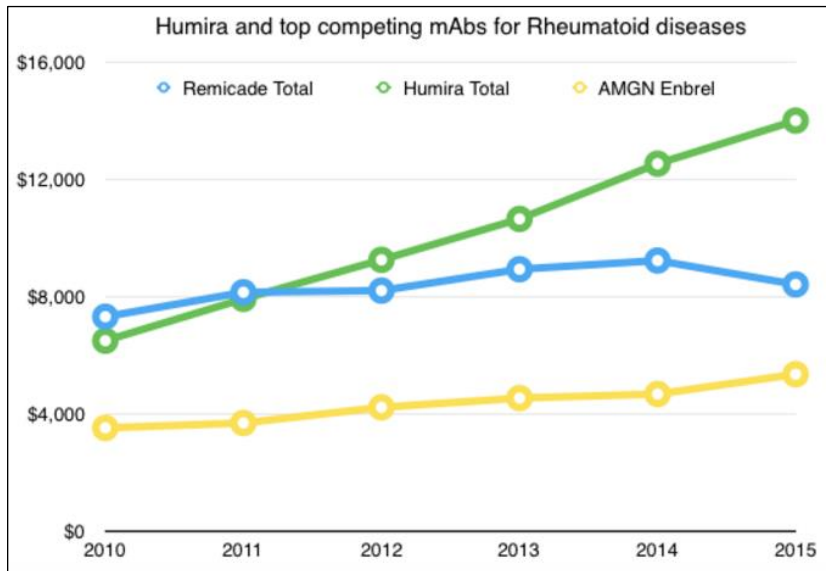


Figure 5: Sales of Humira and Competing mAbs for RA Diseases

Factors which influence the adoption of TNF inhibitors,

1. Adverse effects - Immunogenicity
2. Efficacy and response rate
3. Treatment Frequency
4. Cost

Immunogenicity is one of the main reason why the human mAb, Humira is chosen. Drugs derived from human source are less likely to be rejected by human's body compared to drugs derived from non-human source

The high demand of adalimumab and with Humira losing its exclusivity in December 2016 has attracted the development of Humira's biosimilar. Even though AbbVie's Humira's patent of "composition of matter" expires in December 2016, it still has other patents which protect its right on Humira until

¹ <http://seekingalpha.com/article/3873966-abbvie-stands-abnormally-vulnerable>

2030s. The patent protection AbbVie has on its Humira after December 2016 are indication / method of treatment, formulation, manufacturing and delivery devices.

It is believed that the legal right will keep Humira’s biosimilar at bay until 2022 even though biosimilar got approval from FDA. Table 3 shows the development status of Humira’s biosimilar.

Company	Drug code	Status	Key date	Ref.
Amgen	ABP-501	Filed	November 2015	[2]
Samsung Bioepis/Biogen	SB-5	Filed	Early January 2016	[3]
Sandoz	GP-2017	Phase III	Completion: April 2016	ClinicalTrials.gov: NCT02016105
Fujifilm Kyowa Kirin Biologics	FKB-327	Phase III	Completion: July 2016	ClinicalTrials.gov: NCT02260791
Boehringer Ingelheim	BI-695501	Phase III	Completion: October 2016	ClinicalTrials.gov: NCT02137226
Coherus Biosciences	CHS-1420	Phase III	Completion: March 2017	ClinicalTrials.gov: NCT02489227
Momenta Pharmaceuticals/Shire	M-923/BAX-923	Phase III	Completion: May 2017	ClinicalTrials.gov: NCT02581345
Pfizer	PF-06410293	Phase III	Completion: November 2017	ClinicalTrials.gov: NCT02480153
Mylan/Biocon	MYL-1401A	Phase III	Completion: November 2016	ClinicalTrials.gov: NCT02714322
Oncobiologics/Viropro	ONS-3010	Phase III		[4]
Hetero Drugs	Het-04	Phase III		[5]
AET BioTech/BioXpress Therapeutics	BX-2992	Phase I		[6]
Dong A/Meiji	DMB-3113	Phase I		[7]
LG Life Sciences	LBAL	Phase I		ClinicalTrials.gov: NCT02206867
BioCad	BCD-057	Phase I		ClinicalTrials.gov: NCT02395055
Epirus/Polpharma	BOW-050	Phase I		[8]
Alteogen/Cristalia		Phase I		[9]
Merck Serono	MSB-11022	Phase III	Completion: September 2017	ClinicalTrials.gov: NCT02660580

Table 3: Humira Biosimilars’ Development Status

Factors which influence the choice of a biosimilar,

1. Clinical Trial Data & Interchangeability
2. Price
3. Trust with Innovator Brand

When it comes to adoption of biosimilar, safety and efficacy would be the main factor. Sufficient clinical trial data and approval from authorities will give the patients the confidence to switch to biosimilar.

Besides, significant cost difference will also be the factor to encourage patients to switch to biosimilar.

However, brand name is one of the factor why patients will choose to stick to drug which they have been using for certain period of time and proven the efficacy.

1.3. Product Protections

In the US there are two types of protection for commercial biologic products. The first, and the more well-known of the two, is patent protection that gives the patentee exclusive monopolistic right for 20 years. In the specific case of pharmaceutical-related patents, generally the exclusivity can be extended with supporting patents on indications, methods of treatment, formulations, manufacturing processes,

diagnosis, and devices. However, when the base composition patent is already expired, the patentee would expect the product to be challenged by competitors downplaying the supporting patents. The other is called Biologics Price Competition and Innovation Act (BPCIA) of 2009 by Food and Drug Administration (FDA) which allows marketing exclusivity for biologic products for 12 years. The protection provided by BPCIA may or may not cover the same timeline as BPCIA can be applied at the discretion of the product's original owner, potentially covering exclusivity beyond patent protection. This can be seen as being favorable to the original owner as marketing exclusivity may be able to help provide concrete exclusivity extension for a product in the market beyond its patent protection. In 2011 US government reopened the debate on BPCIA exclusivity protection from 12 years to potentially being reduced to only 7 years, favoring generic biosimilar generic companies to grab revenue from the same piece of pie.²

Ultimately, product protection is currently seen as the government effort in balancing between rewarding innovation and providing affordable healthcare, in the specific context of pharmaceutical industry. Apart from being profitable, in the current time brand image of being humane and consumer-friendly is important to gain favor from consumers, unless if there is no alternative.

² Stephen Barlas, *President Obama Reopens Debate On Patented Biologics*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3086118/>

2. Strategic Management

The biopharmaceutical industry is a rapidly growing industry with immunology being central in our study. The pressure from expiring patents and exclusivity and from biosimilar generic companies trying to jump into the expired patents bandwagon push companies like AbbVie to come up with strategic management especially in the area of intellectual properties. Several strategic management methods will be utilized in this study to come up with recommendations.

2.1. SWOT Analysis

Strengths

- AbbVie is the first into the Adalimumab market.³
- AbbVie holds the core patent family for Adalimumab and huge patent portfolio of 126 patents potentially extending the protection for the product.
- Brand name “Humira” as Adalimumab leading the immunology market.⁴
- Adalimumab is an immunology biologic with human source.⁵
- Having strong R&D, AbbVie can look into developing other monoclonal antibodies from human source from its strong Adalimumab expertise.
- AbbVie can also look into developing other monoclonal antibodies from non-human source in order to complement its existing blockbuster products.

Weaknesses

- Adalimumab’s core composition patent is expiring in 2016.⁶
- AbbVie relies heavily on Humira alone for its immunology market segment.⁷
- AbbVie does not have other product in its present portfolio that may complement or support Humira.⁸

³ Philip J Mease, *Adalimumab in the treatment of arthritis*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1936294/>

⁴ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 38

⁵ Philip J Mease, *Adalimumab in the treatment of arthritis*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1936294/>

⁶ Peter Norman, *Humira: the impending patent battles over adalimumab biosimilars*, 141

⁷ Richard Gonzales, *AbbVie Long-Term Strategy*, 9

Opportunities

- With the likely favorable outcome from the dispute with Amgen, AbbVie can make the victory as showcase to other pharma and block entrance into Adalimumab market.
- AbbVie can look into getting into biosimilar business in order to complement its existing blockbuster products, while at the same time expanding its market share in the biologics sector.
- Rheumatoid Arthritis patients are growing at incidence level of 41 per 100,000 persons per year.⁹
- Crohn's Disease patients are growing at incidence level of 3.1-14.6 per 100,000 persons per year.¹⁰
- As of 2015, Humira holds 29.4% of anti-rheumatics market. With the correct strategy, AbbVie can improve this market capitalization for immunology market in the future.¹¹

Threats

- Cadila's Exemptia, which is an Adalimumab's Biosimilar, was launched in 2014 in India with price one fifth that of Humira.¹²
- Pfizer's Torrent's Adfrar, which is an Adalimumab's Biosimilar, was launched in 2016 in India also with price one fifth that of Humira.¹³
- Amgen's Amjevita, which is an Adalimumab's Biosimilar, has been approved as Humira's Biosimilar by FDA in September 2016.¹⁴

⁸ Ibid.

⁹ Myasoedova E, Crowson CS, Kremers HM, Therneau TM, and Gabriel SE, *Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007*, <http://www.cdc.gov/arthritis/basics/rheumatoid.htm>

¹⁰ Loftus EV Jr, *Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences*, <http://www.cdc.gov/ibd/ibd-epidemiology.htm>

¹¹ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 38

¹² Zeba Siddiqui, *India's Cadila launches first cheaper copy of world's top-selling drug*, 09 December 2014, <http://www.reuters.com/article/2014/12/09/us-cadila-health-humira-india-idUSKBN0JN0X820141209>

¹³ Torrent Pharmaceuticals, *Torrent Pharma Forays Into Super Specialty Segment and Launches Adfrar – Biosimilar Adalimumab*, 12 January 2016, <http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=618431>

¹⁴ FDA, *FDA approves Amjevita, a biosimilar to Humira*, 23 September 2016, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm>

- Samsung Bioepis and Biogen are collaborating to come up with another Adalimumab's Biosimilar, i.e. SB-5, which has been filed with FDA for approval.¹⁵
- Novartis's Sandoz, Coherus and many other biopharmaceutical companies are in the process of developing Adalimumab's Biosimilar generic products.¹⁶
- Eli Lilly and Incyte are developing "Baricitinib", a non-biologic drugs targeting Janus Kinase (JAK1 and JAK2), currently undergoing clinical trial and showing great promise, potentially better results than those of Humira.¹⁷
- Biologics' price generally gets eroded by about 33% upon exclusivity expiry and Biosimilar's entrance into the market. Examples of Biologics with Biosimilars available in the market are Janssen's Remicade and Amgen's Enbrel.¹⁸
- Global socioeconomics of the current time can be a threat to Biologic incumbent such as Humira. With global recession in many countries, reduction in prescription drugs expenditure can be seen as solution to many governments, potentially by subsidizing less expensive drugs version and thereby making generic and biosimilar drugs the preferred choice.¹⁹

¹⁵ Peter Norman, *Humira: the impending patent battles over adalimumab biosimilars*, 142

¹⁶ Ibid.

¹⁷ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 38

¹⁸ Ibid., 6

¹⁹ Bruno Calo-Fernández and Juan Leonardo Martínez-Hurtado, *Biosimilars: Company Strategies to Capture Value from the Biologics Market*, 1399

2.2. Porter's Forces Analysis

Porter's Forces analysis helps to expand "Threats" into greater details to help identify the defensive and aggressive business models recommended for AbbVie. External factors that may affect the market of Humira are evaluated in terms of "Low", "Medium", and "High".

Existing Competitors

Intensity : **MEDIUM**

- Presently there is no competition in the US market.
- Cadila's "Exemptia" is selling in India for one fifth of Humira's price.²⁰
- Pfizer's Torrent's "Adfrar" is also selling in India also for one fifth of Humira's price.²¹

Substitutes

Threat : **MODERATE**

Substitutes in this context are only applicable for new users as incumbent patients generally have to continue the same drugs for treatment, usually lifetime.

- Humira entered the as a substitute for existing immunology biologic drugs at the moment, but it were considered as Biobetter since it was the very first fully human-source immunology biologic drugs.
- Johnson & Johnson's Janssen's "Remicade" (Infliximab), Chugai's and Roche's "Actemra" (Tocilizumab/Atlizumab), Amgen's "Enbrel" (Etanercept), UCB's "Cimzia" (Certolizumab Pegol), and Johnson & Johnson's Janssen's Simponi (Golimumab) are all immunology biologic drugs targeting Rheumatoid Arthritis, and many of them targeting Crohn's disease as well, and joint-, bowel-, and skin- related immunology diseases. All of them, apart from Actemra, are targeting TNF- α .

New Entrants

Threat : **HIGH**

²⁰ Zeba Siddiqui, *India's Cadila launches first cheaper copy of world's top-selling drug*, 09 December 2014, <http://www.reuters.com/article/2014/12/09/us-cadila-health-humira-india-idUSKBN0JN0X820141209>

²¹ Torrent Pharmaceuticals, *Torrent Pharma Forays Into Super Specialty Segment and Launches Adfrar – Biosimilar Adalimumab*, 12 January 2016, <http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=618431>

- Amgen's "Amjevita" has been approved by FDA for marketing from the perspective of BPCIA protection, but still under dispute from the perspective of Intellectual Property protection. Should Amgen be favored by the litigation court over AbbVie, there may be high risk of low cost producers like Cadila and Pfizer's Torrent to bring their Adalimumab's Biosimilar products into the US, first by getting approval from FDA, and then go into the market potentially dropping the market price.
- Samsung Bioepis's and Biogen's "SB-5" has been filed with FDA.²²
- Many other pharmaceutical companies are developing Adalimumab's Biosimilar drugs in Phase 3 clinical trial.²³
- Not-yet-approved Adalimumab's Biosimilar drugs are also waiting for the outcome of AbbVie-Amgen litigation dispute case. Should the outcome favors Amgen, there will be even more new entrants to grab a portion of the pie. However if otherwise, they may relook their investment in the development of Adalimumab's Biosimilar drugs.
- Incyte and Eli Lilly are developing "Baricitinib", an oral JAK1 and JAK2 inhibitor non-Biologic drugs, which shows more promising results than Humira based on its clinical trial. However this is a small-molecule drugs, instead of being Biopharmaceutical.²⁴

Complementors

Threat : **LOW / NON-EXISTENT**

- No complement.

Suppliers

Bargaining Power : **LOW**

- Humira requires several medical devices, such as syringe and pen, to administer to the patients. AbbVie currently subcontract the manufacturing of the medical devices to third-

²² Peter Norman, *Humira: the impending patent battles over adalimumab biosimilars*, 142

²³ Ibid.

²⁴ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 37

party contract manufacturers. The agreements between AbbVie and the subcontractors are exclusively binding.²⁵

- There are about 15 patents expiring between 2024 and 2032 that covers medical devices by AbbVie.²⁶

Customers

Bargaining Power : **HIGH**

- Insurance generally only covers in-country treatment, which means that outside the US substitutes are at the moment not yet a threat to Humira. However, should AbbVie-Amgen litigation dispute case outcome favors Amgen, there is a huge opportunity for foreign Adalimumab's Biosimilar drugs to enter the US immunology market, giving the US patients alternatives with much lower cost.
- In the countries where Humira is not protected, or where IP law enforcement is relatively weak, the patients would prefer to get Exemptia or Adfrar, a much cheaper alternative to Humira.

²⁵ AbbVie 2016 Annual Report, 7

²⁶ Richard Gonzales, *AbbVie Long-Term Strategy*, 14

3. Innovation Patterns and Life Cycle stages of Technology, Product and Organization

3.1. Defining Innovative Patterns of Pharmaceutical industry

The defining pattern of pharmaceutical industry is that it is intimately connected to the advances of the business sectors in biological science and the development of medical products to placate the challenging regulations of regulatory agencies. According to Pharmaceutical Research and Manufacturers of America (2007), unlike other, pharmaceutical inventions requires 13 to 15 years to develop and attain US Food and Drug Administration (FDA) approval. This ultimately means that the effective patent life cycle is around 7-10 years approximately²⁶ Development cost often run high for pharmaceutical inventions and it is necessary to have some forms of safety net from patent protections to recover the preliminary cost.

Since the dawn of the pharmaceutical industry, there have been high expectations that pharmaceutical industry will be able to provide solutions to incurable diseases, improve the productivity of pharmaceutical industry and generate a high return of investment comparable to other technology sectors.²⁷ While there have been significant examples, the overall pharmaceutical industry is still lacking behind other industries in term of generating new products as well as in term of financial performance²⁷²⁸ This is mainly due to the fact that higher developmental cost and the greater time spent doing research to succeed in each of the clinical phases before FDA approval is granted. The Pharmaceutical Research and Manufacturers of America (2007) estimated that it's takes about a billion dollars to generate a new drug and of every ten thousand compounds undergoing research by R&D departments of pharmaceutical companies, only one of them made it to FDA approval. Hence, it is imperative that pharmaceutical firms are eager to ensure that their innovations are well protected through intellectual property rights as well as to receive funding through the disclosure of the findings from their research.

3.2. Technology Life Cycle of Drugs and Value of Pharmaceutical Patents

The technology life cycle of most drugs follow through similar stages as shown in the flow chart below. Most drugs started with research and development stages in the laboratories which are often known as the discovery phases. Once a potential new and novel drug is identified, it is subjected to laboratory and

²⁷ <http://www.ipedr.com/vol14/3-ICIMS2011S00009.pdf>

²⁸ <http://www.nature.com/nbt/journal/v30/n10/full/nbt.2389.html?message-global=remove>

animal experiments to determine its pharmacological and toxicological effects of the potential drugⁱ. The next stage consists of 3 phases: Phase 1 trials include the testing of the pharmacokinetics of the drugs in healthy human volunteers. Phase 2 Trials include carrying out the drug on a limited number of patients to determine the suitable dosing and to check safety aspect on human. Phase 3 trials involved a large group of 1000-10000 patients to establish the efficacy of the drugs and to check for adverse events on human body. The data from phase 3 is especially critical and usually form the basis of the main evidences to the regulators for the approval to bring the drugs to the market. This approval phase may take up to 2 years.

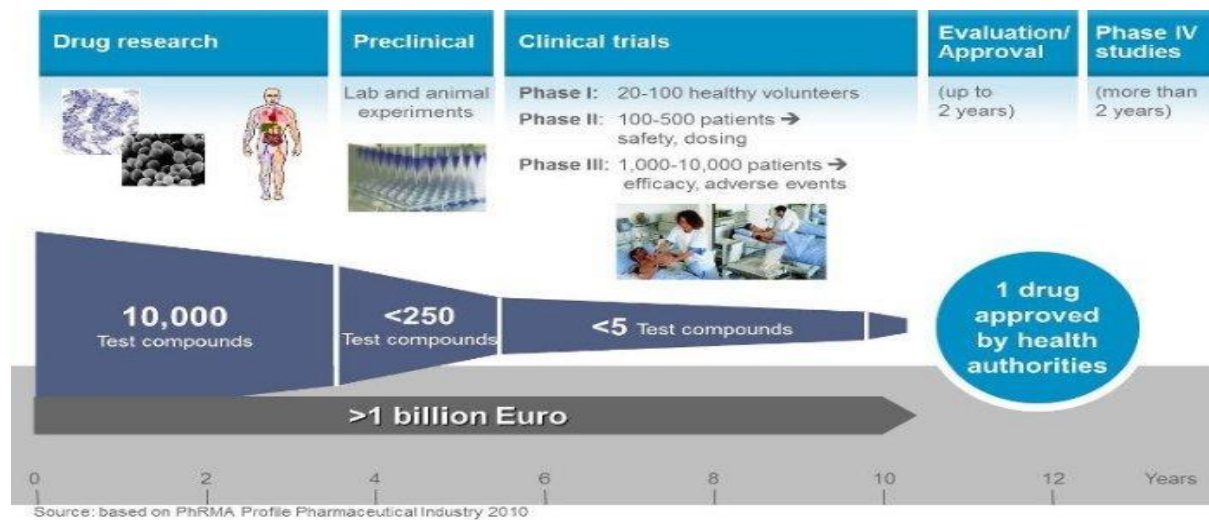


Figure 6: Typical Drug development timelines and success rates

The final phase usually is a post market study which is often denoted as Phase 4 trials. The purpose is to check for long term effects within a population.

Pharmaceuticals industry and its related products as well as its portfolios of patents appear to follow the technology life cycle of most products related to electronics or semiconductor industry. Below is an illustration of the value of pharmaceutical patents through the life cycle of a newly developed drug. An S-curve can be clearly observed from the value of patents from pharmaceutical industry with time. The value of pharmaceuticals patents increases slowly during their discovery phase and grow at a tremendous pace once they are approved for clinical trials. At this stage, nearly a decade had passed since the patents were first filed. Once the patents enter Phase 4, the growth in value becomes increasingly reduced till to the point where the patents are expired and the value of the patents become paltry. Consequently, the risk of using the newly developed drug dropped dramatically as the drugs passed each phase of the approval route. This phenomenon is very much parallel the technological S-

curve of many product industries but with a well-defined time-line that is characterized by the shelf life of the patents.

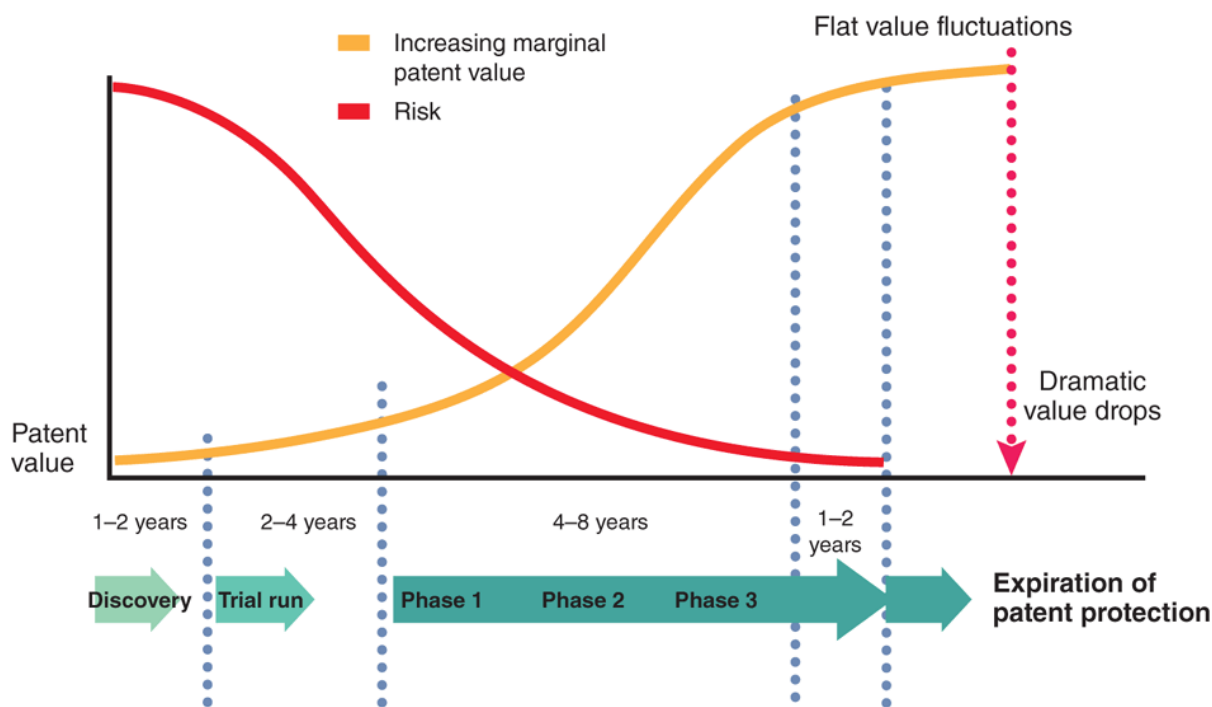


Figure 7: Pharmaceutical patent evaluation and licensing using a stochastic model and Monte Carlo simulations Liangchuan Wu & Lianghong Wu

Yet unlike the technological S-curve of most products, pharmaceutical companies will not be able to make monetary gains during the growth phase in patent values as FDA approval had not been granted. This left the pharmaceutical companies with very little time to commercialize and realize the value of their patents. To circumvent this situation, most pharmaceutical companies employed various methods or strategies to extend their original patent's effectiveness or exclusivity. Some of these methods or strategies include new method of usage for the drug such as when the drug is discovered to be able to cure some other diseases, new patents can be filed to extend the use. New formulation of the drug that boost patient compliance through optimizing the dosage or the ease of delivering the drug into human body can also be another excellent strategy. Other strategies include exploiting stereoselectivity to develop single enantiomers. Most active drug compounds are chiral in nature and can exist in at least 2 structural forms in which the spatial arrangements are mirror image of each other. These 2 compounds are enantiomers and are chemically identical with the exception for their molecular orientation. These single enantiomers version often have increased efficacy and very substantial reduction in side effects. Pharmaceutical companies can explore to develop the enantiomers versions and file patents for the

newly developed enantiomer versions, thereby extending the marketability of the core drugs. One example is Prilosec, an acid reflux drug whose patent expired in 2002 and the company AstraZeneca created an enantiomers version and market the new drug as Nexium²⁸²⁹. [3] This kind of strategy often created controversy, where there are critics who said AstraZeneca is trying to “evergreen” its original patent and aggressively marketing to customers that the Nexium is more effective than the original drug .

3.3. Discussion on the current Life cycle stage of Pharmaceutical Companies

Like most products, industries also go through life cycle stages. Most successful pharmaceutical companies employ a well-tested strategy of placing big bets on a few molecules, marketing them heavily and turning them into blockbusters and this had worked extremely well for many years. However, with declining R&D yield and greater competitions, the pharmaceutical companies are transiting into a new phase. Again, using technological S-curve as a reference, Pharmaceutical industry life cycle stages can be seen as starting out slowly like a relative straight line as companies commence acquiring consumers’ trust. As consumers start believing in them, companies will be able to commercialize their products and there is an extensive period of tremendous growth. Currently, with greater competition and stricter regulations, the pharmaceutical industry’s growth had begun to taper off. This is the stage where most pharmaceutical companies are currently at. The last stage is a period of low or zero growth, liken to the end stage of the S-curve, this is where alternative substitutes and cheaper drugs start to appear in the market.

Pharmaceutical companies understood the direction where the whole industry is heading to. With intense pressures from investors and the window of opportunity narrowing, there had been a wave of mergers and acquisitions in the pharmaceutical industry recently. Most pharmaceutical companies employ this method as a way to keep up with investors’ expectations and to merely survive in the face of the harsh completion. Table 4 illustrates a list of recent mergers and acquisitions of major pharmaceutical companies’ deal done in recent years:

S/N	Mergers and Acquisition deals	Value	Year
1	Teva-Allergan Generics	\$40.5bn	2015
2	Shire-Baxalta	\$32bn	2016

²⁹ <http://www.biopharminternational.com/strategies-extending-life-patents>

3	AbbVie-Pharmacyclics	\$21bn	2015
4	Pfizer-Hospira	\$17bn	2015
5	Valeant-Salix Pharmaceuticals	\$15.8bn	2015
6	Alexion Pharmaceuticals- Synageva BioPharma	\$8.4bn	2015
7	Endo International – Par Pharmaceuticals	\$8.1bn	2015
8	Celgene-Receptos,	\$7.2bn	2015
9	Mylan-Meda	\$7.2bn,	2016
10	Abbott-Alere	\$5.8bn	2016

Table 4: List of Recent Pharmaceutical Mergers and Acquisitions in terms of Values

Source: <http://blog.proclinical.com/top-mergers-and-acquisitions-pharmaceutical-industry>

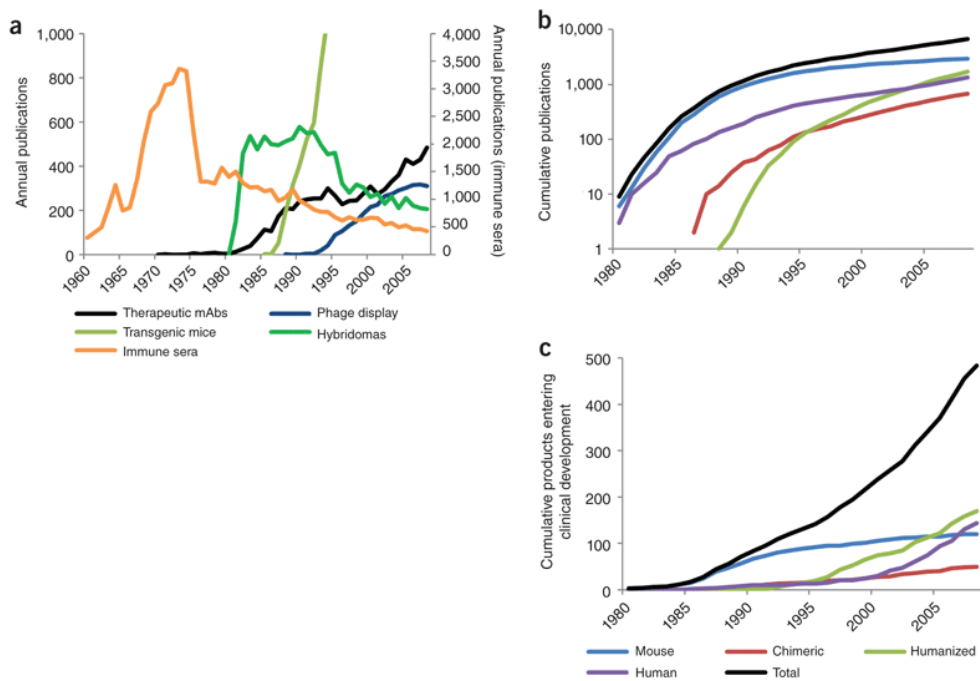
One other reason why the trend of mergers and acquisitions are ongoing is partly due to the expiry of the original patents as well as the motivation to acquire other companies' patents for business expansion. There had been a declining trends of blockbuster drugs being developed in recent years and the stricter regulatory control by governments had make it harder for pharmaceutical companies to gain approval for new drugs. Hence, once the blockbuster drugs' patents from the pharmaceutical companies expired, the drug loses exclusivity and waves of generic drugs will start to enter the market. Usually, generic drugs makers are able to prices their drug cheaper, thereby undercutting the original version's prices by a substantial amount as they usually do not required to go through the same protracted and expensive approval route or clinical trials. Hence, without the discovery of any blockbuster drugs in the pipeline, most big pharmaceutical companies tends to rely on acquisition to retain profitability.

Otherwise, revenue loss as a result of patent expiry can be very significant, one example is the case of Pfizer's Liptor and Celebrex where Pfizer is seen struggling to replace these blockbuster drugs once their patent expiry is due. Consequently, Pfizer tried to acquire U.K Based Asrazeneca which would provide Pfizer a strong oncology channel but the deal fail through and Pfizer had to continue to search for potential targets like Dublin based Actavis. Recently in Aug 2016, Pfizer managed to buy part of

Astrazeneca antibodies business for up to \$1.575 billion that the company said would boost the stable of older products it sells of which some of them had last patent protection³⁰.

3.4. Technology Lifecycle of Monoclonal Antibodies (mAbs)

As science advances into new frontiers, medicine is also progressing towards an era of personalized therapy and targeted cell treatment. The emergence of monoclonal antibody treatment is an essential constituent towards realizing this intent. A monoclonal antibody is a highly specific antibody which is derived from a line of specialized cells and which recognizes only one specific complimentary antigen. In recent years, there have been increasing publications of monoclonal antibodies with regards to other pharmaceutical products such as cell therapy, gene therapy or vaccines. Since monoclonal antibody was first licensed for clinical use more than 30 years ago, the industry has grown exponentially and is worth billions of dollars today.



(a) Annual publications for MATs and precursor technologies. (b) Cumulative publications of ordinal technologies in MATs on PubMed. Note that the early appearance of publications on human mAbs is due to early attempts to produce human mAbs from human hybridomas. The sum of mAb publications (total) is included because the basic product that is delivered as a therapeutic is unchanged. (c) Cumulative clinical trials of ordinal technologies in MATs.

Figure 8: Publications of monoclonal antibody research

http://www.nature.com/nbt/journal/v30/n10/fig_tab/nbt.2389_F4.html

³⁰ <http://www.wsj.com/articles/astrazeneca-sells-part-of-antibiotics-business-to-pfizer-for-up-to-1-575-billion-1472021239>

From the publications of monoclonal antibodies researches and the precursor technologies, one can see that there have been an increasing numbers of such publications over the years. There was a major increase in the number of publications, increasing exponentially during the 1980s and the early 1990s. While human mAbs publications did not results in as many products entering clinical developments during the late 1990s and early 2000s time frame, there has been a large increase from 2005 onwards. This is likely due to the failure of early attempts to develop human mAbs as human hybridomas did not provide sufficient amount of mAbs. Instead, chimeric and humanized mAbs took earlier stage with the aid of recombinant DNA technology. It is only after the arrival of the phage display technology, that large scale manufacturing of human antibodies managed to thrive.

3.5. Patterns of technological innovations in monoclonal Antibodies (mAbs) and mAbs patents

Monoclonal Antibodies can be seen as a major disruption to the pharmaceutical industry as the diminished immunogenicity of humanized and human mAbs enables them to treat chronic disease in addition to the acute diseases market that they initially targeted. These innovations require different administration conventions, as well as new metrics of safety and efficacy, pricing models and distribution channels commensurate with the management of chronic rather than acute disease³¹ [4]. Monoclonal Antibodies' inclination to be highly efficacious and have less side effects than other form of treatment have lead this class of drugs to become the fastest growing biologics. (Biologics is a term to describe genetically-engineered proteins derived from human gene and with high specification to inhibit response of the human immune system). In 2008 alone, the top 5 mAbs generated almost 20 billion dollars in sales and in 2012, the number had increased 3 folds and just one antibody, Humira, alone generated almost 20 billion dollars in sales³²

However, despite monoclonal antibody seemingly huge potentials, patients are limited to their access because of the high cost. Even in developed countries where medical fees are usually covered by national insurance or other healthcare plans, the use of mAbs is posing an escalating burden on national health budgets. Nevertheless, these circumstances are set to change in the coming years as the original monoclonal antibody patents are due for expiry. This provided opportunity for other manufacturers to manufacture generic version of mAbs or biosimilar drugs which can be substantially cheaper to manufacture due to lower research and development (R&D) costs and therefore allow patients to have greater access to them.

Original mAbs manufacturers will have to reinvent their patent strategies to deal with the upcoming situation. The later part of this paper will discuss and describe the various strategies that these manufacturers can employ to outmaneuver the limitations of patents protections. The fact that huge amount of investment is required to bring monoclonal antibodies to the market is sufficient reason that a comprehensive patent strategy is necessary against generic or biosimilar drugs in the market.

In this respect, it is necessary to note that there are complexity and controversy with regards to monoclonal antibodies patents. In 2008 Written Description Training Materials provided by the USPTO,

³¹ Scott, C.T. Nat. Biotechnol. 23, 1037–1039 (2005).

³² <https://www.fenwick.com/FenwickDocuments/Monoclonal-Antibody.pdf>

state that a claim reciting an isolated antibody capable of binding to protein X is adequately described when the specification fully characterizes protein X, even if there are no working examples of actual antibodies that bind protein X³²³³. [7]ⁱⁱ The traditional understanding to this statement is that anyone in possession of an antigen and can fully characterize the structure can claim any antibody to it. The Noelle Case in which Noelle is in litigation with Lederman seem to affirm the understanding of this description. In 2009, when Centocor sue Abbot for infringement of its patents with regards to TNF- α , the United States Supreme Courts rule in favor of Centocor. However 2 years later, the United States Court of Appeal for the Federal Circuit overturned the judgement citing that TNF- α is not a novel antigen and has been known to science for many years. This decision began to raise apprehension among some of the monoclonal antibodies patent owners who had previously granted patents right under the previous understanding of the written description training materials on the validity of their patents. Hence, greater understanding of the patent law and its aspects and coverage is also a crucial part to ensure that monclonal antibody patents litigation goes in the company's favors.

³³ <https://www.uspto.gov/sites/default/files/web/menu/written.pdf>

4. Patent Portfolio Analysis

Analyses of Patent portfolios are useful tools to evaluate both business opportunities and the R&D landscape and trajectory and have been used in the analysis of the landscape of Adalimumab. We have split our analysis into the following segments:

- Data collection and Identification of relevant patents
- Analysis of the patent portfolio by Technology and Function
- Summary of overall patent portfolio

4.1. Data Collection and Identification of Relevant Patent

As the main market of analysis was the USA, it was searched mainly the US patent databases. Our search stream was based on the original base composition patent that expires in 2016. We performed a forward citation on the base patent, followed by a forward and backward citation analysis of the top 10 patents by relative citation strength. Analysis was performed using both the IPTech and Orbit software.

Through the defined patent search streams, it was identified and organized into 158 relevant patents, including all of the disputed patents mentioned in the case of AbbVie vs Amgen. In the landscape of Adalimumab, AbbVie is leading the game with 126 patents with a Relative R&D capability score of 100%. This is seen in their high rate of self-citings and inventor count, indicating the development of the technology within the company. (Table 5).

Applicant	Patents	Others Citings	Self-citings	Inventor Count	Relative R&D capabilities
ABBVIE, INC	126	55	2837	193	100%
GENENTECH, INC.	4	254	1	16	14%
Centocor, Inc.	5	167	5	17	10%
New York University	4	98	5	12	6%
GE HEALTHCARE BIOPROCESS	2	76	0	8	4%
AVENTIS PHARMA S.A.	1	18	0	3	1%
ELCAM MEDICAL AGRICULTURAL COOPERATIVE ASSOCIATION LTD.	2	1	0	9	1%
Amgen Fremont Inc.	1	0	0	17	1%
ANUTRA MEDICAL, INC.	1	0	0	4	0%
VENTURE LENDING & LEASING VII, INC.	2	1	1	4	0%

Table 5: Adalimumab Patent Landscape

4.2. Analysis of the Patent Portfolio by Technology and Function

It was analyzed that AbbVie's patent portfolio by technology and function, utilizing the technological aspects of the patent to correlate the business functions of the product.

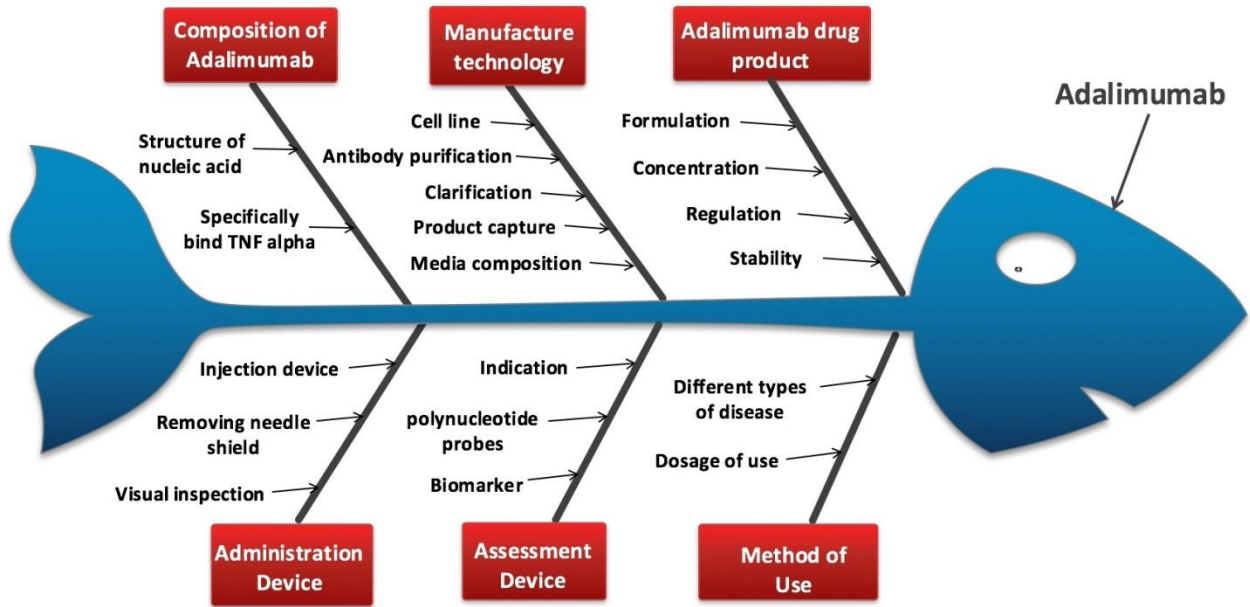


Figure 9: Technology Fishbone Diagram

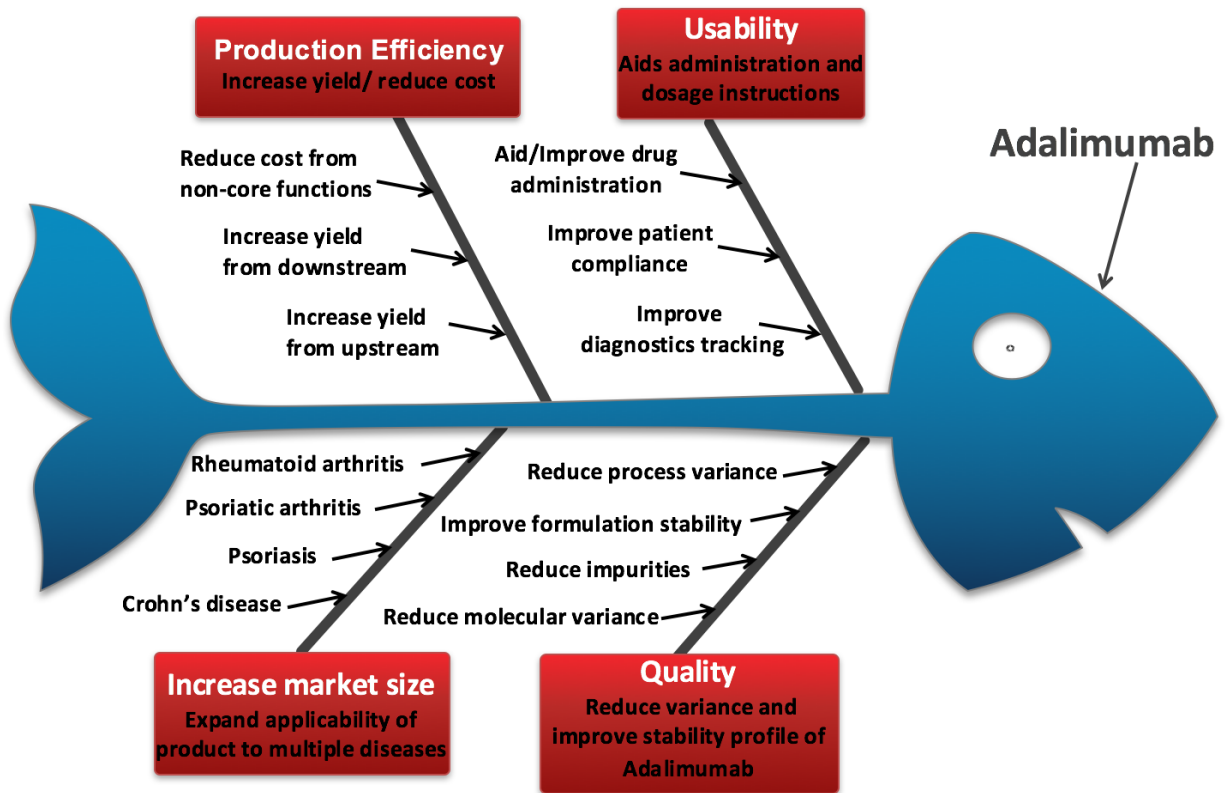


Figure 10: Function Fishbone Diagram

The patent portfolio (126 patents) of **AbbVie** is represented according to their technology and function in the Tech-Function matrix (Table 6)

Tech Function	Base Composition	Manufacturing Technology	Device for Assessment	Device for Administration	Product Formulation	Method (Dosage & Application)
Production Efficiency	8	42			4	
Usability	6	3	15	22	27	36
Increase Market Size (other diseases)	4	1	6	9	9	19
Quality (efficacy)	8	46	5	3	21	

Table 6: Adalimumab Tech-Function Matrix

Note: One patent number is not restricted to 1 technology and 1 function as it could contribute more than one technology and one function.

The four main functions and six technological aspects of the patents are described below.

Function

1. **Production Efficiency** - Patents that improve the manufacturing process of adalimumab. This ranges from the upstream cell culture processes, to the downstream purification and fill finish of the drug. As the manufacture of a single batch of product is extremely costly, any efficiency gains greatly affect the cost to market of the product.
2. **Usability** - Patents that improve the usability of the drug. This comes in the form of improved formulations and methods of delivery that empowers the patient to take charge of their own therapy. Ultimately, this results in improved patient compliance to the dosing regimens/timings which results in better health outcomes.
3. **Increase Market Size (other diseases)** - Patents that increase the market size by expanding the drug indications. The Kefauver-Harris Amendment mandates that FDA - approved drugs must have evidence that they are effective in treating a specified disease/indication. As a result, the FDA only approves new medications that have been shown to be safe and effective for specific indications.
4. **Quality** - Patents that improve the quality of the drug by reducing variation and ensuring the consistent delivery of medicines to the patient. Biologics inherently have a lot of variability in their structure which affects the potency and efficacy of the drug when delivered to a patient. As a result, a significant amount of innovation is required to assess and maintain the quality of the product in an inherently variable process.

Technology

1. **Base Composition** - The base composition of a Biologic forms the key patent of any biopharmaceutical filing. The patents are often the 1st patents to be filed regarding the drugs and detail the structure of the molecule together with the in-vitro and in-vivo pharmacological actions. These are the patents that are often referred to when companies say the drug is going off patent.
2. **Manufacturing Technology** – These patents comprise of technology used in the manufacture of biopharmaceuticals. As the manufacturing process is often extremely complex, significant amounts of innovation is required to develop technology to

effectively bring the product from a small laboratory scale to mass industrial production.

3. **Product Formulation** – Product Formulation patents detail the composition of the base drug, its excipients and any adjuvants that make up the whole drug product delivered to the patient. The formulation can affect the stability and route of administration of the drug to the patient.
4. **Device for Administration** - Administration device patents detail the various engineering aspects of the device used in delivering the drug to the patient. As the route of administration of a drug differs, the devices used to introduce the drug into the patient are also important.
5. **Device for Assessment** - These patents comprise of technology used in the assessment of a patient condition as well as the product. The process of evaluating a patient condition after the administration of a drug is very complex. As such, significant amounts of innovation are required to develop technology to effectively assess the patient.
6. **Method (Dosage & Application)** – Dosing protocols are complex and require the integration of multiple aspects of treatment including pharmacokinetics, pharmacodynamics, patient preferences and technological limitations. These protocols often represent the work of multiple clinical trials and analysis.

Base Composition

Of 126 patents in AbbVie's portfolio, 18 patents are regarding the Base Composition of the drug. (see table xxx). We have ranked the top 10 patents by citation count with the most cited patent being the principal patent in the pool of "Base Composition".

SN	PN	Citing count in U.S.	Title	Function
		Total Citings		
1	06090382	235	Human antibodies that bind human TNF.alpha.	Production efficiency /Usability
2	06258562	200	Human antibodies that bind human TNF.alpha.	Production efficiency /Quality
3	06509015	155	Human antibodies that bind human TNFa	Usability/Increase market size

Table 7: Key Patents (Base Composition)

The principal patent in the "Base Composition" pool is **US6090382** (henceforth referred to as the '382 patent) with a total citing of 235 and can be considered as the core patent of "Adalimumab".

Furthermore, 8/9 of the other patents are extensions of the '382 patent, each focusing on various functional aspects of the technology. This illustrates the importance of the base composition technological aspect; despite being a small subset of the patent portfolio, the technology is able to cover all functions of the drug.

The Main IPC – trend should be taken into consideration in order to determine how technology is evolving in the base composition aspects.

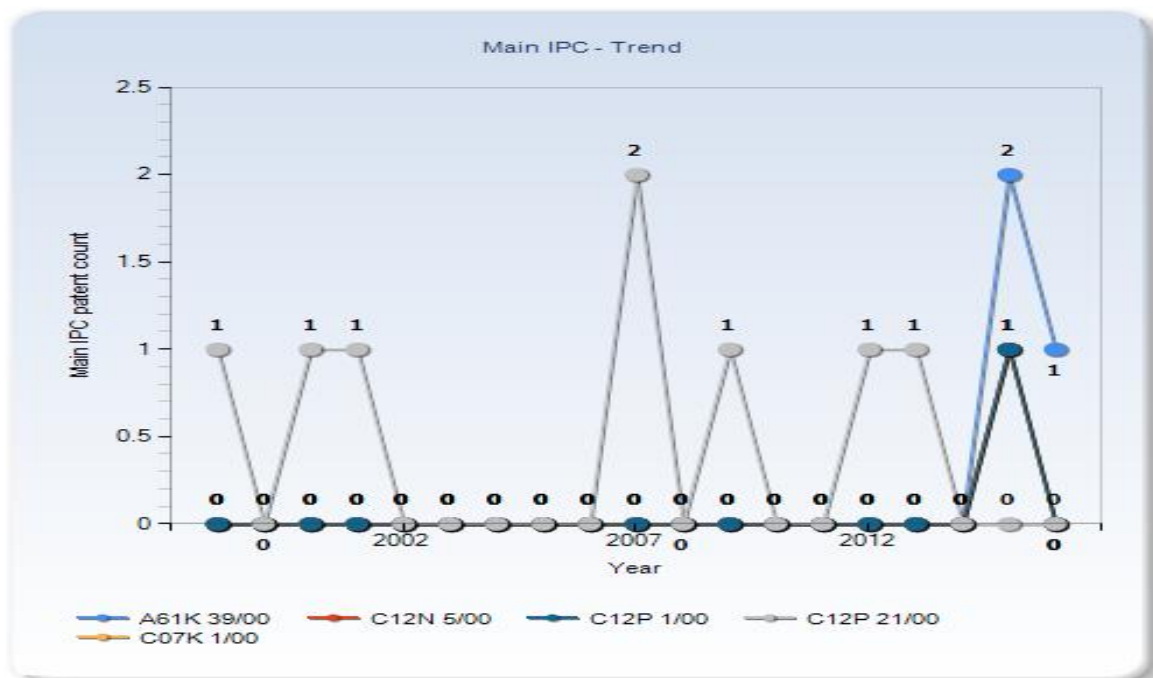


Figure 12: Main IPC trend (Base Composition)

It is interesting to note that from 1998 to 2014, all patents published are concerned with IPC **C12P 21/00** (Preparation of peptides or proteins). Whereas in 2015 and 2016, 6 patents related to the following IPCs were published:

1. **A61K 39/00** (Medicinal Preparations containing antigens or antibodies),
2. **C07K 1/100** (General Processes for the preparation of peptides),
3. **C12N 5/00** (Undifferentiated human, animal or plant cells, eg. Cell lines, Tissues, Cultivation or maintenance thereof; Culture media therefor),
4. **C12P 1/00** (Preparation of compounds or compositions).

This demonstrates an effort by AbbVie to supplement the core patents by developing different functions and improvements to existing core technologies.

Manufacturing Technology

There are total 42 Patent of AbbVie tagged to the manufacturing technological aspect.

It is interesting to note that 4 of the Patents of Manufacturing Technology are involved in lawsuit between Abbvie and Amgen.

SN	PN	Title	1st Application Date	Legal Status
1	US8663945	Methods of Producing Anti-TNF-Alpha Antibodies in Mammalian Cell Culture	2007-09-13	Expiration Date 2027-09-13 ACTIVE
2	US8911964	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	2014-03-26	Expiration Date 2034-09-13 ACTIVE
3	US9359434	Cell Culture Methods to Reduce Acidic Species	2013-03-14	Expiration Date 2033-03-14 ACTIVE
4	US9365645	Methods for controlling the galactosylation profile of recombinantly-expressed proteins	2012-04-26	Expiration Date 2032-04-26 ACTIVE

Table 8: Key Patents by legal interest (Manufacturing Technology)

Within the pool of Manufacturing Technology related Patent, US7863426 is the leading patent with most cited number 31. The patent is cited 113 total citing in U.S.

These patents are process patents which focus on the production efficiency or quality of the product, improving the Cost of goods or reducing the variation of the manufacturing process; critical elements in the manufacture of biologics.

SN	Rank	PN	Patents Citing	Title	Function
1	1	US7863426	113	Antibody Purification	Production efficiency
2	3	US8436149	51	Crystalline anti-hTNF alpha antibodies	Production efficiency
3	2	US8231876	60	Purified antibody composition	Production efficiency/ Quality

Table 9: Key Patents by Citation Strength (Manufacturing Technology)

The top main IPC classification shall be observed from the patents of AbbVie's manufacturing technology segment so that the technological connectivity can be observed here. It is seen that A61K 39/00 is leading in main IPC classification.

Main IPC	Main IPC patent count	Patents	Share
A61K 39/00 (Medical Preparation containing antigens or antibodies)	15	15	44.12%
C12P 21/00 (Preparation of peptides or proteins)	8	8	23.53%
C07K 16/00 (Immunoglobulins, e.g. monoclonal or polyclonal antibodies)	5	5	14.71%
C07K 1/00 (General processes for the preparation of peptides)	3	3	8.82%
C12N 5/00 (Undifferentiated human, animal or plant cells, e.g. cell lines ; Tissues; Cultivation or maintenance thereof; Culture media therefor)	3	3	8.82%
Total	34	34	100%

Table 10: Main IPC classifications

It is interesting that the leading IPC A61K 39/00 has started publishing from only 2014 to 2016. Therefore, medical preparation containing antigens or antibodies becomes the essential part for Manufacturing Technology.

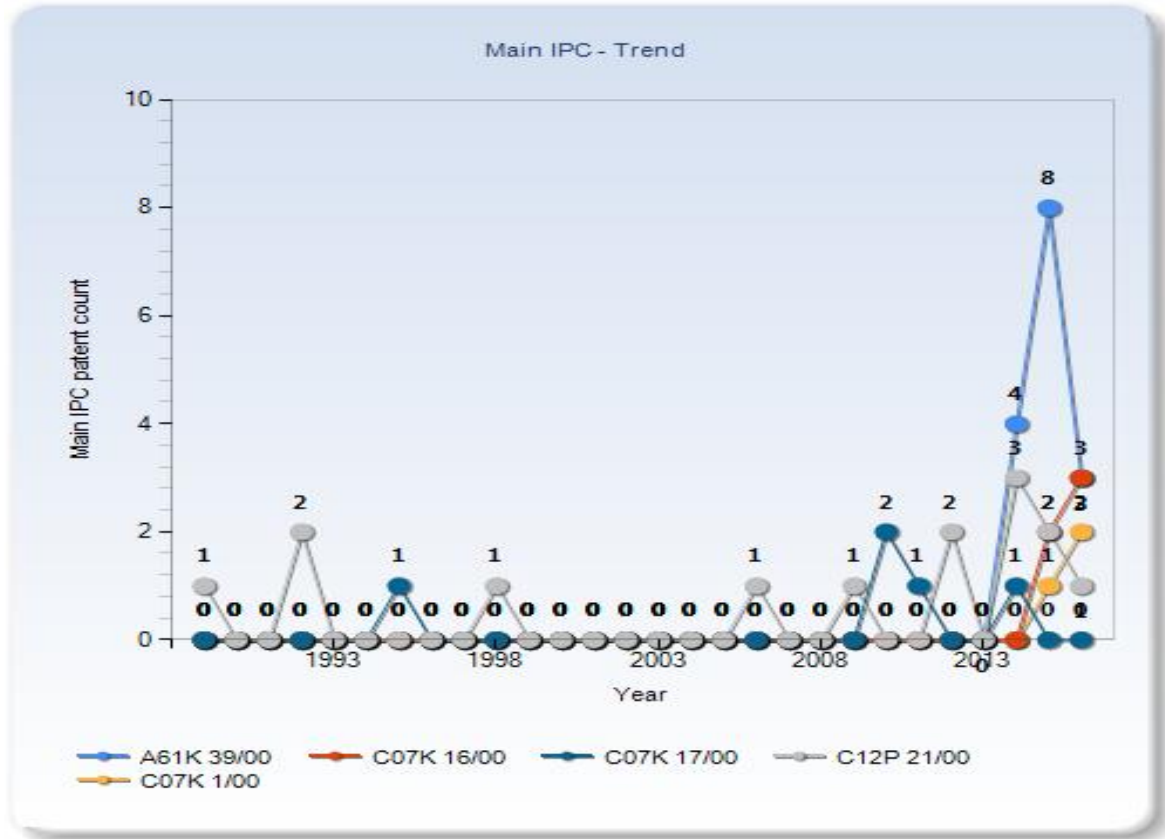


Figure 13: Main IPC trend (Manufacturing Technology)

Product Formulation

Product Formulation is an essential component of any biologic and plays an essential role in the life cycle of any Biologics patent protection strategy. Formulation patents are particularly effective at extending exclusivity of the product. Effective patent life-cycle management requires careful attention to the timing of filings and the content of the application.

SN	PN	Title	1st Application Date	Legal Status
1	US8916157	Formulation of Human Antibodies for Treating TNF- α Associated Disorders	2002-08-16	Expiration Date 2026-05-16 ACTIVE
2	US9220781	Formulation of Human Antibodies for Treating TNF- α Associated Disorders	2002-08-16	Expiration Date 2022-08-16 ACTIVE
3	US9220781	Formulation of Human Antibodies for Treating TNF- α Associated Disorders	2002-08-16	Expiration Date 2022-08-16 ACTIVE
4	US9096666	Purified Antibody Composition	2007-04-04	Expiration Date 2022-04-04 ACTIVE

Table 11: Key Patents by legal interest (Product Formulation)

There are total 39 Patent of AbbVie tagged to the Product formulation aspect. Within the pool, US07588761 is the leading patent with total citing of 113. Similar to the base composition, the formulation component spans across all functions of the patents, illustrating the importance of the Product formulation in the patent portfolio.

SN	PN	Citing count in U.S.	Title	Function
		Total Citing		
1	US7588761	113	Human antibodies that bind human TNF α	Usability/ increase market size
2	US8372401	54	Human antibodies that bind human TNF α	Usability
3	US8436149	51	Crystalline anti-hTNF α antibodies	Production efficiency/ Quality

Table 12: Key Patents by citation strength (Production Formulation)

Additionally, as biopharmaceutical can have different formulations developed at different stages of the product lifecycle, we have observed the filing timings of AbbVie’s formulation patents to evaluate their patent life-cycle management,

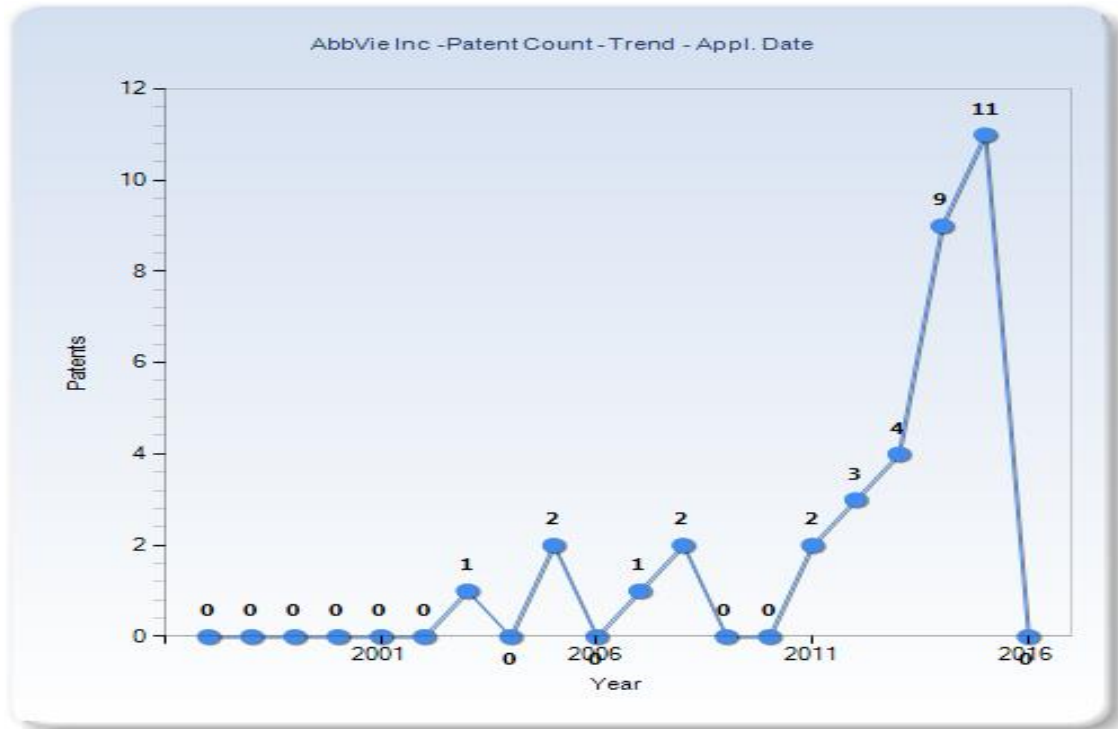


Figure 14: Patent Count trend (Product Formulation)

It is observed that during 2011-2015 is the most active filing period as the base patent is expiring in 2016. We consider this to be part of AbbVie’s fencing strategy against other potential competitors.

Device for Administration

As drug administration is a key component of pharmacological treatment which has a significant impact on patient outcomes. Given the nature of biopharmaceuticals, the devices for administration have to be specific, accurate and robust, delivering an exact amount of drug into the patient every single time. Moreover, given the nature of the formulation, each device has to be calibrated to the drug substance.

The technology contained within these patents, alongside the base composition and formulation patents, ultimately constitute the product being delivered to the patient and hence are important to any pharmaceutical patent portfolio.

SN	PN	Citing count in U.S.		Title	Function
		Total Citing			
1	US8162887	13		Automatic injection devices	Usability, Quality
2	US8636704	11		Automatic injection device	Usability, Market Size
3	US8668670	2		Automatic injection devices	Usability
4	US8679061	12		Automatic injection device	Usability, Market size

Table 13: Key Patent by citation strength (Administration Devices)

Previously, Humira was administered in prefilled syringes, the creation of the injection pen device solved a number of problems like fear of injections/needles and resulted in patients getting optimal doses, with the added benefit of patients liking the product more, thereby increasing the uptake of these devices³⁴. However, as such devices do not constitute the core product that AbbVie was trying to deliver, comparatively less resources were invested into this area, which resulted in less patents being filed.

³⁴ <https://www.ncbi.nlm.nih.gov/pubmed/17359217>



Figure 15: Patent Count trend (Administration Devices)

The very first device patent was published in 2012 while most other patents for devices are published in 2014-2016. The first patent of device administration is also the most cited patent in the US.

Device for Assessment

The patents related to device for assessment could help usability and market share as the product efficiency could be monitored. Patents related to Device for Assessment (AbbVie) are shown as below.

Patent No.	Citing Count in US	Forward Citation	Title	Function
US9405884	0	0	Methods and systems for the analysis of protein samples	Quality
US9399061	0	0	Methods for determining efficacy of TNF-alpha inhibitors for treatment of rheumatoid arthritis	Usability, Market Size
US9170262	0	0	Comparison of Protein Samples	Quality
US8414894	5	51	Human antibodies that bind human TNF α and methods of using same	Quality, Usability,
US7919264	67	98	Methods and compositions for determining the efficacy of a treatment for ankylosing spondylitis using biomarkers	Usability, Market Size

Table 14: Key Patents by citation strength (Assessment Devices)

US7919264 patent is the leading patent in terms of forward citation. It is forward cited by 98 patents of AbbVie.

Method (Dosage & Application)

The patents of Method (Dosage & Application) are also important aspects of Adalimumab drug, extending the approved indications and applications, allowing it to expand its market share. They are directed at compositions of products treating specific diseases. In terms of business connectivity, more diseases can be cured, the more market revenues.

There are total of 35 patents owned by AbbVie in this area. Taken a closer look at citation strength, it is found that **US06509015** (Human antibodies that bind human TNF α) is the leading patent in its field.

In terms of patent litigation, two patents for Method (Dosage & Application) are under dispute between Abbvie and Amgen.

SN	PN	Title	1st Application Date	Legal Status
1	US8889136	Multiple-Variable Dose Regimen for Treating TNF α -Related Disorders	2005-04-08	Expiration Date 2025-04-11 ACTIVE
2	US8986693	Use of TNF α Inhibitor for Treatment of Psoriasis	2014-10-09	Expiration Date 2026-05-16 ACTIVE

Table 15: Key Patents by legal interest (Method)

SN	PN	Citing count in U.S.	Title	Function
		Total Citings		
1	US6509015	155	Human antibodies that bind human TNF α	Usability, Market Size
2	US7541031	114	Methods for treating rheumatoid arthritis using human antibodies that bind human TNF α	Usability, Market Size
3	US7588761	113	Human antibodies that bind human TNF α	Usability, Market Size

Table 16: Key Patents by Citation Strength (Method)

It is observed that **US06509015** belongs to the family of Adalimumab core patent **WO9729131**, published in 1997. It can be considered improved version / extension of core patent. Furthermore, from the patent family, it contributes to development of patents for methods of treating disorders, which are published in 2012-2013.

In terms of timeline, the publication dates of patents for Methods (Dosage & Application) are concentrated in recent 2015. Therefore, it is the strategy of AbbVie to protect the core patents, which are expiring in 2016.

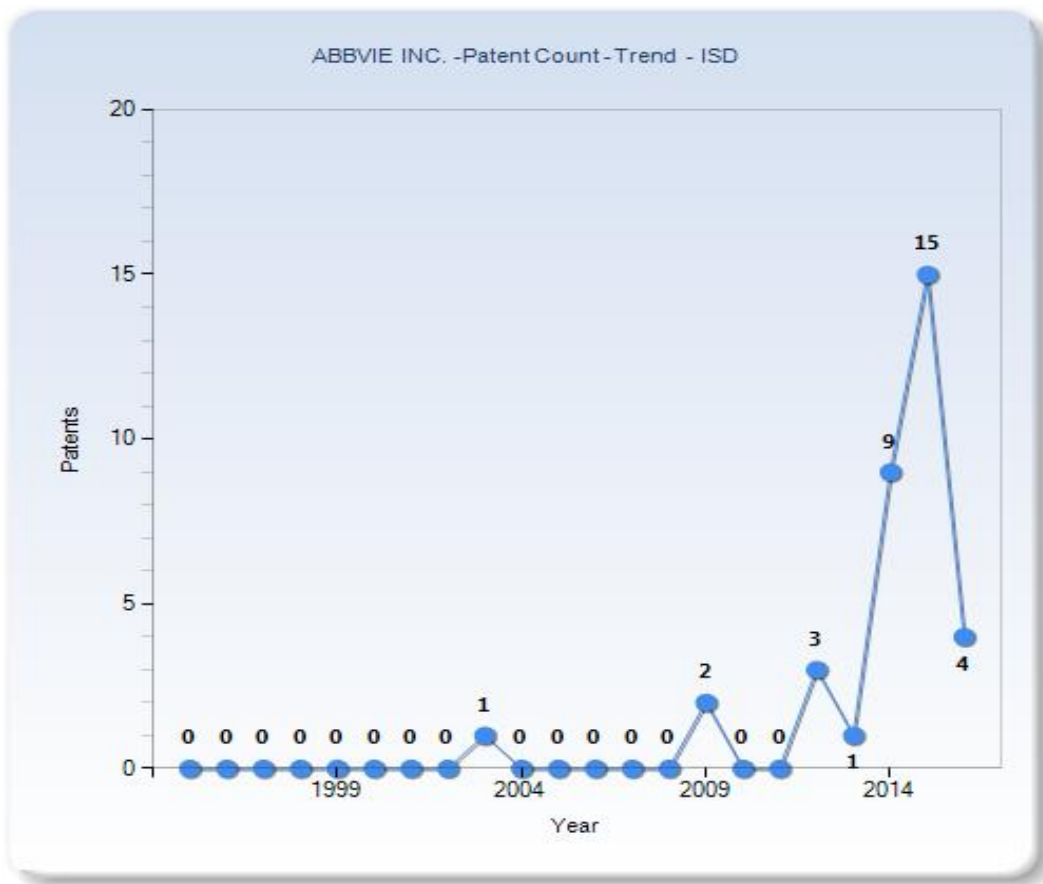


Figure 16 :Patent Count Trend (Method)

4.3. Summary of Patent Portfolio

It is no surprise that AbbVie is the undisputed leader of the patent portfolio surrounding Adalimumab. As its flagship product, AbbVie has made significant human and capital investments into Humira, resulting in a robust patent portfolio. However, as the key original patent is expiring, other companies have begun to move into the market, filing patents surrounding the other functions of the drug. <give examples>

A broad review of the patent portfolio suggests that the direction of the patents are moving towards increasing market size and improving quality by focusing on manufacturing technology, methods and usability. This is enabling AbbVie to extend the lifecycle of their product by preventing other entrants from manufacturing and marketing the product.

Additionally, we see a trend in filing dates, with more patents being filed as the original patent begins to expire. The manufacturing technology and production efficiency patents often represent tacit knowledge/trade secrets that are known during the initial smaller scale production of the product. As the original patent matures, this tacit knowledge is codified into a patent in order to extend the product lifecycle. This may represent a filing strategy of AbbVie.

In general, we find that AbbVie has used a combination of Patent Portfolio Deployment strategies, leveraging their patents via Ad-hoc insertions and pre-emptive fencing. While these strategies have enabled Humira to bring in over \$18Bn a year, it remains to be seen whether they are sufficient in keeping their monopoly control over the market. Already, the FDA has granted approval for a Biosimilar (Amjevita) by Amgen that would significantly erode AbbVie's market share. As mentioned earlier, though AbbVie has sued for patent infringement, the outcome of the case is still pending. <link to recommendations at the end of the report (our stand is that AbbVie will win the lawsuit with some concessions)>

On a longer term, as Humira is approaching the decline phase of its product lifecycle, it is imperative to develop new products to remain competitive in the biopharmaceutical industry. Biosimilars will continue to capture market share of the originators product

5. Technology Trajectory

This chapter will discuss the patterns of technical change in adalimumab as captured by the overall trend and patent citation networks. The logic behind this methodology is that patent documents can provide the best data available on R&D, and patent citations represent indicator of the prior knowledge underlying a specific inventive step. So, if a patent is cited very frequently, it should be regarded as 'technologically' important since it contains the knowledge which forms the basis for subsequent invention.

Since we have defined six technologies in this specific field, so in this part, first we will discuss the technology trajectory in whole adalimumab industry, then the discussion will be focus on the evolution in each technology.

5.1. Patent Count Trend

When study the technology trajectory, using application date as a reference is more convincing. However, there is a significant drop from 2015. The reason is that the USPTO started publishing patent applications 18 months after their earliest filing date from November 2000. So, to make the study of technical change more accurately, we will ignore that line segments which we made transparent.

From a technological viewpoint, S-curve is a regular pattern that characterizes the development and evolution of technologies. According to this model, a technology usually has a life cycle composed of initial adoption, growth, maturity and decline stages. We generate the patent count trend from IP tech, including 158 relevant patents. Then, we draw a curve to reflect the overall trend, according to previous life cycle analysis, we know the technology is approaching the tail end of its innovative cycle, but we still see a high number of applications these 2 years. The reason is that Abbvie has filed lots application around humira to extend its protection, this part will be discussed in patent portfolio session.

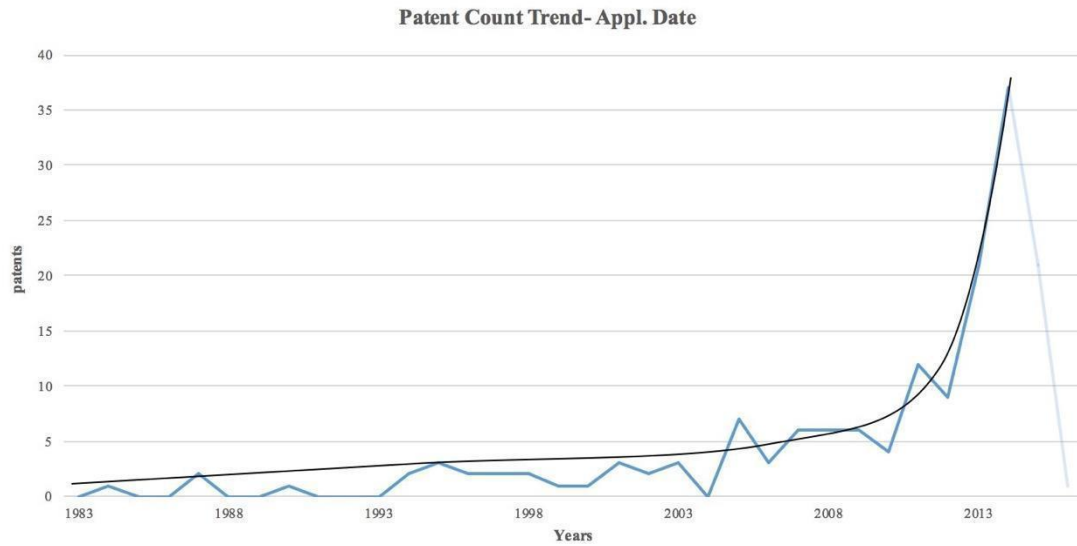


Figure 17: Patent Count Trend

5.2. The evolution pattern of adalimumab technology

We have identified several phases in the evolution of adalimumab technologies from figure 16. Each phase is associated to the introduction of a particular type of component as well as the dominance standard. We will discuss the stages in the general level in this subsection, then will focus on details of the evolution in each technology classification in next subsection.

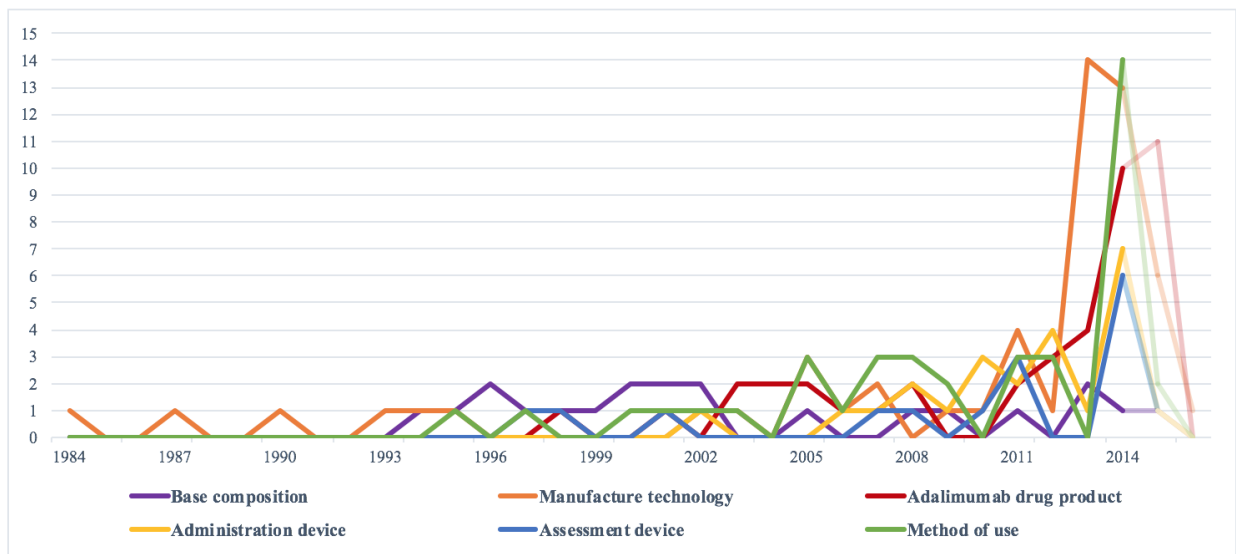


Figure 18: Evolution of technologies used in developing Adalimumab

The basic knowledge of developing adalimumab is how to provide a process for producing a heterologous multichain protein in a single host cell and how to purify the antibody. So during the initial phase from 1984 to 1993, patents are all about that basic biological experiments which belong to manufacture technology. The Second phase, from 1994 to 2007, is characterized by the appearance of first invention in each technology classifications, including the base composition of adalimumab, the first adalimumab drug product and the first administration device---preloaded syringes containing pharmaceutical compositions. Also, the Tumor necrosis factor antagonists are first used in suppressing transplantation immunity and in the treatment of autoimmune diseases. To be more specific, I will explain how the technology's focus shift. After equipped with basic manufacture technology, from 1996 to 2002, industry mainly worked on the base composition of humira; when they known the basic knowledge, their focus shifted to formulate humira drug products. Soon after, humira was used in treating disease. and Almost the same time, the administration device and assess efficiency devices had been developed.

The third phase from 2008 until 2013, witnessed the improvement of each technology. In this stage, the manufacture technology was focus on improving protein purification and crystallization method; Patents about base composition reached its peak and adalimumab has been used in different disease. The fourth phase from 2014 till now is characterized by the significant increase in each technology field except for basic composition. Specifically, Adalimumab can be used in eight diseases now and the manufacture methods had been diversity now.

5.3. The evolution of each technology.

In this section we will examine in detail of six technology category. The aim is to identify the main innovations that have marked the evolution. Normally, technology trajectory has strong relationship to dominant design, so we will define the dominant standard in each classification.

5.3.1. *Technology of Base composition*

The dominant patent in this field is a US patent (06090382) since it has been cited by almost all other patents in this technology field. The earliest patent (05705389) disclosed the structure of nucleic acid which can inhibit production of TNF α and subsequent patent (05795967) disclosed the TNF α antagonists. Dominant patent disclosed the dominant standard that Human antibodies should specifically bind to TNF α and can dissociation and neutralize TNF α activity.

According to the report in 2014 from Chinese Medicine Biotechnol¹, patent applications related to adalimumab composition reached its highest point in the 19th century and then entered a period of steady development. However, from the fig 5 we find that the number of application has been increased from 2012, that's because Abbive's original patent will be expired in 2016, so it had filed several other related patents to extend the patent production.

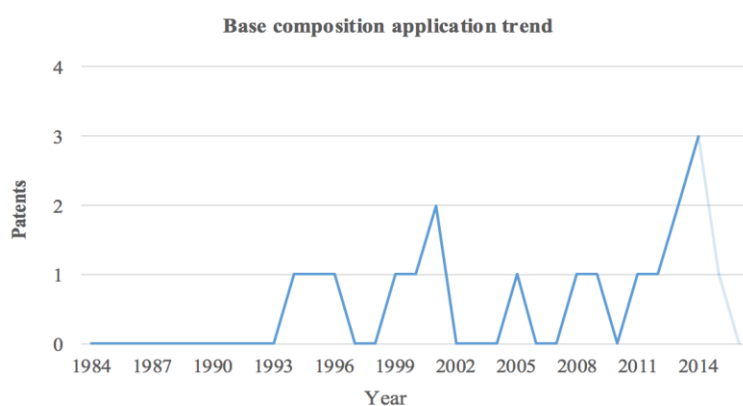


Figure 19: Application Trend of Base Composition

5.3.2. Manufacturing Technology

There are two main stages in this technology category. From 1984 to 2007, the majority of applications are antibody purification. In the beginning, patent used different pH environment to purify antibody. Then the dominant patent (07863426) disclosed using at least one Host Cell Protein which comprising an ion exchange separation step wherein the mixture is subjected to a first ion exchange material, followed by 32 patents in this category. Beginning from 2007, companies are trying to improve adalimumab productivity and the dominant method came up by the patent (08093045) was that producing adalimumab in mammalian cell culture. Since in pharmaceutical industry, any incremental improvement can result in enormous benefits economically. So there remain the need to optimize cell culture media, because it can obtain the greatest amount of protein and the most efficient means of productivity. Improvement including media for growing cells for protein expression and cell culture production media optimized for protein expression.

5.3.3. Adalimumab drug product

The earliest patent (05945098) disclosed a stable intravenously-administrable immune globulin preparations and the subsequent patent (06171586) extent to a stable aqueous pharmaceutical formulation. After seven years, important patent appeared, talked about adalimumab drug itself and this set up a standard of this drug's formulation: the pH range and the K.sub.off range. And it defined very specific regulation like how much lactose/sugar to put into the medicine so that it has the same osmotic pressure. The attention for future will still be the formulation with an extended shelf life. For example, enhanced stability at a broader range temperature and keep stability after several freeze cycle. The recent patent disclosed a liquid aqueous pharmaceutical formulation which has at least 18 months in the liquid state, and is stable following at least 3 freeze cycle of the formulation.

5.3.4. Drug Administration Device

This technology has experienced a lot of improvements along these years. After the dominant device had been introduced by patent (09265887), patents were following the principal that it should be an injection device for providing a subcutaneous injection which includes a syringe movably disposed in a housing and including a barrel portion, a needle and a bung. Improvement then achieved in device's surface which made devices have overmolded gripping surfaces. After that, an apparatus for removing needle shield from a syringe was invented and it allows visual inspection to make it more reliable. In 2014, the syringe fill system incorporates capability for "push-pull", "pull-push", "push-push", and "pull-pull" modes of operation, providing haptic and audible feedback to a user. In recently, since the wearable materials become more attractive, wearable injection devices which can control injecting rates appeared. Devices may adhere to the skin or clothing of a patient and deliver a therapeutic agent into the patient's body by subcutaneous injection at slow, controlled injection rates, and can reduce or eliminate a burning sensation often felt or perceived by patients. The device should be easy to use, pre-fill capable, easy to manufacture, and/or do not require aseptic assembly.

5.3.5. Methods of use

After Tumor necrosis factor antagonists were used to suppress inflammatory immune-potentiated events, researchers were try to use adalimumab to treat disease. As mentioned, adalimumab has been used in treatment of several diseases, and there is still ongoing focus on continuing to innovate with HUMIRA to address critical unmet needs of patients living with serious immune-mediated diseases, for example the group of inflammatory diseases of the eye. Additionally, AbbVie is actively exploring

additional uses of humira in different diseases. This is important as it will help to expand the target market of the drug.

5.3.6.Devices for assessment

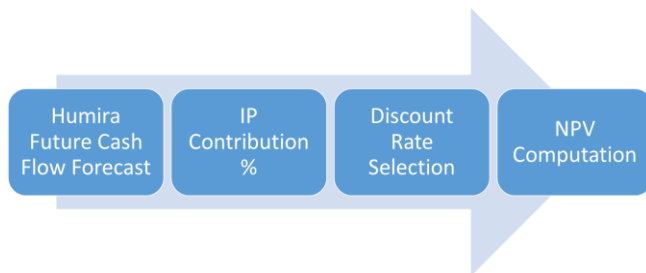
The earliest patent (06607879) disclosed the invention which can be used as hybridizable array elements in a microarray, and it also relates to a method for selecting polynucleotide probes for the composition. In 2006, patent (07919264) which has been cited most to use a collagen degradation biomarker to determine the efficiency in one specific disease. After two years, this methodology has been successfully used in different diseases and improvement in this method has been made and may be apply to more disease in future.

6. IP Valuation

In this section, we are evaluating the worth of AbbVie's patent portfolio surrounding its blockbuster Humira as of 4Q 2016. Both income approach (DCF) and market approach are exploited and compared. In pharmaceutical industry, huge corporations spend years of R&D efforts on different pipeline of drugs, hoping to develop one blockbuster. There is no guaranteed success down each and every pipeline, which made the cost to patenting rather difficult to estimate. It's also impossible to duplicate the R&D investment for another biologics that could replace Humira. Therefore, we did not recommended cost approach.

6.1. Income Approach (DCF Method)

We will follow the 4 steps in DCF method (as shown below) to elaborate how valuation is done.



a. Humira Future Cash Flow Forecast

i. Compound Annual Growth Rate

Market Analyst's Perspective

Market analyst is rather conservative about estimation of sales of Humira, as they see that market erosion from Humira's biosimilars is still a treat. Market analyst predicted that Humira revenue in 2020 will be 13.3 Billion USD³⁵, which gives a compound annual growth rate (CAGR) of -1%.

AbbVie's Perspective

Comparing to market analyst, AbbVie is more positive on their future forecast. They believed that with series of Long Range Planning in place, including continuous R&D efforts, application for new key patents, extensive marketing and advertisement and their strong clinical trial networks, Humira generated revenue should be well protected from biosimilar entry until 2022.

³⁵ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 38

The diagram below illustrates the current patent portfolio of Humira. Key patents in Humira’s current patent portfolio gradually expires from 2016 Dec 31 to 2034. The last patent in the current suite expires 2034. Therefore, it is safe to say that the ‘patent cliff’ resulted by the original formulation patent will not actually taken place. There will not be a tremendous sudden impact on Humira’s sales any market analyst has worried about.

Approved Indication	Rheumatoid Arthritis	Gastro Indications	Psoriasis	Psoriatic Arthritis	Ankylosing Spondylitis	Juvenile Idiopathic Arthritis	Hidradenitis Suppurativa
Composition of Matter	Expires Dec. 31, 2016						
Indication / Method of Treatment	4 patents Earliest Expiry: 2022	6 patents Earliest Expiry: 2022	3 patents Earliest Expiry: 2023	4 patents Earliest Expiry: 2023	3 patents Earliest Expiry: 2022	1 patent Expiry: 2030	1 Patent Expiry: 2031
Formulation	14 Patents Expire 2022 –2028						
Manufacturing	24 patents Expire 2027 – 2034						
Other (Device, Diagnostics, etc.)	15 patents Expire 2024–2032						

Figure 20: Humira Patent Portfolio Expiry dates

Meanwhile, AbbVie is applying for the new formulation patent in U.S. and EU, as well as 2 new indication patents for treating Uveitis and Hidradenitis Suppurativa, which are expected to open up two new markets for Humira. As other biosimilar competitors must have the same route of administration, dosage form and strength as Humira, AbbVie has the advantage to be the market leader in Uveitis and Hidradenitis Suppurativa treatment until beyond 2034.

The net sales of Humira hits 14 billion USD in 2015³⁶. By introducing the de-risked pipeline for Humira, AbbVie forecasted Humira revenue in the year 2020 will be 18.8 Billion USD³⁷, which gives a CAGR about 6%. At this point of time, we see AbbVie’s prediction is more credible as its thought process seems to be more comprehensive.

Beyond 2022, biosimilar may gradually evade into Humira’s current market. It will be difficult for AbbVie to maintain a higher single digit growth rate. A CAGR at around 0.5% is more realistic. Eventually around 2040, the change in market share between Humira and its biosimilars will reach the steady state.

Optimistically, we assume Humira will control 60% of the total market from 2040 onwards, due to its strong hospital network and stickiness of its user base.

³⁶ AbbVie 2015 Annual Report, 39

³⁷ Richard Gonzalez, *AbbVie Long-Term Strategy*, 11

In conclusion, we will apply 3 different CAGR values to calculate the revenue streams during the various phases of the patent landscape and market landscape change from 2016 onwards.

- 2016 – 2022: CAGR1 = 6%
- 2022 – 2034: CAGR2 = 0.5%
- 2034 onwards: CAGR3 = 0%, market share = 60%

ii. Future Humira Cash Flow Streams

In 2015 AbbVie Annual Report, Humira's revenue is reported to be 14 billion USD³⁸, which constitutes to 61.5% of the total revenue of AbbVie. We assume Humira generated cash flow has the same percentage in AbbVie's cash flow, which equals to 7.5 billion x 61.5% = 4.63 billion in the year 2015.

CAGR obtained from the previous part will then be applied on 4.63 billion, to generate the Humira cash flow from 2016 to 2046.

b. IP Contribution %

In general, generic drugs are priced 30% lower than the original biologics.³⁹ Main contributors of the 30% price premium are the intangibles, such as branding, trademarks and patents. Being a major blockbuster, Humira hires the top-tier marketer, to expand its market share even though it is approaching end of product life cycle.⁴⁰ By June 2016, it is said that AbbVie has already spent more than 118 million USD in TV advertisement, which has surpassed its 2015's full-year TV advertisement spending by 20 million USD. Hence, we have the reason to believe that patent contribution % in the price premium will be around 10% on the lower side.

c. Discount Rate Selection

When selecting the discount rate, we take two main factors into considerations: company risk and product development risk.

- AbbVie is a huge established pharmaceutical company and is managed by a top-tier executive team.

³⁸ AbbVie 2015 Annual Report, 39

³⁹ Gabi, *Pricing of biosimilars*, 25 April 2012, <http://gabi-journal.net/news/pricing-of-biosimilars>

⁴⁰ Larry Dobrow, *MM&M 2014 Large Pharma Marketing Team of the Year: Humira*, 01 January 2014, <http://www.mmm-online.com/features/mmm-2014-large-pharma-marketing-team-of-the-year-humira/article/326160/>

- New developments of Humira projects including indications in Uveitis and Hidradenitis and the new formulation are all in the later stages of development, either submitted for FDA approval or already obtained FDA approval. Therefore, risk at this stage is minimum.

Hence, we adopt a 10% discount rate to address the potential risk for Humira, which is at the lower side of industrial norm.⁴¹

d. NPV Computation

By substituting ratios from section b, c into the formula, we have:

$$\sum_{t=1}^T \frac{(I - C)_t}{(1+k_t)^t}$$

I: income C: cost
k: discount coefficient (Inflation, Interest rate or capital market, expected risk)
T: useful life of the technology

Table 14 summarizes the calculation of NPV using DCF method, with the amortization period from 2016 to 2046.

We therefore conclude that Humira's patent portfolio is valued at **6.38 billion USD**.

CAGR-1 = 6%								
Year	2015	2016	2017	2018	2019	2020	2021	2022
Operating Cashflow	7.54	7.99	8.47	8.97	9.51	10.08	10.69	11.33
Operating Cashflow by Humira	4.63	4.91	5.21	5.52	5.85	6.20	6.57	6.97
Patent Contribution	0.46	0.49	0.52	0.55	0.59	0.62	0.66	0.70
No. of Year (t)	-	0	1	2	3	4	5	6
Discount rate = (1+10%) ^{At}	-	1.00	1.10	1.21	1.33	1.46	1.61	1.77
NPV	-	0.49	0.47	0.46	0.44	0.42	0.41	0.39

CAGR-2 = 0.50%												
Year	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
Operating Cashflow	11.39	11.44	11.50	11.56	11.62	11.67	11.73	11.79	11.85	11.91	11.97	12.03
Operating Cashflow by Humira	7.00	7.04	7.07	7.11	7.14	7.18	7.22	7.25	7.29	7.32	7.36	7.40
Patent Contribution	0.70	0.70	0.71	0.71	0.71	0.72	0.72	0.73	0.73	0.73	0.74	0.74
No. of Year (t)	7	8	9	10	11	12	13	14	15	16	17	18
Discount rate = (1+10%) ^{At}	1.95	2.14	2.36	2.59	2.85	3.14	3.45	3.80	4.18	4.59	5.05	5.56
NPV	0.36	0.33	0.30	0.27	0.25	0.23	0.21	0.19	0.17	0.16	0.15	0.13

CAGR-3 = 0%												
Year	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046
Operating Cashflow (60% of market share)	7.22	7.22	7.22	7.22	7.22	7.22	7.22	7.22	7.22	7.22	7.22	7.22
Operating Cashflow by Humira	4.44	4.44	4.44	4.44	4.44	4.44	4.44	4.44	4.44	4.44	4.44	4.44
Patent Contribution	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44
No. of Year (t)	19	20	21	22	23	24	25	26	27	28	29	30
Discount rate = (1+10%) ^{At}	6.12	6.73	7.40	8.14	8.95	9.85	10.83	11.92	13.11	14.42	15.86	17.45
NPV	0.07	0.07	0.06	0.05	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.03

NPV of Revenue Stream from 2016-2046 = **6.38 Billion USD**

Table 17: Calculation of NPV based on DCF method

⁴¹ Tim Opler, Benj Garrett, and Susan Langer, *Valuation Analysis in Pharmaceutical Licensing and M&A Transactions*, January 2014, 57

6.2. Market Approach

For market approach to IP valuation, similar companies with similar biologic products are studied. First, we look at the early stage of auto-immune diseases biologic market, which is the decade of year 2000, where the market size is not yet as developed and as well-defined as present time. And then, we look at the present time auto-immune diseases biologic market, with a market size that has been well established with several blockbusters already in the market.

The two early stage companies that are studied are Centocor, which now becomes Janssen and is part of Johnson & Johnson, and Immunex, which now is part of Amgen. Centocor is known to be the producer of “Remicade” (Infliximab), and after becoming Janssen, also the producer of “Simponi” (Golimumab). Immunex is known to be the producer of “Leukine” and “Enbrel” (Etanercept). The analog to AbbVie would be Knoll being the producer of “Humira” (Adalimumab).

The first transaction happened in 1999 when Centocor merged with Johnson & Johnson, before changing its name to Janssen in 2011. The value of the transaction was about USD 5 billion at the time⁴². Centocor was not in its best condition when the merger happened. One of its major blockbuster biologic drugs, called “Centoxin”, not doing well in the market, causing Centocor to be in deficit. Remicade was the blockbuster drugs that kept them valuable.⁴³ To understand the background behind the transaction, it needs to be understood that Remicade was the first major blockbuster drugs for RA and various other auto-immune diseases. The negative financial condition of Centocor, mixed with the fact that Remicade being the first of the kind, carrying higher risk, may result in the relatively lower transaction value compared to the other two transactions that will be elaborated.

The second transaction happened in 2002 when Immunex was acquired by Amgen for about USD 16 billion at the time⁴⁴. Immunex was in excellent financial condition when the acquisition happened. It had two blockbuster biologic drugs in its sleeve, which are Leukine and Enbrel, the latter alone comprises 75% of its overall revenue in 2000 and year-on-year increase of about 100%.⁴⁵ The fact that it had

⁴² Robert Langreth, *Johnson & Johnson to Purchase Centocor for \$4.9 Billion in Stock*, 22 July 1999, <http://www.wsj.com/articles/SB932559168720832483>

⁴³ <http://www.fundinguniverse.com/company-histories/centocor-inc-history/>

⁴⁴ David P Hamilton, *Amgen Confirms Cash, Stock Deal To Acquire Smaller Rival Immunex*, 18 December 2001, <http://www.wsj.com/articles/SB1008606575817774000>

⁴⁵ <http://www.fundinguniverse.com/company-histories/immunex-corporation-history/>

excellent financial condition and having two blockbusters, may affect its relatively higher transaction value.

The third transaction also happened in 2002 when BASF Knoll was acquired by Abbott for about USD 6.9 billion at the time⁴⁶, before spun off to become AbbVie in 2013. At the time BASF Knoll did not have any blockbuster product, except for D2E7 which was still in trial stage then, and later better known as Adalimumab⁴⁷. D2E7 had a huge potential to becoming the very first human-sourced biologic drugs for various auto-immune diseases, since the earliest ones are either mouse-sourced, humanized-sourced, or chimeric-sourced. And as expected, after Adalimumab is approved by the FDA, it became the best-selling auto-immune biologic drugs worldwide.⁴⁸

The transaction value does not only cover the Intellectual Properties (IPs) purchase, but also include the entirety of assets and resources, and this would include the experts that are in the company, which also include its sales and marketing arm and lobbying capability. In the case of Immunex, its Intangible Assets amounted to only 0.17% of the transaction value.

Based on Immunex's Annual Report in the year 2000, it reported Intangible Assets of USD 27 million.⁴⁹ The revenue of Enbrel in the same year is about 75% of Immunex's overall revenue.⁵⁰ By direct proportionality and assuming the Intangible Assets consist only of IPs, the value of Enbrel's IPs is 75% of USD 27 million, which amounts to be about USD 20 million.

Understanding the value of Enbrel's IP in 2000, we compare it with the value of Enbrel's IP in 2015 when it is already owned by Amgen. Based on Amgen's Annual Report in the year 2015, it reported Intangible Assets of USD 11.64 billion.⁵¹ The revenue of Enbrel in the same year is about 26% of Amgen's overall revenue.⁵² By direct proportionality and assuming the Intangible Assets consists only of IPs, the value of Enbrel's IPs is 26% of USD 11.64 billion, which amounts to be about USD 3 billion. This is 150 times multiplication of its own value in 2000. Despite the exceptionally huge multiplication number, we would like to emphasize that the number is an estimate, and the exact number can fall anywhere in between.

⁴⁶ Thomas M Burton, *Abbott Laboratories Agrees to Buy BASF's Knoll Pharmaceutical Unit*, 15 December 2000, <http://www.wsj.com/articles/SB976832374667325423>

⁴⁷ Joachim Kempeni, *Preliminary results of early clinical trials with the fully human anti-TNF α monoclonal antibody D2E7*, http://ard.bmj.com/content/58/suppl_1/I70.full

⁴⁸ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 38

⁴⁹ Immunex 2000 Annual Report, 48

⁵⁰ *Ibid.*, 38

⁵¹ Amgen 2015 Annual Report, F-4

⁵² *Ibid.*, 4

This is supported by a 2008 forecast of market size growth increase from about USD 6.3 billion in 2004 to USD 34.5 billion in 2014, which amounts to almost 5.5 times multiplication from 2004 to 2014. (Frost & Sullivan N167-52) This is emphasized further by the actual market size of about USD 48.9 billion in 2015, which amounts to almost 7.8 times multiplication from 2004 to 2015, and forecasted market size of about USD 54.5 billion in 2022. Accounting the market size increase already illustrated, and market dominated by blockbuster drugs like Humira, Enbrel, and Remicade, a sharp increase of IP value from the year 2000 value is considered to be sensible.

Therefore, the value of Humira’s IPs can be derived based on market share in 2015 of Humira being 29.4% and Enbrel being 18.5%,⁵³ and assuming that in 2015 the lower floor of Enbrel’s IPs value being USD 200 million and the upper ceiling being USD 3 billion, resulting in IPs value ranging between USD 318 million and USD 4.8 billion.

Verifying with AbbVie’s 2015 Annual Report, given that Humira takes 61% of AbbVie’s overall revenue⁵⁴ and Intangible Asset of USD 19.709 billion,⁵⁵ 61% of USD 19.709 billion results in USD 12.081 billion estimate for Humira’s IP value. This is of course not accounting that Humira’s core patent is expiring while maintaining domination over AbbVie’s revenue, which is shown by overestimation of Humira’s IP value by this simple verification technique.

Owner	Product	% revenue	% market share	Intangible Asset	IP Valuation	Source
AbbVie	Humira	-	-	-	\$ 6.380 billion	income approach DCF method
Amgen	Enbrel	26%	18.5%	\$ 11.641 billion	\$ 3.026 billion	book check
AbbVie	Humira	-	29.4%	-	\$ 4.810 billion	market approach
AbbVie	Humira	61%	-	\$ 19.709 billion	\$ 12.081 billion	book check (verification)

Table 18: Valuations of Humira

⁵³ EvaluatePharma, *World Preview 2016, Outlook to 2022*, 38

⁵⁴ AbbVie 2015 Annual Report, 39

⁵⁵ *Ibid.*, 58

7. Litigation

This session is a review of past patent litigation cases that Abbvie (or Abbott before 2013) has got involved in the past, the IPR challenges from biosimilar producers on Abbvie's Humira patents as well as the ongoing spotlight case between Amgen and Abbvie.

7.1 Litigation against Abbvie: How does Abbvie defend itself?

Ever since the Humira entered market in 2002 and became a big success, the company Abbvie has received constant challenges from the other industrial players. On one hand, it received complaints from other biopharma companies that Humira (either its formulation, or the manufacturing process) have infringed on their patents. On the other side, its existing licensor has also brought up legal proceedings to claim more royalty for the licensed Adlimumab related patent. The increasing number of litigations is a reflection of the interest that it received from the industry. This session is a brief review of four US Court of Appeal for Federal Circuit (CAFC) cases to develop some insights on how Abbvie handles the litigation challenges.

In 2003, Cambridge Antibody Technologies (CAT) filed a law suit claiming that the royalties it was receiving from Abbott were too low. The UK biotech company was the co-developer on Adalimumab drug with Abbott. At the time of the lawsuit, it was receiving a 3.1% royalty payment from Abbott for the sale of Humira product under a licensing agreement on one of its patents (US patent 5,654,407).

⁵⁶ However, CAT claimed that it was entitled to 5.5% percent royalty. Abbott insisted making only 3.1% payment. The district court first ruled in favour of CAT and ordered Abbott to increase its royalty payments, but Abbott appealed. The two companies reached a settlement in October 2005, just one day before the appeal was to start. The final agreed royalty is at 2.688%, which is even lower than that of the initial agreement.⁵⁷ In this case, the big patent portfolio around the Humira product has been used by Abbvie to justify the adjustment of royalty payment, the reason being that the company should be allowed to offset the costs of its work with other partners that helped in the development of Humira.

In December 2008, Bayer Healthcare LLC filed a patent infringement lawsuit against Abbott, claiming

⁵⁶ CAT TRIUMPHS OVER PARSIMONIOUS ABBOTT, 20 December 2004, <http://ipkitten.blogspot.sg/2004/12/cat-triumphs-over-parsimonious-abbott.html>

⁵⁷ Cambridge Antibody Technology and Abbott Agree Regarding Royalties, 26 October 2005, <https://www.thefreelibrary.com/Cambridge+Antibody+Technology+and+Abbott+Agree+Regarding+Royalties.-a0137937381>

that Humira infringes on a Bayer patent "Human Anti-TNF Antibodies", for which it should be awarded compensatory damages.⁵⁸ Amgen subsequently sued back to challenge the validity of Bayer's patent, declaration of non-infringement to "afford relief from the uncertainty and controversy which Bayer's actions have precipitated". The dispute was focus on the interpretation of the term "human monoclonal antibody'. Bayer claimed that the term in the context of the patent broadly covers all antibodies that attach to TNF α to stop inflammation, with no limitation on conditions that it was manufactured. Abbott has contested that such an interpretation is "unduly vague and ambiguous". The Court of appeal has eventually agreed with Abbott and invalidated Bayer's patent.⁵⁹ As a sideline story the corresponding European patent was subsequently also invalidated on the ground of insufficient disclosure upon the challenge from Abbott.⁶⁰

Another dispute happened only a while after this in 2009. Centocor Ortho Biotech, Inc. and New York University is the co-proprietor of a patent covering a chimeric antibody (US No. 7,070,775) for which Abbott was sued for infringement. High court ruled in favor of Centocor, and ordered Abbott to pay compensatory damage in the amount of \$1.6 billion. The decision was reversed upon appeal because that CAFC decides that the person skilled in the art would not have been able to make a fully human antibody based on the description of the chimeric antibody and the rest of the information in the patent.⁶¹ Accordingly, the \$1.67 billion damages awarded by the district court have been negated. Noticeably, Abbott has brought up concurrent lawsuits against Johnson & Johnson ("J&J", which is the parent company of Centocor), claiming J&J's arthritis drug Simponi and psoriasis medicine Stelara, made with human antibodies, are infringing Abbott patents. This has added further pressure to the other party.⁶²

In the last case between Abbvie and the Mathilda and Terence Kennedy Institute of Rheumatology Trust ("Kennedy"), Abbvie has taken a proactive approach to invalidate one of Kennedy's patents (US patent 7,846,442), from which Kennedy has attempted to claim license fees. Kennedy is the owner of U.S.

⁵⁸ Bayer's Complaint: <http://www.patentbaristas.com/wp-content/uploads/2009/01/bayer.pdf>

⁵⁹ CAFC decision, Civil Nos. 09-40002-FDS, 09-40061-FDS 20 October 2010:

<http://www.leagle.com/decision/In%20FDCO%2020101021B13/ABBOTT%20LABORATORIES%20v.%20BAYER%20HEALTHCARE%20LLC>

⁶⁰ NL - Bayer Healthcare v. Abbott, Case No. 356145 HA ZA 10-57, 20 October 2010:

<http://www.eplawpatentblog.com/eplaw/2010/10/nl-bayer-healthcare-v-abbott.html>

⁶¹ The Written Description Requirement for Antibodies (Centocor Part I), 24 Feb 2011:

<https://www.pharmapatentsblog.com/2011/02/24/the-written-description-requirement-for-antibodies-centocor-part-i/>

⁶² Johnson & Johnson loses patent battle with Abbott Laboratories, 21 Feb 2012:

http://www.nj.com/business/index.ssf/2012/02/johnson_johnson_loses_patent_b.html

Patent 6,270,766, directed to methods of treating rheumatoid arthritis by co-administering a disease-modifying antirheumatic drug and an antibody and AbbVie licensed the '766 patent to sell Humira in 2002. After the '766 patent issued, Kennedy obtained the '442 patent, which contains the same "method of treatment" claims, but is claimed to direct towards a more specific patient group. The '766 patent, expires on August 21, 2018. After the '442 patent issued in 2010, Kennedy demanded that AbbVie pay royalties under the '442 patent in order to continue sales of Humira. In response, AbbVie sued Kennedy for DJ that the claims of the '442 patent were invalid over the '766 patent under the doctrine of obviousness-type double patenting, which was affirmed by the district court and the appeal court.⁶³ In its judgement, the court explained, "Kennedy is not entitled to an extra six years of monopoly solely because it filed a separate application unless the two inventions are patentably distinct." Abbvie was relieved from the royalty payment.⁶⁴

Abbvie's success in these cases adds more value to the company and further strengthens its dominating position in the market.

7.2. Inter Partes Review challenge on Humira patents

With the patent cliff (i.e. the expiration of the base composition patent) reaching soon, the biosimilar companies get more incentivized to challenge Abbvie's Humira patents, in the attempt to remove the hurdles on their pathway of the getting the biosimilar to the market. While the court has not decided whether participation in patent dance is compulsory for biosimilar developers, most of the Humira biosimilar producers have elected an alternative strategy to challenge Abbvie's patents by filing inter partes review (IPR) petitions against Abbvie's patents. In comparison with the patent dance, this procedure is less lengthy and less risky to biosimilar producers who may be held liable for infringement.

The first move was led by Amgen Inc. in early 2015. It brought two Inter Partes Review challenges with The USPTO Patent Trial and Appeal Board (PTAB) against two Humira patents covering stable formulations of anti-TNF-alpha antibodies. The patents in suit are U.S. Patent 8,916,157 and U.S. Patent 8,916,158. In its petitions, Amgen asserted that certain claims of both patents were invalid as obvious in view of new third party prior arts. Taken together, the asserted references appear to disclose

⁶³ Federal Circuit Patent Bulletin, 21 Aug 2014: <http://www.wileyrein.com/newsroom-articles-3258.html>

⁶⁴ Abbvie Inc. v. Kennedy Inst. of Rheumatology Trust, No. 2013-1545 (Fed. Cir. Aug. 21, 2014): <http://www.jptos.org/index.php?mact=News,cntnt01,print,0&cntnt01articleid=340&cntnt01showtemplate=false&cntnt01returnid=85>

each aspect of the claimed formulations, but the PTAB did not find sufficient guidance to support the selections required to arrive at the claimed formulations or a basis for finding a reasonable expectation of success.⁶⁵

Although two patents didn't not go through the thorough review by PTAB to re-confirm its validity status, the refusal to institute Amgen's IPR challenge has undoubtedly made these two patents more valuable for Abbvie. It can be seen in the later session about the patent infringement case between Abbvie and Amgen that patent '157 has been chosen by Abbvie out of its 61 core Humira patents for the first round of the patent dance litigation. Interestingly, this IPR challenge brought by Amgen has now turned into a key litigation tool for Abbvie to defend its position as the Humira patent owner.

Another important litigation strategy that Abbvie has adopted is to emphasize Amgen's position in its own precedent case against other biosimilar drug producers. In this case Amgen likely was trying to clear the patent landscape for its own biosimilar, but Amgen is the patent holder in the first case where the Federal Circuit interpreted the biosimilar patent dispute resolution procedures of the BPCIA (Amgen v Sandoz). While the PTAB didn't comment on it in its decisions, AbbVie argued in its Patent Owner Preliminary Responses that Amgen's arguments regarding obviousness and likelihood of success were inconsistent with positions Amgen took when pursuing its own antibody formulation patents.⁶⁶

The probability of finding themselves on both sides of antibody/biosimilar disputes may make other Humira biosimilar producers more cautious about the positions they advance, or at least pause to consider the potential implications of challenging Abbvie on Humira when they are on the other side for another biologic drug.

Following Amgen's footprint, two other biosimilar producers have filed in total six IPR petitions against the Abbvie's Humira patent U.S. in 2015, with two petitions from Boehringer Ingelheim on US Patent no.

⁶⁵ US Patent and Trademark Office, before the Patent Trial and Appeal Board, Amgen Inc Petitioner v AbbVie Biotechnolog Ltd. Patent owner, U.S. Patent 8,916,157 and U.S. Patent 8,916,158, 26 June 2015,

⁶⁶Big Guns Take Aim at Top-Selling Biologic, 18 August 2016, http://www.klgates.com/humira-update-big-guns-take-aim-at-top-selling-biologic-08-19-2016/#_ednref11

8,889,135 and four petitions from Coherus on US Patent no. 8,889,135, US Patent no. 9,017680, US Patent no. 9,073,987 and US Patent No. 9,114,166.^{67 68 69}

Both companies have committed to develop their Adalimumab biosimilars. The German firm Boehringer Ingelheim has completed Phase III clinical trial for their biosimilar drug BI0695501 in October 2016 and is planning submit it for regulatory approval in USA and EP.⁷⁰ Coherus's drug CHS-1402 is expecting to complete Phase III in March 2017.

Both biosimilar producers challenged the validity of patent '135, which covers a bi-weekly dosing methods of treating rheumatoid arthritis with Humira, based on the ground of being obvious other the new third party prior arts. The patent is a cornerstone of the Humira patent estate in relation to "Method of Administering Anti-TNF-alpha Antibodies", consisting of a patent family of six patents. Coherus claimed the patent is invalid because the dosage regimen it covers was a "routine optimization of the therapy" that was known by researchers. Subsequently, it made similar arguments seeking to cancel two other patents (US Patent no. 9,017680 and US Patent no. 9,073,987) in the '135 family.

In contrast to the failure of Amgen's IPR petition, the board determined that Coherus and Boehringer Ingelheim presented sufficient evidence to show a "reasonable likelihood" of unpatentability with respect to the patents in question. In May 2016, PTAB has made the decisions to review the validity of patent '135 and subsequently for the two patents, which has added further risks to Abbvie. If the '135 patent falls in the IPR proceeding, competitors will have a clear way into Abbvie's "Method of administration" technology area. PTAB decision is expected come in 12 months' time in average. Although "method of administration" won't affect the other technology areas which will still be under Abbvie monopoly, the significance defending the validity of the '135 family is still considerable for Humira to maintain its competitive advantage over other biosimilar drugs in this technology area.⁷¹

⁶⁷ PTAB Intitutes Humira Patents, 24 May 2016: <http://www.bigmoleculewatch.com/2016/05/24/ptab-institutes-ipr-on-humira-patent-2/>

⁶⁸ US Patent and Trademark Office, before the Patent Trial and Appeal Board, Boehringer Petitioner v AbbVie Biotechnolog Ltd. Patent owner, US Patent no. 8,889,135

⁶⁹ US Patent and Trademark Office, before the Patent Trial and Appeal Board, Coherus Petitioner v AbbVie Biotechnolog Ltd. Patent owner, US Patent no. 8,889,135, US Patent no. 9,017680, US Patent no. 9,073,987 and US Patent No. 9,114,166

⁷⁰Boehringer Ingelheim's adalimumab biosimilar candidate shows similar efficacy and safety profile to Humira® in pivotal Phase III study, 26 October 2016: http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2016/10-26-2016-boehringer-ingelheims-adalimumab-biosimilar-candidate-shows-similar-efficacy-safety-profile-humira-pivotal-phase-iii-study.html

⁷¹ AbbVie Slides as U.S. Agency Questions Humira Patent, 17 May 2016, <http://www.bloomberg.com/news/articles/2016-05-17/abbvie-patent-on-humira-may-be-invalid-u-s-agency-says>

Up to the current stage, PTAB has instituted five of the IPR proceedings, leaving only Coherus most recent IPR petition on patent '166 pending (the patent covers a formula to make the anti-TNF-alpha antibody). The biosimilar producer will “continue to aggressively press forward with the development and commercialization of our Humira biosimilar consistent with our corporate strategy”, as stated by the Coherus’s CEO.⁷²

On the contrary, there is much less tension between Boehringer and Abbvie, after the two parties entered into a collaboration agreement in March 2016 to develop new biologics (i.e. BI 655066, Anti-IL-23 antibody now in Phase 3 for psoriasis). The collaboration was on the condition of an initial upfront payment of \$595 million by AbbVie.⁷³ In view of the common interest between these two parties, the reason is now apparent why Boehringer did not take any steps further to its IPR challenge on '135 patent.

7.3 The First Humira Patent Dance: Abbvie v Amgen

On 04 August 2016, 20 days after FDA panel members reached an unanimous agreement to approve Amgen’s biosimilar drug ABP 100, Abbvie filed a complaint against Amgen, Inc. asserting that Amgen’s application for approval of a biosimilar version of Humira infringes on AbbVie’s Humira patents, which signifies the start of the first Humira “Patent Dance”.⁷⁴

7.3.1 BPCIA and the Patent Dance

The US biosimilar pathway for biosimilars was established by the Biologics Price Competition and Innovation Act (BPCIA), enacted in 2010 as part of healthcare reform introduced by the Affordable Care Act.

This goal of the BPCI Act is similar to that of the Hatch-Waxman Act (Drug Price Competition and Patent Term Restoration Act of 1984), that established an abbreviated approval pathway for generic drugs

⁷² Abbvie Doubles down on M&A, 29 April 2016:

<https://www.bloomberg.com/gadfly/articles/2016-04-29/abbvie-stemcentrx-deal-part-of-boom-or-bust-m-a-strategy>

⁷³ AbbVie buys rights to Boehringer psoriasis drug for \$595 mln, 07 March 2016: <http://www.reuters.com/article/abbvie-boehringer-psoriasis-idUSL5N16F2N>

⁷⁴ AbbVie Sues Amgen to Fend Off Copy of Blockbuster Humira, 05 August 2016:

<http://www.bloomberg.com/news/articles/2016-08-05/abbvie-sues-amgen-to-fend-off-copy-of-4-billion-humira-drug>

(primarily generic versions of traditional small molecule drugs), i.e. to create an abbreviated pathway for licensure of biosimilar and interchangeable biological products. In addition, it contains a procedure for resolving patent disputes, which is usually referred to as the “Patent Dance”. The objective of this process is to define a means by which the two involved parties established which patents may be infringed by the biosimilar developer’s manufacturing process and seeks to facilitate a negotiated settlement.

BPCIA differentiates the biosimilar approval pathway drastically from generic drugs in many aspects, particularly with a longer period of statutory exclusivity for biosimilars, no 30-month stay for a reference product sponsor upon initiation of litigation, no 180-day market exclusivity period for the first filer of an application for approval of a biosimilar in the absence of interchangeability and most significantly a more passive information exchange mechanism.⁷⁵ A more detailed comparison between these two system is to be found in the Appendix Table 1.

In the context of generic drug approval and litigation, it is the brand drug developer who largely controls the patents that can be litigated, since it is the holder who decides which patents to list in the Orange Book. However, it seems that under BPCIA, more control is given to the biosimilar applicants over the first round of biosimilar application. It has been commented that the the policy consideration is to allow biosimilar applicants to be able to focus their resources on obtaining approval and postpone patent issues until the second round of litigation.

As the initial step of the patent dance, Amgen is to provide the reference product sponsor Abbvie with a copy of the application as well as information describing its manufacturing process, within 20 days after a biosimilar application is accepted by the FDA for review (i.e. 22 January 2016). Amgen has purposely delayed the information exchange process and didn’t send Abbvie any information until 11 April 2016. Relevant information about their manufacturing process was also not provided to Abbvie in order to evaluate the extent of Amgen’s infringement of Abbvie’s patents.⁷⁶

In response to Amgen’s delaying tactics and the passive BPCIA information exchange system, Abbvie’s

⁷⁵ The Biologics Price Competition and Innovation Act: Potential Problems in the Biologic-Drug Regulatory Scheme, September 2015, Northwestern Journal of Technology and Intellectual Property, Volume 13, Issue 2

⁷⁶ AbbVie’s Complaint, ABBVIE INC. and ABBVIE BIOTECHNOLOGY LTD. v. AMGEN INC. and AMGEN MANUFACTURING LTD., in the United States District Court for the District of Delaware, 04 August 2016

strategy is to emphasize that Amgen’s delaying tactics during the information exchange process is contradictory to its standpoint as a biologics developer in the earlier patent dance between Amgen and Sandoz. It has urged Amgen to provide its manufacturing process and negotiate the patents to litigate in good faith.²¹

7.3.2 Abbvie’s 61 “Core” Patents

While it remains contentious whether the BPCIA has struck a well balance between reference biologics product (“RBP”) developer and biosimilar producer, these differences has focused the incentive to settle any patent litigation on the risk of invalidity and/or noninfringement of the reference product sponsor's patents. The RBP developer will have to constantly extend the coverage under their patent portfolio into different technology and function area to strengthen their legal protection, especially when the drug is reaching the patent cliff.

According to the Complaint, it provided Amgen with a list of “61 patents and 5 allowed patent applications from among the more than 100 patents in the Humira estate” and “a 1500 page statement that Amgen’s ABP 501 would infringe more than 1100 claims of patents”.²¹

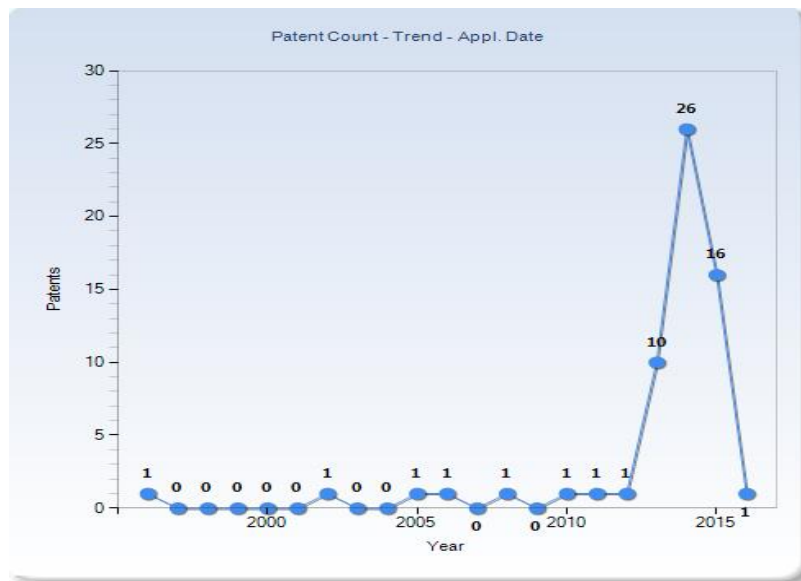


Figure 21: Application Date of the 61 patents (Source: IP tech)

Figure 19 plots out the application date of the 61 “core” patents that Abbvie asserted in its complaint. Although the technology in relation to Adalimumab has taken off as early as 1996, not a lot of patents are identified in Abbvie’s 61 core patents list. Majority of the 61 patents were filed post year 2013, at

which point the Humira product has been in the market for sale for over 10 years. This may result from the following considerations.

Firstly, the patents that are developed in late 90s to early 00s are going to expire soon. By the time Amgen’s ABP 150 reaches the market, some of early patents including the adalimumab base composition patent will not be in force anymore. Damages claimable in case of a finding of infringement are thin and will not justify the huge litigation expenses and thus won’t bring much value to the case. Secondly, as the technology in this field has been evolving in very fast pace, recent patents may be more relevant for discussion. Thirdly, the earlier patents are mostly core patents where the later patents have developed from and improved on. Putting to many of these cornerstone patents into litigation may backfire on the patent owner when the validity of the patents are contested.

7.3.3 The Ten Chosen Patents

BPCIA has granted Amgen the right to decide the number of patents to bring into the first round of litigation. Amgen notified AbbVie that it would be listing six patents on its list of patents to be litigated, which gave AbbVie the right to list up to six patents on its list. Thereafter the parties exchanged their lists of patents, which collectively identified the ten patents below (Table 16). The ten patents that were asserted in the first round of patent litigation under the BPCIA listed in Table 2. They are assigned in the relevant Humira technology to illustrate the direction where two sides are push the case towards.

Relevant Technology	Selected by	Patent No.	Title
Method of use (Dosage)	Abbvie	8961973	Multiple-variable dose regimen for treating TNF α -related disorders
1. Devices for Assessment of Medical efficacy (follow up assessments) 2. Method of use Application for specific diseases	Both	8986693	Use of TNF α inhibitor for treatment of psoriasis
Adalimumab Drug Product (Formulation/drug compositions, e.g like how much lactose/sugar to put into the medicine so that it has the same osmotic pressure as blood)	Abbvie	8916157	Formulation of human antibodies for treating TNF- α associated disorders
	Amgen	9220781	Formulation of human antibodies for treating TNF-alpha associated disorders
	Abbvie	9272041	Formulation of human antibodies for treating TNF-alpha associated disorders
Technology for manufacturing Adalimumab (cell lines/ purification resins and columns/etc)	Both	9096666	Purified antibody composition
	Amgen	8663945	Methods of producing anti-TNF-alpha antibodies in mammalian cell culture
	Abbvie	8911964	Fed-batch method of making human anti-TNF-alpha antibody
	Amgen	9359434	Cell culture methods to reduce acidic species
	Amgen	9150645	Cell culture methods to reduce acidic species

Table 19: Patents in first-round litigation categorized by the relevant technology.

Patents selected by Abbvie cover four of the six technologies that we identified based on the review done on Humira patent landscape. This strategy taken is in the attempt to emphasize Abbvie's right as to the whole of Humira product and its exclusive position across the Humira product value chain.

In comparison, in the six patents that Amgen has chosen, five patents are in relation to the manufacturing process. Amgen as a biologic producer itself, has developed its own expertise in relation to the biologic manufacturing process and has its own patent portfolio. Furthermore, process patents are easier to be designed around to avoid an infringement charge. Both non-infringement and validity of AbbVie's several patents were contested by Amgen in its initial response to AbbVie.²¹ The validity manufacturing process is certainly expected to be an area that Amgen prepares to challenge.

AbbVie, however, are well equipped. Manufacturing technology is the area that AbbVie has heavily invested to innovate along the development of its Humira product. The portfolio analysis has revealed a total number of 42 patents under this category. Apparently, AbbVie has foreseen the issue with process patents and has strategized its patent structure accordingly to fence off potential infringers. The likelihood of AbbVie to succeed in the first round of litigation with such a fencing strategy will be discussed in the following session.

Another strategy that AbbVie used to select the patents for litigation is also worth of noting. AbbVie has brought the patent '157 into the first round litigation. As discussed in the above study, the validity of the patent was questioned by Amgen in one of its earlier IPR petitions. The request was turned down by PTAB after a preliminary assessment in view of the third party prior arts that Amgen submitted.²¹

7.3.4. Legal and Technological Connectivity

To provide a more in depth analysis about AbbVie's position in the first round litigation, the legal and technological connectivity of the 10 chosen patents are plotted out in Figure 20. The patents are arranged in accordance to the application date.

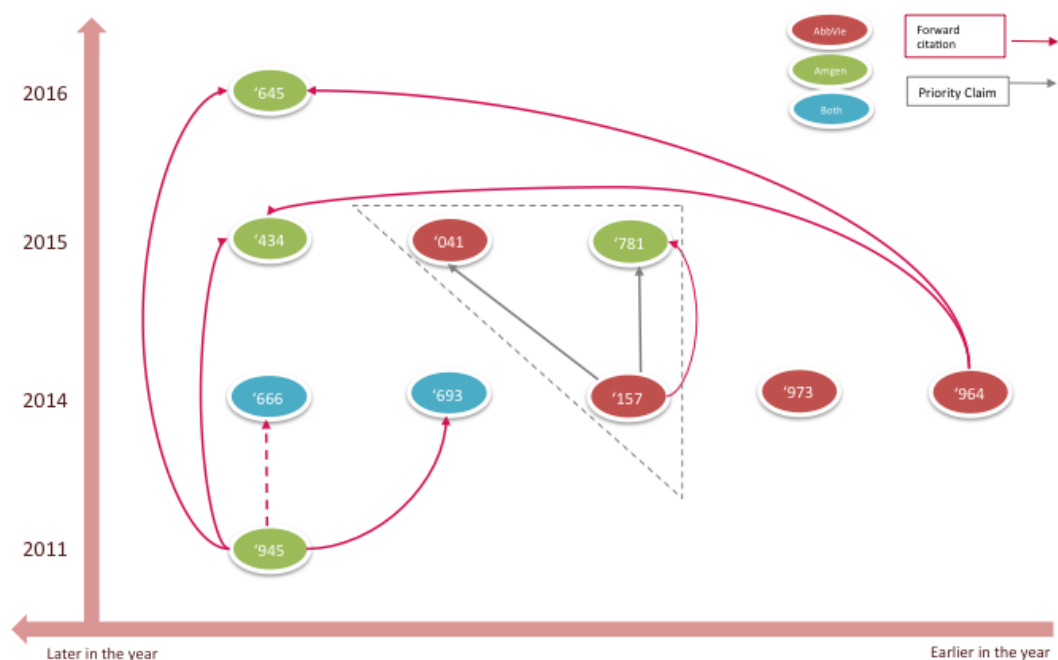


Figure 22: Legal and Technological Connectivity of the 10 chosen patents

It can be seen that the patents in suit can be broadly categorized into two groups, taken into considerations of both their legal and technology connectivity.

First group: Formulation patents - the '157 Family

Patent '157⁷⁷, '781⁷⁸ and '041⁷⁹ are from the same patent family. The big patent family with 18 members (in US) mainly covers stable aqueous pharmaceutical formulations with an extended shelf life, contain high protein concentration, and facilitate easy administration. The different formulations claimed by these patents are all minor variations in the components or concentration.

As shown in the claim scope comparison (Figure 21), '157 claims the broadest scope of protection and both '781 and '041 are a specific composition (organic acid and acetate) at a specific concentration (50mg/ml) under '157, with the added technical benefit of being "suitable for suitable for subcutaneous injection." This means that even if Amgen's ABP 150 product formulation successfully designs around '041 and '781, it is still hard to escape from the broader territory of '157.

⁷⁷ US Patent No. 8916157

⁷⁸ US Patent No. 9220781

⁷⁹ US Patent No. 9272041

One possible strategy that Abbvie may take is to counterclaim invalidity of '041 and '781 as being obvious over each other. However, '157 will still exclude Amgen from using similar formulations.

08916157	2
24. A stable liquid aqueous pharmaceutical formulation comprising	
⊙ (a) 20 to 150 mg/ml of a human IgG1 anti-human Tumor Necrosis Factor alpha (TNF α) antibody,	
⊙ (b) a tonicity agent,	
⊙ (c) a polysorbate, and	
⊙ (d) a buffer system having a pH of 4.0 to 8.0,	
⊙ wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7.	

09220781	1	09272041	1
1. A stable liquid aqueous pharmaceutical formulation comprising		1. A stable liquid aqueous pharmaceutical formulation comprising	
⊙ (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNF α) antibody at a concentration of 50 mg/ml,		⊙ (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNF α) antibody at a concentration of 50 mg/ml,	
⊙ (b) a polyol,		⊙ (b) a polyol,	
⊙ (c) a polysorbate, and		⊙ (c) a polysorbate, and	
⊙ (d) a buffer system comprising an organic acid and having a pH of 4 to 8,		⊙ (d) a buffer system comprising acetate and having a pH of 4 to 8,	
⊙ wherein the antibody is D2E7, and		⊙ wherein the antibody is D2E7, and	
⊙ wherein the formulation is suitable for subcutaneous injection.		⊙ wherein the formulation is suitable for subcutaneous injection.	

Figure 23 Patent Scope Comparison of '157 family

Second Group : Manufacturing Process Patents

Another group identified through the link of citations (pink line in Figure 20) consists of a group of manufacturing process patents. Two key patents in this group are '945 (selected by Amgen)⁸⁰ and '964 (selected by Abbvie)⁸¹. These two key patents are forward cited by the rest of the patents in this group (except for patent '666 which is also identified as a related manufacturing process after reading the patent specification). Subject matters in patent '945 and patent '964 and their scope are to be compared to understand why they were selected by the two parties.

Both '945 and '964 teach how to use cell line to produce the adalimumab antibody media composition. However the inventive concepts embodied in these two patents provide different technical functions. Patent '945 provides methods and compositions for improving protein expression in cell culture, particularly mammalian cell culture. The novel and inventive part that this patent claims is the outcome, i.e. the characteristics of cell culture composition resulting from the process. If Amgen wants to design around the patent, it simply needs to prove that its process has achieved a lower/higher result.

⁸⁰ US Patent No. 8911964

⁸¹ US Patent No. 8663945

In comparison, patent '964 covers a well monitored and controlled Fed-batch process for making adalimumab antibody media composition. The main focus of the patent is process variables, more specifically how to monitor and maintain certain glucose concentration in cell culture composition, which is much more difficult to be designed around as compared with patent '945. In addition, currently the only feasible alternative to Fed-batch process is the Continuous Manufacturing Technology.⁸² This alternative is still in its initial development stage and is not widely adopted for the mass production of human monoclonal antibody. Adalimumab biosimilar producers are not likely to have a workaround with the feb-batch process in their own manufacturing line.

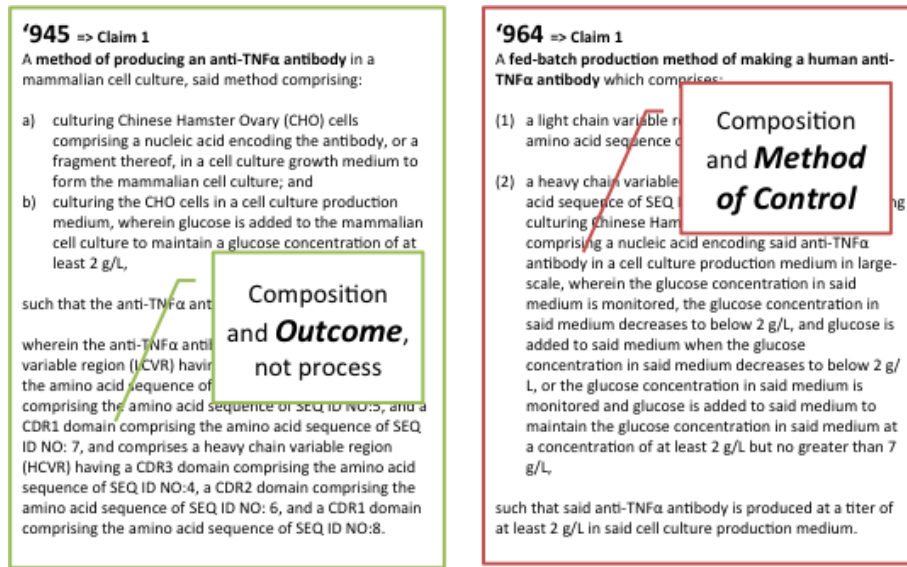


Figure 24: Comparison between '945 and '964

Amgen has also selected '666⁸³, '434⁸⁴ and '645⁸⁵ in the 61 patents list, which are all logical progression for manufacturing process improvements from '945. From Figure 21, it can be seen that '645 and '434 combines the technical improvements from both '945 (selected by Amgen) and '964 (selected by AbbVie). The technical bits introduced into these two patents by '964 consist of the better methods of control from Feb-batch process, which will enhance the strength of the two patents and cause Amgen's design around strategy in these two patents at least a partial (if not complete) failure. Further analysis could be done to study the interaction and scope of the patents within this group, which is not yet covered by this report.

⁸² Comparison of Batch Culture and Continuous Cultivation, 01 May 2000: <http://userpages.umbc.edu/~xkang/ENCH772/advantage.htm>

⁸³ US Patent No. 9096666

⁸⁴ US Patent No. 9359434

⁸⁵ US Patent No. 9150645

Lastly, the patents cited by AbbVie included a usage patent '693⁸⁶, covering one of the indications (psoriasis) of the Humira. The non-obviousness of this patent is also expected to be under great dispute. Amgen will certainly challenge that the new indications including psoriasis is obvious to the skilled workers in the art. Defending the validity of such usage patents are crucial to sustain Humira's market share for the treatment of the different diseases.

7.3.4 What will be the next step in the Patent Dance?

Based on our analysis above, Amgen is unlikely to escape from the legal protection that AbbVie's IP portfolio covers. In the area of manufacturing patents which Amgen seems to be focussing on in the first round litigation, it is anticipated that Amgen may also challenge the validity of the patents while contesting a non-infringement case. However, in the subsequent litigations that AbbVie intends to bring up when Amgen's ABP 150 goes to market, AbbVie still have patents with strong legal protection in its portfolio to use as a weapon.

The lack of Amgen's manufacturing process information is a challenge that AbbVie is facing at the current stage. As it learns more of its competitor's process in the first round of litigation, it will be more capable of strategizing the patent selection when going into the second round of litigation.

Considering the huge Humira market value and the huge value of AbbVie's Humira patent estate, the amount of compensatory damage and lost licensing profit will be a big impact to Amgen's business if the court concludes any of the 10 AbbVie's patents in suit has been infringed. As the case develops further, AbbVie's interlocutory injunction request, if granted, will be a powerful weapon to stop Amgen from selling the biosimilar drug, and will further pressurize Amgen to come into a licensing negotiation with AbbVie.

On 01 November 2016, the parties jointly proposed a bench trial commencing the week of November 4, 2019, with completion of fact discovery by January 15, 2018 and expert discovery by May 24, 2019. AbbVie noted that the proposed schedule is for the ten patents-in-suit and that "when Amgen provides notice of commercial marketing (which it is required to do 180 days before launch), AbbVie will bring suit on the remaining patents."⁸⁷

⁸⁶ US Patent No. 8986693

⁸⁷ ABBVIE V. AMGEN: THE PARTIES REQUEST A BENCH TRIAL IN NOVEMBER 2019, 31 October 2016 : <http://www.bigmoleculewatch.com/2016/10/31/abbvie-v-amgen-the-parties-request-a-bench-trial-in-november-2019/>

Hatch-Waxman: Brand and Generic Drugs	BPCIA: Biologics and Biosimilars
5 years marketing exclusivity for new active moiety;	12 years marketing exclusivity for new “biological structures.”
Generic drug application possible provided that the filing is accompanied by the patent challenge	Biosimilars application only possible after the 12 years exclusivity
The first generic “filer” receives six months of generic market exclusivity.	For the first “interchangeable” (a more difficult classification to obtain than mere biosimilarity) product has been approved, no subsequent interchangeable applications will be approved until one year after the first commercial marketing by the first licensee.
There is patent certifications to FDA indicating potential patent challenges. the FDA is required to suspend review and approval of the ANDA for 30 months unless shortened or lengthened by court order.	No automatic stay of approval if agreement is not achieved and patent infringement actions arise as a result.
All the PDA approved Brand and Generic Drugs are archived in the library called Orange book, listing patents including claims to the active ingredient, product or approved uses of the product	Exchange of information is not-voluntary: More specifically, information that describes the processes used to manufacture the biosimilar products are disclosed in the biosimilar application, whereas relevant patents are determined by the reference biological product (RBP) holder in the patent dance.
The NDA holder can bring suit on all patents the ANDA applicant included in the orange book certification.	Up to 12 patents can be asserted in the first round of patent litigation. Additional patents can be asserted after the biosimilar applicant gives its post-approval 180-day pre-marketing notice in the second round litigation

Table 20: Comparison of the procedural rights under Hatch-Waxman Act and BPCIA.

8. Discussion and Conclusions

One of the goals of this report was to evaluate the IP portfolio and strategy of Humira. We have shown the depth of Humira's portfolio given the complexity and competitiveness of the biopharmaceutical landscape and the extent of its patent protection, and believe that despite the many challenges to its position, it will maintain its market share till at least 2020.

A second goal of the paper was to discuss the IP management of AbbVie and propose possible paths forward. With the knowledge of AbbVie's competitive advantage, we have proposed possible IP strategies and considerations going forward. Given the relative pubescence of biopharmaceuticals and its regulations, we believe this to be essential in the long term growth of the company and to maintain their position as a market leader.

Overall, AbbVie has performed very well in its strategy to promote and protect their product. With a continuous growth of over \$16Bn in product sales since its inception, AbbVie's execution of their IP strategy and risk management has proven successful. Their defensive patenting strategy, coupled with their innovation trajectory has resulted in a patent portfolio of over 100 patents around the various technologies associated with Humira. We believe that their patterns of innovation and patent strengths will result in delaying market entry to the USA till at least 2020.

Yet, as the biopharmaceutical landscape is becoming increasingly complex and competitive, both major and minor players are beginning to realize the important of IP strategy and management. As such, AbbVie cannot rely on a single success and must amongst other things, capitalize on the following opportunities in IP strategy to remain a market leader (Figure 23).

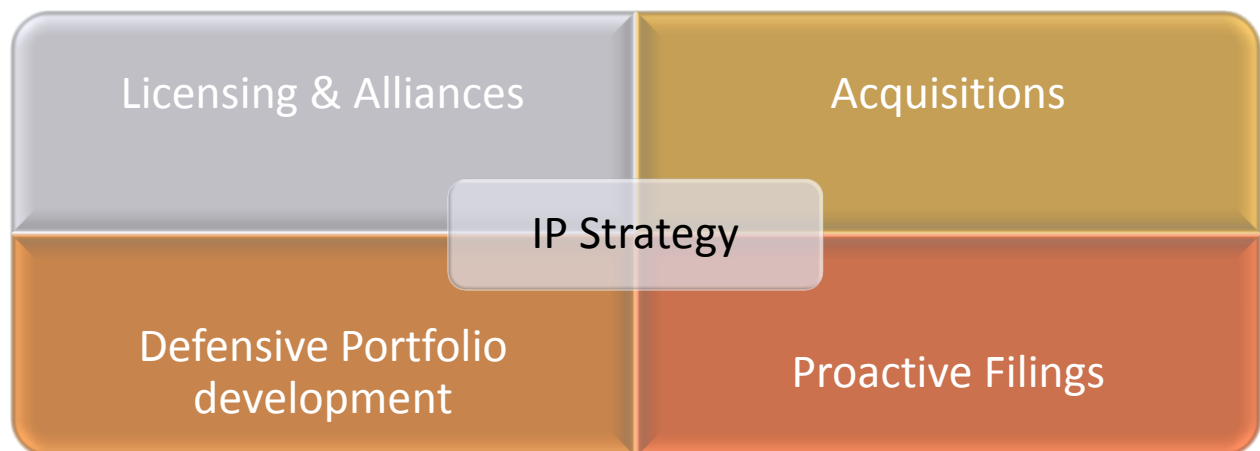


Figure 25 : Opportunities in IP Strategy

1. IP Licensing and strategic alliances

AbbVie is already a market leader in the immunotherapeutic segment. However, it is very reliant on its strong market presence and distribution channels in the USA and EU, with a majority of its revenue coming from these markets.

With the rapid growth of the Asian economic machine, AbbVie should look towards the east and capitalize on the market experience and distribution channels of Asian pharmaceutical companies to expand its market footprint. This involves active market licensing of their products and forming strategic alliances with the more established pharmaceutical distributors and marketing firms in Asia. While AbbVie has started some steps in this, there are still significant opportunities for expansion.

Yet, regulations in the east are in its adolescence and are relatively untested. As such, AbbVie should work to build a mutually beneficial relationship with the regulators as part of their strategy. Additionally, Humira is one of the best-in-class treatments for a number of diseases and may set the standard for treatments in future.

2. Acquisitions

AbbVie has an abundance of resources largely due to its success in Humira, but also because of its strong history with Abbott. As such, it has evolved a large R&D organization that bears the risk of closed innovation and should look at open innovative strategies to mitigate its risk of stagnation.

With such large reserves, AbbVie should explore the acquisition of smaller, more mobile pharmaceutical companies that have developed competing compounds and their associated patents. This serves to either eliminate the competition or leverage the work of others to expand their pipeline.

3. Defensive portfolio development

AbbVie spends a lot on R&D. Given the extremely low rates of success, for every rare blockbuster that makes it to the market, AbbVie should adopt a similar strategy as it did for Humira. However, given that IP strategy is gaining ground in the marketplace and with more spotlights being shone on the biopharmaceutical industry, it needs to develop truly innovative technologies to mitigate the risk of IPRs and invalidations.

4. Proactive filings

The timing of patent filings is an important factor in Biopharmaceutical IP strategy. In addition to cost of maintenance of the patent, the timing of additional filings can determine the length of market monopoly of the drug. AbbVie should explore possible options based on the strength of their innovations in context of the market and their competitors.

Finally, as interpretations to recent regulations become more certain, AbbVie's strategy needs to be dynamic to adapt to developments in landmark rulings and interpretations. We believe that an integration of the aforementioned factors will give AbbVie the edge in current and future market conditions.
