“Drug Lag” Analysis of Monoclonal Antibodies in the United States and Europe

by

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Submitted to the College of Health and Human Services

Eastern Michigan University

In partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

in

Clinical Research Administration

April, 2019

Ypsilanti, Michigan

Acknowledgments

I would like to thank Dr. Irwin Martin for providing me with the support and guidance throughout the project. He has always been available to help whenever I needed help in writing or research. I would also like to help Dr. Jean Rowan and Dr. Stephen Sonstein for guidance throughout my master's program.

Abstract

The review time of new drug applications (NDA) in the United States (US) and market authorization applications (MAA) in European Union (EU) were compared for monoclonal antibodies (mAbs). The Food and Drug Administration (FDA) had been criticized in the past for longer review times to approve drugs than the European Medicines Agency (EMA). The main objective of this study was to see how the FDA compared to the EMA in approving "cutting edge products". The FDA review time for mutually approved mAbs was calculated by searching the NDA submission dates and approval dates from Drugs@FDA. In a similar manner, MAA submission and approval dates were searched from European public assessment reports (EPAR) from the EMA website, and the review time were calculated. The review times for mAbs approved in both the US and EU were compared using descriptive statistics. The results revealed that FDA review time mean (in days) was 269, while the EMA review time mean (in days) was 427. Of the review times of the 63 mAbs that were compared, the FDA took longer than the EMA to review just four mAbs. Thus, there is no drug lag in approval of new technology products in the US. In fact, it seems the US may be a more efficient reviewer of these products.

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Chapter 1: Introduction

The United States Food and Drug Administration (US-FDA) is an agency within the United States Department of Health and Human Services that oversees the manufacturing and distribution of food, pharmaceuticals, medical devices, tobacco, and other consumer products and veterinary medicine. The European Medicines Agency (EMA) is the European Union (EU) agency for the evaluation of medicinal products. The new drug application (NDA) is the formal final step taken by a drug sponsor, which involves applying to the Food and Drug Administration (FDA) to get approval required to market a new drug in the United States (US). Marketing authorization application (MAA) is an authorization application submitted to the EMA for the purpose of obtaining approval from the European Commission to market the drug in the countries located within the EU. "Review time" is the time taken by the FDA to review NDAs (Center for Drug Evaluation, and Research, 2016), or the EMA to review MAAs from submission to marketing approval (European Medicines Agency, 2018d). The FDA had been criticized for taking longer review times than the EMA in the 1970s. Recent work, however, has shown this difference to have disappeared. It remains unknown, however, if high technology drugs are reviewed with equal efficiency by both agencies. Hence, there is a need to compare the review times of the FDA and EMA to see if there is a difference in the review times of high technology drugs between both the agencies. As an example of high technology drugs, review of monoclonal antibodies (mAbs) was used to compare the agencies. In this study, mAbs approved from the years 1997 to 2018 in both the US and EU were compared.

Chapter 2: Background

The US FDA had been criticized as inefficient compared to its European counterpart, the EMA (Wardell, 1973). A survey study published in 1973 was conducted in Britain (20 teaching hospitals) and in an American university medical center in the US, which included five therapeutic areas: angina, hypertension, asthma, pyelonephritis, and gastric ulcers (Wardell, 1973). Out of these therapeutic areas, certain drugs were unavailable in the US like salbutamol for asthma, beta blockers for angina, co-trimoxazole for pyelonephritis, carbenoxolone for gastric ulcers, and beta blockers and bethanidine for hypertension. Most American physicians were not knowledgeable about these drugs and wanted to have these drugs available to them. In another study completed in 1976, the US lagged behind Britain for approval of products in important categories including cardiovascular drugs, peptic ulcer, and central nervous system drugs, therapies for depression, epilepsy, and migraines (Wardell, 1978).

A report on the US-FDA drug approvals was submitted in 1980 to the Subcommittee on Science, Research, and Technology of the House Committee on Science and Technology (Comptroller General of the United States, 1980). It stated that the FDA approval process was lengthy, and important drugs (providing major or modest therapeutic gains over drugs already being marketed) and less important drugs took the same amount of time to get approved. Lengthy approvals delayed the benefits important drugs could provide to the public. According to this report, many important drugs such as disopyramide, to treat abnormal heart rhythm, were available more than five years earlier in the United Kingdom. Propranolol, an important advance in treating high blood pressure at the time of its introduction, was available more than seven years earlier in the United Kingdom. Sodium valproate, used to treat epilepsy, was available about six years earlier in Switzerland. The report stated that the FDA guidelines being unclear,

lack of efficient communication between the FDA and the industry, lengthy chemistry and manufacturing control reviews, incomplete NDAs, industry's slow rate of resolving deficiencies, intense congressional and consumer scrutiny of the drug approval process, adverse relationship between the FDA and the drug industry, and the FDA's conservative approach to drug regulation might have caused the delay in approving the drugs in the US (Comptroller General of the United States, 1980).

The review times for both the FDA and EMA were compared in a study for active treatment drugs for oncology approved in the US and EU (Roberts, Allen, & Sigal, 2011). The study identified 35 new oncology drugs that were approved by either the FDA or EMA from the years 2003 to 2010. All of the drugs that were approved by both the agencies were available to the patients in the US first. They concluded that pharmaceutical companies submit their clinical findings to the FDA prior to submitting those to EMA. Also, they discussed that the FDA consistently took less time than the EMA to review (Roberts, Allen, & Sigal, 2011).

Another study conducted to compare the total review times for all applications involving novel therapeutic agents approved from 2001 to 2010 by the FDA, EMA, and Health Canada (Downing et al., 2012). The analysis of the study included 225 approvals by the FDA, 186 by the EMA, and 99 by Health Canada. Among the applications, there were 289 unique agents. The study concluded that median length of time for completion of the first review was 303 days for applications approved by the FDA, 366 days for those approved by the EMA, and 352 days for those approved by Health Canada. The median total review time was also shorter at the FDA than at EMA or Health Canada. Among the 289 unique novel therapeutic agents, 190 were approved in both the US and EU, of which 121 were first approved in the US. Similarly, 154

were approved in both the US and Canada, of which 132 were first approved in the US (Downing et al., 2012).

In our program, a "drug lag" analysis had been done for new molecular entities (NMEs) of mutually approved drugs in the US and EU. In the study, NMEs' approval time between the US and EU was compared for drugs approved from 1993 to 2015 (Deore, 2016). The study demonstrated that drug approval delays no longer exist in the US when compared to the EU for the years 1993 through 2015. The number of first NME approvals in the US was greater and any drug approval delay was higher in the EU (Deore, 2016).

In a later analysis (Deore, 2017), the review time for both the agencies was compared in terms of therapeutic class and type of review for the drugs approved from 1994 to 2015 for approved drugs in both regions. The study revealed that the US had no review time delay compared to the EU. The US-FDA conducted a faster review in almost all therapeutic areas. Based on the type of review, the US-FDA also took less review time for priority, standard, and orphan drugs.

In an attempt to further examine the review differences between the FDA and EMA, it was postulated that high technology drugs might be reviewed more efficiently in the US than in the EU due to the internal review expertise of the FDA. Therefore, the current project compared the review time taken by both the FDA and EMA to approve mAbs, an example of a high technology class of drugs, from 1997 to 2018. Abciximab (Reopro) was the first mAb approved in the US in 1994. Since abciximab was not approved in the EU, this was not included in this analysis. Thus, 1997 was the first year any mAb was approved by both the agencies.

Chapter 3: Introduction to Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) were first discovered in 1970 by the scientists at the Roche-funded Basel Institute for Immunology (Genentech, 2019). The initial mAbs being produced from mice caused immune reactions in humans. Hence, research was done to humanize the mAbs by producing chimeric mouse-human monoclonal antibodies and then fully human recombinant mAbs.

Monoclonal antibody names are comprised of four main sections: Prefix / Target class / Source / Stem. Most currently marketed antibody names end (stem) with “mab”, which indicates that the drug is a monoclonal antibody. The next-to-last syllable refers to the source of the antibody. It refers to the species on which the structure of the antibody was based. For example: “o” refers to nearly 100% mouse source for the antibody structure, “xi” refers to antibodies that are partially human-like and partially other organism-like in structure, “zu” antibodies are humanized, or approximately 90% human-like, and “u” antibodies are fully human in nature. The “target class” refers to the therapeutic use of the drug and/or the targeted types of disease states. Some commonly used examples include “tu” or “tum” drugs used to treat cancer, “li” drugs that impact the immune system and “ci” drugs that affect the circulatory or cardiovascular system. The prefix is the first one or two syllables. The name is proposed by the manufacturer developing the drug. (Curler & Thompson, 2016).

Use of mAbs is not limited to one therapeutic area. Initial mAbs were used as immunomodulatory agents to prevent rejection after solid organ transplantation. Further development produced mAbs to prevent tissue damage in diseases like rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, multiple sclerosis, and psoriasis.

Therapeutic use of mAbs is also broadening for asthma, atopic dermatitis, migraine headaches, hypercholesterolemia, osteoporosis, and viral or bacterial infections (National Institute of Health, 2018). As of 2018, more than 60 therapeutic monoclonal antibodies were approved in the US (National Institute of Health, 2018). Since the discovery in 1970, improved and direct techniques are being used to identify, select, optimize, and manufacture mAbs. The advanced technology and greater understanding of the development have led to precise tailoring of mAbs' activity. The clinical trial of the drug ZMapp containing three different mAbs appeared to show a drop in mortality among infected volunteers who received the experimental therapeutic in the Ebola outbreak in 2014-2016 (National Institute of Allergy and Infectious Diseases (NIAID), 2018). Preclinical research showed the probability of mAbs' role in protecting from the Zika virus, and influenza treatment and prevention. A number of mAbs have been created to specifically target antigens on cancer cells and/or to selectively deliver radiotherapy to them (Pento, 2017). Human Immunodeficiency Virus (HIV) mAbs technology discovered several hybridomas that produce mAbs useful in HIV research as well (National Institute of Health- Office of Intramural Research Office of Technology Transfer, 2018).

Chapter 4: Drug Review Process in the US

The Prescription Drug User Fee Act (PDUFA) launched in 1992 proved to be of great help in biopharmaceutical innovation systems in the US. PDUFA was passed by Congress in 1992 and authorized the FDA to collect fees from companies that produce certain human drugs and biological products. Since the passage of PDUFA, user fees have played an important role in expediting the drug approval process. PDUFA is reauthorized every 5 years. On August 18, 2017, PDUFA was reauthorized through September 2022 (Office of the Commissioner, 2019). Under PDUFA, the FDA started to review applications in two categories: standard review, and priority review. Under standard review, the FDA's goal is to review the application in 10 months; and under priority review, the goal to review is 6 months. The application is considered under priority review if the drug would be of significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications (Office of the Commissioner, 2018b). Many mAbs have gone through priority review, which means the FDA's goal was to take action on most of the mAbs application within 6 months of filing compared to 10 months under standard review.

A. The FDA Modernization Act of 1997

One of the main initiatives of the FDA Modernization Act of 1997 was to modernize the regulation of biological products. The act eliminated the requirement for establishment applications, batch certifications, and monograph requirements for insulin and antibiotics. It also reduced the need for environmental assessments as part of a product application (Office of the Commissioner, 2018b). Since mAbs are biologics, this act made it easier for the companies to develop mAbs. The act codified the FDA's regulations and practice to increase patient access to

experimental drugs and medical devices and expanded databases on clinical trials. It also provided for advance notices to the patients about the drugs being discontinued in the near future on which they rely on for life support or serious conditions. Even though the act made it easier for the industry to develop and get the drugs approved, it did not lower the standards by which medical products were to be introduced for public use. For each drug to be approved, companies must have two adequate and well-controlled studies to prove the product's safety and effectiveness (Office of the Commissioner, 2018a)

B. Transfer of Therapeutic Products to the Center for Drug Evaluation and Research

In 2003, some of the therapeutic biological products were transferred to the Center for Drug Evaluation and Research (CDER) from the Center for Biologics Evaluation and Research (CBER). Since then, the CDER has been regulating the transferred biological therapeutic products including premarket review and continuing oversight. CDER and CBER consult and support each other for regulation issues of the products (CBER, 2018). Monoclonal antibodies for in-vivo use are reviewed by CDER under this transfer (US Food and Drug Administration, 2017).

Chapter 5: Drug Approval Process in Europe

The law to charge fees by the EMA to provide regulatory services to authorize medicines was enacted in 1995. The rules relating to the agency's fees are governed by the fee regulation (Council Regulation [EC] No 297/95) and its implementing rules, as well as the pharmacovigilance fee regulation (Regulation [EU] No 658/2014, European Medicines Agency, 2018c).

In the EU, there are two routes for authorizing medicines: a centralized route and a national route. Since most mAbs are being developed for HIV, cancer, auto-immune diseases, and infectious diseases, therefore, mAbs would be reviewed through the centralized authorization procedure (European Medicines Agency, 2018a). The Committee for Medicinal Products for Human Use (CHMP) is the European Medicines Agency's (EMA) committee responsible for human medicines. It replaced the former Committee for Proprietary Medicinal Products (CPMP) in May 2004. The CHMP plays a vital role in the authorization of medicines, assessing modifications to existing marketing authorization, considering the recommendations of the EMA's Pharmacovigilance Risk Assessment Committee on the market, recommending to the European Commission changes to a medicine's marketing authorization, or its suspension or withdrawal from the market. The CHMP also evaluates medicines authorized at the national level referred to EMA for a harmonized position across the EU (European Medicines Agency, 2018b).

The MAA is mandatory to be reviewed under centralized procedure for human medicines containing a new active substance to treat HIV or acquired immune deficiency syndrome (AIDS), cancer, diabetes, neurodegenerative diseases, auto-immune diseases, viral diseases,

medicines derived from biotechnology processes, such as genetic engineering, advanced-therapy medicines, such as gene-therapy, somatic cell therapy, or tissue-engineered medicines, and orphan medicines (medicines for rare diseases) (European Medicines Agency, 2018a). Drugs that are significant therapeutic, scientific, or technical innovations, whose authorization would be in the interest of the public or animal health at the EU level, also qualify for the centralized procedure.

Under the centralized authorization procedure, pharmaceutical companies submit a single application market authorization application (MAA) to the EMA. Once approved, MAA holders can make the drugs available throughout the EU (European Medicines Agency, 2018a). The MAA holders do not need to submit separate applications in the member states of the EU under this procedure. The authorization granted by the European Commission is valid in all member states of the EU and European Economic Area (EEA) countries of Iceland, Liechtenstein, and Norway.

Currently, most of the new, innovative medicines pass through the centralized authorization procedure in order to be marketed in the EU (European Medicines Agency, 2018a). After the MAA submission, the Pharmacovigilance Risk Assessment Committee (PRAC) provides input on aspects related to risk management and the Committee for Advanced Therapies (CAT) on advanced therapy medicines. This whole procedure takes up to 210 days. After the evaluation, the CHMP issues a scientific opinion on whether the medicine may be authorized or not. The EMA sends the opinion to the European Commission, which issues the marketing authorization. Within 67 days of CHMP opinion, European Commission decisions are published in the Community Register of medicinal products of human use, and the EMA publishes a European

public assessment report (EPAR). The goal to approve a drug through this procedure is 277 days (European Medicines Agency, n.d.).

Chapter 6: Methodology

To compare the review times, the NDA submission dates and the approval dates for the mAbs by the FDA were searched from the FDA website at Drugs@FDA from 1994 through 2018; and the mAbs' names, dates of submission, and dates of approval were collected in an Excel sheet. In a similar manner, the MAA submission dates and approval dates for the mAbs approved in Europe were searched in the European Public Assessment Reports from the initial authorization documents at the EMA website starting from 1997 through 2018. Since the first mAb was approved by EMA was in 1997, the analysis for the study was done starting from 1997. The lists were compared and only products approved in both regions between 1997 and 2018 were considered for analysis. Further description of how data were gathered, may be found in Deore (2016) and Deore (2017). Days taken by both the agencies to review the mAbs were calculated using "Days Calculator" by inputting the submission dates and approval dates. The approval date and review time were both compared by calculating the difference in review days of both the agencies for all the mAbs approved in both the regions. In this project, the data of 63 mAbs were found available at both the FDA and EMA websites and was compared. The project used descriptive statistics to analyze and present the results.

Chapter 7: Results

The review times of 63 mAbs approved from the years 1997 to 2018 was compared by descriptive statistics. The first mAb approved in 1994 in the US was not approved in the EU. Therefore, the analysis conducted in the study started from the year 1997.

The FDA review time mean (in days) was 269.06 with a median of 241.0 days (Figures 1 and 2). The shortest review times taken by the FDA was 76 days for blinatumomab, 128 for denosumab, 128 for atezolizumab, and 131 for daratumumab (Appendix B). The longest review time taken by the FDA for mAbs was 728 days for ustekinumab, 571 for sarilumab, 476 for iIbritumomab tiuxetan, 458 for brodalumab, and 456 for daclizumab (Appendix B). Of the 63 mAbs studied, the FDA approved 1 mAb in less than 100 days, 7 in 100 to 150 days, 16 in 150 to 200 days, 11 in 200 to 250 days, 5 in 250 to 300 days, 6 in 300 to 350 days, 11 in 350 to 400 days, 4 in 400 to 450 days, 1 in 550 to 600 days and 1 in 700 to 750 days' range (Figure 2). The FDA review time ranged from 76 to 728 days (Appendix B).

Under PDUFA, the FDA's goal is to complete standard reviews in 10 months, and priority reviews in 6 months (Office of the Commissioner, 2019). Based on the study results, of the 63 mAbs approved, 11 were approved in 76 to 173 days (within 6 months), 29 in 182 to 279 days (6 to 10 months), 17 in 304 to 381 days (10 to 13 months), 4 in 429-476 days (14 to 16 months), 1 in 571 days (19 months), and 1 in 728 days (24 months) (Appendix B).

The EMA review time mean (in days) was 426.76 with a median of 429.0 days (Figures 1 and 3). The shortest review time taken by the EMA was 246 days for lanadelumab (SHP643), 247 for emicizumab, 264 for idarucizumab, 267 for siltuximab, and 269 for eculizumab (Appendix B). The longest review time taken by the EMA was 755 days for natalizumab, 624 for

ocrelizumab, 618 for dinutuximab, 613 for brodalumab, and 598 for daratumumab (Appendix B). Of the 63 mAbs studied, the EMA approved 2 mAbs in 200 to 250 days, 6 in 250 to 300 days, 8 in 300 to 350 days, 7 in 350 to 400 days, 18 in 400 to 450 days, 7 in 450 to 500 days, 7 in 500 to 550 days, 4 in 550 to 600 days, 3 in 600 to 650 days, and 1 in 750 to 800 days' range (Figure 3). The EMA review time ranged from 246 to 755 days (Appendix B).

The EMA's goal to approve a drug through the centralized procedure is 277 days (about 9 months). The results of this study revealed that of the 63 mAbs compared, 5 were approved in 246 to 269 days (within 277 days' limit), 17 in 286 to 386 days, 26 in 394 to 484 days, 11 in 503 to 598 days, 3 in 613 to 624 days, and 1 in 755 days (Appendix B).

Of the review times of 63 mAbs that were compared, the FDA took longer than the EMA to review four mAbs. For the remaining 59 mAbs, the EMA took longer than the FDA to review. There was a difference of 157.7 days in means (426.76-269.06) of the mAbs review days. Thus, the FDA approved these applications on average over 5 months sooner than the EMA.

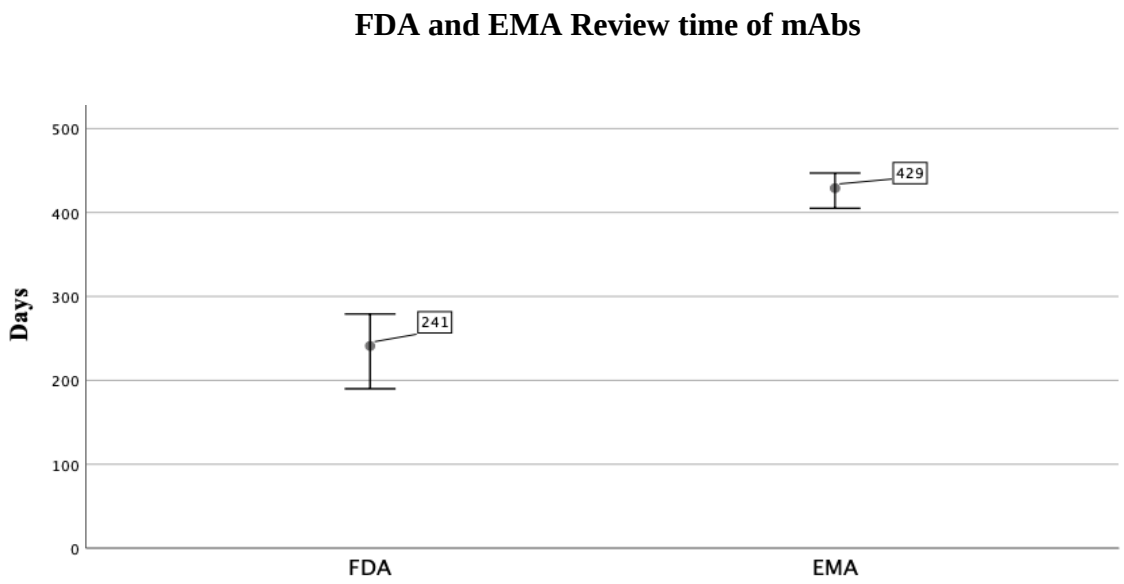

Figure 1: Median time in days (± 95% CI) for FDA and EMA review times

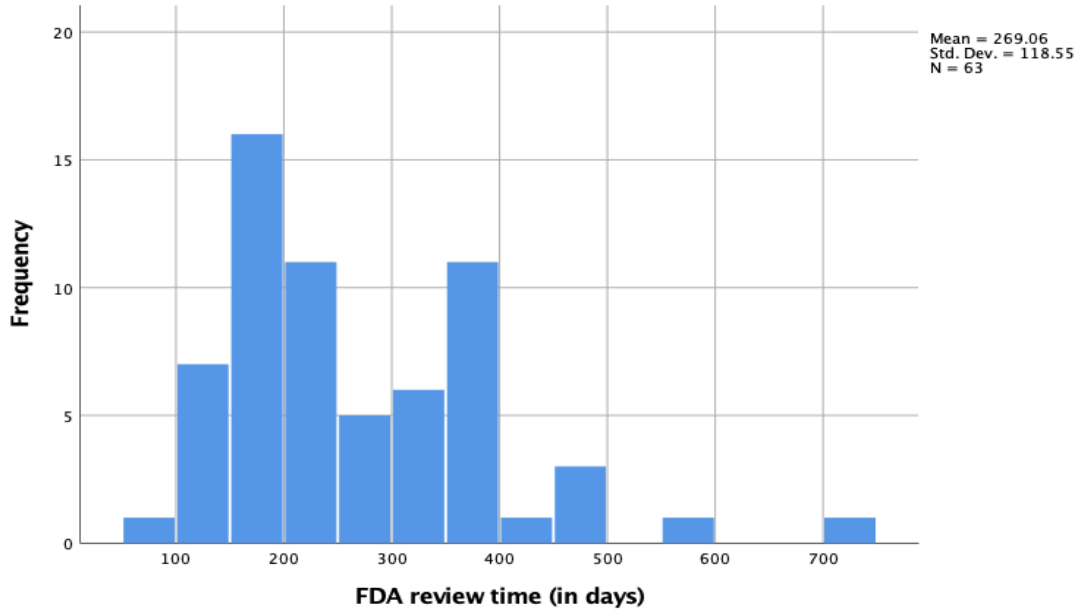

Figure 2: FDA review time (in days) for mAbs

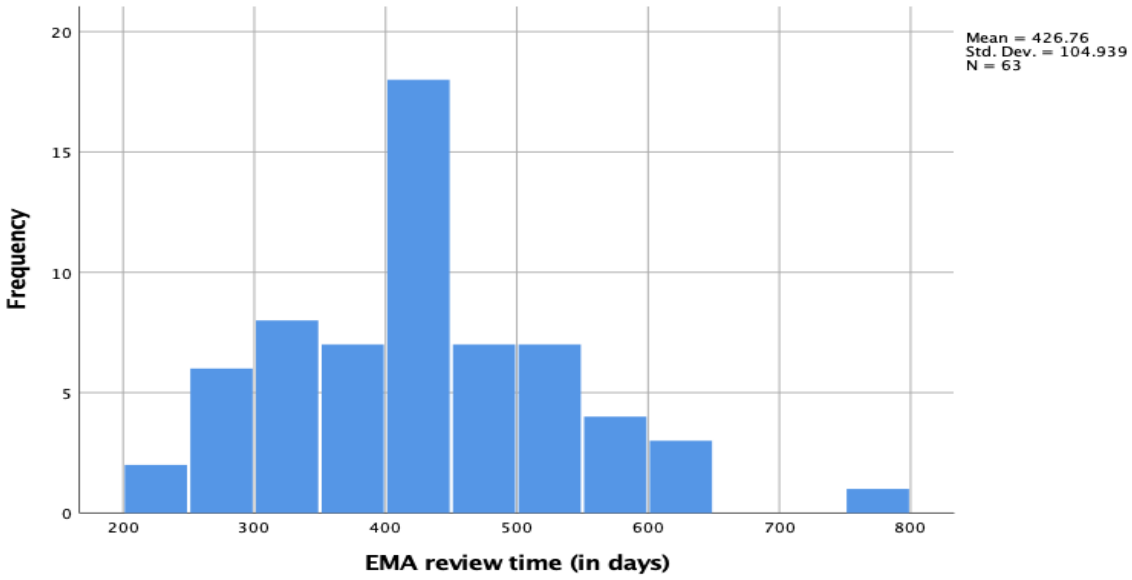

Figure 3: EMA review time (in days) for mAbs

Chapter 8: Discussion

This study compared the review times for the mAbs to see if there was a difference between the FDA and EMA from the years 1997 to 2018. The results revealed that the EMA had taken longer review times to review (59 out of 63 mAbs compared) than the FDA. After PDUFA came into effect, the FDA review and approval times have improved greatly. With PDUFA implementation, the FDA could hire more experts to review the applications and improve the information technology through upgrading the FDA website. Under PDUFA, the FDA's goal is to complete standard reviews in 10 months and priority reviews in 6 months. According to the results of this study, the average review time for the FDA was less than 9 months.

All the mAbs go through a centralized procedure in the EU. Under this procedure the CHMP (with the help of CAT and PRAC) evaluates MAA (European Medicines Agency, n.d.). The CHMP within EMA aims for 210 days to evaluate MAA. The European Commission has 67 days to authorize the marketing of the drug after it receives a positive scientific opinion from the EMA. Therefore, the goal to approve a drug through this procedure is 277 days (about 9 months). According to the results of this study, the average review time for the EMA was 14 months.

The study results from the first part of this project (Deore, 2016) revealed that nearly 79% of the new molecular entities (NMEs) were first approved in the US. The median approval difference per year calculated was significantly higher in the EU. The average approval difference per year for the EU was higher at 12 months in comparison to 4 months in the US. The study concluded that there is now no delay in the approval of new drugs in the US when compared to the EU, and the drug delay is statistically significantly higher in the EU.

The study results from the second part of this project (Deore, 2017) revealed that the US had no review delay compared to the EU for the year 1994 to 2015. The US-FDA conducted a faster review in almost all the therapeutic areas. Of the 210 drugs reviewed, 160 drugs took less review time in the US, whereas in the EU 50 drugs. Average review delay for the US was 3.09 months, and for EU was 4.92 months. The study concluded that the review delay for Europe was statistically significantly higher than in the US.

After studying the review process of both the agencies, and the results of the studies, the different organizations in the EMA involved to review, and authorize marketing of drugs, may cause the review process to be slower as compared to the FDA where review and the approval are done by a single organization within the FDA. Perhaps both organizations have now reached their optimal review time. It is likely that without bureaucratic streamlining in the EMA, the FDA will remain more efficient agency for regulatory reviews.

Chapter 9: Conclusion

Previous work done as first and second parts of this study (Deore, 2016), and (Deore, 2017), shows a little difference in review times of the FDA and EMA. This study was conducted to find out if it was still true in high technology products. Monoclonal antibodies were used as an example of high technology drugs in this study to compare the review time of both the agencies. The results revealed that the US-FDA is faster by over 5 months on average than EMA. The EU bureaucracy process may slow down the review process so that reviews are unlikely to ever match the FDA without organizational changes.

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Appendices

Appendix A: mAbs approved both in the US and EU from 1997 to 2018

Monoclonal Antibody	Brand name in USA	Brand name in Europe
Rituximab	Rituxan	MabThera
Basiliximab	Simulect	Simulect
Palivizumab	Synagis	Synagis
Infliximab	Remicade	Remicade
Trastuzumab	Herceptin	Herceptin
Gemtuzumab Ozogamicin	Mylotarg	Mylotarg
Alemtuzumab	Campath	MabCampath
Ibritumomab Tiuxetan	Zevalin	Zevalin
Adalimumab	Humira	Trudexa
Cetuximab	Erbitux	Erbitux
Natalizumab	Tysabri	Tysabri
Ranibizumab	Lucentis	Lucentis
Panitumumab	Vectibix	Vectibix
Eculizumab	Soliris	Soliris
Certolizumab Pegol	Cimzia	Cimzia
Golimumab	Simponi	Simponi
Canakinumab	Ilaris	Ilaris
Ustekinumab	Stelara	Stelara
Ofatumumab	Arzerra	Arzerra
Tocilizumab	Actemra	RoActemra
Denosumab (Prolia)	Prolia	Prolia
Denosumab (Xgeva)	Xgeva	Xgeva
Belimumab	Benlysta	Benlysta
Ipilimumab	Yervoy	Yervoy
Brentuximab Vedotin	Adcetris	Adcetris
Pertuzumab	Perjeta	Perjeta
Ado-Trastuzumab Emtansine	Kadcyla	Kadcyla
Obinutuzumab	Gazyva	Gazyvaro
Ramucirumab	Cyramza	Cyramza
Siltuximab	Sylvant	Sylvant
Vedolizumab	Entyvio	Entyvio

Appendix A: mAbs approved both in the US and EU from 1997 to 2018

Appendix A continued: mAbs approved both in the US and EU from 1997 to 2018

Monoclonal Antibody	Brand name in USA	Brand name in Europe
Pembrolizumab	Keytruda	Keytruda
Blinatumomab	Blincyto	Blincyto
Nivolumab	Opdivo	Opdivo
Secukinumab	Cosentyx	Cosentyx
Dinutuximab	Unituxin	Unituxin
Alirocumab	Praluent	Praluent
Evolocumab	Repatha	Repatha
Idarucizumab	Praxbind	Praxbind
Mepolizumab	Nucala	Nucala
Daratumumab	Darzalex	Darzalex
Necitumumab	Portrazza	Portrazza
Elotuzumab	Empliciti	Empliciti
Reslizumab	Cinquair	Cinqaero
Ixekizumab	Taltz	Taltz
Atezolizumab	Tecentriq	Tecentriq
Daclizumab	Zinbryta	Zenapax
Olaratumab	Lartruvo	Lartruvo
Bezlotoxumab	Zinplava	Zinplava
Brodalumab	Siliq	Kyntheum
Avelumab	Bavencio	Bavencio
Dupilumab	Dupixent	Dupixent
Ocrelizumab	Ocrevus	Ocrevus
Durvalumab	Imfinzi	Imfinzi
Sarilumab	Kevzara	Kevzara
Guselkumab	Tremfya	Tremfya
Inotuzumab Ozogamicin	Besponsa	Besponsa
Benralizumab	Fasenra	Fasenra
Emicizumab	Hemlibra	Hemlibra
Tildrakizumab-asmn	Ilumya	Ilumetri
Burosumab-twza+A63	Crysvita	Crysvita
Erenumab-aooe	Aimovig	Aimovig
Lanadelumab(+A65SHP643)	Takhzyro	Takhzyro

Appendix B: Review time in US and EU for each product in the study

Monoclonal antibody	NDA submission	NDA approval	NDA review time (in days)	MAA submission	MAA approval	MAA review time (in days)	Difference: (FDA review time - EMA review time)
Rituximab	5-06-97	11-26-97	205	2-27-97	6-02-98	461	-256
Basiliximab	11-12-97	5-12-98	182	10-07-97	10-09-98	368	-186
Palivizumab	12-19-97	6-19-98	183	7-31-98	8-13-99	379	-196
Infliximab	12-30-97	8-24-98	238	3-05-98	8-13-99	527	-289
Trastuzumab	5-04-98	9-25-98	145	2-11-99	8-28-00	565	-420
Gemtuzumab Ozogamicin	8-30-99	5-17-00	262	12-01-16	4-19-18	505	-243
Alemtuzumab	6-21-99	6-23-00	369	3-23-00	7-06-01	471	-102
Ibritumomab Tiuxetan	11-01-00	2-19-02	476	3-07-03	1-16-04	316	160
Adalimumab	3-28-02	12-31-02	279	3-28-02	9-01-03	523	-244
Cetuximab	8-14-03	2-12-04	183	7-01-03	6-29-04	454	-271
Natalizumab	5-24-04	11-23-04	184	6-03-04	6-27-06	755	-571
Ranibizumab	8-11-05	6-30-06	324	2-08-06	1-22-07	349	-25
Panitumumab	3-29-06	9-27-06	183	4-28-06	12-03-07	319	-136
Eculizumab	9-15-06	3-16-07	183	9-25-06	6-20-07	269	-86
Certolizumab Pegol	4-30-07	4-22-08	359	6-06-08	10-01-09	483	-124
Golimumab	6-25-08	4-24-09	304	3-03-08	10-01-09	578	-274
Canakinumab	12-17-08	6-17-09	183	12-04-08	10-23-09	324	-141
Ustekinumab	9-29-07	9-25-09	728	12-04-07	1-15-09	409	319
Ofatumumab	1-30-09	10-26-09	270	2-05-09	4-19-10	439	-169
Tocilizumab	7-09-09	1-08-10	184	11-29-07	1-15-09	414	-230
Denosumab (Prolia)	1-25-10	6-01-10	128	1-09-09	5-26-10	503	-375
Denosumab (Xgeva)	1-25-10	6-01-10	128	6-04-10	7-13-11	405	-277
Belimumab	6-09-10	3-09-11	274	6-04-10	7-13-11	405	-131
Ipilimumab	6-25-10	3-25-11	274	5-05-10	7-12-11	434	-160
Brentuximab Vedotin	2-28-11	8-19-11	173	5-31-11	10-25-12	514	-341
Pertuzumab	12-06-11	6-08-12	186	12-01-11	3-04-13	460	-274
Ado-Trastuzumab Emtansine	8-24-12	2-22-13	183	8-30-12	11-15-13	443	-260
Obinutuzumab	4-22-13	10-03-13	165	4-25-13	7-22-14	454	-289
Ramucirumab	3-27-13	4-11-14	381	8-23-13	12-19-14	484	-103
Siltuximab	8-30-13	4-23-14	237	8-29-13	5-22-14	267	-30
Vedolizumab	6-20-13	5-20-14	355	3-06-13	5-22-14	443	-88

Appendix B: Review time in US and EU for each product in the study

Appendix B continued: Review time in US and EU for each product in the study

Monoclonal antibody	NDA submission	NDA approval	NDA review time (in days)	MAA submission	MAA approval	MAA review time (in days)	Difference: (FDA review time - EMA review time)
Pembrolizumab	2-27-14	9-04-14	190	6-04-14	7-16-15	408	-218
Blinatumomab	9-19-14	12-03-14	76	10-09-14	11-23-15	411	-335
Nivolumab	7-30-14	12-22-14	146	9-02-14	6-19-15	291	-145
Secukinumab	10-22-13	12-24-14	429	10-23-13	1-14-15	449	-20
Dinutuximab	4-11-14	3-10-15	344	12-05-13	8-14-15	618	-274
Alirocumab	11-24-14	7-24-15	243	12-02-14	9-23-15	296	-53
Evolocumab	8-27-14	8-27-15	366	8-29-14	7-17-15	323	43
Idarucizumab	2-19-15	10-16-15	240	3-02-15	11-20-15	264	-24
Mepolizumab	11-04-14	11-04-15	366	11-03-14	12-01-15	394	-28
Daratumumab	7-09-15	11-16-15	131	9-09-15	4-28-17	598	-467
Necitumumab	12-02-14	11-24-15	358	12-01-14	2-15-16	442	-84
Elotuzumab	6-29-15	11-30-15	155	7-03-15	5-11-16	314	-159
Reslizumab	3-29-15	3-02-16	340	6-30-15	8-15-16	413	-73
Ixekizumab	3-23-15	3-22-16	366	4-23-15	4-25-16	369	-3
Atezolizumab	1-12-16	5-18-16	128	4-20-16	9-21-17	520	-392
Daclizumab	2-27-15	5-27-16	456	9-04-97	2-26-99	541	-85
Olaratumab	2-24-16	10-19-16	239	1-29-16	11-09-16	286	-47
Bezlotoxumab	11-22-15	10-21-16	335	11-17-15	1-18-17	429	-94
Brodalumab	11-16-15	2-15-17	458	11-13-15	7-17-17	613	-155
Avelumab	9-23-16	3-23-17	182	10-06-16	9-18-17	348	-166
Dupilumab	7-29-16	3-28-17	243	11-04-16	9-27-17	328	-85
Ocrelizumab	4-28-16	3-28-17	335	4-25-16	1-08-18	624	-289
Durvalumab	10-13-16	5-01-17	201	9-01-17	9-21-18	386	-185
Sarilumab	10-30-15	5-22-17	571	6-24-16	6-23-17	365	206
Guselkumab	11-16-16	7-13-17	240	11-23-16	11-10-17	353	-113
Inotuzumab Ozogamicin	12-20-16	8-17-17	241	4-14-16	6-28-17	441	-200
Benralizumab	11-16-16	11-14-17	364	11-24-16	1-08-18	411	-47
Emicizumab	6-23-17	11-16-17	147	6-22-17	2-23-18	247	-100
Tildrakizumab-asmn	3-23-17	3-20-18	363	3-06-17	9-17-18	561	-198
Burosumab-twza+A63	8-17-17	4-17-18	183	11-30-16	2-19-18	447	-264
Erenumab-aooe	5-17-17	5-17-18	366	5-23-17	7-26-18	430	-64
Lanadelumab(+A65SHP643)	12-26-17	8-23-18	241	3-12-18	11-22-18	246	-5