Drug Lag Analysis of New Molecular Entities (NMEs) in the United States and Europe- Extension Project

by

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Abstract

Introduction

Review time determines the time taken to review the NDA application from NDA submission to completion of the review. The FDA had been criticized for taking double the time to review compared to EU.

Objectives

The primary objective of the study was to analyze the review delay in the US as well as in the EU for mutually approved drugs from the year 1994 to 2015. The study also analyzed the review delay in terms of therapeutic class and type of review.

Methods

The data for this study was collated from the regulatory websites - FDA and EMA. The approval letters from the Drugs@FDA and initial marketing-authorization documents available at the European public assessment reports (EPAR) on the EMA website were collected and compared in MS Excel 2013. Then the data was analyzed to determine the review delay in terms of two variables. One variable was the number (%) of drug first reviewed in the US as well as in EU. The other variable was the review delay in terms of therapeutic class and type of review. Non-parametric Wilcoxon Signed Ranks Test was used for determining statistical significance in review delay.

Results

From year 1994 to 2015, the median review time for the US was 9.88 months whereas for EU, 14.55 months. Out of 210 drugs, 160 (76.19%) drugs took less review time in the US, whereas in EU, 50 (23.81%) drugs. Average review delay for US was 3.09 months, whereas for EU, 4.92 months. Review delay by ATC classification code in the US was for 3 classes whereas in EU for the remaining 12 classes. Hundred and four (104) priority drugs had review delay in EU, whereas 18 drugs had in the US. Fifty - four (54) standard drugs had review delay in EU whereas 32 drugs had in the US. Based on the sample size of 210, Wilcoxon Signed Ranks test indicates that the review delay for Europe (MAA review time) (mean rank 125.81) was statistically significantly higher than the US (NDA review time) (mean rank 99.15); Z= -5.43 and p value < 0.000 at 95 % confidence interval.

Conclusions

The study revealed that the US had no review delay compared to EU for the year 1994 to 2015. The FDA had taken statistically significantly less review time in comparison to EU. The US-FDA conducted faster review in almost all the therapeutic areas. Based on the type of review, US-FDA took less review time for priority, standard and orphan drugs. The regulatory agencies of the US and Europe should take efforts to harmonize the review process which can minimize the review delay in EU.

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Chapter 1: Introduction

The US Congress enacted the Prescription Drug User Fee Act (PDUFA) in 1992, which permited the FDA to collect user fees from companies (US FDAd). PDUFA is reauthorized every 5 years. According to Downing, Aminawung, Shah, Braunstein, Krumholz, & Ross (2012), every renewal had focus on specific areas. The focus of PDUFA IV renewal in 2007 was on safety of drug and post marketing surveillance. For the PDUFA V renewal in 2012, the focus was to improve the competence and efficiency of the NDA review process. The user fees made a significant impact on the review cycle of NDA applications. When the sponsor submits an NDA application, the FDA takes 60 days to make a decision whether to file the NDA and then the application is reviewed. There are 2 types of review cycle: priority review and standard review. In 1992, the FDA authorized designation of priority review refers to "those drugs that, if approved, would lead to significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications" (US FDAb). Priority reviews should take 6 months to review the application. Standard review refers to "applications for drugs that do not meet the priority review designation criteria" (US FDA, 2013). Standard reviews should take 10 months to review the application. While in the EMA, it should take 210 days for the evaluation of marketing authorization applications (MAAs) via centralized procedure. There is an accelerated assessment for medicines that are of main concern for public health, particularly ones that are therapeutic innovations (EMAb) which generally takes 150 evaluation days, rather than 210. According to Downing, Aminawung, Shah, Braunstein, Krumholz, & Ross (2012), the first review time is defined as "the number of days between submission of the NDA application and completion of the first review (the date on which the regulatory agency notified the applicant of the decision)". For the EMA, the

completion date for the first review is the date the agency issues an initial recommendation. For applications that need multiple reviews, “total review time” is defined as the combined length of all the regulatory review cycles required for approval. An earlier analysis (Deore, 2016) compared the difference between the approval dates in the US and EU. To provide additional insight, this project aimed to find the difference between total review times in the US and EU with regards to therapeutic area, type of review and also for the individual drug.

Chapter 2: Background

The regulators try to approve safe and effective drugs for the marketplace. Past tragedies such as thalidomide (1962) led to stringent laws related to approval of drugs. It had been claimed that the FDA took longer to review the applications and thus leading to additional time taken for drugs to reach the market, which was termed the "Drug Lag" (Wileman and Mishra, 2010). Wardell in 1970 first described the drug lag, and since then it has been a debated issue (Tsuji and Tsutani, 2010). It was claimed that the FDA was taking double the time taken by EMA to approve drugs (Zakaria, 2011). While the FDA review process attempts to screen drugs that are not safe or effective, this thourough review may hinder a patient's access to the safe and effective drugs, especially for those patients with serious or life threatening diseases for whom no other treatment is available (Kesselheim, Wang, Franklin, & Darrow, 2015). Some were critical that this long approval process unnecessarily holds up patient access to new medications that may have improved their health (Rawson, 2000). The availability of a drug in one country and not in another country is seemed to be unfair to the patients of the other country who are deprived of the drug (Trotta, Leufkens, Schellens, Laing, & Tafuri, 2011). Physicians want effective medications for their patients and patients want effective medications in order to get better quickly (Rawson, 2000). Although physicians and patients want timely access to effective medications, it is difficult to determine what speed is right for the medications to get approved (Downing, Aminawung, Shah, Braunstein, Krumholz, & Ross, 2012). When a drug is approved in one country for a specific indication and not in the other country, it may raise a question whether the drug had an acceptable benefit-risk profile and, if yes, then questions may be raised by the scientific and public community about why the other regulatory did not approve it (Trotta, Leufkens, Schellens, Laing, & Tafuri (2011). The earlier project showed that the approval dates were statistically significantly later in

EU than the US (Deore, 2016) and found that an approval delay did not exist in the US. This project provided additional analysis to the earlier project (Deore, 2016) and considered the following data:

1. Determined the US-FDA review time (i.e., number of days between NDA submission and approval),
2. Determined the EMA review time (i.e., number of days between marketing authorization application submission and marketing authorization approval),
3. Compared the review time at both the agencies (FDA and EMA) to determine if differences existed,
4. Determined review times differences by the therapeutic area by considering and comparing NMEs approved in a particular therapeutic areas at both agencies, and
5. Determined review time differences for NMEs approved via priority review at either agency by considering the type of review (priority vs. standard).

Chapter 3: Methodology

A. Data source:

i. Approval letters of the NMEs available at the Drugs@FDA on the FDA website (US FDAc)

ii. Initial marketing-authorization documents available at the European public assessment reports on the EMA website (EMAc)

iii. ATC code (ATC)

B. Data collection:

For consistency, the mutually approved NMEs were selected as in the earlier project (Deore, 2016). This project analyzed the approval letters available at the Drugs@FDA on the FDA website and initial marketing-authorization application (MAA) documents available at the European public assessment reports on the EMA website.

For four drugs (Orlaam, Trovan, Tikosyn and Bextra) MAA date were not available as they were withdrawn from the market and three drugs (Cresemba, Zydelig and Sivextro) were found duplicate. These 7 drugs from the earlier project (Deore, 2016) were excluded from the analyses of this project.

From the FDA website, at the Drugs@FDA, the mutually approved NMEs were searched. Then under the approval history, the approval letters were searched for the NDA submission date. An Excel sheet was created in which these data were captured. Under the approval history, the type of review was specified. This review type was extracted to the same Excel sheet in different column. For each of the 210 mutually approved NME, the same procedure was followed.

Under the European public assessment reports (EPAR), the mutually-approved NME was selected. After searching the specific drug, under the assessment history, initial marketing-authorization documents (IMAD) were searched. In IMAD, the document: EPAR - Procedural steps taken before authorization was searched. In that document, in the section submission of the dossier, the marketing authorization application date was searched and captured in the Excel sheet. In the EPAR, the authorization details of the NME were searched for the therapeutic area. The therapeutic area of each NME was captured in the same Excel sheet. For each of the 210 mutually approved NME, the same procedure was followed.

The NDA submission dates and drug approval dates were used to determine the review times in US and EU, respectively. These data were then used for calculating the differences in US and EU review times. The type of review and the therapeutic area of the NME were used to determine the review differences in terms of NMEs approved via priority review and within therapeutic areas.

C. Data Analysis

i. Review time analysis in the US and EU

The US review time was determined by taking the difference between NDA approval and the NDA submission in the US. The EU review time was determined by taking the difference between the MAA approval and the MAA submission in EU. Two data points were used for calculation of the review time differences, one was the US review time and the other was the EU review time. These differences in review time were used to determine the review time differences by therapeutic area and for NMEs approved via priority or standard review. The type of review for two drugs (Agenerase and Votrient) were not provided and hence excluded from the analyses.

According to guidelines for Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) assignment 2013, the ATC classification system was suggested by the WHO as an international standard for drug utilization studies. In the ATC classification system, active substances are differentiated into various groups based on their therapeutic, pharmacological and chemical properties. Therapeutic means the system or organ class on which they act. The study considered these ATC code to analyse therapeutic area review differences.

ii. Statistical Analysis

Descriptive statistics was used to analyze the data and present the results. Non-parametric Wilcoxon Signed Ranks test was used to determine statistical significance in the review time differences between the US and EU by assigning rank based on review time.

D. Ethical Consideration

This study neither contains primary subject data nor includes research participants and focused on analysing public data available at Food and Drug Administration (FDA) (US FDAa) and European Medicines Agency (EMA) (EMAa). IRB review was therefore unnecessary.

Chapter 4: Results

New drug application (NDA) review time in the US and Marketing authorization application (MAA) review time in EU are shown in Appendix 1. From year 1994 to 2015, for 210 drugs, NDA review time ranged from 1.40 to 98.90 months; mean review time was 12.98 months and median was 9.88 months. However, MAA review time ranged from 5.03 to 30.40 months; mean review time was 14.82 months and median was 14.55 months. Appendix 1 also showed the difference between MAA and NDA review time. Out of 210 mutually approved NME, 160 (76.19%) drugs took less review time in the US, whereas 50 (23.81%) drugs took less review time in EU. The review difference for the US ranged from 0.10 to 17.97 months and for EU, from 0.10 to 85.5 months.

As shown in Appendix 2, average of review delay for individual drugs in the US was 3.09 months, whereas for EU, it was 4.92 months.The mean of yearly average review delay for US was 2.93 months whereas for EU, 4.68 months. In the total 22 years, US had review delay for 6 years, and EU had for 16 years.

Based on the sample size of 210, a Wilcoxon Signed Ranks test indicates that the review time for Europe (MAA approval time) (mean rank 125.81) was statistically significantly higher than the US (NDA approval time) (mean rank 99.15), $Z = -5.43$ and p value < 0.000 at 95 % confidence interval.

Review delay by ATC classification code in the US was found for 3 classes (Genitourinary system and reproductive hormones, Musculoskeletal system and ‘Other’) whereas the EU had longer reviews for the remaining 12 classes (Table 1).

For the genitourinary system and reproductive hormones class, a total of 5 drugs were mutually approved out of which 3 drugs had longer review times in the US, and 2 drugs had longer reviews in the EU (Table 1). For musculoskeletal system class, 1 drug (Zometa) was mutually approved and had 5.1 month longer review time in the US (Appendix 3). For 'Other' class, 12 drugs were mutually approved out of which 7 drug had longer review time in the US whereas 5 drugs had in EU (Table 1).

For the antineoplastic agent class, out of 44 mutually approved drugs, 41 drugs had longer review time in EU. For HIV/AIDS class, out of 23 mutually approved drugs, 22 drugs had longer review time in EU. For the immuno-modulating agent class, out of 11 mutually approved drugs, 10 drugs had longer review time in EU. For nervous system class, out of 24 mutually approved drugs, 13 drugs had longer review time in EU whereas 11 drugs had in the US (Table 1).

Table 1: Review delay by ATC classification code

	ATC Classification Code	Number of Drugs		
		Total	**Review Delay for the US**	**Review Delay for EU**
1	Alimentary tract and metabolisma	28	9	19
2	Antiinfectives	22	4	18
3	Antineoplastic agents	44	3	41
4	Blood and blood forming organs	9	3	6
5	Cardiovascular system	10	3	7
6	Dermatological drugs	2	0	2
7	Genitourinary system and reproductive hormones	5	3	2
8	HIV/AIDS	23	1	22
9	Immuno modulating agents	11	1	10
10	Musculoskeletal system	1	1	0
11	Nervous system	24	11	13
12	Opthalmology	6	1	5
13	Other	12	7	5
14	Respiratory system	5	2	3
15	Systemic hormonal preparations, excluding reproductive hormones and insulins	8	1	7

Out of 210 drugs, the type of review for two drugs (Agenerase and Votrient) was not available hence 208 drugs were considered. Out of 208 drugs, 122 were approved by priority review whereas 86 by standard review (Table 2). Of 122 priority review drugs, 104 drugs had longer review times in the EU, whereas 18 drugs had longer reviews in the in the US. Of 122 priority review drugs, 50 drugs were 'Orphan Drugs' for which EU had review delays for 40 drugs and the US had longer reviews for 10 drugs (Table 2). Of 86 standard review drugs, 54 had longer review times in the EU whereas 32 drugs had longer reviews in the US. Of 86 standard review drugs, 15 drugs were 'Orphan Drugs' for which EU had review delays for 12 drugs and the US had longer reviews for 3 drugs (Table 2).

Table 2: Review delay by type of review

Type of Review		Total Drugs	Number of Drugs	Review delay in the US	Review delay in EU
Priority (P)	P, Orphan	122	50	10	40
	P		72	8	64
Standard (S)	S, Orphan	86	15	3	12
	S		71	29	42

Chapter 5: Discussion

The purpose of this project was to analyze the impact of review time on a possible drug lag in the US when compared to the EU for mutually approved drugs from year 1994 to 2015. This study revealed EMA had significantly longer review times than the FDA for the time period in question. As shown in Appendix 1, from year 1994 to 2015, the mean review time for the FDA was 12.98 months compared to 14.82 months for EMA. Out of the 210 mutually approved drugs, 160 (76.19%) drugs had less review time in the US whereas 50 (23.81%) drugs had less review time in EU. The review time difference ranged from 0.10 to 17.97 months in the US compared to 0.10 to 85.5 months for EU (Appendix 1). As shown in Appendix 2, not only was the review time more for EU, but the average review delay in the EU (4.92 months) was also significantly higher than the US (3.09 months) from the year 1994 to 2015. The study showed that for the 22 years of analysis, the FDA had review delay for 6 years, whereas EMA had for 16 years (Appendix 2). Since 1992, FDA had taken efforts to reduce the review time. During initial period of PDUFA I (1992-1997), FDA had review delay for 2 years (1994 and 1997). Thereafter, for PDUFA II, III, and IV, in 15 years, FDA had review delay for 3 years (2000, 2004, and 2011). It showed that the PDUFA has positive effect in reducing review delay (FDA Performance Report 2000, 2006; Appendix 2). For PDUFA V (2012-2017), FDA had review delay for 8 drugs out of 60 drugs which shows even for PDUFA V the review delay will be probably for EU and not for the US.

The FDA had also been criticized for taking longer time to review and to approve life saving drugs like oncology drugs (Roberts, Allen, & Sigal, 2011). This study revealed that out of the 15 therapeutic classes, the FDA had review delay for 03 classes (genitourinary system and reproductive hormones, musculoskeletal system and ‘other’ class) whereas EMA had delay for the remaining 12 classes (Table 1) including the important classes (antineoplastic agents, HIV/AIDS,

immuno-modulating agents, and nervous system). It shows that EMA had delay for approving life-saving drugs whereas the US had a delay for comparatively less critical classes (genitourinary system and reproductive hormones, musculoskeletal system and 'other' class). It was claimed that the FDA had shorter review time than EU for cancer and hematologic diseases, but not for other therapeutic areas (Downing, Aminawung, Shah, Braunstein, Krumholz, & Ross, 2012). As shown in Table 1, for HIV/AIDS drugs, out of 23 mutually approved, 22 drugs had longer review time in EU, whereas only 1 drug had longer review time in the US. For antineoplastic drugs, out of 44 drugs, 41 drugs had longer review time in EU and only 3 drugs had in the US. FDA had always attempted to perform a faster review of drugs having greater therapeutic potential (Roberts, Allen, & Sigal, 2011). Among 11 mutually approved immuno-modulating drugs, 10 drugs had longer review time in EU and only 1 drug had longer review time in the US. For nervous system class, out of 24 mutually approved drugs, exceptionally 11 drugs had longer review time in the US but EU also had longer review time for 13 drugs. The other studies also confirmed that the FDA approved new drugs more speedily than any other regulatory agencies including EMA (Howes, 2015). These results showed that even for critical ATC classes, the FDA reviewed the drugs faster than EMA. The reason of getting life-saving drugs or critical class drugs approved in the US quicker may be due to prioritizing the drugs by categorizing the application as priority or standard. The results support the statement. For priority applications, the results confirmed that 104 drugs had review delay in EU whereas 18 drugs had in the US (Table 2). Even for priority orphan drugs, out of 50 drugs, 40 drugs had review lag in EU compared to 10 drugs in the US. For standard orphan drugs, out of 15, EMA had review lag for 12 drugs whereas the FDA had for 3 drugs (Table 2). In an article from The Los Angeles Times, it was stated that the FDA approved more "orphan" drugs compared to the EMA (Healy, 2017). Despite the debate that US had a drug lag, the US was

relatively fast in approving drugs (Schweitzer, Schweitzer, & Le Guellec, 2016). It was demonstarted that the FDA completes regulatory reviews more rapidly than EMA (Downing, Aminawung, Shah, Braunstein, Krumholz, & Ross, 2012). The study results also supports and concludes that the FDA approves drugs faster than EMA by taking less review time. The results also showed that the drugs approved by priority review in the US were significantly higher than EU (Table 2). The earlier project (Deore, 2016) demonstarated that US significantly approved most of the drugs first compared to EU and there was approval delay for EU. The overall results demonstrated that there was no approval and review delay in US instead EU had significant drug lag (approval and review delay) for mutually approved NME for the period in question.

Although the study aimed to find whether a review delay exists either for EMA or FDA, but it also recommends finding out the root cause. PDUFA was successful attempt by US-FDA (FDA Performance Report 2000, 2006). It allowed FDA to collect the user fees which made a significant impact on the efficiency of review process. There should be more efforts across all the regulators to initiate such kind of initiatives which will accelerate the review process and also help patients to receive drugs as early as possible. The harmonization of application process can also help in accelerating the review or approval process. Due to variations in regulations in EU, within EU and US, the pharmaceutical company has to apply separately which increases the overall cost of the drug. After paying the high cost, in return drug does not get approved at the same time and patients are deprived from the innovative drugs. Unfortunately, there is no ideal world but harmonization in the drug review process among EU, within EU and in the US can aid in reducing the longer review time which will bring potentially new drugs to the patients in need. It might not resolve the issue completely and additional measures may be required by all individual regulatory agencies to resolve it.

Chapter 6: Conclusion

The FDA had always been criticized for taking longer review time compared to EMA. Thereby depriving patients for potentially new life saving drugs. This study aimed to find out the review delay, and whether it exists in the US or in EU. The results revealed that the FDA had no review delay compared to EMA. In fact, the FDA had taken statistically significantly less review time compared to EMA. Additionally, the FDA reviewed the significantly higher number of drugs in most of the therapeutic areas. US-FDA also reviewed priority, standard and orphan drugs faster. The study concludes there was review delay in EU for individual drugs, in therapeutic areas and for type of review. However, the patient's needs should be considered regardless of geographical locations. There should be strategies across all regulatory agencies such as harmonizing the review process which can minimize the review delay and eventually help patients to receive the innovative or life saving drugs at the earliest.

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Appendices

Appendix 1: Review time difference in the US and EU

Year	Brand Name	Active Ingredients	NDA Submission (US)	NDA Approval (US)	NDA Review time in the US (Months)	MAA Submission (EU)	MAA Approval (EU)	MAA Review time in EU (Months)	Difference in Review Time (EU-US; months)
1994	Cerezyme	imiglucerase	5/21/1993	5/23/1994	12.23	1/6/1997	11/17/1997	10.50	-1.73
1994	Zerit	stavudine	12/28/1993	6/24/1994	5.93	7/31/1995	5/8/1996	9.40	3.47
1994	Cystagon	cysteamine bitartrate	1/23/1993	8/15/1994	18.97	2/1/1996	6/23/1997	16.93	-2.03
1995	Cellcept	mycophenolate mofetil	11/10/1994	5/3/1995	5.80	10/31/1994	2/14/1996	15.70	9.90
1995	Epivir	lamivudine	7/7/1995	11/17/1995	4.43	6/30/1995	8/8/1996	13.50	9.07
1995	Invirase	saquinavir mesylate	8/31/1995	12/6/1995	3.23	9/15/1995	10/4/1996	12.83	9.60
1995	Rilutek	riluzole	6/29/1995	12/12/1995	5.53	7/3/1995	6/10/1996	11.43	5.90
1996	Norvir	ritonavir	12/21/1995	3/1/1996	2.37	2/26/1996	8/26/1996	6.07	3.70
1996	Crixivan	indinavir sulfate	1/31/1996	3/13/1996	1.40	3/1/1996	10/4/1996	7.23	5.83
1996	Taxotere	docetaxel	7/27/1994	5/14/1996	21.90	9/7/1994	11/27/1995	14.87	-7.03
1996	Hycamtin	topotecan hydrochloride	12/22/1995	5/28/1996	5.27	1/5/1996	11/12/1996	10.40	5.13
1996	Humalog	insulin lispro recombinant	3/14/1995	6/14/1996	15.27	11/1/1994	4/30/1996	18.20	2.93
1996	Viramune	nevirapine	2/23/1996	6/21/1996	3.97	6/4/1997	2/5/1998	8.20	4.23
1996	Vistide	cidofovir	10/4/1995	6/26/1996	8.87	12/28/1995	4/23/1997	16.07	7.20
1996	Zyprexa	olanzapine	9/22/1995	9/30/1996	12.47	9/22/1995	9/27/1996	12.37	-0.10
1997	Aldara	imiquimod	7/26/1996	2/27/1997	7.20	5/20/1997	9/18/1998	16.20	9.00
1997	Viracept	nelfinavir mesylate	12/20/1996	3/14/1997	2.80	2/13/1997	1/22/1998	11.43	8.63
1997	Quadramet	samarium sm-153 lexidronam pentasodium	6/13/1995	3/28/1997	21.80	11/21/1996	2/5/1998	14.70	-7.10
1997	Fareston	toremifene citrate	1/3/1995	5/29/1997	29.23	12/1/1994	2/14/1996	14.67	-14.57
1997	Plavix	clopidogrel bisulfate	4/28/1997	11/17/1997	6.77	4/9/1997	7/15/1998	15.40	8.63
1997	Teslascan	mangafodipir trisodium	9/15/1995	11/26/1997	26.77	6/28/1996	5/22/1997	10.93	-15.83
1997	Evista	raloxifene hydrochloride	6/8/1997	12/9/1997	6.13	6/5/1997	8/5/1998	14.20	8.07
1997	Prandin	repaglinide	7/1/1997	12/22/1997	5.80	6/2/2000	1/29/2001	8.03	2.23

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1997	Emadine	emedastine difumarate	3/22/1996	12/29/1997	21.57	11/26/1997	1/27/1999	14.23	-7.33
1998	Tasmar	tolcapone	6/3/1996	1/29/1998	20.17	5/31/1996	8/27/1997	15.10	-5.07
1998	Refludan	lepirudin recombinant	12/31/1996	3/6/1998	14.33	12/20/1995	3/13/1997	14.97	0.63
1998	Viagra	sildenafil citrate	9/29/1997	3/27/1998	5.97	9/29/1997	9/14/1998	11.67	5.70
1998	Azopt	brinzolamide	1/26/1997	4/1/1998	14.33	11/25/1998	3/9/2000	15.67	1.33
1998	Xeloda	capecitabine	10/28/1997	4/30/1998	6.13	9/29/1999	2/2/2001	16.40	10.27
1998	Integrilin	eptifibatide	4/1/1996	5/18/1998	25.90	1/7/1998	7/1/1999	18.00	-7.90
1998	Arava	leflunomide	3/10/1998	9/10/1998	6.13	2/6/1998	9/2/1999	19.10	12.97
1998	Sustiva	efavirenz	6/11/1998	9/17/1998	3.27	6/29/1998	5/28/1999	11.10	7.83
1998	Renagel	sevelamer hydrochloride	11/3/1997	10/30/1998	12.03	6/30/1998	1/28/2000	19.23	7.20
1998	Micardis	telmisartan	9/26/1997	11/10/1998	13.67	10/9/1997	12/16/1998	14.43	0.77
1998	Thyrogen	thyrotropin alfa	12/12/1997	11/30/1998	11.77	12/1/1997	3/9/2000	27.63	15.87
1998	Ziagen	abacavir sulfate	6/24/1998	12/17/1998	5.87	6/29/1998	7/8/1999	12.47	6.60
1999	Panretin	alitretinoin	5/26/1998	2/2/1999	8.40	2/8/1999	10/11/2000	20.37	11.97
1999	Agenerase	amprenavir	10/15/1998	4/15/1999	6.07	10/30/1998	10/20/2000	24.03	17.97
1999	Xenical	orlistat	11/26/1996	4/23/1999	29.27	12/12/1996	7/29/1998	19.80	-9.47
1999	Avandia	rosiglitazone maleate	11/25/1998	5/25/1999	6.03	12/3/1998	7/11/2000	19.53	13.50
1999	Actos	pioglitazone hydrochloride	1/15/1999	7/15/1999	6.03	3/30/1999	10/13/2000	18.77	12.73
1999	Sonata	zaleplon	12/30/1997	8/13/1999	19.70	1/5/1998	3/12/1999	14.37	-5.33
1999	Rapamune	sirolimus	12/15/1998	9/15/1999	9.13	12/23/1998	3/13/2001	27.03	17.90
1999	Comtan	entacapone	10/24/1997	10/19/1999	24.17	4/4/1997	9/22/1998	17.87	-6.30
1999	Tamiflu	oseltamivir phosphate	4/29/1999	10/27/1999	6.03	2/9/2001	6/20/2002	16.53	10.50
1999	Keppra	levetiracetam	2/1/1999	11/30/1999	10.07	1/25/1999	9/29/2000	20.43	10.37
1999	Optimark	gadoversetamide	2/28/1998	12/8/1999	21.60	5/2/2006	7/23/2007	14.90	-6.70
1999	Inomax	nitric oxide	6/16/1997	12/23/1999	30.67	1/5/2000	8/1/2001	19.13	-11.53
1999	Targretin	bexarotene	6/22/1999	12/29/1999	6.33	11/24/1999	3/29/2001	16.37	10.03

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2000	Zonegran	zonisamide	3/19/1997	3/27/2000	36.80	11/6/2003	3/10/2005	16.33	-20.47
2000	Visudyne	verteporfin	8/14/1999	4/12/2000	8.07	8/6/1999	7/27/2000	11.87	3.80
2000	Lantus	insulin glargine recombinant	4/9/1999	4/20/2000	12.57	3/29/1999	6/9/2000	14.60	2.03
2000	Exelon	rivastigmine tartrate	4/7/1997	4/21/2000	37.00	4/1/1997	5/12/1998	13.53	-23.47
2000	Cetrotide	cetrorelix	10/28/1999	8/11/2000	9.60	2/2/1998	4/13/1999	14.50	4.90
2000	Kaletra	lopinavir/ritonavir mylan	5/31/2000	9/15/2000	3.57	6/27/2000	3/20/2001	8.87	5.30
2000	Trisenox	arsenic trioxide	3/27/2000	9/25/2000	6.07	12/1/2000	3/5/2002	15.30	9.23
2000	Starlix	nateglinide	12/17/1999	12/22/2000	12.37	12/22/1999	4/3/2001	15.60	3.23
2001	Lumigan	bimatoprost	9/18/2000	3/16/2001	5.97	12/11/2000	3/8/2002	15.07	9.10
2001	Travatan	travoprost	7/6/2000	3/16/2001	8.43	12/4/2000	11/27/2001	11.93	3.50
2001	Zometa	zoledronic acid	12/21/1999	8/20/2001	20.27	12/21/1999	3/20/2001	15.17	-5.10
2001	Viread	tenofovir disoproxil fumarate	4/30/2001	10/26/2001	5.97	5/4/2001	2/5/2002	9.23	3.27
2001	Tracleer	bosentan	11/17/2000	11/20/2001	12.27	2/8/2001	5/15/2002	15.37	3.10
2001	Invanz	ertapenem sodium	11/30/2000	11/21/2001	11.87	12/6/2000	4/18/2002	16.60	4.73
2001	Arixtra	fondaparinux sodium	2/15/2001	12/7/2001	9.83	2/14/2001	3/21/2002	13.33	3.50
2002	Orfadin	nitisinone	12/27/1999	1/18/2002	25.10	6/6/2003	2/21/2005	20.87	-4.23
2002	Faslodex	fulvestrant	3/28/2001	4/25/2002	13.10	2/4/2003	3/10/2004	13.33	0.23
2002	Vfend	voriconazole	11/17/2000	5/24/2002	18.43	10/25/2000	3/19/2002	17.00	-1.43
2002	Xyrem	sodium oxybate	9/30/2000	7/17/2002	21.83	3/11/2004	10/13/2005	19.37	-2.47
2002	Hepsera	adefovir dipivoxil	3/20/2002	9/20/2002	6.13	3/26/2002	3/6/2003	11.50	5.37
2002	Abilify	aripiprazole	10/31/2001	11/15/2002	12.67	12/5/2001	6/4/2004	30.40	17.73
2003	Fuzeon	enfuvirtide	9/13/2002	3/13/2003	6.03	9/23/2002	5/27/2003	8.20	2.17
2003	Somavert	pegvisomant	12/22/2000	3/25/2003	27.43	3/12/2001	11/13/2002	20.37	-7.07
2003	Emend	aprepitant	9/27/2002	3/26/2003	6.00	10/30/2002	11/11/2003	12.57	6.57

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2003	Iressa	gefitinib	8/2/2002	5/5/2003	9.20	5/6/2008	6/24/2009	13.80	4.60
2003	Velcade	bortezomib	1/21/2003	5/13/2003	3.73	1/31/2003	4/26/2004	15.03	11.30
2003	Reyataz	atazanavir sulfate	12/20/2002	6/20/2003	6.07	4/29/2002	3/2/2004	22.43	16.37
2003	Emtriva	emtricitabine	9/3/2002	7/2/2003	10.07	12/6/2002	10/24/2003	10.73	0.67
2003	Aloxi	palonosetron hydrochloride	9/26/2002	7/25/2003	10.07	7/29/2003	3/22/2005	20.07	10.00
2003	Zavesca	miglustat	4/20/2001	7/31/2003	27.73	6/29/2001	11/20/2002	16.97	-10.77
2003	Levitra	vardenafil hydrochloride	9/24/2001	8/19/2003	23.13	12/28/2001	3/6/2003	14.43	-8.70
2003	Cubicin	daptomycin	12/19/2002	9/12/2003	8.90	12/1/2004	1/19/2006	13.80	4.90
2003	Cialis	tadalafil	6/28/2001	11/21/2003	29.20	6/28/2001	11/12/2002	16.73	-12.47
2004	Alimta	pemetrexed disodium	9/29/2003	2/4/2004	4.27	7/29/2003	9/20/2004	13.97	9.70
2004	Ketek	telithromycin	2/28/2000	4/1/2004	49.80	3/24/2000	7/9/2001	15.73	-34.07
2004	Apidra	insulin glulisine recombinant	6/18/2003	4/16/2004	10.10	6/5/2003	9/27/2004	16.00	5.90
2004	Vidaza	azacitidine	12/26/2003	5/19/2004	4.83	1/9/2008	12/17/2008	11.43	6.60
2004	Cymbalta	duloxetine hydrochloride	11/12/2001	8/3/2004	33.17	10/10/2003	12/17/2004	14.47	-18.70
2004	Tarceva	erlotinib hydrochloride	7/29/2004	11/18/2004	3.73	8/26/2004	9/19/2005	12.97	9.23
2004	Macugen	pegaptanib sodium	6/17/2004	9/17/2004	3.07	8/31/2004	1/31/2006	17.27	14.20
2004	Prialt	ziconotide acetate	12/28/1999	12/28/2004	60.90	5/9/2003	2/21/2005	21.80	-39.10
2004	Ventavis	iloprost	6/30/2004	12/29/2004	6.07	12/20/2001	9/16/2003	21.17	15.10
2004	Lyrica	pregabalin	10/30/2003	12/30/2004	14.23	2/27/2003	7/6/2004	16.50	2.27
2005	Mycamine	micafungin sodium	4/29/2002	3/16/2005	35.07	4/11/2006	4/25/2008	24.83	-10.23
2005	Baraclude	entecavir	9/30/2004	3/29/2005	6.00	9/30/2004	6/26/2006	21.13	15.13
2005	Byetta	exenatide synthetic	6/29/2004	4/28/2005	10.10	11/2/2005	11/20/2006	12.77	2.67
2005	Tygacil	tigecycline	12/15/2004	6/15/2005	6.07	12/17/2004	4/24/2006	16.43	10.37
2005	Levemir	insulin detemir recombinant	12/5/2002	6/16/2005	30.80	11/7/2002	6/1/2004	19.07	-11.73

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2005	Aptivus	tipranavir	12/21/2004	6/22/2005	6.10	11/3/2004	10/25/2005	11.87	5.77
2005	Nevanac	nepafenac	2/25/2005	8/19/2005	5.83	12/18/2006	12/11/2007	11.93	6.10
2005	Increlex	mecasermin recombinant	2/24/2005	8/30/2005	6.23	12/7/2005	8/3/2007	20.13	13.90
2005	Exjade	deferasirox	4/29/2005	7/7/2005	2.30	4/28/2005	8/28/2006	16.23	13.93
2005	Nexavar	sorafenib tosylate	7/6/2005	12/1/2005	4.93	9/7/2005	7/19/2006	10.50	5.57
2005	Revlimid	lenalidomide	4/7/2005	12/27/2005	8.80	2/28/2006	6/14/2007	15.70	6.90
2006	Sutent	sunitinib malate	8/10/2005	1/26/2006	5.63	8/30/2005	7/19/2006	10.77	5.13
2006	Dacogen	decitabine	11/14/2005	5/2/2006	5.63	5/31/2011	9/20/2012	15.93	10.30
2006	Azilect	rasagiline mesylate	9/5/2003	5/16/2006	32.80	10/10/2003	2/21/2005	16.67	-16.13
2006	Prezista	darunavir ethanolate	12/22/2005	6/23/2006	6.10	1/4/2006	2/12/2007	13.47	7.37
2006	Sprycel	dasatinib	12/28/2005	6/28/2006	6.07	1/12/2006	11/20/2006	10.40	4.33
2006	Noxafil	posaconazole	12/21/2005	9/15/2006	8.93	7/2/2004	10/25/2005	16.00	7.07
2006	Januvia	sitagliptin phosphate	12/16/2005	10/16/2006	10.13	3/6/2006	3/21/2007	12.67	2.53
2006	Invega	paliperidone	11/30/2005	12/19/2006	12.80	5/4/2006	6/25/2007	13.90	1.10
2007	Tekturna	aliskiren hemifumarate	2/10/2006	3/5/2007	12.93	9/5/2006	8/22/2007	11.70	-1.23
2007	Neupro	rotigotine	1/19/2005	5/9/2007	28.00	9/29/2004	2/15/2006	16.80	-11.20
2007	Torisel	temsirolimus	10/5/2006	5/30/2007	7.90	10/5/2006	11/19/2007	13.67	5.77
2007	Doribax	doripenem	12/12/2006	10/12/2007	10.13	6/27/2007	7/25/2008	13.13	3.00
2007	Isentress	raltegravir potassium	4/13/2007	10/12/2007	6.07	4/25/2007	12/20/2007	7.97	1.90
2007	Tasigna	nilotinib hydrochloride monohydrate	9/29/2006	10/29/2007	13.17	10/5/2006	11/19/2007	13.67	0.50
2007	Kuvan	sapropterin dihydrochloride	5/25/2007	12/13/2007	6.73	10/30/2007	12/2/2008	13.30	6.57
2008	Intelence	etravirine	7/17/2007	1/18/2008	6.17	7/26/2007	8/28/2008	13.30	7.13
2008	Relistor	methylnaltrexone bromide	3/30/2007	4/24/2008	13.03	5/4/2007	7/2/2008	14.17	1.13
2008	Vimpat	lacosamide	9/28/2007	10/28/2008	13.20	5/2/2007	8/29/2008	16.17	2.97
2008	Toviaz	fesoterodine fumarate	3/17/2006	10/31/2008	31.97	3/9/2006	4/20/2007	13.57	-18.40

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2008	Mozobil	plerixafor	6/16/2008	12/15/2008	6.07	6/5/2008	7/31/2009	14.03	7.97
2008	Firmagon	degarelix acetate	2/14/2008	12/24/2008	10.47	2/27/2008	2/17/2009	11.87	1.40
2009	Afinitor	everolimus	6/27/2008	3/30/2009	9.20	7/1/2008	8/3/2009	13.27	4.07
2009	Samsca	tolvaptan	10/23/2007	5/19/2009	19.13	1/28/2008	8/3/2009	18.43	-0.70
2009	Multaq	dronedarone hydrochloride	6/27/2008	7/1/2009	12.30	7/3/2008	11/26/2009	17.03	4.73
2009	Onglyza	saxagliptin hydrochloride	6/30/2008	7/31/2009	13.20	7/1/2008	10/1/2009	15.23	2.03
2009	Vibativ	telavancin hydrochloride	12/6/2006	9/11/2009	33.67	10/27/2009	9/2/2011	22.50	-11.17
2009	Votrient	pazopanib hydrochloride	12/18/2008	10/19/2009	10.17	2/27/2009	6/14/2010	15.73	5.57
2009	Qutenza	capsaicin	10/13/2008	11/16/2009	13.30	8/30/2007	5/15/2009	20.80	7.50
2010	Victoza	liraglutide recombinant	3/23/2008	1/25/2010	22.43	5/23/2008	6/30/2009	13.43	-9.00
2010	Vpriv	velaglucerase alfa	8/31/2009	2/26/2010	5.97	10/30/2009	8/26/2010	10.00	4.03
2010	Carbaglu	carglumic acid	6/17/2009	3/18/2010	9.13	10/5/2001	1/24/2003	15.87	6.73
2010	Gilenya	fingolimod	12/18/2009	9/21/2010	9.23	12/22/2009	3/17/2011	15.00	5.77
2010	Pradaxa	dabigatran etexilate mesylate	12/15/2009	10/19/2010	10.27	2/1/2007	3/18/2008	13.70	3.43
2010	Latuda	lurasidone hydrochloride	12/30/2009	10/28/2010	10.07	9/27/2012	3/21/2014	18.00	7.93
2010	Halaven	eribulin mesylate	3/30/2010	11/15/2010	7.67	3/30/2010	3/17/2011	11.73	4.07
2011	Datscan	ioflupane i-123	3/6/2009	1/14/2011	22.63	11/24/1998	7/27/2000	20.37	-2.27
2011	Edarbi	azilsartan kamedoxomil	4/22/2010	2/25/2011	10.30	9/29/2010	12/7/2011	14.47	4.17
2011	Daliresp	roflumilast	7/15/2009	2/28/2011	19.77	9/30/2010	2/28/2011	5.03	-14.73
2011	Caprelsa	vandetanib	7/7/2010	4/6/2011	9.10	9/1/2010	2/17/2012	17.80	8.70
2011	Zytiga	abiraterone acetate	12/18/2010	4/28/2011	4.37	9/17/2010	9/5/2011	11.77	7.40
2011	Victrelis	boceprevir	11/10/2010	5/13/2011	6.13	11/23/2010	7/18/2011	7.90	1.77
2011	Edurant	rilpivirine hydrochloride	7/23/2010	5/20/2011	10.03	9/2/2010	11/28/2011	15.07	5.03
2011	Xarelto	rivaroxaban	7/28/2008	7/1/2011	35.60	10/31/2007	9/30/2008	11.17	-24.43
2011	Zelboraf	vemurafenib	4/27/2011	8/17/2011	3.73	5/4/2011	2/17/2012	9.63	5.90

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2011	Firazyr	icatibant acetate	10/22/2007	8/25/2011	46.77	7/27/2007	7/11/2008	11.67	-35.10
2011	Xalkori	crizotinib	3/30/2011	8/26/2011	4.97	7/28/2011	10/23/2012	15.10	10.13
2011	Ferriprox	deferiprone	1/29/2009	10/14/2011	32.93	2/6/1998	8/25/1999	18.83	-14.10
2012	Picato	ingenol mebutate	3/25/2011	1/23/2012	10.13	7/27/2011	11/15/2012	15.90	5.77
2012	Inlyta	axitinib	4/14/2011	1/27/2012	9.60	4/19/2011	9/3/2012	16.77	7.17
2012	Erivedge	vismodegib	9/8/2011	1/30/2012	4.80	12/1/2011	7/12/2013	19.63	14.83
2012	Kalydeco	ivacaftor	10/18/2011	1/31/2012	3.50	10/27/2011	7/23/2012	9.00	5.50
2012	Amyvid	florbetapir f-18	10/7/2011	4/6/2012	6.07	1/4/2012	1/14/2013	12.53	6.47
2012	Kyprolis	carfilzomib	9/26/2011	7/20/2012	9.93	1/22/2015	11/19/2015	10.03	0.10
2012	Stribild	cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate	10/26/2011	8/27/2012	10.20	11/24/2011	5/24/2013	18.23	8.03
2012	Xtandi	enzalutamide	5/21/2012	8/31/2012	3.40	6/26/2012	6/21/2013	12.00	8.60
2012	Bosulif	bosutinib monohydrate	11/17/2011	9/4/2012	9.73	7/28/2011	3/27/2013	20.27	10.53
2012	Aubagio	teriflunomide	8/12/2011	9/12/2012	13.23	2/1/2012	8/26/2013	19.07	5.83
2012	Stivarga	regorafenib	4/27/2012	9/27/2012	5.10	5/3/2012	8/26/2013	16.00	10.90
2012	Fycompa	perampanel	5/25/2012	10/22/2012	5.00	5/24/2011	7/23/2012	14.20	9.20
2012	Cometriq	cabozantinib s-malate	5/21/2012	11/29/2012	6.40	10/29/2012	3/21/2014	16.93	10.53
2012	Iclusig	ponatinib hydrochloride	7/30/2012	12/14/2012	4.57	8/30/2012	7/1/2013	10.17	5.60
2012	Signifor	pasireotide diaspartate	2/17/2012	12/14/2012	10.03	9/30/2010	4/24/2012	19.07	9.03
2012	Sirturo	bedaquiline fumarate	6/28/2012	12/28/2012	6.10	8/28/2012	3/5/2014	18.47	12.37
2012	Eliquis	apixaban	9/28/2011	12/28/2012	15.23	2/25/2010	5/18/2011	14.90	-0.33
2013	Tecfidera	dimethyl fumarate	2/24/2012	3/27/2013	13.23	2/28/2012	1/30/2014	23.40	10.17
2013	Invokana	canagliflozin	5/31/2012	3/29/2013	10.07	6/22/2012	11/15/2013	17.03	6.97
2013	Xofigo	radium ra-223 dichloride	12/14/2012	5/15/2013	5.07	12/12/2012	11/13/2013	11.20	6.13

Year	Brand Name	Active Ingredients	NDA Submission (US)	NDA Approval (US)	NDA Review time in the US (Months)	MAA Submission (EU)	MAA Approval (EU)	MAA Review time in EU (Months)	Difference in Review Time (EU-US; months)
2013	Mekinist	trametinib dimethyl sulfoxide	8/2/2012	5/29/2013	10.00	2/7/2013	6/30/2014	16.93	6.93
2013	Tafinlar	dabrafenib mesylate	7/29/2012	5/29/2013	10.13	7/24/2012	8/26/2013	13.27	3.13
2013	Tivicay	dolutegravir sodium	12/16/2012	8/12/2013	7.97	12/17/2012	1/16/2014	13.17	5.20
2013	Brintellix	vortioxetine hydrobromide	10/2/2012	9/30/2013	12.10	8/24/2012	12/18/2013	16.03	3.93
2013	Adempas	riociguat	2/8/2013	10/8/2013	8.07	2/5/2013	3/27/2014	13.83	5.77
2013	Opsumit	macitentan	10/19/2012	10/18/2013	12.13	10/25/2012	12/20/2013	14.03	1.90
2013	Vizamyl	flutemetamol f-18	10/26/2012	10/25/2013	12.13	11/23/2012	8/22/2014	21.23	9.10
2013	Imbruvica	ibrutinib	6/28/2013	11/13/2013	4.60	10/29/2013	10/21/2014	11.90	7.30
2013	Olysio	simeprevir sodium	3/28/2013	11/22/2013	7.97	4/24/2013	5/14/2014	12.83	4.87
2013	Sovaldi	sofosbuvir	4/8/2013	12/6/2013	8.07	4/19/2013	1/16/2014	9.07	1.00
2013	Anoro	umeclidinium bromide; vilanterol trifenatate	12/18/2012	12/18/2013	12.17	1/8/2013	5/8/2014	16.17	4.00
2014	Hetlioz	tasimelteon	5/31/2013	1/31/2014	8.17	5/1/2014	7/3/2015	14.27	6.10
2014	Imbruvica	ibrutinib	6/28/2013	2/12/2014	7.63	5/2/2014	10/21/2014	5.73	-1.90
2014	Neuraceq	florbetaben f-18	12/21/2012	3/19/2014	15.10	1/7/2013	2/20/2014	13.63	-1.47
2014	Otezla	apremilast	3/20/2013	3/21/2014	12.20	12/2/2013	1/15/2015	13.63	1.43
2014	Zykadia	ceritinib	12/24/2013	4/29/2014	4.20	3/4/2014	5/6/2015	14.27	10.07
2014	Zontivity	vorapaxar sulfate	5/10/2013	5/8/2014	12.10	11/28/2013	1/19/2015	13.90	1.80
2014	Sivextro	tedizolid phosphate	10/18/2013	6/20/2014	8.17	1/31/2014	3/23/2015	13.87	5.70
2014	Zydelig	idelalisib	9/11/2013	7/23/2014	10.50	10/28/2013	9/18/2014	10.83	0.33
2014	Jardiance	empagliflozin	3/5/2013	8/1/2014	17.13	3/5/2013	5/22/2014	14.77	-2.37
2014	Orbactiv	oritavancin diphosphate	12/6/2013	8/6/2014	8.10	2/4/2014	3/19/2015	13.60	5.50
2014	Cerdelga	eliglustat tartrate	9/19/2013	8/19/2014	11.13	9/20/2013	1/19/2015	16.20	5.07
2014	Otezla	apremilast	3/20/2013	3/21/2014	12.20	12/2/2013	1/15/2015	13.63	1.43
2014	Hetlioz	tasimelteon	5/31/2013	1/31/2014	8.17	5/1/2014	7/3/2015	14.27	6.10

Year	Brand Name	Active Ingredients	NDA Submission (US)	NDA Approval (US)	NDA Review time in the US (Months)	MAA Submission (EU)	MAA Approval (EU)	MAA Review time in EU (Months)	Difference in Review Time (EU-US; months)
2014	Akynzeo	netupitant; palonosetron hydrochloride	9/27/2013	10/10/2014	12.60	12/13/2013	5/27/2015	17.67	5.07
2014	Harvoni	ledipasvir; sofosbuvir	2/7/2014	10/10/2014	8.17	2/28/2014	11/17/2014	8.73	0.57
2014	Ofev	nintedanib esylate	5/2/2014	10/15/2014	5.53	5/5/2014	1/15/2015	8.50	2.97
2014	Esbriet	pirfenidone	11/4/2009	10/15/2014	60.20	2/26/2010	2/28/2011	12.23	-47.97
2014	Lynparza	olaparib	2/3/2014	12/19/2014	10.63	9/3/2013	12/16/2014	15.63	5.00
2015	Lenvima	lenvatinib mesylate	8/14/2014	2/13/2015	6.10	8/15/2014	5/28/2015	9.53	3.43
2015	Farydak	panobinostat lactate	3/22/2014	2/23/2015	11.27	5/5/2014	8/28/2015	16.00	4.73
2015	Cresemba	isavuconazonium sulfate	7/8/2014	3/6/2015	8.03	7/16/2014	10/15/2015	15.20	7.17
2015	Orkambi	ivacaftor; lumacaftor	11/5/2014	7/2/2015	7.97	11/5/2014	11/19/2015	12.63	4.67
2015	Entresto	sacubitril; valsartan	12/17/2014	7/7/2015	6.73	12/16/2014	11/19/2015	11.27	4.53
2015	Odomzo	sonidegib phosphate	9/26/2014	7/24/2015	10.03	5/5/2014	8/14/2015	15.53	5.50
2015	Daklinza	daclatasvir dihydrochloride	2/13/2015	7/24/2015	5.37	12/3/2013	8/22/2014	8.73	3.37
2015	Tresiba	insulin degludec	9/29/2011	9/25/2015	48.57	9/26/2011	1/21/2013	16.10	-32.47
2015	Genvoya	cobicistat; elvitegravir; emtricitabine; tenofovir alafenamide fumarate	11/5/2014	11/5/2015	12.17	11/28/2014	11/19/2015	11.87	-0.30
2015	Cotellic	cobimetinib fumarate	12/11/2014	11/10/2015	11.13	9/2/2014	11/20/2015	14.80	3.67
2015	Bridion	sugammadex sodium	10/31/2007	12/15/2015	98.90	6/21/2007	7/25/2008	13.33	-85.57

Appendix 2: Review delay in the US and EU

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
1994	Cerezyme	1.73	1.25	0	1.16
	Zerit	0		3.47	
	Cystagon	2.03		0	
1995	Cellcept	0	0	9.90	8.62
	Epivir	0		9.07	
	Invirase	0		9.60	
	Rilutek	0		5.90	
1996	Norvir	0	0.89	3.70	3.63
	Crixivan	0		5.83	
	Taxotere	7.03		0	
	Hycamtin	0		5.13	
	Humalog	0		2.93	
	Viramune	0		4.23	
	Vistide	0		7.20	
	Zyprexa	0.1		0	
1997	Aldara	0	4.98	9.00	4.06
	Viracept	0		8.63	
	Quadramet	7.1		0	
	Fareston	14.57		0	
	Plavix	0		8.63	
	Teslascan	15.83		0	
	Evista	0		8.07	
	Prandin	0		2.23	
	Emadine	7.33		0	
1998	Tasmar	5.07	1.08	0	5.76
	Refludan	0		0.63	
	Viagra	0		5.70	
	Azopt	0		1.33	
	Xeloda	0		10.27	
	Integrilin	7.9		0	
	Arava	0		12.97	
	Sustiva	0		7.83	

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
	Renagel	0		7.20	
	Micardis	0		0.77	
	Thyrogen	0		15.87	
	Ziagen	0		6.60	
1999	Panretin	0	3.025	11.97	8.07
	Agenerase	0		17.97	
	Xenical	9.47		0	
	Avandia	0		13.50	
	Actos	0		12.73	
	Sonata	5.33		0	
	Rapamune	0		17.90	
	Comtan	6.3		0	
	Tamiflu	0		10.50	
	Keppra	0		10.37	
	Optimark	6.7		0	
	Inomax	11.53		0	
	Targretin	0		10.03	
2000	Zonegran	20.47	5.49	0	3.56
	Visudyne	0		3.80	
	Lantus	0		2.03	
	Exelon	23.47		0	
	Cetrotide	0		4.90	
	Kaletra	0		5.30	
	Trisenox	0		9.23	
	Starlix	0		3.23	
2001	Lumigan	0	0.728	9.10	3.89
	Travatan	0		3.50	
	Zometa	5.1		0	
	Viread	0		3.27	
	Tracleer	0		3.10	
	Invanz	0		4.73	
	Arixtra	0		3.50	
2002	Orfadin	4.23	1.355	0	3.89
	Faslodex	0		0.23	

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
	Vfend	1.43		0	
	Xyrem	2.47		0	
	Hepsera	0		5.37	
	Abilify	0		17.73	
2003	Fuzeon	0	3.25	2.17	4.71
	Somavert	7.07		0	
	Emend	0		6.57	
	Iressa	0		4.60	
	Velcade	0		11.30	
	Reyataz	0		16.37	
	Emtriva	0		0.67	
	Aloxi	0		10.00	
	Zavesca	10.77		0	
	Levitra	8.7		0	
	Cubicin	0		4.90	
	Cialis	12.47		0	
2004	Alimta	0	9.187	9.70	6.3
	Ketek	34.07		0	
	Apidra	0		5.90	
	Vidaza	0		6.60	
	Cymbalta	18.7		0	
	Tarceva	0		9.23	
	Macugen	0		14.20	
	Prialt	39.1		0	
	Ventavis	0		15.10	
	Lyrica	0		2.27	
2005	Mycamine	10.23	1.996	0	7.3
	Baraclude	0		15.13	
	Byetta	0		2.67	
	Tygacil	0		10.37	
	Levemir	11.73		0	
	Aptivus	0		5.77	
	Nevanac	0		6.10	
	Increlex	0		13.90	

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
	Exjade	0		13.93	
	Nexavar	0		5.57	
	Revlimid	0		6.90	
2006	Sutent	0	2.016	5.13	4.73
	Dacogen	0		10.30	
	Azilect	16.13		0	
	Prezista	0		7.37	
	Sprycel	0		4.33	
	Noxafil	0		7.07	
	Januvia	0		2.53	
	Invega	0		1.10	
2007	Tekturna	1.23	1.775	0	2.53
	Neupro	11.2		0	
	Torisel	0		5.77	
	Doribax	0		3.00	
	Isentress	0		1.90	
	Tasigna	0		0.50	
	Kuvan	0		6.57	
2008	Intelence	0	3.066	7.13	3.43
	Relistor	0		1.13	
	Vimpat	0		2.97	
	Toviaz	18.4		0	
	Mozobil	0		7.97	
	Firmagon	0		1.40	
2009	Afinitor	0	1.695	4.07	3.41
	Samsca	0.7		0	
	Multaq	0		4.73	
	Onglyza	0		2.03	
	Vibativ	11.17		0	
	Votrient	0		5.57	
	Qutenza	0		7.50	
2010	Victoza	9	1.285	0	4.57
	Vpriv	0		4.03	
	Carbaglu	0		6.73	

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
	Gilenya	0		5.77	
	Pradaxa	0		3.43	
	Latuda	0		7.93	
	Halaven	0		4.07	
2011	Datscan	2.27	7.55	0	3.59
	Edarbi	0		4.17	
	Daliresp	14.73		0	
	Caprelsa	0		8.70	
	Zytiga	0		7.40	
	Victrelis	0		1.77	
	Edurant	0		5.03	
	Xarelto	24.43		0	
	Zelboraf	0		5.90	
	Firazyr	35.1		0	
	Xalkori	0		10.13	
	Ferriprox	14.1		0	
2012	Picato	0	0.019	5.77	7.67
	Inlyta	0		7.17	
	Erivedge	0		14.83	
	Kalydeco	0		5.50	
	Amyvid	0		6.47	
	Kyprolis	0		0.10	
	Stribild	0		8.03	
	Xtandi	0		8.60	
	Bosulif	0		10.53	
	Aubagio	0		5.83	
	Stivarga	0		10.90	
	Fycompa	0		9.20	
	Cometriq	0		10.53	
	Iclusig	0		5.60	
	Signifor	0		9.03	
	Sirturo	0		12.37	
	Eliquis	0.33		0	
2013	Tecfidera	0	0	10.17	5.46

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
	Invokana	0		6.97	
	Xofigo	0		6.13	
	Mekinist	0		6.93	
	Tafinlar	0		3.13	
	Tivicay	0		5.20	
	Brintellix	0		3.93	
	Adempas	0		5.77	
	Opsumit	0		1.90	
	Vizamyl	0		9.10	
	Imbruvica	0		7.30	
	Olysio	0		4.87	
	Sovaldi	0		1.00	
	Anoro	0		4.00	
2014	Hetlioz	0	2.98	6.10	3.17
	Imbruvica	1.9		0	
	Neuraceq	1.47		0	
	Otezla	0		1.43	
	Zykadia	0		10.07	
	Zontivity	0		1.80	
	Sivextro	0		5.70	
	Zydelig	0		0.33	
	Jardiance	2.37		0	
	Orbactiv	0		5.50	
	Cerdelga	0		5.07	
	Otezla	0		1.43	
	Hetlioz	0		6.10	
	Akynzeo	0		5.07	
	Harvoni	0		0.57	
	Ofev	0		2.97	
	Esbriet	47.97		0	
	Lynparza	0		5.00	
2015	Lenvima	0	10.758	3.43	3.37
	Farydak	0		4.73	
	Cresemba	0		7.17	

		US		EU	
Year	**Brand Name**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**	**Review Delay (Month)**	**Yearly Average Review Delay (Month)**
	Orkambi	0		4.67	
	Entresto	0		4.53	
	Odomzo	0		5.50	
	Daklinza	0		3.37	
	Tresiba	32.47		0	
	Genvoya	0.3		0	
	Cotellic	0		3.67	
	Bridion	85.57		0	
1994 - 2015		3.09	2.93	4.92	4.68

Appendix 3: Review delay by Anatomical Therapeutic Chemical (ATC) classification code

ATC Classification Code	Brand Name	Review Delay in the US	Review Delay in EU
Alimentary tract and metabolisma	Cerezyme	1.73	0
	Cystagon	2.03	0
	Humalog	0	2.93
	Prandin	0	2.23
	Xenical	9.47	0
	Avandia	0	13.50
	Actos	0	12.73
	Lantus	0	2.03
	Starlix	0	3.23
	Orfadin	4.23	0
	Emend	0	6.57
	Aloxi	0	10.00
	Zavesca	10.77	0
	Apidra	0	5.90
	Byetta	0	2.67
	Levemir	11.73	0
	Januvia	0	2.53
	Kuvan	0	6.57
	Relistor	0	1.13
	Onglyza	0	2.03
	Victoza	9	0
	Vpriv	0	4.03
	Carbaglu	0	6.73
	Invokana	0	6.97
	Jardiance	2.37	0
	Cerdelga	0	5.07
	Akynzeo	0	5.07
	Tresiba	32.47	0
Antiinfectives	Vistide	0	7.20
	Tamiflu	0	10.50
	Invanz	0	4.73
	Vfend	1.43	0
	Hepsera	0	5.37
	Cubicin	0	4.90
	Ketek	34.07	0
	Mycamine	10.23	0

ATC Classification Code	Brand Name	Review Delay in the US	Review Delay in EU
	Baraclude	0	15.13
	Tygacil	0	10.37
	Noxafil	0	7.07
	Doribax	0	3.00
	Vibativ	11.17	0
	Victrelis	0	1.77
	Sirturo	0	12.37
	Olysio	0	4.87
	Sovaldi	0	1.00
	Sivextro	0	5.70
	Orbactiv	0	5.50
	Harvoni	0	0.57
	Cresemba	0	7.17
	Daklinza	0	3.37
Antineoplastic agents	Taxotere	7.03	0.00
	Hycamtin	0	5.13
	Fareston	14.57	0
	Xeloda	0	10.27
	Panretin	0	11.97
	Targretin	0	10.03
	Trisenox	0	9.23
	Faslodex	0	0.23
	Iressa	0	4.60
	Velcade	0	11.30
	Alimta	0	9.70
	Tarceva	0	9.23
	Nexavar	0	5.57
	Revlimid	0	6.90
	Dacogen	0	10.30
	Sprycel	0	4.33
	Torisel	0	5.77
	Tasigna	0	0.50
	Mozobil	0	7.97
	Firmagon	0	1.40
	Afinitor	0	4.07
	Votrient	0	5.57
	Halaven	0	4.07
	Zytiga	0	7.40

ATC Classification Code	Brand Name	Review Delay in the US	Review Delay in EU
	Zelboraf	0	5.90
	Xalkori	0	10.13
	Inlyta	0	7.17
	Erivedge	0	14.83
	Kyprolis	0	0.10
	Xtandi	0	8.60
	Bosulif	0	10.53
	Stivarga	0	10.90
	Iclusig	0	5.60
	Xofigo	0	6.13
	Mekinist	0	6.93
	Tafinlar	0	3.13
	Imbruvica	0	7.30
	Imbruvica	1.9	0.00
	Zykadia	0	10.07
	Zydelig	0	0.33
	Lynparza	0	5.00
	Farydak	0	4.73
	Odomzo	0	5.50
	Cotellic	0	3.67
Blood and blood forming organs	Plavix	0	8.63
	Refludan	0	0.63
	Integrilin	7.9	0.00
	Arixtra	0	3.50
	Ventavis	0	15.10
	Pradaxa	0	3.43
	Xarelto	24.43	0
	Eliquis	0.33	0
	Zontivity	0	1.80
Cardiovascular system	Micardis	0	0.77
	Tracleer	0	3.10
	Tekturna	1.23	0
	Samsca	0.7	0
	Multaq	0	4.73
	Edarbi	0	4.17
	Firazyr	35.1	0
	Adempas	0	5.77
	Opsumit	0	1.90

ATC Classification Code	Brand Name	Review Delay in the US	Review Delay in EU
	Entresto	0	4.53
Dermatological drugs	Aldara	0	9.00
	Picato	0	5.77
Genitourinary system and reproductive hormones	Evista	0	8.07
	Viagra	0	5.70
	Levitra	8.7	0
	Cialis	12.47	0
	Toviaz	18.4	0
HIV／AIDS	Zerit	0	3.47
	Epivir	0	9.07
	Invirase	0	9.60
	Norvir	0	3.70
	Crixivan	0	5.83
	Viramune	0	4.23
	Viracept	0	8.63
	Sustiva	0	7.83
	Ziagen	0	6.60
	Agenerase	0	17.97
	Kaletra	0	5.30
	Viread	0	3.27
	Fuzeon	0	2.17
	Reyataz	0	16.37
	Emtriva	0	0.67
	Aptivus	0	5.77
	Prezista	0	7.37
	Isentress	0	1.90
	Intelence	0	7.13
	Edurant	0	5.03
	Stribild	0	8.03
	Tivicay	0	5.20
	Genvoya	0.3	0
Immunomodulating agents	Cellcept	0	9.90
	Arava	0	12.97
	Rapamune	0	17.90
	Vidaza	0	6.60
	Gilenya	0	5.77
	Aubagio	0	5.83
	Tecfidera	0	10.17

ATC Classification Code	Brand Name	Review Delay in the US	Review Delay in EU
	Otezla	0	1.43
	Otezla	0	1.43
	Ofev	0	2.97
	Esbriet	47.97	0
Musculoskeletal system	Zometa	5.1	0
Nervous system	Rilutek	0	5.90
	Zyprexa	0.1	0
	Tasmar	5.07	0
	Sonata	5.33	0
	Comtan	6.3	0
	Keppra	0	10.37
	Zonegran	20.47	0
	Exelon	23.47	0
	Xyrem	2.47	0
	Abilify	0	17.73
	Cymbalta	18.7	0
	Prialt	39.1	0
	Lyrica	0	2.27
	Sutent	0	5.13
	Azilect	16.13	0
	Invega	0	1.10
	Neupro	11.2	0
	Vimpat	0	2.97
	Qutenza	0	7.50
	Latuda	0	7.93
	Fycompa	0	9.20
	Brintellix	0	3.93
	Hetlioz	0	6.10
	Hetlioz	0	6.10
Opthalmology	Emadine	7.33	0.00
	Azopt	0	1.33
	Visudyne	0	3.80
	Lumigan	0	9.10
	Travatan	0	3.50
	Nevanac	0	6.10
Other	Quadramet	7.1	0
	Teslascan	15.83	0
	Renagel	0	7.20

ATC Classification Code	Brand Name	Review Delay in the US	Review Delay in EU
	Optimark	6.7	0
	Macugen	0	14.20
	Exjade	0	13.93
	Datscan	2.27	0.00
	Ferriprox	14.1	0.00
	Amyvid	0	6.47
	Vizamyl	0	9.10
	Neuraceq	1.47	0.00
	Bridion	85.57	0.00
Respiratory system	Inomax	11.53	0.00
	Daliresp	14.73	0.00
	Kalydeco	0	5.50
	Anoro	0	4.00
	Orkambi	0	4.67
Systemic hormonal preparations, excluding reproductive hormones and insulins	Thyrogen	0	15.87
	Cetrotide	0	4.90
	Somavert	7.07	0.00
	Increlex	0	13.90
	Caprelsa	0	8.70
	Cometriq	0	10.53
	Signifor	0	9.03
	Lenvima	0	3.43

Appendix 4: Review delay by type of review (priority and standard)

Type of Review	Brand Name	Review Delay in the US	Review Delay in EU
Priority	Zerit	0	3.47
	Cellcept	0	9.90
	Epivir	0	9.07
	Invirase	0	9.60
	Norvir	0	3.70
	Crixivan	0	5.83
	Taxotere	7.03	0
	Hycamtin	0	5.13
	Viramune	0	4.23
	Viracept	0	8.63
	Evista	0	8.07
	Prandin	0	2.23
	Viagra	0	5.70
	Xeloda	0	10.27
	Integrilin	7.9	0
	Arava	0	12.97
	Sustiva	0	7.83
	Ziagen	0	6.60
	Xenical	9.47	0
	Avandia	0	13.50
	Actos	0	12.73
	Tamiflu	0	10.50
	Visudyne	0	3.80
	Kaletra	0	5.30
	Lumigan	0	9.10
	Travatan	0	3.50
	Viread	0	3.27
	Arixtra	0	3.50
	Hepsera	0	5.37
	Fuzeon	0	2.17
	Emend	0	6.57
	Iressa	0	4.60
	Reyataz	0	16.37
	Cubicin	0	4.90
	Tarceva	0	9.23
	Macugen	0	14.20
	Prialt	39.1	0

Type of Review	Brand Name	Review Delay in the US	Review Delay in EU
	Lyrica	0	2.27
	Mycamine	10.23	0
	Baraclude	0	15.13
	Tygacil	0	10.37
	Aptivus	0	5.77
	Nevanac	0	6.10
	Sutent	0	5.13
	Prezista	0	7.37
	Noxafil	0	7.07
	Torisel	0	5.77
	Isentress	0	1.90
	Kuvan	0	6.57
	Intelence	0	7.13
	Afinitor	0	4.07
	Multaq	0	4.73
	Gilenya	0	5.77
	Pradaxa	0	3.43
	Halaven	0	4.07
	Datscan	2.27	0
	Zytiga	0	7.40
	Victrelis	0	1.77
	Erivedge	0	14.83
	Amyvid	0	6.47
	Xtandi	0	8.60
	Eliquis	0.33	0
	Xofigo	0	6.13
	Tivicay	0	5.20
	Olysio	0	4.87
	Sovaldi	0	1.00
	Sivextro	0	5.70
	Orbactiv	0	5.50
	Harvoni	0	0.57
	Entresto	0	4.53
	Daklinza	0	3.37
	Bridion	85.57	0
Priority; Orphan	Cerezyme	1.73	0
	Cystagon	2.03	0
	Rilutek	0	5.90
	Refludan	0	0.63

Type of Review	Brand Name	Review Delay in the US	Review Delay in EU
	Thyrogen	0	15.87
	Panretin	0	11.97
	Rapamune	0	17.90
	Inomax	11.53	0
	Targretin	0	10.03
	Trisenox	0	9.23
	Zometa	5.1	0
	Orfadin	4.23	0
	Xyrem	2.47	0
	Somavert	7.07	0
	Velcade	0	11.30
	Alimta	0	9.70
	Vidaza	0	6.60
	Ventavis	0	15.10
	Increlex	0	13.90
	Exjade	0	13.93
	Nexavar	0	5.57
	Revlimid	0	6.90
	Sprycel	0	4.33
	Mozobil	0	7.97
	Vpriv	0	4.03
	Carbaglu	0	6.73
	Caprelsa	0	8.70
	Zelboraf	0	5.90
	Firazyr	35.1	0
	Xalkori	0	10.13
	Kalydeco	0	5.50
	Stivarga	0	10.90
	Cometriq	0	10.53
	Iclusig	0	5.60
	Sirturo	0	12.37
	Adempas	0	5.77
	Imbruvica	0	7.30
	Hetlioz	0	6.10
	Imbruvica	1.9	0
	Zykadia	0	10.07
	Cerdelga	0	5.07
	Hetlioz	0	6.10
	Ofev	0	2.97

Type of Review	Brand Name	Review Delay in the US	Review Delay in EU
	Esbriet	47.97	0
	Lynparza	0	5.00
	Lenvima	0	3.43
	Farydak	0	4.73
	Cresemba	0	7.17
	Orkambi	0	4.67
	Cotellic	0	3.67
Standard	Humalog	0	2.93
	Vistide	0	7.20
	Zyprexa	0.1	0
	Aldara	0	9.00
	Quadramet	7.1	0
	Plavix	0	8.63
	Teslascan	15.83	0
	Emadine	7.33	0
	Tasmar	5.07	0
	Azopt	0	1.33
	Renagel	0	7.20
	Micardis	0	0.77
	Sonata	5.33	0
	Comtan	6.3	0
	Keppra	0	10.37
	Optimark	6.7	0
	Zonegran	20.47	0
	Lantus	0	2.03
	Exelon	23.47	0
	Cetrotide	0	4.90
	Starlix	0	3.23
	Invanz	0	4.73
	Faslodex	0	0.23
	Vfend	1.43	0
	Emtriva	0	0.67
	Aloxi	0	10.00
	Levitra	8.7	0
	Cialis	12.47	0
	Ketek	34.07	0
	Apidra	0	5.90
	Cymbalta	18.7	0
	Byetta	0	2.67

Type of Review	Brand Name	Review Delay in the US	Review Delay in EU
	Levemir	11.73	0
	Azilect	16.13	0
	Januvia	0	2.53
	Invega	0	1.10
	Tekturna	1.23	0
	Neupro	11.2	0
	Doribax	0	3.00
	Relistor	0	1.13
	Vimpat	0	2.97
	Toviaz	18.4	0
	Firmagon	0	1.40
	Samsca	0.7	0
	Onglyza	0	2.03
	Vibativ	11.17	0
	Victoza	9	0
	Latuda	0	7.93
	Edarbi	0	4.17
	Daliresp	14.73	0
	Edurant	0	5.03
	Xarelto	24.43	0
	Picato	0	5.77
	Inlyta	0	7.17
	Stribild	0	8.03
	Aubagio	0	5.83
	Fycompa	0	9.20
	Tecfidera	0	10.17
	Invokana	0	6.97
	Brintellix	0	3.93
	Vizamyl	0	9.10
	Anoro	0	4.00
	Neuraceq	1.47	0
	Otezla	0	1.43
	Zontivity	0	1.80
	Jardiance	2.37	0
	Otezla	0	1.43
	Akynzeo	0	5.07
	Odomzo	0	5.50
	Tresiba	32.47	0
	Genvoya	0.3	0

Type of Review	Brand Name	Review Delay in the US	Review Delay in EU
Standard; Orphan	Fareston	14.57	0
	Tracleer	0	3.10
	Abilify	0	17.73
	Zavesca	10.77	0
	Dacogen	0	10.30
	Tasigna	0	0.50
	Qutenza	0	7.50
	Ferriprox	14.1	0
	Kyprolis	0	0.10
	Bosulif	0	10.53
	Signifor	0	9.03
	Mekinist	0	6.93
	Tafinlar	0	3.13
	Opsumit	0	1.90
	Zydelig	0	0.33