“Drug Lag” analysis of New Molecular Entities between the United States and Europe

by

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Abstract

Introduction

In the United States, the Food and Drug Administration (FDA) and in Europe, the European Medicines Agency (EMA) are responsible for approving new drugs. At one time the FDA was criticized as it was taking a longer time for approving or reviewing new drugs.

Objectives

The study was primarily designed to analyze the approval delay in the United States compared to European Union for New Molecular Entities (NMEs) approved by both agencies from the years 1993 through 2015. In addition, the study analyzed whether there is a statistical significant difference between the two agencies in terms of approval delays.

Methods

The study data were collected from EMA and FDA websites and compared in MS Excel 2013™ for NMEs approved by both agencies. Study data were analyzed for - i) number of first approved NMEs for each region out of total approved NMEs and ii) the difference between the dates of approval. To examine any statistical significance in approval times, the non-parametric Wilcoxon Signed Ranks Test for Paired Samples was used.

Results

The study showed that from the years 1993 through 2015, a total 217 NMEs were approved in both the US and EU (N=217); 171 (78.80%) of these were first approved in the US whereas 46 (21.20%) were first approved in the EU. For the stated period, the average time a US approval followed an EU approval was 4.06 months; whereas for the EU, the average approval delay was 12.16 months. The median approval time a US approval followed an EU approval was 0 months,

whereas for EU the median approval delay was 5.72 months. Wilcoxon Signed-Ranks Test indicated that the median approval delay for EU (*Med=5.72*) was statistically significantly higher than the US (*Med=0*), Z = 6408, p < .0001.

Conclusions

The study demonstrated that a 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 statistically significantly higher in the EU.

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Chapter 1: Introduction

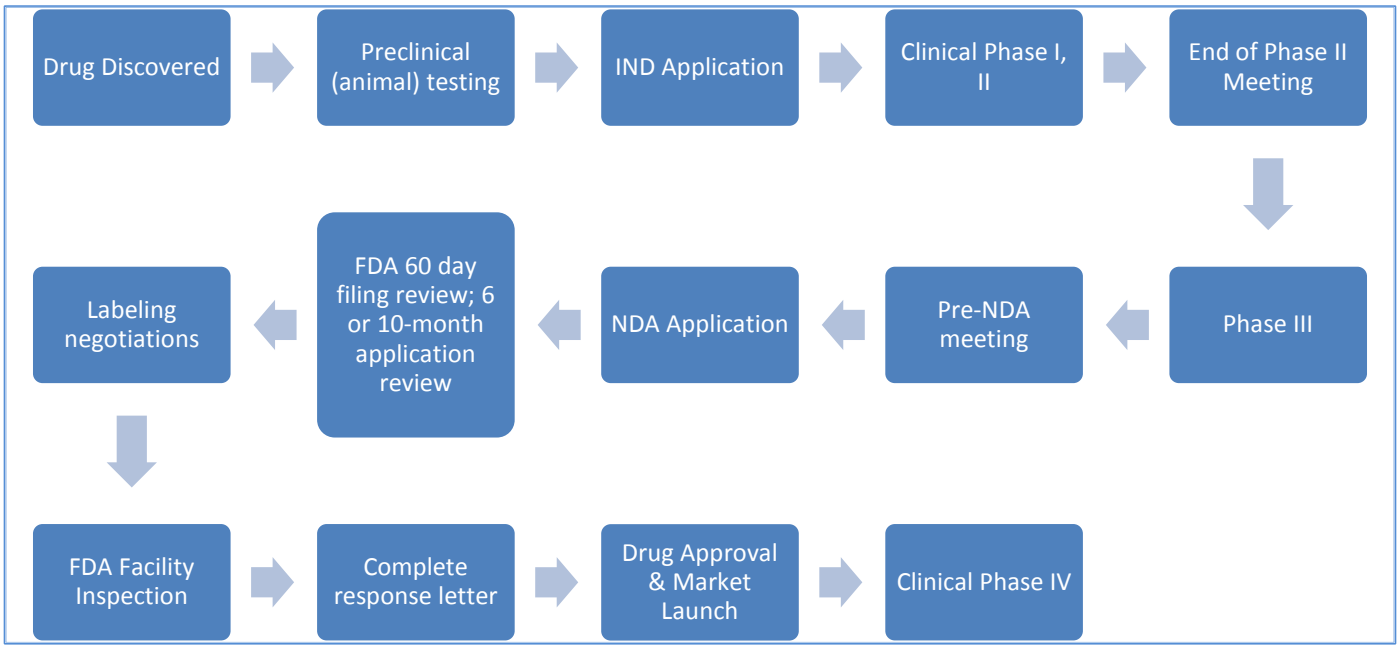
It is the responsibility of drug regulatory agencies to approve only safe and effective drugs. In the United States, the Food and Drug Administration (FDA) and in Europe, the European Medicines Agency (EMA) are responsible for approving new drugs.

A. The new drug approval process in the United States

In 1820, the first edition of US Pharmacopoeia was published which focused on chemical purity. In 1906, the US Congress passed the Pure Food and Drug Act which required purity of food and drugs and prohibited interstate commerce of misbranded or adulterated foods and drugs. In 1938, the Food, Drug, and Cosmetic Act was passed with requirement that a drug should be tested for safety. In 1962, after the Kefauver-Harris Drug Amendments to the Act, manufacturers had to prove that the drug was safe and effective (Lipsky, 2001; & Stringer, 2008). Currently, the US FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) ensure that new drugs on market have been tested for safety and effectiveness. The US FDA not only prevents quackery but also provides information about drugs to clinicians and the patients so that they may be used wisely (http://www.fda.gov/). The drug approval process in the US is outlined in Figure 1.

Figure 1: New Drug approval Process in the United States

Source: US-FDA



B. New Drug approval process in the European Union

Prior to 1995, in the European Union (EU), per council directive 75/319/EEC, drugs were approved for marketing at the National level. For a drug to reach the entire European Union (27 countries), a company had to submit a marketing authorization to each National authority separately. Later, per council regulation (EEC) No 2309/93, issued on 22 July 1993, drugs were permitted to be approved either by the centralized authorization process or by the national authorization processes in the European Union under the drug harmonizing approval process (http://www.ema.europa.eu/).

i. Centralized authorization process

The European Medicines Agency (EMA) is responsible for the authorization of human and veterinary drugs which results in a single marketing authorization valid in all EU countries and European Economic Area (EEA) countries including Iceland, Liechtenstein and Norway. In this

process, a pharmaceutical company submits an application for scientific review to the relevant EMA committee resulting in one scientific opinion. Based on scientific committee approval, the European Commission (EC) issues a marketing authorization which is valid in all EU countries. Drug products which are innovative or used for advanced-therapy or developed using biotechnology or another high-technology process or listed in EMA guidance must go through the centralized process. Drugs which do not fall within the mandatory scope of the centralized process may be approved by a National authorization processes, Decentralized process or Mutual Recognition process (http://www.ema.europa.eu/).

ii. National authorization process

This type of approval is granted to a particular member state country where the drug was intended to be marketed. The approval is granted by a single EU member state regulatory authority. A drug which was intended for one country's market does not fall within the mandatory scope of the centralized procedure may be approved by this process (http://www.ema.europa.eu/).

iii. Decentralized process

In this process, companies apply for simultaneous approval of a drug in more than one country. To go through this process, the drug should not yet have been approved in any EU country and should also not fall within the mandatory scope of the centralized procedure. ("European Medicines Agency", 2014). In this process one "reference" member state leads the assessment and consults with other member states where the application is submitted for approval. After all the member states agree on the assessment, the company is issued a national

marketing authorization in those countries where application was submitted ("A Look at the European Medicines Agency", 2015).

iv. Mutual-recognition process

A drug company which has marketing approval in one EU Member Country may apply for approval to be granted in other EU countries only when it does not fall within the mandatory scope of the centralized procedure**.** In this process, a company applies to different EU countries where drug is intended to be marketed. Then other EU member countries request for the marketing approval and assessment report from EU country where the drug was already being marketed. Then those EU member countries propose approval by mutual recognition, if no EU member country has serious objections on the drug's approval. Finally, the drug is approved in other EU member countries (http://www.ema.europa.eu/).

C. Objective

The primary objective of this study was to analyze the difference in approval time between the United States and the European Union for New Molecular Entities (NMEs) approved in both regions during the years 1993 through 2015. The secondary objective is to analyze whether there is a statistical significant difference in approval delays.

Chapter 2: Background

The United States has a strict regulatory system for drug approval. The FDA had been criticized for taking a long time to approve or review of new drugs. These delays resulted in fewer new drugs per year in the US compared to Europe. In the mid-l970s, studies were conducted which showed a significant delay of new drugs to the US market compared to the United Kingdom (Wardell, 1973 & 1974). Thereafter, several studies demonstrated that the review and approval time was longer in the US. The launching of fewer new drugs was ultimately affecting clinicians and the patients as they were not getting access to the new drugs in a timely manner. Critics concluded that the delay was either due to the extra time taken by regulatory agencies or more stringent laws which existed in the US (Wardell, 1974). There was also a study which concluded that the UK benefited by their less stringent regulatory policies for launching new drugs and by monitoring their drugs more effectively via post marketing surveillance (Wardell, 1974). Additionally, it was stated by Wardell (1979) at Congressional hearings that new drugs were available first in abroad for a wide range of therapeutic indications. Wardell (1974 & 1979) stated that the number of approved indications, approval rates, exclusivity and new approved drugs was higher in the EU than the US. This statement was initially rejected by Congress and FDA (Kennedy, 1978 & 1979). Later, Congress and eventually the FDA accepted the reality of delays in launching new drugs in the US and started to evaluate the cause. As part of a corrective action plan, Congress passed the Prescription Drug User Fee Act (PDUFA) in 1992, which allowed the FDA to collect fees from pharmaceutical companies for the review of new drug applications. Thereafter, PDUFA has been re-authorized every five years. On 9 July 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA), which re-authorized PDUFA through September 2017. PDUFA V will continue to offer timely reviews of new drugs and biologic license applications

("Prescription Drug User Fee Act", 2015). The approval and reauthorization of PDUFA has played a significant role in expediting the new drug or biologic approval process (http://www.fda.gov/).

After 1993, the European Union harmonized the drug approval process and drugs could be approved by a centralized authorization procedure. In 1995, the EMEA (later EMA) was established and decisions on new drug approvals could be made at the EU level. Due to this centralized authorization process, national regulatory authority resources were saved. Some regulatory agencies were either directly operating on marketing approvals whereas other were cooperating in mutual recognition or in de-centralized drug approval process (http://www.ema.europa.eu/).

Since changes in the drug approval process after EMEA was established in 1995 and first PDUFA had been implemented in the US in 1992, the new drug approvals timing in the US and EU have not been compared.

Chapter 3: Methodology

In this study, New Molecular Entity (NME) approval data were collected from the years 1993 through 2015 (retrieved on 09 Feb 2016).

A. New Molecular Entity (NME)

New Molecular Entity (NME) in this study refers to an application with an active moiety that has not been previously approved or legally marketed in the US in any drug either as a single ingredient or as part of a combination (http://www.fda.gov/). For this study, the NMEs refers to active moieties which have been approved by both the EMA and FDA.

B. Data sources

i. European Public Assessment Reports (EPARs) available at the EMA website http://www.ema.europa.eu/ema/.

ii. "Drugs@FDA" data published on the US FDA website http://www.fda.gov/.

C. Data collection

In the stated study period, NMEs were retrieved from the FDA website Drugs@FDA. NDAs were found by reviewing Drug Approval Reports by Month, in the section Original New Drug Approvals (NDAs and BLAs) by Month. The drug names which were assigned NDA Type 1 (meaning NME) were copied onto MS Excel 2013™ Sheet 1. A total of 662 NMEs were collected from the FDA website. In other Excel Sheet 2, 1073 drugs that were approved by EMA from the above source were recorded. After comparing Excel Sheets 1 and 2, 217 drugs were found to be approved by both EMA and FDA. NMEs that were refused, suspended or withdrawn were excluded from the study. The approval dates for study drugs were re-verified by using

Excel function control find (Ctrl F**)**. The trade name, active ingredients, approval dates in the US and the EU were compiled in one Excel Sheet for analysis of data.

D. Data Analysis

i. Analysis of approval dates in the US and EU

This study analyzed any drug approval delay in the US when compared to the EU. The data were analyzed for two variables- i) number and percentage of initial approved NMEs for each region out of total approved NMEs in both regions and ii) the time between the dates of approval. For example, as the US was the first to approve the drug Orlaam® (levomethadyl acetate hydrochloride) in 7/9/1993 and the EU approved the same drug in 7/1/1997, the approval delay for each region was 0 for the US and 48.43 months for the EU. The drug approval 'delay' was calculated by subtracting the US approval date from EU approval date for the statistical analysis. The approval delay was obtained for each NMEs approved in both regions. The median and average approval delay was calculated. A yearly drug delay was calculated as the average approval delay for all NMEs approved in that year. The annual difference was based on the year in which the NME was first approved in either region.

ii. Statistical Analysis

The non-parametric test Wilcoxon Signed Ranks Test for Paired Samples was used to determine any statistical significance in the approval delay, by assigning rank on the basis of where the NME was first approved between the two regions as well as the approval difference.

E. Ethical Considerations

This study did not involve participation of research subjects or primary subject data and entirely focused on analysis of data which was publically provided by EMA in European Public Assessment Reports (EPARs) via website http://www.ema.europa.eu/ema/ and by FDA via website http://www.fda.gov/.

Chapter 4: Results

The Appendix contains the list of NMEs approved (N=217) in the US and EU from the years 1993 through 2015. The number of NME's first approved in the US and the EU is shown in Table 1 and Figure 2.

Table 1: Number of NMEs first approved in the US and the EU.

Year	NMEs First Approved in the US	NMEs First Approved in the EU
1993	1	0
1994	3	0
1995	4	0
1996	5	3
1997	8	2
1998	10	2
1999	11	3
2000	6	2
2001	7	1
2002	5	1
2003	8	4
2004	7	3
2005	10	1
2006	6	2
2007	6	1
2008	4	2
2009	6	1
2010	4	3
2011	7	5
2012	14	3
2013	14	0
2014	16	4
2015	9	3
Total	**171**	**46**
Percentage (%) of first approvals	**78.80%**	**21.20%**

Note: New Molecular Entities (NMEs) refers to applications with an active moiety that had not been previously approved or legally marketed in either region as a single ingredient or as part of a combination.

Table 1 summarizes the total number of NME approvals in the US and EU. Out of the total 217 NMEs (N=217), 171 (78.80%) were first approved in the US, whereas 46 (21.20%) were first approved in the EU.

From the years 1993 through 1999, the number of NME initial approvals gradually increased in the US (Figure 2). From the years 2000 until 2011, the number of NME initial approvals were stable except for the year 2005 (n=10). For the years 2012, 2013 and 2014, the NME initial approvals were relatively high. The NME initial approval rate for EU was stable from the year 1996 until 2015 except for the year 2011 (n=5). The overall number of NME initial approvals in the US were greater compared to the EU (Figure 2).

Figure 2: Number of NMEs First Approved in the US and the EU.

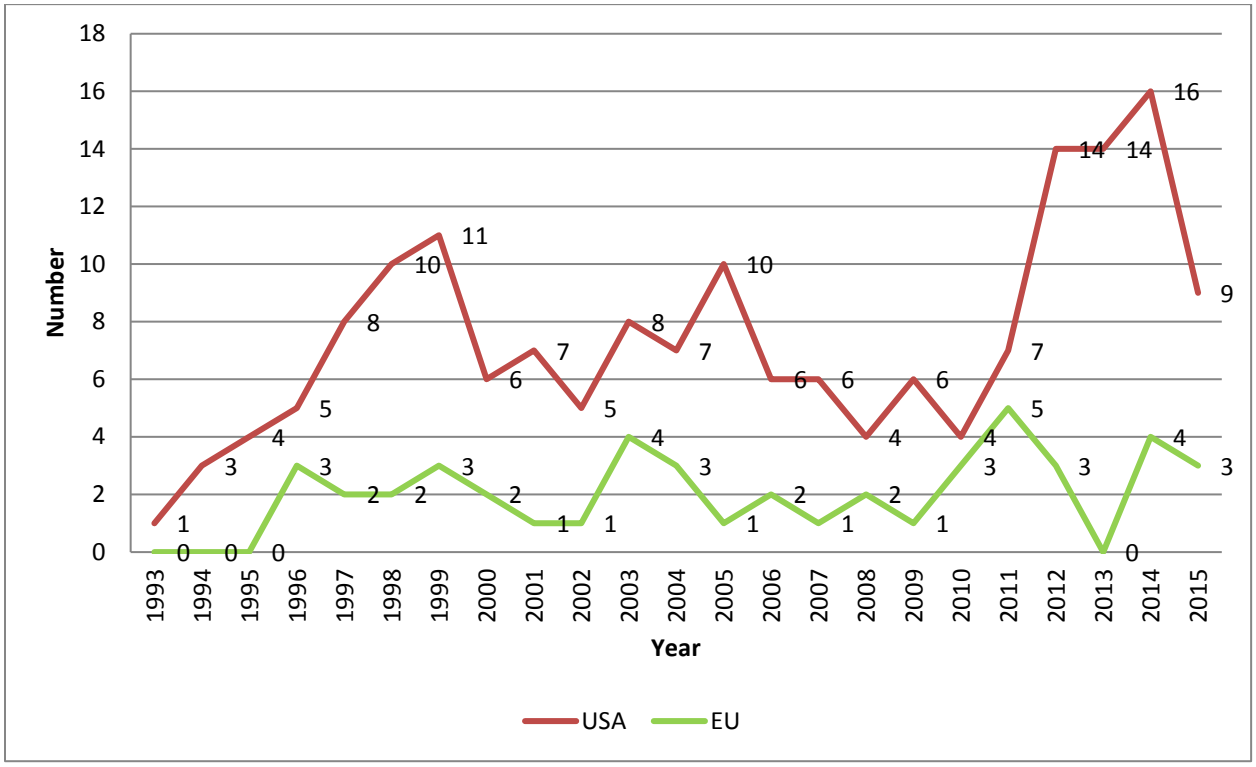


Table 2 summarizes the difference in approval times for NMEs. For the year studied, the average approval delay for all NMEs when the US was not the first to approve was 4.06 months, whereas for EU the average delay was 12.16 months.

Table 2: Change in the relative approval times of NMEs for the US and EU, 1993 through 2015

		US		EU	
Year	NME's	First approval	Average Approval Delay (Months)	First approval	Average Approval Delay (Months)
1993	1	1	0	0	48.43
1994	3	3	0	0	33.34
1995	4	4	0	0	8.63
1996	8	5	0.90	3	6.03
1997	10	8	2.19	2	11.33
1998	12	10	1.43	2	11.29
1999	14	11	1.94	3	18.43
2000	8	6	4.98	2	11.58
2001	8	7	0.64	1	6.83
2002	6	5	0.37	1	20.74
2003	12	8	2.57	4	13.14
2004	10	7	5.48	3	7.75
2005	11	10	1.15	1	15.73
2006	8	6	3.23	2	13.46
2007	7	6	2.13	1	5.12
2008	6	4	3.44	2	3.19
2009	7	6	0.88	1	6.53
2010	7	4	17.92	3	8.19
2011	12	7	28.89	5	4.44
2012	17	14	1.79	3	10.35
2013	14	14	0	0	6.37
2014	20	16	2.38	4	5.81
2015	12	9	11.14	3	2.93
1993-2015	217	171 (78.80%)	4.06	46 (21.20%)	12.16

Note: Average drug delay refers to the number in months for all NME's approved that year between the first approved NMEs and approval in the other region. If a region was first to approve, the delay is zero.

Figure 3 shows the annual average difference in approval times for NMEs initially approved in each region. Although the average approval delay for EU (12.16 months) was higher than the US (4.06 months) for the stated study period, the overall trend for EU drug approval delay decreased. The average approval delay for the US was less than EU throughout the study period except for the years 2010, 2011 and 2015 where it was more than 11 months (Table 2; Figure 3).

Figure 3: Average differences in approval times for the US and the EU

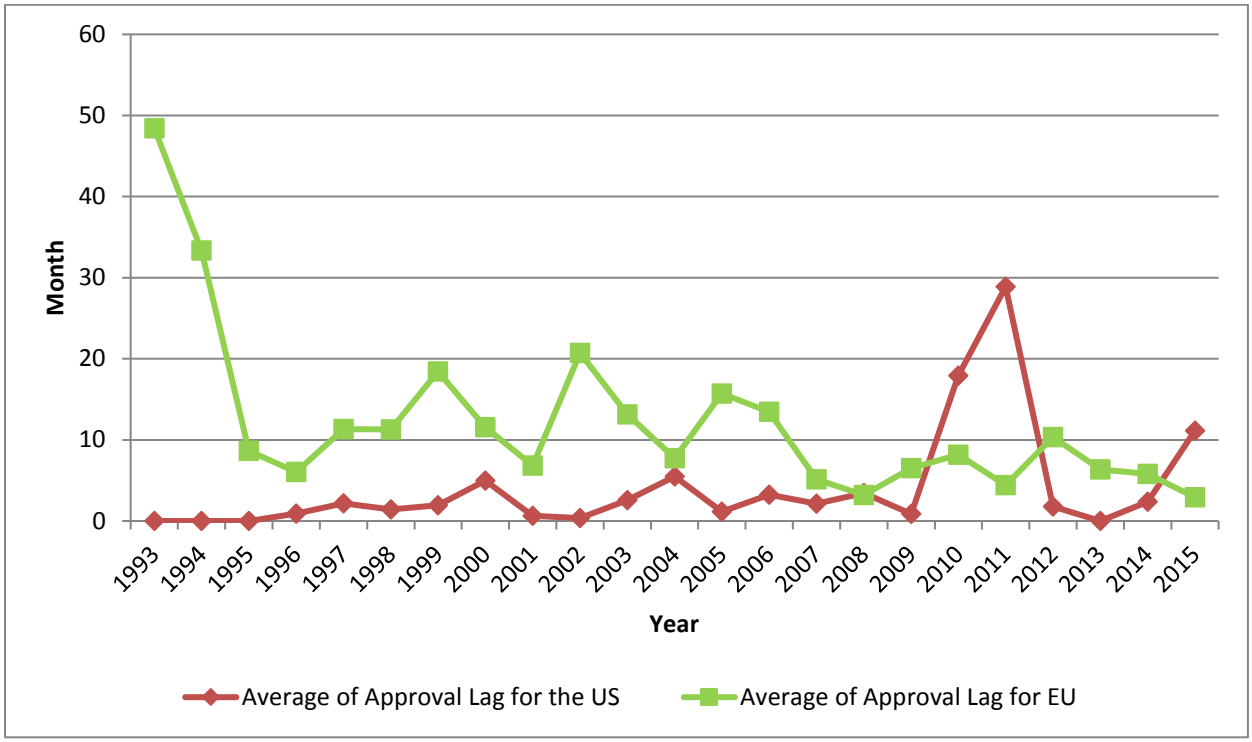


Table 3 summarizes the overall delay in terms of the number of approvals and the average approval delay for the stated study period. A total of 217 NMEs were approved in both regions. Of those, the initial approvals were generally in the US (N=171; 78.80%). When not approved first, the average approval delay in the US was only 4.06 months whereas the EU the delay averaged 12.16 months. The median approval delay for the US was zero, whereas for EU it was 5.72 months. Wilcoxon Signed-Ranks Test indicated that the median approval delay for EU (*Med=5.72*) was statistically significantly higher than the US (*Med=0*), Z = 6408, p < .0001.

Table 3: Relative difference in approval times between US and EU for the NMEs

	US	EU
Number of approved NMEs	217	217
Number of first approvals	171	46
Percentage (%) of first approvals	78.80%	21.20%
Median approval lag (months)	0	5.72
Average approval lag (months)	4.06	12.16

Note: Median drug delay refers to the number in months for all NMEs approved that year between the first approved NMEs and approval in the other region. If a region was first to approve, the median delay was zero.

Chapter 5: Discussion

The purpose of this study was to analyze number and difference in the approval times for NMEs approved in both the US and EU from the years 1993 through 2015. The number of NMEs first approved in the US was much higher than EU. Nearly 79% of the NMEs were first approved in the US. The median approval difference per year calculated was significantly higher in the EU. The median approval difference for NME approvals in the US per year was constantly zero for the stated study period whereas it was 5.72 months for the EU. The average approval difference per year for the EU was higher at 12 months in comparison to 4 months in the US.

An earlier study examined 159 new drugs approved in the US, EU, and Japan for the years 1999 through 2007 (Tsuji and Tsutani, 2010). This study showed that 47% of the drugs were first approved in the US with a median approval delay for the other drugs of 0.2 months, EU was the first to approve 46% of the drugs with a delay of 1.8 months while Japan was the first to approve only 0.4% of the drugs with an approval delay of 50.7 months. These data are consistent with the findings of the present study, even though these authors looked at all approvals and not just NMEs. Additionally, this study has shown that the conclusions from 1999-2007 are likely still valid.

NME application submission dates were not available on the FDA and EMA websites. Therefore, the study assumed that the submission dates for each NME were similar in each region. To determine whether the drug approval delay was due to review time and not differential submission times, further analysis would need to be conducted using the application submission date as well as approval date. It is likely, however, that the primary reason for the difference in approval times is the review time. US review and approval times improved greatly since PDUFA implementation. PDUFA allowed the FDA to hire more reviewers and upgrade

information technology which accelerated the application review process without compromising review quality (www.fda.gov/). As a result, the NME initial approvals in the US increased from the year 1993 until 1999 (Fig-2). The gradual increase in approvals might be due to the pending applications with the FDA before 1993, which were later reviewed (FDA Performance Report 2000). Under PDUFA II, review times were reduced and the FDA met or surpassed nearly all its review performance goals (FDA Performance Report 2000). PDUFA III aimed to improve FDA-sponsor interactions, the application review process, and post market surveillance (FDA Performance Report 2006). In the year 2012, 2013 and 2014, the maximum numbers of NMEs were first approved in the US. In the year 2012 (PDUFA V), via FDA Safety and Innovation Act (FDASIA), the "Breakthrough Therapies" provision was added (FDASIA, Section 902, 21 U.S.C. 356(a)) which helped in accelerating the new drug approval process in these drugs (FDA annual summary report 2015).

In the EU, after council regulation, (EEC) No 2309/93, enforced on 22 July 1993, the drug approval process was harmonized and new drugs were approved by centralized authorization procedure. The average approval delay for the EU when compared to the US decreased (Fig.3) for the year 2010, 2011, and 2015. It had been debated whether EMA's drug approval processes allows quicker approval than those of the FDA (Zakaria, 2011). The study data demonstrated that not only the number of NMEs getting approved first in the US were greater but also improving more quickly than in the EU. (See also Downing, 2012). Additionally, EMA's centralized and national approval process requires labelling in each language of the region. That may add to the approval delay (Trotta, 2011).

Another reason for fewer initial NME approvals in EU could be the origin or nationality of the manufacturer company. If the drug is invented by the US origin company, the application

may be filed first in the US. The detailed analyses of the relationship between the company origin and initial approval might help answering this question. The cost or subsidies provided by government for clinical trials may play important roles. Therefore, there is a need to evaluate where the clinical development was initially started and later where the NME was first approved. This analysis did not incorporate application date, nationality of inventor companies, drug development interest in all therapeutic areas, first clinical developmental initiation or the cost of clinical trial. Additional analysis of the NME data may require these supporting data.

The ICH process has done much to harmonize requirements between the two regions. Although it should be considered, after harmonization, there will always be some significant difference in the decision making of the two agencies due to cultural differences and cost factor exist between the US, EU and within EU (Pignatti, 2013).

Chapter 6: Conclusion

Waiting for new drug approvals is a concern of patients, clinicians, pharmaceutical companies, as well as the regulators. In the 1970s, the FDA had been criticized for causing a delay in the approval of new drugs. The results of this analysis revealed that there is now no delay in the approval of new drugs the US when compared to the EU. The rate of initial NME approvals in the US was greater and the drug delay was statistically significantly higher in EU. There may now be a "drug lag" in the EU which might require action taken by the EMA.

References

A Look at the European Medicines Agency. (2015, January 15). Retrieved from http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm246776.htm.

Downing, N. S., Aminawung, J. A., Shah, N. D., Braunstein, J. B., Krumholz, H. M., & Ross, K. S. (2012). Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies. *The New England Journal of Medicine*, 366, 2284-2293.

European Medicines Agency. (n.d.). Retrieved February 03, 2016, from http://www.ema.europa.eu/ema/.

Kennedy, D. (1978). A Calm Look at 'Drug Lag' *JAMA*, 239(5), 423-426.

Kennedy, D (1979). Statement at hearing on the Food and Drug Administration's new drug approval process, before the Subcommittee on Science, Research, and Technology of the Committee on Science and Technology, *US House of Representatives, Washington, DC, GPO*.

Lipsky, M. S., & Sharp, L. K. (2001). From idea to market: The drug approval process. *Journal of the American Board of Family Medicine*, 14(5), 362-367.

Lloyd, I. (2013). Citeline Pharma R&D Annual Review 2014 Supplement: New Active Substances Launched During 2013. *Citeline Pharma R&D Annual Review 2014 Supplement: New Active Substances Launched During 2013*, 1-12.

Pignatti, F. (2013, February 12). *Harmonization across regions*. Speech presented at Implementing a National Cancer Clinical Trials System for the 21st Century: IOM Session # 6, Washington, DC.

Prescription Drug User Fee Act (PDUFA). (2015, December 30). Retrieved from http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/

Stringer, S. (1998). What has been happening with over-the-counter drug regulation. *Food and Drug Law Journal*, 53(4), 633-641.

The European regulatory system for medicines A consistent approach to medicines regulation across the European Union. (2014). *European Medicines Agency*, 437313, 1-6.

Trotta, F., Leufkens, H. G., Schellens, J. H., Laing, R., & Tafuri, G. (2011). Evaluation of oncology drugs at the European Medicines Agency and US Food and Drug Administration: When differences have an impact on clinical practice. *Journal of Clinical Oncology*, 29(16), 2266-2272.

Tsuji, K., & Tsutani K. (2010). Approval of new drugs 1999–2007: comparison of the US, the EU and Japan situations. *Journal of Clinical Pharmacology and Therapeutics*, 35, 289-301.

U.S. Food and Drug Administration. (n.d.). Retrieved February 03, 2016, from http://www.fda.gov/.

Wardell, W. (1973). Introduction of new therapeutic drugs in the United States and Great Britain: An international comparison. *Clinical Pharmacology and Therapeutics,* 14(5), 773-79.

Wardell, W. (1974). Therapeutic implication of the drug lag. *Clinical Pharmacology and Therapeutics*, 15(1), 73-96.

Wardell, W. (1978). The drug lag revisited: Comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976. *Clinical Pharmacology and Therapeutics*, 24(5), 499-524.

Wardell, W. (1979). Statement on the Food and Drug Administration's process for approving new drugs. Hearings before the Subcommittee on Science, Research and Technology of the Committee on Science and Technology, *US House of Representatives*. *96th Congress 1st Session. Washington DC*: GPO, 51-91, 455-7, 488- 849

Zakaria, F. (2011). Finding a strategy for growth. *The Washington Post*. Retrieved February 3, 2016.

Appendix

List of approved NME's by both the agency FDA and EMA

Year	Trade Name	Active Ingredients	Date Approved in the US	Date Approved in EU	Difference (EU minus US in Months)
1993	Orlaam	levomethadyl acetate hydrochloride	7/9/1993	7/1/1997	48.43
1994	Cerezyme	imiglucerase	5/23/1994	11/17/1997	42.47
1994	Zerit	stavudine	6/24/1994	5/8/1996	22.80
1994	Cystagon	cysteamine bitartrate	8/15/1994	6/23/1997	34.77
1995	Cellcept	mycophenolate mofetil	5/3/1995	2/14/1996	9.57
1995	Epivir	lamivudine/zidovudine teva	11/17/1995	8/8/1996	8.83
1995	Invirase	saquinavir mesylate	12/6/1995	10/4/1996	10.10
1995	Rilutek	riluzole	12/12/1995	6/10/1996	6.03
1996	Norvir	ritonavir	3/1/1996	8/26/1996	5.93
1996	Crixivan	indinavir sulfate	3/13/1996	10/4/1996	6.83
1996	Taxotere	docetaxel	5/14/1996	11/27/1995	-5.63
1996	Hycamtin	topotecan hydrochloride	5/28/1996	11/12/1996	5.60
1996	Humalog	insulin lispro recombinant	6/14/1996	4/30/1996	-1.50
1996	Viramune	nevirapine	6/21/1996	2/5/1998	19.80
1996	Vistide	cidofovir	6/26/1996	4/23/1997	10.03
1996	Zyprexa	olanzapine	9/30/1996	9/27/1996	-0.10
1997	Aldara	imiquimod	2/27/1997	9/18/1998	18.93
1997	Viracept	nelfinavir mesylate	3/14/1997	1/22/1998	10.47
1997	Quadramet	samarium sm-153 lexidronam pentasodium	3/28/1997	2/5/1998	10.47
1997	Fareston	toremifene citrate	5/29/1997	2/14/1996	-15.67
1997	Plavix	clopidogrel bisulfate	11/17/1997	7/15/1998	8.00
1997	Teslascan	mangafodipir trisodium	11/26/1997	5/22/1997	-6.27
1997	Evista	raloxifene hydrochloride	12/9/1997	8/5/1998	7.97
1997	Trovan	trovafloxacin mesylate	12/18/1997	7/3/1998	6.57
1997	Prandin	repaglinide	12/22/1997	1/29/2001	37.80
1997	Emadine	emedastine difumarate	12/29/1997	1/27/1999	13.13
1998	Tasmar	tolcapone	1/29/1998	8/27/1997	-5.17
1998	Refludan	lepirudin recombinant	3/6/1998	3/13/1997	-11.93
1998	Viagra	sildenafil citrate	3/27/1998	9/14/1998	5.70
1998	Azopt	brinzolamide	4/1/1998	3/9/2000	23.60
1998	Xeloda	capecitabine	4/30/1998	2/2/2001	33.63

Year	Trade Name	Active Ingredients	Date Approved in the US	Date Approved in EU	Difference (EU minus US in Months)
1998	Integrilin	eptifibatide	5/18/1998	7/1/1999	13.63
1998	Arava	leflunomide	9/10/1998	9/2/1999	11.90
1998	Sustiva	efavirenz	9/17/1998	5/28/1999	8.43
1998	Renagel	sevelamer hydrochloride	10/30/1998	1/28/2000	15.17
1998	Micardis	telmisartan	11/10/1998	12/16/1998	1.20
1998	Thyrogen	thyrotropin alfa	11/30/1998	3/9/2000	15.50
1998	Ziagen	abacavir sulfate	12/17/1998	7/8/1999	6.77
1999	Panretin	alitretinoin	2/2/1999	10/11/2000	20.57
1999	Agenerase	amprenavir	4/15/1999	10/20/2000	18.47
1999	Xenical	orlistat	4/23/1999	7/29/1998	-8.93
1999	Avandia	rosiglitazone maleate	5/25/1999	7/11/2000	13.77
1999	Actos	pioglitazone hydrochloride	7/15/1999	10/13/2000	15.20
1999	Sonata	zaleplon	8/13/1999	3/12/1999	-5.13
1999	Rapamune	sirolimus	9/15/1999	3/13/2001	18.17
1999	Tikosyn	dofetilide	10/1/1999	11/29/1999	1.97
1999	Comtan	entacapone	10/19/1999	9/22/1998	-13.07
1999	Tamiflu	oseltamivir phosphate	10/27/1999	6/20/2002	32.23
1999	Keppra	levetiracetam	11/30/1999	9/29/2000	10.13
1999	Optimark	gadoversetamide	12/8/1999	7/23/2007	92.80
1999	Inomax	nitric oxide	12/23/1999	8/1/2001	19.57
1999	Targretin	bexarotene	12/29/1999	3/29/2001	15.20
2000	Zonegran	zonisamide	3/27/2000	3/10/2005	60.30
2000	Visudyne	verteporfin	4/12/2000	7/27/2000	3.53
2000	Lantus	insulin glargine recombinant	4/20/2000	6/9/2000	1.67
2000	Exelon	rivastigmine tartrate	4/21/2000	5/12/1998	-23.67
2000	Cetrotide	cetrorelix	8/11/2000	4/13/1999	-16.20
2000	Kaletra	lopinavir/ritonavir mylan	9/15/2000	3/20/2001	6.20
2000	Trisenox	arsenic trioxide	9/25/2000	3/5/2002	17.53
2000	Starlix	nateglinide	12/22/2000	4/3/2001	3.40
2001	Travatan	travoprost	3/16/2001	11/27/2001	8.53
2001	Lumigan	bimatoprost	3/16/2001	3/8/2002	11.90
2001	Zometa	zoledronic acid	8/20/2001	3/20/2001	-5.10
2001	Viread	tenofovir disoproxil fumarate	10/26/2001	2/5/2002	3.40
2001	Bextra	valdecoxib	11/16/2001	3/27/2003	16.53

Year	Trade Name	Active Ingredients	Date Approved in the US	Date Approved in EU	Difference (EU minus US in Months)
2001	Tracleer	bosentan	11/20/2001	5/15/2002	5.87
2001	Invanz	ertapenem sodium	11/21/2001	4/18/2002	4.93
2001	Arixtra	fondaparinux sodium	12/7/2001	3/21/2002	3.47
2002	Orfadin	nitisinone	1/18/2002	2/21/2005	37.67
2002	Faslodex	fulvestrant	4/25/2002	3/10/2004	22.83
2002	Vfend	voriconazole	5/24/2002	3/19/2002	-2.20
2002	Xyrem	sodium oxybate	7/17/2002	10/13/2005	39.47
2002	Hepsera	adefovir dipivoxil	9/20/2002	3/6/2003	5.57
2002	Abilify	aripiprazole	11/15/2002	6/4/2004	18.90
2003	Fuzeon	enfuvirtide	3/13/2003	5/27/2003	2.50
2003	Somavert	pegvisomant	3/25/2003	11/13/2002	-4.40
2003	Emend	aprepitant	3/27/2003	11/11/2003	7.63
2003	Iressa	gefitinib	5/5/2003	6/24/2009	74.73
2003	Velcade	bortezomib	5/13/2003	4/26/2004	11.63
2003	Reyataz	atazanavir sulfate	6/20/2003	3/2/2004	8.53
2003	Emtriva	emtricitabine	7/2/2003	10/24/2003	3.80
2003	Aloxi	palonosetron hydrochloride	7/25/2003	3/22/2005	20.20
2003	Zavesca	miglustat	7/31/2003	11/20/2002	-8.43
2003	Levitra	vardenafil hydrochloride	8/19/2003	3/6/2003	-5.53
2003	Cubicin	daptomycin	9/12/2003	1/19/2006	28.67
2003	Cialis	tadalafil	11/21/2003	11/12/2002	-12.47
2004	Alimta	pemetrexed disodium	2/4/2004	9/20/2004	7.63
2004	Ketek	telithromycin	4/1/2004	7/9/2001	-33.23
2004	Apidra	insulin glulisine recombinant	4/16/2004	9/27/2004	5.47
2004	Vidaza	azacitidine	5/19/2004	12/17/2008	55.77
2004	Cymbalta	duloxetine hydrochloride	8/3/2004	12/17/2004	4.53
2004	Tarceva	erlotinib hydrochloride	11/18/2004	9/19/2005	10.17
2004	Macugen	pegaptanib sodium	12/17/2004	1/31/2006	13.67
2004	Prialt	ziconotide acetate	12/28/2004	2/21/2005	1.83
2004	Ventavis	iloprost	12/29/2004	9/16/2003	-15.67
2004	Lyrica	pregabalin	12/30/2004	7/6/2004	-5.90
2005	Mycamine	micafungin sodium	3/16/2005	4/25/2008	37.87
2005	Baraclude	entecavir	3/29/2005	6/26/2006	15.13
2005	Byetta	exenatide synthetic	4/28/2005	11/20/2006	19.03
2005	Tygacil	tigecycline	6/15/2005	4/24/2006	10.43

Year	Trade Name	Active Ingredients	Date Approved in the US	Date Approved in EU	Difference (EU minus US in Months)
2005	Levemir	insulin detemir recombinant	6/16/2005	6/1/2004	-12.67
2005	Aptivus	tipranavir	6/22/2005	10/25/2005	4.17
2005	Nevanac	nepafenac	8/19/2005	12/11/2007	28.13
2005	Increlex	mecasermin recombinant	8/30/2005	8/3/2007	23.43
2005	Exjade	deferasirox	11/2/2005	8/28/2006	9.97
2005	Nexavar	sorafenib tosylate	12/20/2005	7/19/2006	7.03
2005	Revlimid	lenalidomide	12/27/2005	6/14/2007	17.80
2006	Sutent	sunitinib malate	1/26/2006	7/19/2006	5.80
2006	Dacogen	decitabine	5/2/2006	9/20/2012	77.77
2006	Azilect	rasagiline mesylate	5/16/2006	2/21/2005	-14.97
2006	Prezista	darunavir ethanolate	6/23/2006	2/12/2007	7.80
2006	Sprycel	dasatinib	6/28/2006	11/20/2006	4.83
2006	Noxafil	posaconazole	9/15/2006	10/25/2005	-10.83
2006	Januvia	sitagliptin phosphate	10/16/2006	3/21/2007	5.20
2006	Invega	paliperidone	12/19/2006	6/25/2007	6.27
2007	Tekturna	aliskiren hemifumarate	3/5/2007	8/22/2007	5.67
2007	Neupro	rotigotine	5/9/2007	2/15/2006	-14.93
2007	Torisel	temsirolimus	5/30/2007	11/19/2007	5.77
2007	Doribax	doripenem	10/12/2007	7/25/2008	9.57
2007	Isentress	raltegravir potassium	10/12/2007	12/20/2007	2.30
2007	Tasigna	nilotinib hydrochloride monohydrate	10/29/2007	11/19/2007	0.70
2007	Kuvan	sapropterin dihydrochloride	12/13/2007	12/2/2008	11.83
2008	Intelence	etravirine	1/18/2008	8/28/2008	7.43
2008	Relistor	methylnaltrexone bromide	4/24/2008	7/2/2008	2.30
2008	Vimpat	lacosamide	10/28/2008	8/29/2008	-2.00
2008	Toviaz	fesoterodine fumarate	10/31/2008	4/20/2007	-18.67
2008	Mozobil	plerixafor	12/15/2008	7/31/2009	7.60
2008	Firmagon	degarelix acetate	12/24/2008	2/17/2009	1.83
2009	Afinitor	everolimus	3/30/2009	8/3/2009	4.20
2009	Samsca	tolvaptan	5/19/2009	8/3/2009	2.53
2009	Multaq	dronedarone hydrochloride	7/1/2009	11/26/2009	4.93
2009	Onglyza	saxagliptin hydrochloride	7/31/2009	10/1/2009	2.07
2009	Vibativ	telavancin hydrochloride	9/11/2009	9/2/2011	24.03
2009	Votrient	pazopanib hydrochloride	10/19/2009	6/14/2010	7.93
2009	Qutenza	capsaicin	11/16/2009	5/15/2009	-6.17

Year	Trade Name	Active Ingredients	Date Approved in the US	Date Approved in EU	Difference (EU minus US in Months)
2010	Victoza	liraglutide recombinant	1/25/2010	6/30/2009	-6.97
2010	Vpriv	velaglucerase alfa	2/26/2010	8/26/2010	6.03
2010	Carbaglu	carglumic acid	3/18/2010	1/24/2003	-87.00
2010	Gilenya	fingolimod	9/21/2010	3/17/2011	5.90
2010	Pradaxa	dabigatran etexilate mesylate	10/19/2010	3/18/2008	-31.50
2010	Latuda	lurasidone hydrochloride	10/28/2010	3/21/2014	41.33
2010	Halaven	eribulin mesylate	11/15/2010	3/17/2011	4.07
2011	Datscan	ioflupane i-123	1/14/2011	7/27/2000	-127.43
2011	Edarbi	azilsartan kamedoxomil	2/25/2011	12/7/2011	9.50
2011	Daliresp	roflumilast	2/28/2011	2/28/2011	0.00
2011	Caprelsa	vandetanib	4/6/2011	2/17/2012	10.57
2011	Zytiga	abiraterone acetate	4/28/2011	9/5/2011	4.33
2011	Victrelis	boceprevir	5/13/2011	7/18/2011	2.20
2011	Edurant	rilpivirine hydrochloride	5/20/2011	11/28/2011	6.40
2011	Xarelto	rivaroxaban	7/1/2011	9/30/2008	-33.47
2011	Zelboraf	vemurafenib	8/17/2011	2/17/2012	6.13
2011	Firazyr	icatibant acetate	8/25/2011	7/11/2008	-38.00
2011	Xalkori	crizotinib	8/26/2011	10/23/2012	14.13
2011	Ferriprox	deferiprone	10/14/2011	8/25/1999	-147.77
2012	Picato	ingenol mebutate	1/23/2012	11/15/2012	9.90
2012	Inlyta	axitinib	1/27/2012	9/3/2012	7.33
2012	Erivedge	vismodegib	1/30/2012	7/12/2013	17.63
2012	Kalydeco	ivacaftor	1/31/2012	7/23/2012	5.80
2012	Amyvid	florbetapir f-18	4/6/2012	1/14/2013	9.43
2012	Kyprolis	carfilzomib	7/20/2012	11/19/2015	40.57
2012	Stribild	cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate	8/27/2012	5/24/2013	9.00
2012	Xtandi	enzalutamide	8/31/2012	6/21/2013	9.80
2012	Bosulif	bosutinib monohydrate	9/4/2012	3/27/2013	6.80
2012	Aubagio	teriflunomide	9/12/2012	8/26/2013	11.60
2012	Stivarga	regorafenib	9/27/2012	8/26/2013	11.10
2012	Fycompa	perampanel	10/22/2012	7/23/2012	-3.03
2012	Cometriq	cabozantinib s-malate	11/29/2012	3/21/2014	15.90
2012	Signifor	pasireotide diaspartate	12/14/2012	4/24/2012	-7.80
2012	Iclusig	ponatinib hydrochloride	12/14/2012	7/1/2013	6.63

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2012	Eliquis	apixaban	12/28/2012	5/18/2011	-19.67
2012	Sirturo	bedaquiline fumarate	12/28/2012	3/5/2014	14.40
2013	Tecfidera	dimethyl fumarate	3/27/2013	1/30/2014	10.30
2013	Invokana	canagliflozin	3/29/2013	11/15/2013	7.70
2013	Xofigo	radium ra-223 dichloride	5/15/2013	11/13/2013	6.07
2013	Tafinlar	dabrafenib mesylate	5/29/2013	8/26/2013	2.97
2013	Mekinist	trametinib dimethyl sulfoxide	5/29/2013	6/30/2014	13.23
2013	Tivicay	dolutegravir sodium	8/12/2013	1/16/2014	5.23
2013	Brintellix	vortioxetine hydrobromide	9/30/2013	12/18/2013	2.63
2013	Adempas	riociguat	10/8/2013	3/27/2014	5.67
2013	Opsumit	macitentan	10/18/2013	12/20/2013	2.10
2013	Vizamyl	flutemetamol f-18	10/25/2013	8/22/2014	10.03
2013	Imbruvica	ibrutinib	11/13/2013	10/21/2014	11.40
2013	Olysio	simeprevir sodium	11/22/2013	5/14/2014	5.77
2013	Sovaldi	sofosbuvir	12/6/2013	1/16/2014	1.37
2013	Anoro	umeclidinium bromide; vilanterol trifenatate	12/18/2013	5/8/2014	4.70
2014	Hetlioz	tasimelteon	1/31/2014	7/3/2015	17.27
2014	Imbruvica	ibrutinib	2/12/2014	10/21/2014	8.37
2014	Neuraceq	florbetaben f-18	3/19/2014	2/20/2014	-0.90
2014	Otezla	apremilast	3/21/2014	1/15/2015	10.00
2014	Zykadia	ceritinib	4/29/2014	5/6/2015	12.40
2014	Zontivity	vorapaxar sulfate	5/8/2014	1/19/2015	8.53
2014	Sivextro	tedizolid phosphate	6/20/2014	3/23/2015	9.20
2014	Sivextro	tedizolid phosphate	6/20/2014	3/23/2015	9.20
2014	Zydelig	idelalisib	7/23/2014	9/18/2014	1.90
2014	Zydelig	idelalisib	7/23/2014	9/18/2014	1.90
2014	Jardiance	empagliflozin	8/1/2014	5/22/2014	-2.37
2014	Orbactiv	oritavancin diphosphate	8/6/2014	3/19/2015	7.50
2014	Cerdelga	eliglustat tartrate	8/19/2014	1/19/2015	5.10
2014	Otezla	apremilast	9/23/2014	1/15/2015	3.80
2014	Hetlioz	tasimelteon	10/2/2014	7/3/2015	9.13
2014	Akynzeo	netupitant; palonosetron hydrochloride	10/10/2014	5/27/2015	7.63
2014	Harvoni	ledipasvir; sofosbuvir	10/10/2014	11/17/2014	1.27
2014	Esbriet	pirfenidone	10/15/2014	2/28/2011	-44.17

Year	Trade Name	Active Ingredients	Date Approved in the US	Date Approved in EU	Difference (EU minus US in Months)
2014	Ofev	nintedanib esylate	10/15/2014	1/15/2015	3.07
2014	Lynparza	olaparib	12/19/2014	12/16/2014	-0.10
2015	Lenvima	lenvatinib mesylate	2/13/2015	5/28/2015	3.47
2015	Farydak	panobinostat lactate	2/23/2015	8/28/2015	6.20
2015	Cresemba	isavuconazonium sulfate	3/6/2015	10/15/2015	7.43
2015	Cresemba	isavuconazonium sulfate	3/6/2015	10/15/2015	7.43
2015	Orkambi	ivacaftor; lumacaftor	7/2/2015	11/19/2015	4.67
2015	Entresto	sacubitril; valsartan	7/7/2015	11/19/2015	4.50
2015	Odomzo	sonidegib phosphate	7/24/2015	8/14/2015	0.70
2015	Daklinza	daclatasvir dihydrochloride	7/24/2015	8/22/2014	-11.20
2015	Tresiba	insulin degludec	9/25/2015	1/21/2013	-32.57
2015	Genvoya	cobicistat; elvitegravir; emtricitabine; tenofovir alafenamide fumarate	11/5/2015	11/19/2015	0.47
2015	Cotellic	cobimetinib fumarate	11/10/2015	11/20/2015	0.33
2015	Bridion	sugammadex sodium	12/15/2015	7/25/2008	-89.97

Source: US-FDA, and EMA

Note: For the above table, trade name refers to approved New Molecular Entities (NMEs) in both the US and EU, which refers to application with an active moiety that had not been previously approved or legally marketed in any drug as either a single ingredient or as part of a combination.