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RESEARCH ARTICLE

The New Drug Lag: EU Lags in Review Times of Monoclonal Antibodies

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Abstract

Background FDA had been criticized for its slow review of new drugs. Critics complained of a "drug lag" from which US patients suffered when compared to Europeans. Since the advent of PDUFA, however, the FDA has demonstrated a possible slight advantage in review time when compared to the EMA.

Methods Submission and approval dates for monoclonal antibodies were collected from the FDA and EMA websites.

Results When using monoclonal antibodies as examples of complex, yet important new therapeutic agents, it was determined that the FDA reviews these agents on average 5 months faster than the EMA.

Conclusion The review processes within each agency may have reached their highest efficiencies without making further changes in a review system.

Keywords FDA · EMA · Regulatory review · Monoclonal antibodies

Background

The difference in new molecular entities (NMEs) approval times between the USA and the European Union has been of interest for decades. The FDA had been criticized for lengthier approvals. In the mid-l970s, the USA suffered a significant delay of new drugs to the market when compared to the UK [1, 2]. This delay became known as the "Drug Lag." Critics inferred that the delay was either due to the extra time taken by regulatory agencies or more stringent laws that existed in the USA [3]. Wardell [2, 4] stated that the number of approved indications, approval rates, and new drug approvals were higher in the UK/Europe than in USA. While initially rejected by Congress and FDA [5, 6], the FDA eventually acknowledged delays in new drugs approvals. 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 and use those fees to hire additional staff to review new drug applications. Thereafter, PDUFA has been re-authorized every 5 years. Also in the mid-1990s, the European Union harmonized its drug approval process; drugs could be approved by a centralized authorization procedure. In 1995, the EMEA (later EMA) was established to approve centralized applications.

Recent studies have shown slight advantages in review times by the FDA. Oncology products seem to be available first in the USA [7]. Novel therapeutic agents approved between 2001 and 2010 were approved more quickly by the FDA than the EMA or Health Canada [8]. In our laboratory, new molecular entities approved in both the USA and EU were compared for approvals from 1993 to 2015. Approval dates generally favored the USA [9]. Additionally, review times for both agencies were compared in terms of therapeutic class and type of review for the drugs approved from 1994 to 2015. The FDA review times were faster in almost all therapeutic areas. The FDA took less time for priority, standard, and orphan drugs [10].

To further examine the review differences between the FDA and EMA, it was postulated that high technology drugs might be reviewed more efficiently in the USA than in the EU due to the internal review expertise of the FDA and lack of multiple layers of review seen in the EMA review system. Therefore, we compared the review times taken by both the FDA and EMA to approve monoclonal antibodies (mAb) from 1997 to 2018. These agents were chosen as they are likely the most complex reviews for

This study has not been previously presented in any fashion.

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the agencies, from a quality, safety, and efficacy perspective. Abciximab (Reopro) was the first mAb approved in the USA in 1994. Since abciximab was not approved in the EU, this was not included in this analysis. Thus, 1997 was the first year that any mAb was approved by both the agencies.

Methods

US NDA submission dates and approval dates for mAbs were collected from the FDA website, "Drugs@FDA" (http://www.fda.gov/) from 1997 through 2018. EU marketing authorization application (MAA) submission dates and approval dates for mAbs approved during the same period were collected from the European Public Assessment Reports from the initial authorization documents at the EMA website (http://www.ema.europa.eu/ema/). These lists were compared and only products approved in both regions were considered for analysis. Using this technique, 63 mAbs were available for comparison.

Results

FDA and EMA submission and approval dates for the 63 mAbs are listed in Table 1.

FDA review time mean was 269 days with a median of 241 days and ranged from 76 to 728 days. The shortest review time taken by the FDA was 76 days for blinatumomab. The longest review time taken by the FDA for mAbs was 728 days for ustekinumab, 571 for sarilumab, 476 for ibritumomab tiuxetan, 458 for brodalumab, and 456 for daclizumab. To demonstrate the approval time trends, the 63 mAbs approved by the FDA are grouped by 50-day review times in Fig. 1.

EMA review time mean was 427 days with a median of 429 days and ranged from 246 to 755 days. The shortest review time taken by the EMA was 246 days for lanadelumab (SHP643). The longest review time taken by the EMA was 755 days for natalizumab, 624 for ocrelizumab, 618 for dinutuximab, 613 for brodalumab, and 598 for daratumumab. To demonstrate the approval time trends, the 63 mAbs approved by the EMA are grouped by 50-day review times in Fig. 2.

For these 63 mAbs, the FDA took longer than the EMA to review four mAbs. For the remaining 59 mAbs, the EMA took longer. There was a mean difference of 158 review days. Thus, the FDA approved these applications on average over 5 months sooner than the EMA.

Discussion

The FDA has made great progress in improving the efficiency and speed of NDA reviews since the advent of PDUFA. Under PDUFA, the FDA's goal is to complete standard reviews in 10 months and priority reviews in 6 months. For these 63 mAbs, the average review time for the FDA was less than 9 months.

In the EU, all the mAbs go through a centralized procedure. Under this procedure, the CHMP (with the help of the CAT and PRAC) evaluates MAAs [11]. The CHMP goal for review is 210 days to evaluate an MAA. The European Commission has 67 days to authorize the marketing of the drug after it receives a positive scientific opinion from the EMA. Therefore, the goal to approve a drug through this procedure is 277 days (approximately 9 months). For these 63 mABs, the average review time for the EMA was 14 months.

Given that the agents compared require complex applications, yet are generally submitted for unmet medical needs, it may be that both agencies are operating at their most efficient levels during these reviews. The FDA system, even when requiring input from external Advisory Committees, may be an inherently more efficient system than the multiple reviews involved in a typical EMA approval. Improved efficiency by the FDA benefits American patients as well as the NDA sponsors.

Conclusion

The FDA averages over 5 months faster in the review of monoclonal antibodies when compared to the EMA. The EU bureaucratic process may slow down the review so that reviews are unlikely to match the FDA without organizational changes.

Table 1. Review Times by FDA (NDA) and EMA (MAA) for Monoclonal Antibodies.

Monoclonal Antibody	NDA Submission	NDA Approval	NDA Review Time (in Days)	MAA Submission	MAA Approval	MAA Review Time (in Days)	Difference: (FDA Review Time – EMA Review Time)
Rituximab	5-06-97	11-26-97	205	2-27-97	6-02-98	461	– 256
Basiliximab	11-12-97	5-12-98	182	10-07-97	10-09-98	368	– 186
Palivizumab	12-19-97	6-19-98	183	7-31-98	8-13-99	379	– 196
Infliximab	12-30-97	8-24-98	238	3-05-98	8-13-99	527	– 289
Trastuzumab	5-04-98	9-25-98	145	2-11-99	8-28-00	565	– 420
Gemtuzumab Ozogamicin	8-30-99	5-17-00	262	12-01-16	4-19-18	505	– 243
Alemtuzumab	6-21-99	6-23-00	369	3-23-00	7-06-01	471	– 102
Ibritumomab Tiuxetan	11-01-00	2-19-02	476	3-07-03	1-16-04	316	160
Adalimumab	3-28-02	12-31-02	279	3-28-02	9-01-03	523	– 244
Cetuximab	8-14-03	2-12-04	183	7-01-03	6-29-04	454	– 271
Natalizumab	5-24-04	11-23-04	184	6-03-04	6-27-06	755	– 571
Ranibizumab	8-11-05	6-30-06	324	2-08-06	1-22-07	349	– 25
Panitumumab	3-29-06	9-27-06	183	4-28-06	12-03-07	319	– 136
Eculizumab	9-15-06	3-16-07	183	9-25-06	6-20-07	269	– 86
Certolizumab Pegol	4-30-07	4-22-08	359	6-06-08	10-01-09	483	– 124
Golimumab	6-25-08	4-24-09	304	3-03-08	10-01-09	578	– 274
Canakinumab	12-17-08	6-17-09	183	12-04-08	10-23-09	324	– 141
Ustekinumab	9-29-07	9-25-09	728	12-04-07	1-15-09	409	319
Ofatumumab	1-30-09	10-26-09	270	2-05-09	4-19-10	439	– 169
Tocilizumab	7-09-09	1-08-10	184	11-29-07	1-15-09	414	– 230
Denosumab (Prolia)	1-25-10	6-01-10	128	1-09-09	5-26-10	503	– 375
Denosumab (Xgeva)	1-25-10	6-01-10	128	6-04-10	7-13-11	405	– 277
Belimumab	6-09-10	3-09-11	274	6-04-10	7-13-11	405	– 131
Ipilimumab	6-25-10	3-25-11	274	5-05-10	7-12-11	434	– 160
Brentuximab Vedotin	2-28-11	8-19-11	173	5-31-11	10-25-12	514	– 341
Pertuzumab	12-06-11	6-08-12	186	12-01-11	3-04-13	460	– 274
Ado-Trastuzumab Emtansine	8-24-12	2-22-13	183	8-30-12	11-15-13	443	– 260
Obinutuzumab	4-22-13	10-03-13	165	4-25-13	7-22-14	454	– 289
Ramucirumab	3-27-13	4-11-14	381	8-23-13	12-19-14	484	– 103
Siltuximab	8-30-13	4-23-14	237	8-29-13	5-22-14	267	– 30
Vedolizumab	6-20-13	5-20-14	355	3-06-13	5-22-14	443	– 88
Pembrolizumab	2-27-14	9-04-14	190	6-04-14	7-16-15	408	– 218
Blinatumomab	9-19-14	12-03-14	76	10-09-14	11-23-15	411	– 335
Nivolumab	7-30-14	12-22-14	146	9-02-14	6-19-15	291	– 145
Secukinumab	10-22-13	12-24-14	429	10-23-13	1-14-15	449	– 20
Dinutuximab	4-11-14	3-10-15	344	12-05-13	8-14-15	618	– 274
Alirocumab	11-24-14	7-24-15	243	12-02-14	9-23-15	296	– 53
Evolocumab	8-27-14	8-27-15	366	8-29-14	7-17-15	323	43
Idarucizumab	2-19-15	10-16-15	240	3-02-15	11-20-15	264	– 24
Mepolizumab	11-04-14	11-04-15	366	11-03-14	12-01-15	394	– 28
Daratumumab	7-09-15	11-16-15	131	9-09-15	4-28-17	598	– 467
Necitumumab	12-02-14	11-24-15	358	12-01-14	2-15-16	442	– 84
Elotuzumab	6-29-15	11-30-15	155	7-03-15	5-11-16	314	– 159
Reslizumab	3-29-15	3-02-16	340	6-30-15	8-15-16	413	– 73
Ixekizumab	3-23-15	3-22-16	366	4-23-15	4-25-16	369	– 3

Table 1. (continued)

Monoclonal Antibody	NDA Submission	NDA Approval	NDA Review Time (in Days)	MAA Submission	MAA Approval	MAA Review Time (in Days)	Difference: (FDA Review Time – EMA Review Time)
Atezolizumab	1-12-16	5-18-16	128	4-20-16	9-21-17	520	– 392
Daclizumab	2-27-15	5-27-16	456	9-04-97	2-26-99	541	– 85
Olaratumab	2-24-16	10-19-16	239	1-29-16	11-09-16	286	– 47
Bezlotoxumab	11-22-15	10-21-16	335	11-17-15	1-18-17	429	– 94
Brodalumab	11-16-15	2-15-17	458	11-13-15	7-17-17	613	– 155
Avelumab	9-23-16	3-23-17	182	10-06-16	9-18-17	348	– 166
Dupilumab	7-29-16	3-28-17	243	11-04-16	9-27-17	328	– 85
Ocrelizumab	4-28-16	3-28-17	335	4-25-16	1-08-18	624	– 289
Durvalumab	10-13-16	5-01-17	201	9-01-17	9-21-18	386	– 185
Sarilumab	10-30-15	5-22-17	571	6-24-16	6-23-17	365	206
Guselkumab	11-16-16	7-13-17	240	11-23-16	11-10-17	353	– 113
Inotuzumab Ozogamicin	12-20-16	8-17-17	241	4-14-16	6-28-17	441	– 200
Benralizumab	11-16-16	11-14-17	364	11-24-16	1-08-18	411	– 47
Emicizumab	6-23-17	11-16-17	147	6-22-17	2-23-18	247	– 100
Tildrakizumab-asmn	3-23-17	3-20-18	363	3-06-17	9-17-18	561	– 198
Burosumab-twza + A63	8-17-17	4-17-18	183	11-30-16	2-19-18	447	– 264
Erenumab-aooe	5-17-17	5-17-18	366	5-23-17	7-26-18	430	– 64
Lanadelumab (+A65SHP643)	12-26-17	8-23-18	241	3-12-18	11-22-18	246	– 5

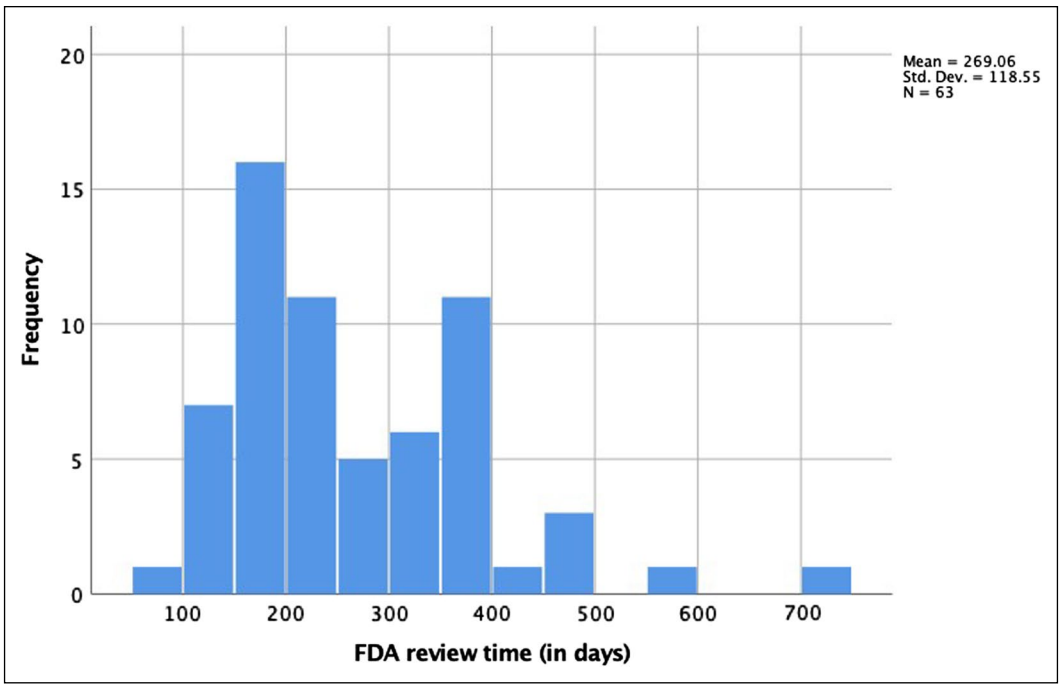

Figure 1. FDA Review Time (in Days) for mAbs.

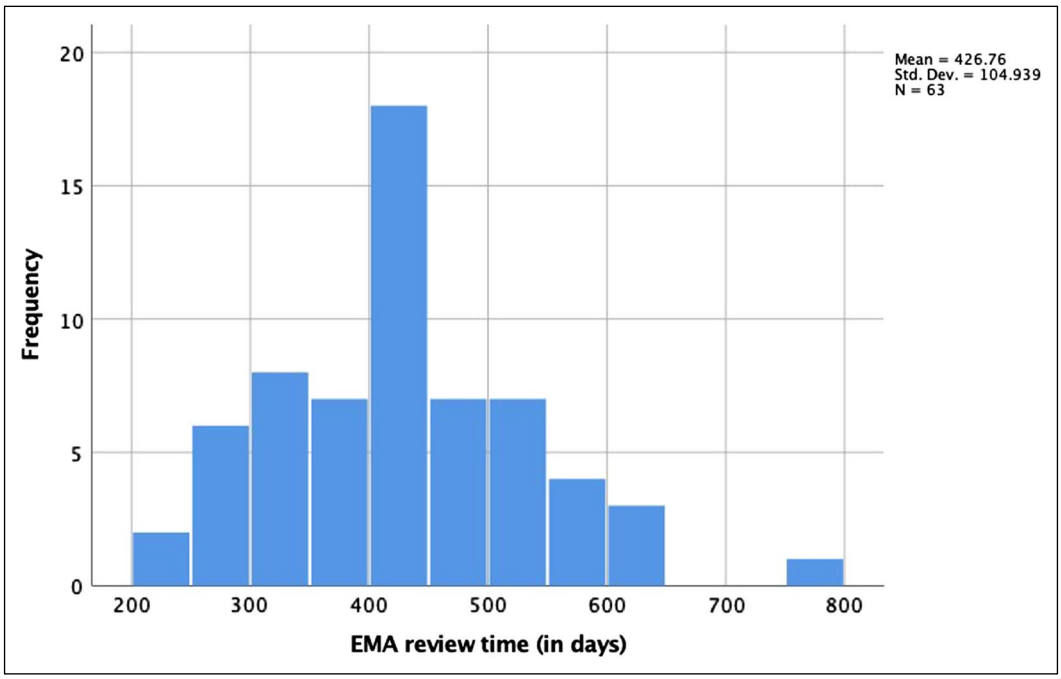

Figure 2. EMA Review Time (in Days) for mAbs.

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Compliance with Ethical Standards

Conflict of interest

No author has any conflicts of interest. ICMJE forms are enclosed.

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