Comparison of novel oncology drugs that received dual approval from the US accelerated approval and EU conditional marketing authorisation pathways, 2006–2021: a cross-sectional study

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ABSTRACT

Objective We aimed to provide insight into differences in drug review decision-making by the US Food and Drug Administration’s (FDA) accelerated approval (AA) pathway and the European Medicines Agency’s (EMA) conditional marketing authorisation (CMA) pathway, and to add to the current knowledge base of drug approval processes.

Design, setting, participants This cross-sectional study thoroughly examines novel oncology drugs with dual approval through FDA AA and EMA CMA between 2006 and 2021. Statistical analysis was performed from June to July 2022.

Primary and secondary outcome measures The study examined the regulatory differences between regions for dually approved novel oncology drugs, including approval decisions, pivotal efficacy clinical trials, speed of review and postmarketing obligations.

Results During this time period, there was a difference in the use of the FDA AA and the EMA CMA (FDA: EMA: 41.2%: 70.0%, p<0.05). Of the 25 drugs approved by both the FDA AA and the EMA CMA, 22 (88.0%) of the regulatory decisions were based on the same pivotal clinical trials. But there were more differences in the requirements for postmarketing obligations, with the EMA’s postmarketing obligations focusing more on the efficacy and safety of the drug (EMA: FDA: 63.0%: 27.0%, p<0.05) and the FDA’s postmarketing obligations focusing more on the efficacy (FDA: EMA: 73.0%: 23.9%, p<0.05). In addition, both the USA and EU had some postmarketing obligations completed beyond the schedule (30.4% and 19.2% in the USA and EU, respectively), with the longest delays lasting 3.7 years (0.2–3.7 years) and 3.3 years (0.04–3.3 years) in the USA and EU, respectively.

Conclusions The FDA and EMA have different orientations and benefit–risk balance considerations in the use of AA or CMA. It is also the case that the shortcomings in the design and implementation of postmarketing studies have made it a challenge to obtain the evidence needed to confirm a drug’s benefits.

INTRODUCTION

Cancer is one of the main causes of mortality worldwide. According to the Global Cancer Report 2020, released by the WHO’s International Agency for Research on Cancer, cancer incidence and mortality rates are rising each year, and the total number of cases worldwide could increase by 60% over the next 20 years.

As a result, it has been a priority for the pharmaceutical industry and regulatory agencies to develop, manufacture and approve new drugs for the treatment of such diseases. Many countries have developed different ways to speed up the review and approval of drugs to meet urgent medical needs. A key strategy for bringing novel oncology drugs to market more quickly is through the US Food and Drug Administration’s (FDA) accelerated approval (AA) pathway and the European Medicines Agency’s (EMA) conditional marketing authorisation (CMA) pathway.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To fully assess the similarity and differences in the review opinions of the drug reviewers of the two regions, we reviewed the medical review documents and public assessment reports for each drug at both agencies.

⇒ This article focused on the differences in the review of pivotal clinical trials and the requirements and fulfilment of postmarketing obligations in the Food and Drug Administration (FDA) accelerated approval and European Medicines Agency (EMA) conditional marketing authorisation.

⇒ Our study only included drugs in the initial application and has not been extended to drugs in the supplemental application.

⇒ Our study was limited to oncology, and it remains unknown whether the findings would apply to other indications.

⇒ Because of data constraints, this study did not analyse products that did not receive FDA and EMA approval.

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The US AA programme was established in 1992. According to Article 901 of the FDA’s Safety and Innovation Act, drugs used to treat serious or life-threatening diseases may be given AA based on reasonable surrogate or intermediate clinical endpoints that forecast clinical benefits. However, postmarketing confirmatory studies are required to confirm the benefit of drugs with AA.3

The EU’s CMA pathway was proposed in 2004 by the European Commission, and legally adopted in 2006. Only newly developed drugs that are marketed and designed for the treatment of severely debilitating or life-threatening conditions, emergency use in response to public health threats or orphan drugs, are eligible. CMA is given for 1 year with specific obligations if the benefits of immediate clinical use outweigh the risks of having incomplete data. EMA also reviews the CMA on an annual basis. Overall, the FDA AA and the EMA CMA share the goal of providing earlier access to potentially life-saving therapies. The greatest commonality between the two review decisions is that they both provisionally approve drugs based primarily on surrogate endpoints and non-comprehensive clinical trial data.5,6 However, unlike the AA in the USA, only new molecular entities can be considered for CMA in the EU and a time limit for the validity of the CMA is specified. In addition, most FDA AA approvals rely on endpoints that are likely to predict clinical benefit, while the EMA CMA relies on the results of benefit–risk assessments. Therefore, it is of great interest to examine the differences between them in terms of review decisions, review criteria and postmarketing management. But most previous studies, however, have concentrated on experience with US AA or EU CMA,8–10 or have individually examined special review pathways in a particular country,11–13 without conducting a thorough comparison of decisions made by both processes. This study sought to provide a systematic and comprehensive comparison of the regulatory differences between the FDA AA and EMA CMA by analysing information on novel oncology drugs that received dual approval during 2006–2021, including regulatory pathways, pivotal clinical trials, postmarketing obligations and drug status.

METHODS
Study design and sample
In this cross-sectional study, data on novel drugs and biologics approved based on surrogate endpoints published by the Center for Drug Evaluation and Research, EMA annual reports and related information on the FDA and EMA websites were retrieved between 1 January 2006 and 31 December 2021. After collecting the list of drugs approved by FDA AA or EMA CMA for the first time (excluding supportive care products, new formulations and ancillary drugs), this paper further screened out the information on drugs approved by both FDA AA and EMA CMA and organised basic information of these listed drugs in terms of the time of approval, approved indications and market status. Since the status of these novel oncology drugs was continuously updated, the data was tracked till July 2022.

Identification of pivotal clinical trials and primary study endpoints
We searched the Drugs@FDA database and the EMA website to obtain initial and supplementary approval letters, the multidisciplinary review documents, the medical review documents published by the FDA, and the European Public Assessment Report published by the EMA, thus further identifying specific information about the pivotal clinical trials for dual approval, including trial type, trial phase, blinding and main study endpoint. Generally, these trials are marked as ‘pivotal’ in the drug review report. If a drug review report is not clearly labelled as a pivotal clinical trial, then trials described in the report as critical to approval are prioritised as the pivotal trials. Primary trial endpoints are categorised as clinical endpoints (the characteristics or variables that describe or reflect how an individual feels, functions or survives) and surrogate endpoints (a marker, such as a laboratory measurement, radiographic image, physical sign or other measures, ie, not itself a direct measurement of clinical benefit).14,15

Identification of postmarketing obligations under AA or CMA
By reviewing the FDA approval letter and the EMA postmarketing obligations obtained in the two documents were matched with those of the clinical trials in the USA. ClinicalTrials.gov database to determine the specific characteristics of the postmarketing obligations under AA or CMA (including trial type, trial phase and blinding), the significant time points of the studies (including study start date, actual primary completion date and the actual or estimated study completion dates) and the current stage of progress (including completed, recruiting, completed recruitment, not yet recruited).

Patient and public involvement
No patients were involved in any aspect of this study.

Statistical analysis
Using descriptive statistics, we described the characteristics of new oncology drugs that received FDA AA and EMA CMA, as well as their pivotal clinical trials and postmarketing obligations. A χ² test was used to analyse differences in FDA AA and EMA CMA characteristics, including approval pathways, marketing status, orphan
status, pivotal clinical trials characteristics and postmarketing obligations characteristics and fulfilment. The Mann-Whitney U test was used to determine differences in review time between the FDA and EMA. A two-tailed \( p < 0.05 \) was considered statistically significant. All data processing analyses were performed from 1 June 2022 to 31 July 2022, using Excel and SPSS V.24.0.

### RESULTS

#### Overview of approvals

Between 2006 and 2021, the FDA approved 68 novel oncology drugs with initial applications through AA, the EMA authorised 40 novel oncology drugs with CMA (online supplemental tables S1 and S2). During the same period, of the 68 oncology drugs approved by the FDA AA, 28 drugs were approved in the EU through CMA, 2 drugs were approved through accelerated assessment, 17 drugs were approved under the regular approval pathway and 21 drugs were not granted marketing authorisation in the EU, including Pralatrexate (Folotyn), which was denied marketing because the Committee for Medicinal Products for Human Use found insufficient evidence that its benefits outweighed its risks. Among the 40 oncology drugs approved by EMA CMA, 28 drugs were approved in the USA through AA, 9 drugs were approved through other expedited pathways, 2 drugs were approved through the regular approval pathway and 1 drug was not approved in the USA (table 1).

As of the date of our tracking, of the 68 oncology drugs approved by FDA AA, 10 drugs (14.8%) were withdrawn due to difficulties in completing confirmatory trials or the results of which did not demonstrate a clinical benefit for the drug, as well as serious drug safety risks, 29 drugs (42.6%) were converted to full approval and are normally on the market and 16 drugs (23.9%) are still in AA. Of the 40 oncology drugs approved by the EMA CMA, 3 drugs (7.5%) were withdrawn due to difficulties in proving clinical benefit or voluntary withdrawal by the holder for commercial reasons, 21 drugs (52.5%) were converted to full approval and are normally on the market and 16 drugs (40.0%) are still in the CMA. The specific withdrawals are shown in online supplemental table S3.

At the same time, a total of 28 novel oncology drugs involving 30 indications have received both FDA AA and EMA CMA, involving 21 solid cancers and 9 haematological cancers. Among solid cancers, non-small cell lung cancer was the most common (8/21, 38.1%), while among haematological cancers, multiple myeloma was the majority (3/9, 33.3%). Also, there were 23 orphan drugs designated by FDA and 8 orphan drugs designated by EMA, and these 8 drugs were also designated as orphan drugs by FDA. From the viewpoint of marketing status, 25 drugs were normally marketed in Europe and America, olaratumab and rucaparib were withdrawn in both EU and USA due to the results of confirmatory trials failing to verify the benefits of the drugs, and ofatumumab was voluntarily applied for withdrawal from the market in the EU for commercial reasons by the holder but is still listed and sold in the USA.

#### Use and stack of other expedited programmes

To better compare the differences between FDA AA and EMA CMA, this section and the following discuss only the 25 drugs (covering 27 indications) that received dual approval and are not withdrawn in Europe and the USA.

In the USA, of the 27 dual-approved drug-indication pairs, only 2 (7.4%) AAs were not overlaid with any other expedited pathway, 25 (92.6%) AAs were overlaid with at least one other expedited pathway, 14 (51.9%) AAs were overlaid with more than 2 other expedited pathways, and 1 (3.7%) AA was overlaid with three other expedited routes. Of these, the most common way was to stack priority review and breakthrough therapy designation.

In the EU, only 5 (18.5%) CMAs were overlaid with one other expedited pathway, and 22 (81.5%) CMAs were not overlaid with any other expedited pathway.
Overall, the FDA used multiple expedited pathways to market more frequently, this is consistent with other studies, and the EMA had less overlapping use of special review pathways.

### Approval time and review duration

Generally, 24 of the 25 dual-approved new oncology drugs were submitted for marketing at the FDA before they were submitted in the EU, and 23 were approved at the FDA before the EMA. Looking at the time taken for the review, among the 25 dual-approved oncology drugs, the FDA median review time was 175 days and EMA was 411 days, with FDA review time significantly shorter than EU (175 vs 411 days, \( p=0.000 \)) (figure 1).

### Characteristics and results of pivotal clinical trials

Of the 25 drugs with dual approval, 35 clinical trials were identified as pivotal by the FDA, with 68.0% of the drugs using 1 pivotal clinical trial, 24.0% using 2 pivotal clinical trials and 8.0% using 3 clinical trials. Thirty-two clinical trials were identified as pivotal by the EMA, with 80.0% of the drugs using one pivotal clinical trial, 12.0% using two pivotal clinical trials and 8.0% using three clinical trials. Specifically, the pivotal clinical trials identified by both agencies were mainly in phase II (FDA: EMA: 45.7%: 43.8%), and the proportion of single-arm trials was over 90% (FDA: EMA: 91.4%: 93.7%), with relatively few randomised controlled trials (FDA: EMA: 8.6%: 6.3%). In addition, none of the pivotal trials of the 25 drugs had overall survival (OS) as the primary endpoint at either agency, but rather the objective response rate (ORR), was predominant (FDA: EMA: 65.8%: 65.8%). Some drugs had multiple endpoints as the primary study endpoint, usually a combination of ORR and duration of response (DOR) (FDA: EMA: 7.3%: 5.3%) (table 2).

#### Table 2  The characteristics and results of pivotal clinical trials of 25 dual-approved drugs

<table>
<thead>
<tr>
<th>Stage of trial</th>
<th>FDA AA</th>
<th>EMA CMA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>7 (20.0%)</td>
<td>7 (21.9%)</td>
<td>0.850</td>
</tr>
<tr>
<td>Phase I/II</td>
<td>10 (28.6%)</td>
<td>10 (31.3%)</td>
<td>0.811</td>
</tr>
<tr>
<td>Phase II</td>
<td>16 (45.7%)</td>
<td>14 (43.8%)</td>
<td>0.872</td>
</tr>
<tr>
<td>Phase III</td>
<td>2 (5.7%)</td>
<td>1 (3.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Type of clinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-arm trial</td>
<td>32 (91.4%)</td>
<td>30 (93.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Randomised controlled</td>
<td>3 (8.6%)</td>
<td>2 (6.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Study endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>24 (58.5%)</td>
<td>23 (60.5%)</td>
<td>0.857</td>
</tr>
<tr>
<td>PFS</td>
<td>1 (2.4%)</td>
<td>1 (2.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>ORR + DOR</td>
<td>3 (7.3%)</td>
<td>2 (5.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>CR</td>
<td>2 (4.9%)</td>
<td>2 (5.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Safety endpoints</td>
<td>9 (22.0%)</td>
<td>9 (23.7)</td>
<td>0.854</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4.9%)</td>
<td>1 (2.6%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

#### Efficacy

| Objective response rate, % | FDA AA: 45.7 (44.0–47.4) | EMA: 50.3 (48.6–52.0) | 0.571 |

#### Safety

| AEs ≥3, no patients (%) | FDA: 3098/6380, 48.6 | EMA: 3194/6566, 48.6 | 0.09   |
| SAEs, no patients (%)   | FDA: 1532/6380, 24.0 | EMA: 1267/6566, 19.3 | 0.39   |

AA, accelerated approval; AE, adverse event; CMA, conditional marketing authorisation; CR, complete response; DOR, duration of response; EMA, European Medicines Agency; FDA, Food and Drug Administration; ORR, objective response rate; PFS, progression-free survival; SAE, serious adverse event.
From the results of the pivotal clinical trials, there was no significant difference in the pivotal clinical efficacy of the dual-approved drugs between FDA AA and EMA CMA (ORR: FDA vs EMA: 45.7% vs 50.3%, p>0.05). In addition, there was also no significant difference in safety outcomes between FDA AA and EMA CMA (Grade≥3 AEs: FDA vs EMA: 48.6% vs 48.6%, p>0.05; SAEs: FDA vs EMA: 24.0% vs 19.3%, p>0.05).

Overall, regulatory decisions for 22 of the 25 matched drugs (88.0%) were based on the same pivotal trials, and there were no significant differences in pivotal clinical efficacy and safety outcomes for any of the approved drugs. For the remaining three groups of drugs, the differences in pivotal trials were due to the differing reviews of evidence packages submitted by applicants by the two agencies. For example, for ceritinib, Study C2845 and Study M2301 in the data package were both considered ‘pivotal’ by the FDA, but Study M2301 was considered ‘supportive’ by the EMA, where Study C2845 was ‘pivotal’. In addition, even though both agencies made approvals based on the same pivotal clinical trials, the FDA and EMA differed slightly in their selection of the primary study endpoint. For example, for everolimus, both agencies identified CLDK378×2101 as pivotal study, but the FDA considered the primary study endpoint to be ORR, while the EMA considered the primary study endpoint to include ORR and DOR (online supplemental table S4).

Postmarketing obligations
Since drugs undergoing AA and CMA do not yet fully satisfy the requirements for full approval, applicants must discuss and agree on the details of postmarketing obligations with the regulatory agencies and carry them out as required, thus providing a basis for conversion of the drug to full approval.18 Among the 25 novel oncology drugs that received both FDA AA and EMA CMA, there exist differences in the requirements and completion of their postmarketing obligations in the USA and EU.

Characteristics of postmarketing obligations
Overall, of the 25 dual-approved drugs, the FDA required 37 postmarketing obligations and the EMA required 46 postmarketing obligations. Among them, the postmarketing obligations of 8 drugs were consistent in these two agencies, 4 drugs had completely different postmarketing obligations, 13 drugs had overlapping postmarketing obligations, but not completely consistent, of which 11 drugs had more obligations required by EMA (online supplemental table S5). In terms of the purpose of the requirements, 27 (73.0%) of the postmarketing obligations required by the FDA were to verify the efficacy of the drug and 10 (27.0%) were to determine the efficacy and safety of the drug. Eleven (23.9%) of the postmarketing obligations required by the FDA were to verify the efficacy of the drug, 29 (63.0%) were to determine the efficacy and safety of the drug, and 6 (13.1%) were specifically for determining drug safety requirements.

In general, although the pivotal evidence at the time of EMA and FDA approval was essentially the same, there were significant differences between EMA and FDA in the number of postmarketing obligations required and clinical study objectives. First, these 11 drugs had more postmarketing obligations at the EMA than at the FDA, with the FDA requiring only one of the multiple postmarketing studies required by the EMA sometimes. Taking pemigatinib as an example, the EMA required the submission of the outcomes of two clinical studies, FIGHT-202 and FIGHT-302, while the FDA only required that of FIGHT-302. The second is the difference in the purpose of the study. FDA required more efficacy studies than the EMA (FDA: EMA: 73.0%: 23.9%, p<0.05), EMA required more obligations to verify the efficacy and safety (EMA: FDA: 63.0%: 27.0%, p<0.05).

Characteristics of clinical studies
Matching the postmarketing obligations required by regulators with the studies registered on ClinicalTrials.gov website, it was found that the 37 postmarketing studies required by the FDA involved 38 clinical trials and 1 observational study. Thirty-eight clinical studies included four new clinical trials conducted after approval and 34 studies conducted before approval, which were mainly randomised controlled trials (28/38, 73.7%). In terms of study endpoints, most studies used a single endpoint (surrogate endpoint or clinical endpoint) as the primary study endpoint (35/38, 92.1%), while some studies used multiple surrogate endpoints or a combination of surrogate and clinical endpoints as the primary study endpoint (3/38, 7.9%). Specifically, surrogate endpoints continued to account for the highest proportion of postmarketing studies, up to 73.2%, and the largest proportion of them, was PFS (up to 70.0%). Four studies also used the clinical endpoint as the primary study endpoint.

The 46 postmarketing studies required by the EMA involved 44 clinical studies and 5 other studies. Forty-four clinical studies included 3 new clinical trials conducted after approval and 41 preapproval continuation studies, which were also mainly randomised controlled trials (25/44, 56.8%). Similar to the USA, single endpoints were usually used as the primary study endpoints (42/44, 95.5%). And the majority of these studies utilized surrogate endpoints (39/48, 81.3%), with PFS being the most frequently employed (21/39, 53.8%). Three studies used a clinical endpoint alone or in combination with a surrogate endpoint as the primary study endpoint (table 3).

Fulfilment of postlisting obligations
To oblige holders to actively complete their postmarketing obligations, both FDA and EMA have set the time for the submission of final reports. We found that the average time frame for the FDA to request a final report was 3.4 years, compared with 2.7 years for the EMA. For most studies, both the FDA and EMA required a final report within 3 years (FDA:EMA: 59.5%-63.0%), but the FDA allowed a greater percentage of final reports to be...
submitted within 5 years to meet postmarketing obligations (FDA:EMA: 27.0%:17.4%).

Of the 37 postmarketing obligations required by the FDA, 23 obligations were completed, 2 obligations were released, 7 obligations were on track to meet the required timeline, 2 obligations were delayed due to the delay of study protocol submission and 3 obligations were in pending status. Among the 23 completed postmarket studies, 7 studies were submitted in excess of the FDA's required submission date, with an average delay of 0.8 years (0.2–3.7 years).

Of the 46 postmarketing obligations required by the EMA, 26 were completed, 18 were on track to meet the required time and 2 experienced delays. Of the 26 completed postmarketing obligations, 5 study submissions exceeded the EMA-required submission date by an average of 0.8 years (0.04–3.3 years).

In contrast, there was no significant difference in the completion rate of FDA and EMA postmarketing obligations (FDA: EMA: 62.2%: 56.6%, p<0.05), but FDA conducted significantly more trials on schedule than FDA (EMA: FDA: 27.0%:18.9%, p<0.05) (table 4).

Conversion of AA/CMA to full approvals

Overall, 14 drugs were converted to full approval at both FDA and EMA based on the postmarketing obligations that had been met. Among them, 12 drugs were converted to full approval at both FDA and EMA, 2 drugs were converted only in the FDA (lorlatinib and trastuzumab deruxtecan), and two drugs were converted only in the EMA (polatuzumab vedotin and avelumab). Specifically, lonafarnib was not converted to full approval in the EU because a single-arm clinical study was not completed, which was not required by the FDA. Also, trastuzumab deruxtecan was not converted to full approval in the EU because a randomised controlled trial, which was completely different from the FDA's postmarketing obligations, was not completed. In the USA, polatuzumab vedotin was not converted to full approval because a single-arm clinical study was not completed in the FDA although the postmarketing obligations were the same at both agencies, the FDA website showed that the obligation was on schedule and not converted to full approval.

Of the 13 drugs that were converted to full approval (1 drug for which no information has been reported in the EU and USA), in the USA, 1 drug was converted based on significant improvement in the primary endpoint OS in the confirmatory trial; 12 drugs were based on significant improvement of surrogate endpoints in confirmatory trials, with the majority of the surrogate endpoints being PFS (11/12, 91.7%). In the EU, one drug was based on a significant improvement of the primary endpoint OS in the confirmatory trial; nine drugs were based on a significant improvement of the progression-free survival (PFS) in confirmatory trials, and two drugs were based on the improvement of the ORR. The DOR of one drug (avelumab) was worse than predicted but was approved for conversion by the EMA based on its positive risk–benefit ratio.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Characteristics of postmarketing studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>EMA</td>
</tr>
<tr>
<td>Study design</td>
<td>n=38</td>
</tr>
<tr>
<td>Single-arm trial</td>
<td>10 (26.3%)</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>28 (73.7%)</td>
</tr>
<tr>
<td>Study type</td>
<td>n=38</td>
</tr>
<tr>
<td>New</td>
<td>4 (10.5%)</td>
</tr>
<tr>
<td>Ongoing</td>
<td>34 (89.5%)</td>
</tr>
<tr>
<td>Study endpoints</td>
<td>n=41</td>
</tr>
<tr>
<td>Surrogate endpoints</td>
<td>30 (73.2%)</td>
</tr>
<tr>
<td>Clinical endpoints</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>Co-endpoints*</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>Safety endpoints</td>
<td>7 (17.0%)</td>
</tr>
</tbody>
</table>

*A co-endpoint is a combination of a clinical endpoint and a surrogate endpoint.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The fulfilment of FDA AA and EMA CMA postmarketing obligations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>EMA</td>
</tr>
<tr>
<td>Status</td>
<td>N=37</td>
</tr>
<tr>
<td>Completed</td>
<td>23 (62.2%)</td>
</tr>
<tr>
<td>Running on schedule</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Running with delays</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Pending</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Released</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Time limit for submission required by the regulator</td>
<td>N=37</td>
</tr>
<tr>
<td>≤3 years</td>
<td>22 (59.5%)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>≥5 years</td>
<td>10 (27.0%)</td>
</tr>
<tr>
<td>Actual submission time</td>
<td>N=21*</td>
</tr>
<tr>
<td>≤3 years</td>
<td>19 (90.5%)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>–</td>
</tr>
<tr>
<td>≥5 years</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Overdue rates</td>
<td>7 (30.4%)</td>
</tr>
</tbody>
</table>

*FDA: two completed postmarketing obligations were submitted on time but without the specific submission date for the final report, and EMA: one completed postmarketing obligation was submitted on time but without the specific submission date for the final report.

AA, accelerated approval; CMA, conditional marketing authorisation; EMA, European Medicines Agency; FDA, Food and Drug Administration.
DISCUSSION

For dual-approved drugs, there were certain commonalities between FDA AA and EMA CMA. In both US AA and EU CMA, premarketing pivotal clinical trials were mainly single-arm clinical ones (FDA: EMA: 91.4%: 93.7%) and postmarketing studies were mainly randomised controlled clinical trials (FDA: EMA: 73.7%: 56.8%). In addition, there was no significant difference in the completion rate of their postmarketing obligations (FDA: EMA: 62.2%: 56.5%, p>0.05) and the conversion rate of varieties to full approval (FDA: EMA: 56.0%: 56.0%, p>0.05). Also, surrogate endpoints, such as ORR, PFS, were more often used for pivotal drug clinical trials and postmarketing studies in both the US AA and EU CMA processes. This may be because both regions have biomarker development and qualification processes which clarify what information should be required for the use of biomarkers as surrogate endpoints.

Although FDA AA and EMA CMA have many commonalities, there also exist some differences. First, the number of novel oncology drugs with FDA AA between 2006 and 2021 was significantly greater than that with EMA CMA, and only 28 (41.2%) of the 68 drugs marketed through FDA AA were approved through CMA in EMA, and the EU Rarely stacked multiple expedited pathways compared with the USA (EMA: FDA: 18.5%: 92.6%, p < 0.05). This suggests some differences in the use of special pathways by the FDA and EMA, which is consistent with the findings of a study comparing EMA and FDA application decisions for new drug launches between 2014 and 2016. Second, the FDA approval efficiency was also significantly higher than the EMA in terms of access time and review speed (175 vs 411 days, p=0.000). This is consistent with the findings of Lythgoe et al. It was just based on the higher efficiency of FDA approval that 92.6% of drugs were chosen to be marketed in the USA. This could be related to the fact that the USA has the world’s largest drug market and is also the world’s largest funder of biomedical research. In addition, the USA is the only major economy without any central direct drug price negotiations, so its pricing is not restricted, which means that drugs are usually launched in the USA first. And because some countries often use reference pricing approaches to set drug prices, drug prices in other countries usually take into account the price of the first launch country. If a drug is marketed for the first time in the USA, even if the price is negotiated in other countries, based on the original high price, the price reduction is not significant. This has also prompted more companies to choose to market in the USA first. However, shorter review duration and earlier FDA approvals mean that more drugs are withdrawn, and the FDA AA withdrawal rate is significantly higher than that in the EU (14.8%: 7.5%).

What is more, there exist differences in the postmarketing obligations required by the FDA and EMA. Usually, the postmarketing obligations required by the EMA focus on the efficacy and safety of the drug, while those required by the FDA focus on the efficacy of the drug. This may be explained by differences in the orientation and risk–benefit balance between the two agencies for AA or CMA. When applying for FDA AA, it is more important to consider if the surrogate endpoint can accurately predict the clinical benefit, and when applying for EMA CMA, it is more important to consider the positive risk–benefit ratio and unmet medical needs. Since establishing the AA pathway in 1992, the USA also has more experience in AAs and the FDA has been more willing to accept risk and uncertainty in its reviews. This finding closely aligns with the considerations made by Hoekman et al. Thus, the FDA and EMA should consider developing a more robust communication system to ensure that the two agencies are in closer alignment.

Drug access is significantly aided by AA and CMA. However, our study showed that both processes have drawbacks. First, drugs that receive AA or CMA based on incomplete trial data, and their specific benefits need to be further confirmed. Thus, postmarketing studies have a very important role in confirming the safety and efficacy of drugs. However, of the completed postmarketing obligations, 30.4% of the novel oncology drugs were overdue in the USA, with the longest overdue period being as high as 3.7 years. In the EU, 19.2% of the postmarketing studies were overdue, with the longest overdue period being 3.3 years. Also, 50% of withdrawn drugs in the USA were taken off the market due to the recruitment difficulties of postmarketing confirmatory trials that led to the delay of the trials to verify the benefits of their drugs. What is more, some studies found that a portion of drugs failed to meet their primary endpoints in postmarketing studies, but the FDA approved conversion to full approval or delayed the withdrawal of approval. These findings suggest that the duration of product licences and the deadline for postmarketing studies should be reconsidered. A similar issue was discussed by Chenyang et al. On 29 December 2022, the USA announced the Consolidated Appropriations Act, 2023, which revises the AA pathway. One of the key reforms focuses on ensuring that sponsors comply with the prespecified conditions set out in the postaccelerated study approval research plan for confirmatory studies. Therefore, to fully prepare for AA or CMA, and subsequent conversion to full approval, pharmaceutical firms should communicate with regulators early in the drug development process to discuss the possibility of an AA or CMA, target appropriate supportive and confirmatory clinical trials, and initiate postmarketing studies before the granting of an AA or CMA as possible. Holders should be encouraged to carry out postmarketing studies in a timely and systematic way so that regulators can balance the risk–benefit profile of drugs based on complete information. In addition, regulators should review this on a regular basis. If a product remains on the market for a long period of time without validating its clinical benefit, the licence should be automatically withdrawn at that point, without the need for the manufacturer to choose to withdraw or convene an advisory committee meeting.
The second drawback to AA and CMA is that the frequency of surrogate endpoints such as ORR and PFS, was greater in both pivotal drug clinical trials and postmarketing studies. This raises the question of how a definite clinical benefit is determined and whether actual clinical outcomes or surrogate endpoints should be used for postmarketing confirmatory clinical trials. There is controversy in the literature about the use of surrogate endpoints for cancer drugs. Some studies have found it challenging to use OS and quality of life as clinical endpoints in actual practice, and that using surrogate endpoints could be beneficial. But most researchers have been negative about the use of surrogate endpoints and questioned their validity. The FDA’s internal statistical review also found no patient-level correlation between changes in surrogate markers and clinical outcomes in the pivotal trial of aducanumab (Aduhelm, Biogen). Some studies have also picked up on this. In general, OS and patient-related data should be part of the evidence, regardless of which clinical endpoint is used as the primary endpoint. Thus, when employing biomarkers for drugs with AA and CMA, there should be agreement on the process for choosing the biomarker and adequately showing the relationship between the biomarker and the clinical outcomes the biomarker is being used to predict. If possible, OS or health-related quality of life should be included as one of the study outcomes in postmarketing confirmatory studies to establish meaningful clinical benefits. In addition, real-world data should be used as a supplement to experimental evidence to verify the clinical benefits of new drugs.

Third, our study found that both the EMA and FDA review reports gave only a cursory explanation of the postmarketing obligations, usually lacked enough detail to identify the trial stage, study type, study endpoints and patient allocation. Moreover, several clinical studies did not disclose their NCT numbers, which makes it challenging to find the correct clinical trial on the ClinicalTrials.gov website. Thus, the FDA and EMA should enhance the transparency of postmarketing studies for AA or CMA of drugs, appropriately update relevant outcomes, and provide a detailed description of the study design, trial endpoints, study population and other information required for the postmarketing study. If possible, the NCT number should be included in the approval document to help patients, doctors and researchers find the details.

This study has several limitations. First, this study only includes initial drug application and has not been extended to the supplemental application. Second, the analysis was restricted to oncological studies and it remains unknown whether the findings would apply to other indications such as HIV, tuberculosis or influenza. Variability in prevalence, unmet medical needs, accessibility of alternative treatment choices or the degree of scientific understanding of different diseases, may result in differences in AA or CMA procedures. Further, because of data constraints, this study did not analyse products that did not receive FDA and EMA approval. Thus, it remains unknown whether and how often pharmaceutical firms and regulators consider making unapproved drugs.

CONCLUSIONS
Between 2006 and 2021, there were some differences in the use of the AA pathway and the requirements for postmarketing obligations between the FDA and EMA. In addition, when postmarketing obligations were conducted, some studies were overdue for completion in both the USA and EU, a result that is sufficient to allow us to reflect on the effective duration of AA and CMA, as well as the duration of the completion of postmarketing obligations for such products.

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