

ARTICLE

A detailed analysis of expedited regulatory review time of marketing authorization applications for new anticancer drugs in the US and EU

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Abstract

The aim of this study was to assess the effect of expedited regulatory approval programs used by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), type of product (small molecule or biotechnology-derived product) and consulting scientific advisory committees on the regulatory review time of the marketing authorization applications (MAAs) for new anticancer drugs. A dataset composed of 76 new anticancer drugs was constructed. The date of submission of the MAAs in the United States and the European Union were comparable. The typical review time of MAAs was 136 days shorter in the United States (201 days [median]) than in the European Union (337 days [median]). The type of product did not have a high impact on the review time. The review time of the MAAs for drugs undergoing priority review in the United States or accelerated assessment in the European Union at the stage of review of MAA was generally shorter than that for drugs following the standard regulatory pathway. The regulatory pathway using at least one expedited regulatory program at the stages of drug development, review of MAA, and approval of drug in the United States (172 days [median]), and that at the stages of review of MAA and approval of drug in the European Union (183 days [median]) enabled the shortest review time of MAAs. Referral to advisory committee meeting increased the review time of MAAs for drugs undergoing one or more expedited regulatory approval programs in the United States and the European Union close to that for drugs undergoing the standard regulatory approval pathway.

Study Highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

The US Food and Drug Administration (FDA) has more expedited regulatory approval programs than the European Medicines Agency (EMA), suggested to result in earlier availability of anticancer drugs in the United States compared to in the European Union.

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WHAT QUESTION DID THIS STUDY ADDRESS?

The effect of expedited regulatory approval programs, type of product, and consulting scientific advisory committees on the regulatory review time of the marketing authorization applications (MAAs) for new anticancer drugs in the United States and the European Union.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

It was shown that the review of MAAs for new anticancer drugs was finalized typically 136 days later and expedited regulatory programs were less frequently employed in the European Union compared to in the United States. The regulatory pathways leading to shortest review time of MAAs for new anticancer drugs were identified.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

A field of improvement for the regulatory framework in the European Union to enable earlier drug availability was indicated. Insight for the industry into combinations of expedited regulatory approval programs advantageous to apply for was provided.

INTRODUCTION

Cancer is a major cause of death worldwide, accounting for around 10 million deaths in 2020.¹ A large number of drugs are being developed to treat cancer, which subsequently must go through an approval process performed by regulatory agencies to be marketed. The United States and the European Union have their own regulatory agencies that support drug development and marketing authorization procedures for new medicines, namely, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively. Both agencies have expedited regulatory approval programs for drugs with high potential patient value, which support the development of such drugs, or provide shorter review times of marketing authorization applications (MAAs) or preliminary approval.^{2,3}

The FDA has five principal regulatory approval programs: fast track designation (introduced in 1987), accelerated approval (introduced in 1992), priority review designation (introduced in 1992), breakthrough therapy designation (introduced in 2012),⁴ and regenerative medicine advanced therapy (RMAT) designation (introduced in 2017).⁵ The EMA has four regulatory initiatives that streamline the approval process: exceptional circumstances (introduced in 1995),⁶ accelerated assessment (introduced in 2005),⁷ conditional marketing authorization (introduced in 2006),⁸ and PRIority Medicines scheme (PRIME; introduced in 2016).⁹ Priority review (United States) and accelerated assessment (European Union) reduce review time to 6 months (vs. 10 months for standard review) and 150 days (vs. 210 days for standard review), respectively; accelerated approval (United States) and conditional approval

(European Union) allow preliminary approval while confirmatory studies are ongoing; and fast track (United States), breakthrough therapy (United States), and PRIME (European Union) aim to shorten the duration of clinical trials.¹⁰ These expedited regulatory approval programs can be used at different stages leading to marketing authorization: before the submission of the MAA to support the drug development, or after the submission of the MAA to reduce its standard review time at the FDA or the EMA or to provide preliminary approval of drugs. Thus, different combinations of programs (i.e., pathways), are possible. However, it is not clear which program or pathway drives the total review time of MAAs by a regulatory agency.

Another observation is that the FDA has more expedited regulatory approval programs than the EMA, which is suggested to result in earlier availability of anticancer drugs in the United States compared to in the European Union. Several publications have investigated and confirmed this effect, although the datasets used were very small,^{2,3,11,12} and, therefore, it is difficult to determine the relevance of the expedited regulatory approval programs or other important factors, such as type of product (small molecule or biotechnology-derived product) and advisory committee meetings. Although the review time of MAAs by regulatory agencies might be important, from the drug availability perspective, the date of submission of MAAs should also be considered.

Here, a detailed analysis of the effect of different expedited regulatory approval programs, type of product, and consulting the scientific advisory committees on the regulatory review time of the MAAs for new anticancer drugs in the United States and the European Union is presented.

METHODS

The new anticancer drugs for which the Committee for Medicinal Products for Human Use (CHMP) of the EMA gave a positive opinion between January 2010 and December 2019 were previously described by Garsen et al.¹³ The inclusion criteria were specified as follows: (i) article 8(3) full or full-mixed application as legal basis; (ii) new active substance; and (iii) products developed to treat cancer. Information on the date of start of procedure and CHMP opinion, type of product (small molecule or biotechnology-derived product), regulatory approval program (PRIME, accelerated assessment and conditional approval), and the Inter-Committee Scientific Advisory Group on Oncology (IC-SAG) meeting was extracted from the European Public Assessment Report (EPAR) and the summary of the CHMP opinion available on the EMA website.

For all anticancer drugs which complied to the inclusion criteria listed above, the Drugs@FDA database between May 2006 and July 2019 was utilized and information on the date of submission of MAA and approval of drug, type of MAA (new drug application [NDA] for small molecules, and biologic license application [BLA] for biotechnology-derived products), regulatory approval program (fast track designation, breakthrough therapy designation, priority review and accelerated approval), and the Oncologic Drugs Advisory Committee (ODAC) meeting was extracted from the FDA approval letters and administrative correspondence.

The review time of MAA in the United States and the European Union was calculated as the number of days that elapsed from the submission of MAA to the approval of the drug by the FDA, and as the number of days that elapsed from the start of procedure to the CHMP opinion, respectively.

The expedited regulatory approval programs were categorized based on their employment at different stages leading to marketing authorization: (i) drug development

(fast track designation and/or breakthrough therapy designation in the United States, and PRIME in the European Union); (ii) review of MAA (priority review in the United States and accelerated assessment in the European Union); and (iii) approval of drug (accelerated approval in the United States and conditional approval in the European Union; [Table 1](#)). The dataset used in this study does not assess the RMAT designation of the FDA and does not contain any drugs that underwent the exceptional circumstances program of the EMA. Each MAA was classified to follow either a standard or an expedited regulatory approval pathway (i.e., combinations of programs).

RESULTS

Construction of the dataset

A total of 96 new anticancer drugs for which the CHMP of the EMA gave a positive opinion between January 2010 and December 2019 was previously described by Garsen et al.¹³ Two drugs (ixazomib and neratinib) were excluded because they initially (i.e., before re-examination), received a negative CHMP opinion. Nine drugs (asparaginase, cabozantinib [Cabometyx], daunorubicin and cytarabine, dinutuximab beta [Qarziba], everolimus, irinotecan, paclitaxel, pegaspargase, and propranolol hydrochloride) were excluded, as they were not considered as a new active substance in the corresponding European Public Assessment Reports (EPARs; $n = 85$ new anticancer drugs with a positive CHMP opinion).

For 85 new anticancer drugs given a positive CHMP opinion, the FDA database between May 2006 and July 2019 was utilized. Four drugs (pixantrone, tegafur/gimeracil/oteracil, padeliporfin, and lenvatinib [Kisplyx]) were not approved by the FDA, one drug (durvalumab) had a different indication, and two drugs (sipuleucel-t and tivozanib) had insufficient information on regulatory

TABLE 1 Categories of expedited regulatory approval programs

Stages leading to marketing authorization			
	Drug development	Review of MAA	Approval of drug
FDA	Fast track designation, breakthrough therapy designation, RMAT designation	Priority review	Accelerated approval
EMA	PRIME	Accelerated assessment	Conditional approval
Program benefits	Promotes and accelerates drug development benefits <ul style="list-style-type: none"> Rolling review by FDA 	Reduces review time of MAA <ul style="list-style-type: none"> 6 months instead of standard 10 months by FDA 150 days instead of standard 210 days by EMA 	Leads to preliminary approval of drug <ul style="list-style-type: none"> Confirmatory studies planned or ongoing

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; MAA, marketing authorization application; PRIME, PRiORity Medicines; RMAT, regenerative medicine advanced therapy.

actions in the FDA database. Two drugs (atezolizumab and idelalisib) were excluded from the analysis as for each drug there was one MAA for two different indications in the EMA database and two MAAs for each indication in the FDA database ($n = 76$ new anticancer drugs approved by the FDA and the EMA).

The dataset is composed of 76 new anticancer drugs with both positive CHMP opinion and FDA approval (Figure S1; Table S1).

Date of start of the procedure by the EMA and date of submission of the MAA to the FDA

The date of start of the procedure by the EMA in the European Union and date of submission of the MAA to the FDA in the United States were comparable, except for gilteritinib, palbociclib, carfilzomib, and decitabine (335, 372, 1249, and 2045 days later in the European Union, respectively). The MAAs for 63 drugs were submitted to the FDA before the start of procedures by the EMA, whereas for 13 drugs, the MAAs were submitted to the FDA after the start of procedures by the EMA. The submission of MAAs to the FDA occurred 44 days (median) before start of procedures by the EMA.

Review time of MAA and type of product

The review time of MAAs was 201 days (median) in the United States and 337 days (median) in the European Union. The typical review time of MAAs for new anticancer drugs was 136 days longer in the European Union than in the United States. About two-thirds of the products were small molecules ($n = 49$), whereas one-third of the products were biotechnology-derived products ($n = 27$). The type of product (i.e., small molecule or biotechnology-derived product), did not have a high impact on the review time (Figure 1).

Review time of MAA and expedited regulatory approval programs

The review time of MAAs by the FDA for 68 drugs (89%) undergoing one or more expedited regulatory approval programs (i.e., fast track designation, breakthrough therapy designation, priority review, or accelerated approval) was 192 days (median). The CHMP of the EMA gave a positive opinion for 33 drugs (43%) via at least one expedited regulatory approval program (i.e., PRIME, accelerated assessment or conditional approval) and the review

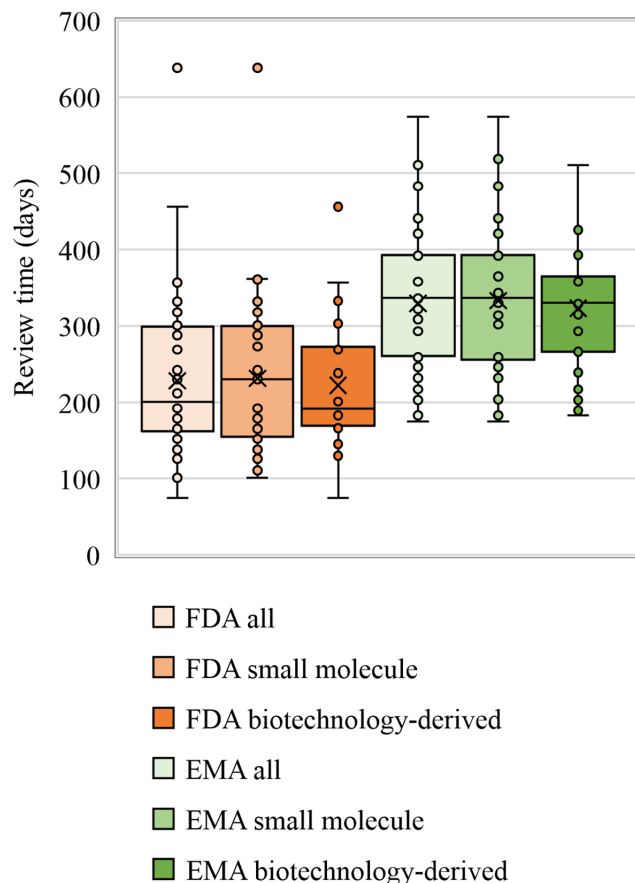


FIGURE 1 Review time of MAA for new anticancer drugs (small molecules and biotechnology-derived products) by the FDA and the EMA. Data are presented as median \pm standard error of the median (SE). Small molecules ($n = 49$) and biotechnology-derived products ($n = 27$). EMA, European Medicines Agency; FDA, US Food and Drug Administration; MAA, marketing authorization application.

time of MAAs for these drugs was 315 days (median). These data show that more drugs underwent expedited regulatory approval programs in the United States and the typical review time of MAAs for such drugs was 123 days shorter in the United States than in the European Union. For drugs undergoing the standard regulatory approval pathway, the review time was 304 days (median) and 343 days (median) by the FDA and the EMA, respectively.

Early at the drug development stage, expedited regulatory approval programs promoting and accelerating drug development (i.e., fast track designation and breakthrough therapy designation in the United States and PRIME in the European Union) were used for 51 drugs in the United States, whereas only three drugs benefited from PRIME in the European Union. At the stage of review of MAA, programs reducing review time (i.e., priority review in the United States and accelerated assessment in the European Union) were used for 59 drugs in the United States and only for 13 drugs in the European Union. At the stage

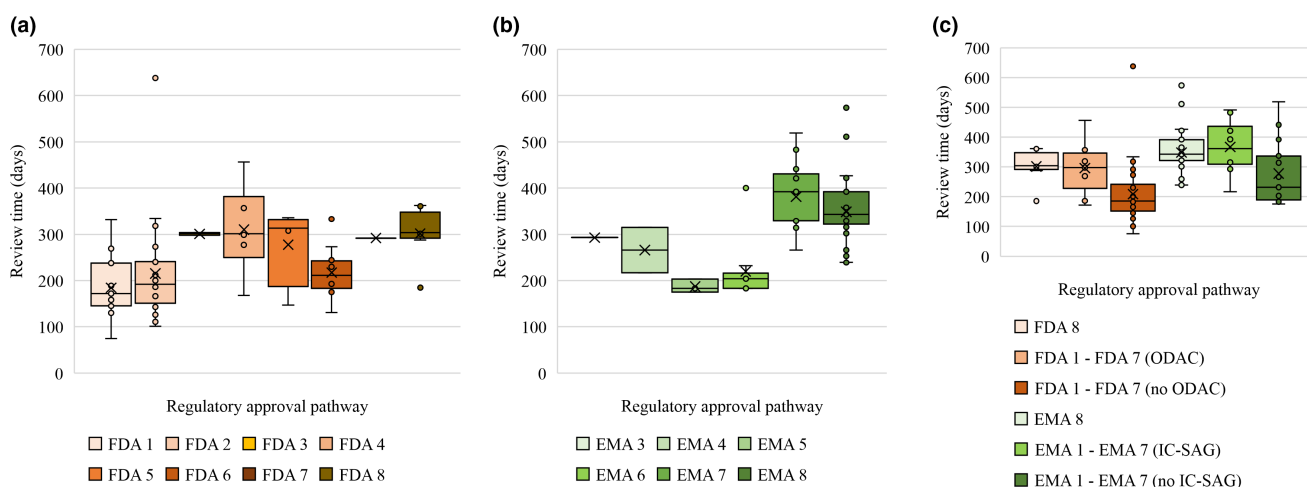
of approval of drug, where programs leading to preliminary approval of drugs can be used, review of MAAs for 26 drugs were finalized with accelerated approval in the United States and those for 21 drugs with conditional approval in the European Union (Figure 2).

Review time of MAA and regulatory approval pathways

In addition, the review time of MAAs by both regulatory agencies via different regulatory approval pathways (FDA 1 – FDA 8 in the United States: combinations of fast track designation, breakthrough therapy designation, priority review, and accelerated approval; and EMA 1 – EMA 8 in the European Union: combinations of PRIME, accelerated assessment and conditional approval) followed during consecutive stages leading to marketing authorization were compared. In the United States, the review time of the MAAs for new anticancer drugs undergoing priority review was in

general shorter than that for those following the standard regulatory pathway (FDA 8, 304 days [median]; Figure 2a). Using one or more expedited regulatory approval programs at the stage of drug development but not at the stage of review of MAA (FDA 3 or FDA 4) did not have a high impact in the review time of MAAs. The MAAs for the new anticancer drugs undergoing at least one expedited regulatory program at each stage (FDA 1) were reviewed the fastest by the FDA (a median of 172 days): fast track designation and/or breakthrough therapy designation at the stage of drug development, followed by priority review at the stage of review of MAA, and thereafter by accelerated approval at the stage of approval of drug (Figure 2a). The review time of MAAs for new anticancer drugs following the regulatory pathways FDA 2 or FDA 6, both using priority review at the stage of review of MAA, were comparably short (192 days [median] and 212 days [median], respectively; Figure 2a).

In the European Union, most of the new anticancer drugs were reviewed via the standard regulatory pathway. However, the review time of the MAAs for new anticancer



Regulatory Approval Pathway	Stages Leading to Marketing Authorization			Number of Drugs	Median Review Time (days)	Number of Drugs in Advisory Meetings
	Drug Development	Review of MAA	Approval of Drug			
FDA 1	Fast track and/or breakthrough therapy designation	Priority review	Accelerated approval	19	172	2
FDA 2	Fast track and/or breakthrough therapy designation	Priority review	Standard	24	192	0
FDA 3	Fast track and/or breakthrough therapy designation	Standard	Accelerated approval	2	301	1
FDA 4	Fast track and/or breakthrough therapy designation	Standard	Standard	6	301	2
FDA 5	Standard	Priority review	Accelerated approval	4	314	2
FDA 6	Standard	Priority review	Standard	12	212	1
FDA 7	Standard	Standard	Accelerated approval	1	291	0
FDA 8	Standard	Standard	Standard	8	304	3
EMA 1	PRIME	Accelerated assessment	Conditional approval	0	NA	0
EMA 2	PRIME	Accelerated assessment	Standard	0	NA	0
EMA 3	PRIME	Standard	Conditional approval	1	293	1
EMA 4	PRIME	Standard	Standard	2	266	1
EMA 5	Standard	Accelerated assessment	Conditional approval	3	183	0
EMA 6	Standard	Accelerated assessment	Standard	10	204	1
EMA 7	Standard	Standard	Conditional approval	17	392	7
EMA 8	Standard	Standard	Standard	43	343	5

FIGURE 2 Review time of MAA for new anticancer drugs by the FDA and EMA following different regulatory pathways. (a) Review time by the FDA. (b) Review time by the EMA. (c) Review time by the FDA and the EMA undergoing at least one expedited regulatory program and advisory committee meetings. Data are presented as median ± SE. EMA, European Medicines Agency; FDA, US Food and Drug Administration; IC-SAG, Inter-Committee Scientific Advisory Group on Oncology; MAA, marketing authorization application; ODAC, Oncologic Drugs Advisory Committee.

drugs undergoing accelerated assessment (EMA 5 and EMA 6) was shorter (183 days [median] and 204 days [median], respectively) than that for new anticancer drugs following the standard regulatory pathway (EMA 8, 343 days [median]; [Figure 2b](#)). Using accelerated assessment at the stage of review of MAA, and thereafter using conditional approval at the stage of approval of drug resulted in the shortest review time of MAAs for new anticancer drugs the by EMA (the regulatory pathway EMA 5; [Figure 2b](#)).

Review time of MAA and advisory committee meetings

The effect of consulting scientific advisory committees (ODAC by the FDA and IC-SAG the EMA) on the review time of MAAs was evaluated. 11 (14%) and 15 (20%) new anticancer drugs required advisory committee meeting in the United States and in the European Union, respectively ([Figure 2c](#)). Seven of these drugs were referred by both regulatory agencies to the advisory committee meeting (axitinib, brentuximab vedotin, ofatumumab, olaparib, panobinostat, pazopanib, and vandetanib; [Table S1](#)). The drugs following the regulatory pathways FDA 2 (fast track designation and/or breakthrough therapy designation at the stage of drug development, followed by priority review at the stage of review of MAA), FDA 7 (accelerated approval at the stage of approval of drug) or EMA 5 (accelerated assessment at the stage of review of MAA and conditional approval at the stage of approval of drug) were not referred to an advisory committee meeting ([Figure 2c](#)).

Nine of 68 (13%) and 10 of 33 (30%) new anticancer drugs undergoing one or more expedited regulatory approval programs (FDA 1 – FDA 7 and EMA 1 – EMA 7) were referred to an advisory committee meeting by the FDA and the EMA, respectively. The typical review time of MAAs for these drugs was 113 days and 130 days (based

on median values) longer in the United States and the European Union, respectively, if referred to an advisory committee meeting ([Figure 2c](#)). Referral to the advisory committee meeting had a lower impact on the review time of MAAs for drugs undergoing the standard regulatory approval pathway (5 day shorter and 22 days longer [based on median values] in the United States and the European Union, respectively).

The issues raised to the scientific advisory committees were distinct to the United States and the European Union, and the most common questions were related to risk–benefit assessment in the United States and clinical data package, target population/indication, and evidence of clinical efficacy in the European Union ([Table 2](#)).

DISCUSSION

Expedited regulatory approval programs can be employed by the FDA or the EMA at different stages leading to marketing authorization: (i) drug development (fast track designation and/or breakthrough therapy designation in the United States, and PRIME in the European Union); (ii) review of MAA (priority review in the United States and accelerated assessment in the European Union); and (iii) approval of drug (accelerated approval in the United States and conditional approval in the European Union; [Table 1](#)). Different combinations of programs (i.e., pathways) are possible. However, it is not clear which program or pathway drives the total review time of MAAs by regulatory agencies. The objective of this study was to analyze the effect of different expedited regulatory approval programs, type of product, and consulting scientific advisory committees on the regulatory review time of the MAAs for new anticancer drugs in the United States and the European Union.

The review time of MAA in the United States and the European Union for 76 new anticancer drugs with

TABLE 2 Issues raised to the scientific advisory committees in the United States (ODAC) and the European Union (IC-SAG)

Number of drugs referred to advisory committee meeting (regulatory agency)		Pharmacology ^a	Clinical data package ^b	Target population and indication	Risk–benefit assessment	Clinical safety	Clinical efficacy
7 (both the FDA and the EMA)	US	1	1	1	4	1	1
	EU	1	4	3	1	2	7
4 (only the FDA)	US	1	1	0	4	2	1
8 (only the EMA)	EU	0	4	5	0	2	8
Total 11 (the FDA)	US	2	2	1	8	3	2
Total 15 (the EMA)	EU	1	8	8	1	4	15

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; IC-SAG, Inter-Committee Scientific Advisory Group on Oncology; ODAC, Oncologic Drugs Advisory Committee; US, United States.

^aIncluding dosing and route of administration.

^bFor example, lack of randomization, issue with study design, adequate control, bias, size of the database, and the choice of end points.

a positive CHMP opinion and approved by the FDA (Table S1) were calculated as the number of days that elapsed from the submission of MAA to the approval of the drug by the FDA, and as the number of days that elapsed from the start of procedure to the CHMP opinion, respectively. It should be noted that generally 13 EMA working days^{14,15} are required for (technical) validation of MAA in the European Union between the submission of MAA and the start of procedure, and the European Commission decision is obtained within 67 days of receipt of CHMP opinion.¹⁶ Therefore, the review time of MAAs in the European Union would generally be more than 73 days longer than the timelines reported in this study if the time required for the validation of MAA and for Commission Regulation (EC) decision was included in its calculation.

The prioritization of obtaining marketing authorization in different regions might depend, among others, on the commercial interest and clinical trial strategy in the corresponding region. For most companies, the US market is commercially more interesting than the EU market,¹⁷ and, therefore, the submission of the MAA in the United States might be prioritized compared to that in the European Union. The results show that typically the MAAs for new anticancer drugs were submitted 44 days (median) earlier to the FDA before the start of procedures by the EMA. Taking the time required for the validation of MAAs in the European Union into account, the date of submission of the MAAs in the United States and the European Union were comparable. Our results are in line with Uyl-de Groot et al. that conducted a retrospective study of 12 selected newly registered (2011–2017) cancer drugs and demonstrated that the date of submission of the MAAs to the FDA and the EMA were almost comparable and the time to first registration was 181 days (average) in the United States and 378 days (average, including the time required for the validation of MAA and EC decision) in the European Union, with a difference of 197 days.²

The typical review time of MAAs for new anticancer drugs was 136 days shorter in the United States (201 days [median]) than in the European Union (337 days [median]), and the type of product (i.e., small molecule or biotechnology-derived product), did not have a high impact on the review time (Figure 1). These results are in line with previous studies that compared the review time of MAAs by the FDA and the EMA. Joppi et al. identified 66 novel drugs approved in both the United States (from 2015 to 2017) and the European Union and found that the review time of MAAs by the EMA was 121.5 days (median) longer (including the time required for the validation of MAA and EC decision in the European Union) than that by the FDA.³

The results of this study highlight that each regulatory agency has elaborated an original regulatory framework

for new anticancer drugs. The FDA used one or more expedited regulatory approval programs for 89% of the new anticancer drugs, whereas the EMA only for 43%. The FDA utilized expedited regulatory approval programs at the stage of drug development and review of MAA much more frequently than the EMA did (Figure 2a,b). The differences in the application of expedited regulatory programs in the United States and the European Union have been previously studied.¹² Leo et al.¹² analyzed 17 novel drugs for use in breast cancer approved between 1995 and 2018 and found statistically significant differences in the utilization of expedited regulatory programs at the stage of drug development and review of MAA by the FDA and the EMA. Similarly, Hwang et al. found that 57% of new drugs approved from 2007 through 2017 in the United States qualified for at least one expedited program, whereas this percentage was only 15% of new drugs approved in the European Union.¹⁸

In the United States and the European Union, the review time of the MAAs for drugs following regulatory pathways that included an expedited regulatory program at the stage of review of MAA (i.e., priority review in the United States and accelerated assessment in the European Union) was generally shorter than that for drugs following the standard regulatory pathway (Figure 2a,b). The regulatory pathways that enabled the shortest review time of MAAs were the FDA 1 in the United States ($n = 19$, 172 days [median], at least one expedited regulatory program at each stage) and the EMA 5 in the European Union ($n = 3$, 183 days [median], accelerated assessment at the stage of review of MAA and conditional approval at the stage of approval of drug).

The FDA and the EMA consulted the scientific advisory committees (ODAC and the IC-SAG, respectively) for 14% and 20% of new anticancer drugs, respectively, for distinct issues (Figure 2c; Table 2). Referral to an advisory committee meeting increased the review time of MAAs for drugs undergoing one or more expedited regulatory approval programs in the United States and the European Union (113 days and 130 days [based on median values], respectively) close to that for drugs undergoing the standard regulatory approval pathway (Figure 2c).

This study, based on the one of the largest datasets, showed that the review of MAAs for new anticancer drugs was finalized typically 136 days later and that expedited regulatory programs were much less frequently used in the European Union compared to in the United States, indicating a potential field of improvement for the regulatory framework in the European Union to enable earlier drug availability. Delay in marketing authorization of anticancer drugs in the European Union compared to in the United States was previously estimated to result in loss of thousands of life years in the

European Union.² In addition, the regulatory pathways leading to the shortest review time of MAAs for new anticancer drugs by the FDA and the EMA were identified, providing insight for the industry into combinations of expedited regulatory approval programs that might be advantageous to apply for. Although not studied here, regulatory procedures, price regulations, and health technology assessments are other important factors affecting to the availability of drugs to patients after obtaining marketing authorization.

AUTHOR CONTRIBUTIONS

F.C.G., E.D., and A.Z. wrote the manuscript. A.Z. designed the research. F.C.G. performed the research. F.C.G. and E.D. analyzed the data.

CONFLICT OF INTEREST

F.C.G. and E.D. are employees of Zwiery Regulatory Consultancy. A.Z. is the CEO and owner of Zwiery Regulatory Consultancy.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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