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Original Article

Differential times of submission and approval of CFTR modulators for the treatment of Cystic Fibrosis in the United States and the European Union

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ABSTRACT

Background: The objective of this study was to assess the differential times of submission and approval of CFTR modulators in the United States (US) and the European Union (EU).
Methods: By collecting publicly available data from the websites of the Food and Drug Administration and the European Medicines Agency, we quantified differential times in submission, review duration, and approvals of initial marketing authorization and variation of indications of CFTR modulators in the US and the EU by December 31, 2023.
Results: Applications regarding marketing of 4 CFTR modulators were submitted 103 (SD ±143) days later in the EU than in the US: 31 (SD ±39) days later for initial approval, and 124 (SD ±155) days for supplemental indications. The regulatory review process was completed in 181 days [IQR, 179 - 182] in the US and 325 days [IQR, 276 - 382] in the EU: 167 days [IQR, 102 - 232] in the US and 346 days [IQR, 302 - 400] in the EU for first approvals, 181 days [IQR, 181 - 182] in the US and 324 days [IQR, 264 - 382] in the EU for supplemental indication approvals. CFTR modulators were approved 267 (SD 143) days later in the EU than in the US: 220 (SD ±76) days for initial approval and 280 (SD ±157) days for supplemental indications.
Conclusion: We found significant differences in times of submission and for approval of CFTR modulators between the US and EU, whereby initial approvals and subsequent indication approvals were always first granted in the US

1. Background

Expediting the review and approval of new medicines for serious and life-threatening conditions has become a major regulatory challenge in the United States (US) and the European Union (EU) [1]. To prioritize access to the most promising medicines, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have established specific programs that improve interactions with sponsors, accept more adaptive evidence, and shorten regulatory review time for approval (Box 1) [1]. However, differences in the timing of decisions between the US and the EU remain a source of debate among policymakers, the pharmaceutical industry, and patients [2].

In 2012, with the marketing of the first Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator, ivacaftor, discussions on US and EU new drug approval timeliness entered the field of CF [3,4]. Designed to correct the malfunctioning protein caused by variants in the CFTR gene, four CFTR modulator therapies (ivacaftor, lumacaftor plus ivacaftor, tezacaftor plus ivacaftor, and elexacaftor plus tezacaftor plus ivacaftor) are approved in the US and the EU [4,5]. The

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different FDA and EMA regulatory decision-making process and time potentially impact patients' access [4]. For extending the therapeutic indications towards rarer genotypes, FDA has accepted data from non-clinical models, while EMA requires clinical data [6–8]. Although data from the same clinical trials were used for regulatory purposes, the different timing of approval of CFTR modulators has minimally been investigated [6].

Differential timing of approval of medicines between FDA and EMA is associated with submission times of applications to regulators and the subsequent regulatory review duration [2,9,10]. The more we comprehend such dynamics in the field of CF, the better we can advocate that policymakers implement of evidence-based strategies to improve timely access to CFTR modulators for people with CF (pwCF). In this study, we analyzed the different submission times and regulatory review duration regarding the first marketing authorizations and subsequent indication approvals of CFTR modulators in the US and the EU, and factors associated with different approval times.

2. Methods

2.1. Data sources and extraction

Data on regulatory decisions made by December 31, 2023 regarding CFTR modulators were retrieved from publicly available documents: approval letters and Prescribing Information for FDA, and the European Public Assessment Reports (EPAR) for EMA [11,12]. Applications accepted by FDA and based on non-clinical models were excluded. Two authors (EC, SG) manually abstracted data and double-checked for inconsistencies.

For each FDA and EMA submission, we collected the therapeutic indication, the dates of submission, the associated expedited program, and formal marketing authorization of the first approval and variations of indication. Authorizations were divided into "first approval" – when the CFTR received the first authorization for marketing and "variations of indications" the subsequent decisions modifying the initial therapeutic indications for the same active substance. New Drug Application (NDA) status and different pharmaceutical forms were not considered for such stratification. In the case of CFTR modulators, the therapeutic indication is based on specific CFTR gene variants and the age of the eligible population. A detailed description of the methodology used to collect and organized data upon the different US and the EU process is reported in appendix (Supplementary material) [2,13].

2.2. Statistical analysis

We considered the number of days as the measure of the analysis. Following the temporal sequence of events, we first analyzed the mean difference in the submission of applications for CFTR modulators to FDA and EMA to all the applications commonly granted by both institutions. The analysis was repeated with stratification according to the characteristics of the applications (i.e., initial approval or supplemental indication approvals, genotype, and age) for all the CFTR modulator products. By applying the same stratification, we then assessed the regulatory review duration and differences between the US and the EU, as well as the impact of such differences on the differential times of approval in the US and the EU.

To calculate the regulatory review duration, we considered all the applications granted by FDA and EMA for CFTR modulators. For the US, we calculated the time elapsed from the date of submission of the application to the formal approval by the FDA, whereas, for the EU, the time elapsed from the date of submission to the EMA to the marketing authorization granted by the European Commission. We then calculated

Box 1
US Food and Drug Administration and European Medicines Agency expedited programs

US Food and Drug Administration	European Medicines Agency
Priority Review (1992) *Qualifying criteria: s*ignificant improvement in safety or efficacy for the treatment, diagnosis, or prevention of serious conditions *Benefits:* shorter FDA review timeframe: 6 months vs standard 10 months	**Accelerated Assessment** (2004) *Qualifying criteria:* major interest in public health, particularly in the therapeutic innovation field *Benefits: s*horter EMA review timeframe:150 days vs standard 210 days
Accelerated Approval (1992) *Qualifying criteria:* meaningful advantage over available therapies and demonstrated effect on a surrogate endpoint reasonably likely to predict clinical benefit *Benefits: a*pproval based on surrogate endpoint or intermediate clinical endpoint	**Authorisation under Exceptional Circumstances** (2004) *Qualifying criteria:* inability to provide comprehensive data under normal conditions of use, because of the rarity or the collection of full information is not possible or unethical *Benefits: l*ess comprehensive evidence at the time of Marketing Authorization compared with normal requirement
Fast-Track (1997) *Qualifying criteria:* potential to address serious conditions and fill an unmet medical need, based on preclinical data *Benefits:* frequent interactions with FDA during drug development, rolling review	**Conditional Marketing Authorisation** (2006) *Qualifying criteria:* benefit to public health of immediate availability outweighs the risk of less comprehensive data than usual *Benefits: l*ess comprehensive evidence at the time of Marketing A uthorization compared with normal requirement
Breakthrough Therapy (2012) *Qualifying criteria:* Treatment of serious or life-threatening diseases AND substantial improvement on a clinically significant endpoint over available therapies *Benefits:* Intensive actions to expedite the development process: all Fast-Track program features, intensive FDA guidance, organizational commitment involving senior managers	**PRIME – PRIority MEdicines** (2016) *Qualifying criteria:* major therapeutic advantage over existing treatments, or fulfilment of an unmet medical need, assessed on the basis of early clinical data. *Benefits:* early and proactive support of the EMA for the development, possible eligibility to accelerated assessment applications

the impact of difference in the submission time and regulatory review duration as a percentage of the whole-time difference in approval. With the same approach, we investigated the impact of the scientific component on the whole regulatory process, i.e., the duration of the scientific review duration. For the FDA, it coincides with the regulatory review duration, while for the EMA, it was defined as the time elapsed from the start of the procedure (day 0) to the release of the Committee for Medicinal Products for Human Use (CHMP) opinion.

Summary statistics, such as mean and standard deviations (SD), were used to describe differential times in approval and times in submission in the US and the EU, while median and interquartile ranges (IQR) were used to describe review duration. Due to small numbers, subgroup comparisons and confidence interval calculations were carried out using the Wilcoxon test or comparison by Student's t-distribution, respectively, and an interval calculation using Student's t-distribution.

3. Results

In the study period, a total of 19 applications of four CFTR modulators seeking initial approval or supplemental indication approval were licensed by FDA and 18 by EMA. Four applications (i.e., one for each CFTR modulator at each regulator) were for initial marketing authorization, whereas the remaining 15 in the US and 14 in the EU concerned supplemental indication approvals; at the time of the analysis, the most recent application for the use of ivacaftor for pwCF aged ≥ 1 month was approved in the US but not in the EU.

As shown in Fig. 1, the development of CFTR modulators has evolved from targeting with ivacaftor the variants that are similar in their dysfunction to Gly551Asp (G551D, the original indication), towards the most common Phe508del (F508del) variant in those of European ancestry (in homozygous and heterozygous status) in association with CFTR correctors, and including an even younger population.

3.1. Differences in submission times

Except for the first approval of lumacaftor/ivacaftor, whose application was submitted to FDA and EMA on the same date, all the applications were first submitted by the sponsor in the US (Fig. 1). For those approvals granted by both FDA and EMA, including the simultaneous application of lumacaftor/ivacaftor, applications were submitted 103 (SD ±143) days later in the EU than in the US. This time lag decreased to 31 (SD ±39) days for initial marketing authorization, and increased to 124 (SD ±155) days for variations of indication. The marked delays for variations of indication were triggered by applications addressing F508del genotypes, submitted, on average, to EMA 107 (SD ±159) days later than to FDA for lumacaftor/ivacaftor, 176 (SD ±211) days for tezacaftor/ivacaftor, and 152 days (SD ±171) for elexacaftor/tezacaftor/ivacaftor (Table S1).

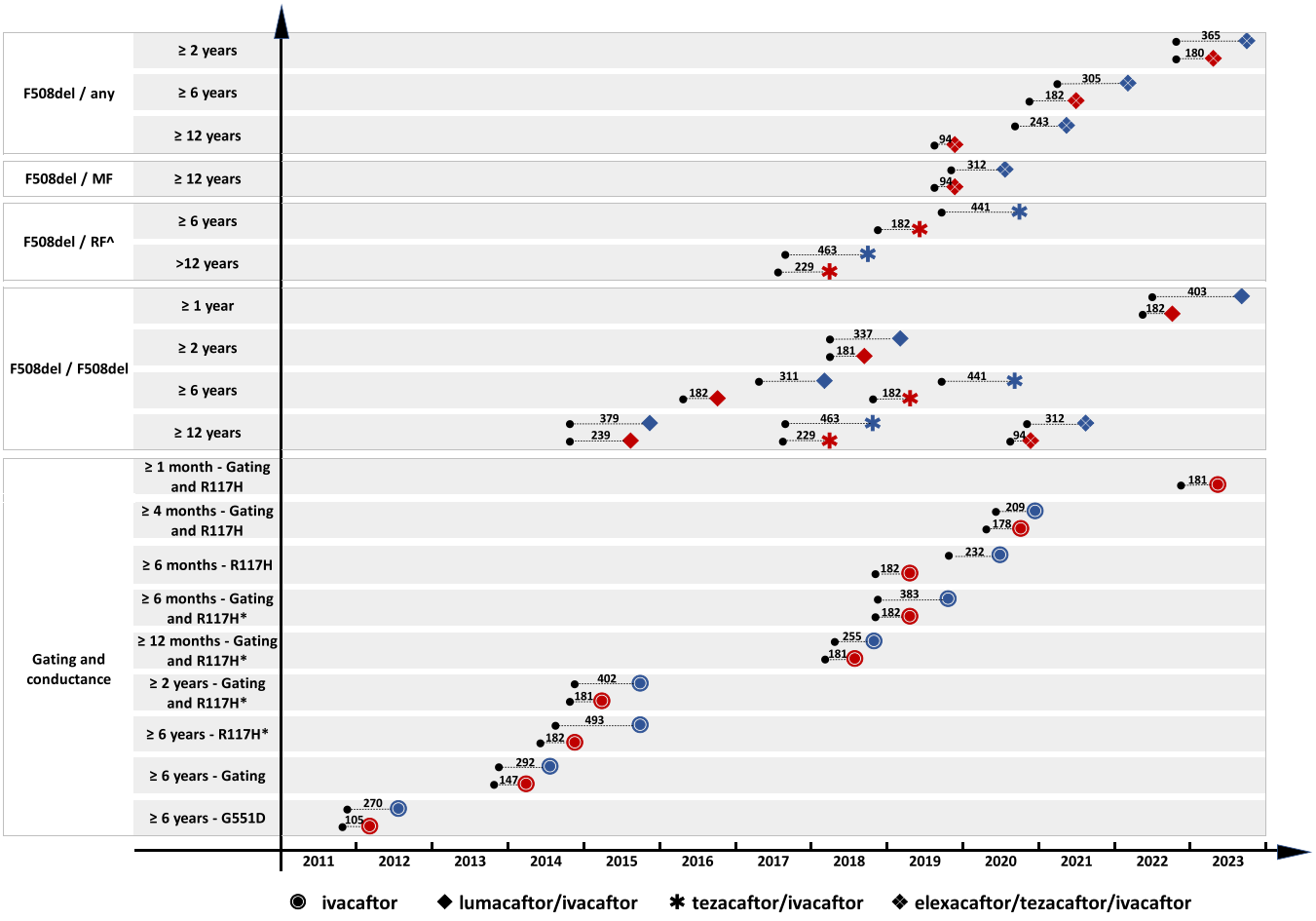

Fig. 1. Submission times and FDA and EMA regulatory review duration for CFTR modulators. Black dots represent the dates of submission of the application, while the red and blue symbols represent the time of approval in the US and the EU respectively. Dashed lines correspond to the days of regulatory review durations. Acronyms: Minimal Function (MF); Residual Function (RF).
Eligible Gating mutations: G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P; * in the EU, approved for individuals aged ≥18 year; ^ in the EU, includes RF mutations responsive to tezacaftor/ivacaftor: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 327226A→G, or 3849+10kbC→T, while in the US indication does not mention the mandatory presence of F508del mutation in heterozygosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Regulatory and scientific review duration

Once submitted, the overall median length of time of regulatory review for the four CFTR modulator applications was 181 days [IQR, 179 - 182] in the US and 325 days [IQR, 276 - 382] in the EU. For applications regarding initial marketing authorizations, the median length was 167 days [IQR, 102 - 232] for the FDA and 346 days [IQR, 302 - 400] for the EU system, while for supplemental indication approvals, 181 days [IQR, 181 - 182] for FDA and 324 days [IQR, 264 - 382] for EMA. Overall, regulatory review was completed in 163 [IQR, 158 - 168] more days in the EU than the US to approve an application of CFTR modulators; this period increased to 189 days [IQR, 177 - 202] for the first approval and reduced to 156 days [IQR, 151 - 161] for supplemental indication approvals. The relative impact of the three phases of the EU regulatory review was 6 % for procedure validation, 77 % for scientific review, and 17 % for the European Commission's approval (Fig. 2).

When focusing on the scientific review duration, which corresponds to the regulatory review time in the US, for the EMA the median length was 252 days [IQR, 196 - 300] for all the indications, 270 days [IQR, 226 - 312] for initial approval ($p = 0.20$), and 252 days [IQR, 196 - 300] for supplemental indication approvals. With stratification for all the different characteristics analyzed, we observed a significant difference between the FDA and EMA scientific review duration for all the genotypes and for indications addressing pwCF aged 6–11 years (Table 1).

In the US, all four CFTR modulators were granted "priority review" designation, shortening the FDA review timeframe from a standard 10-month period to 6 months, as well as "fast-track" and "breakthrough therapy" designations, which provide the implementation of actions to expedite development process and review including frequent interactions with FDA during drug development.

On the other hand, in the EU, only ivacaftor benefited from "accelerated assessment", a designation shortening the EMA review timeframe from the standard 210 days to 150 days. For the combinations lumacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor, despite initially being granted "accelerated assessment" designation, the subsequent major observations raised by the CHMP during the assessment led to additional clock stops, thus switching the scientific review duration back into the 210-day standard assessment. The combination tezacaftor/ivacaftor was considered not eligible for this designation, as it was deemed to be of no major public health interest.

Indeed, while no interruptions were found for FDA, when subtracting the clock stop periods from EMA procedures, its regulatory review duration decreased from 325 days [IQR, 276 - 382] to 284 [IQR, 232 - 306] for all the applications (−13 %); from 346 days [IQR, 302 - 400] to 271 days [245 - 315] for first approvals (−22 %) and from 324 [IQR, 264 - 382] to 284 [IQR, 228 - 306] for variations of indications (−12 %).

Without clock stops, the difference in regulatory review duration between FDA and EMA would decrease from 163 days [IQR, 158 - 168] to 98 days [IQR, 94 - 103] for all the applications, from 189 days [IQR, 177 - 202] to 122 days [IQR, 110 - 134] for first approvals, and from 156 days [IQR, 151 - 161] to 91 days [IQR, 87 - 96] for variations of indication.

3.3. Differences in approval timings

Overall, CFTR modulators were approved in the EU 267 (SD ±143) days after US approvals. This differential timing decreased to 220 (SD ±76) days for first approvals and increased to 280 (SD ±157) days for variations of indication. The shortest differential timing in approval regarded applications targeting non-F508del genotypes - which were approved in the EU 208 days (SD ±118) days after the US - whereas the lengthiest one regarded applications targeting heterozygous F508del genotypes: +344 (SD ±154) days (Fig. 3, Table S2).

In all cases, the regulatory review duration most impacted the interval timings in approval in both absolute and percentage terms: out of the overall 267 days of difference in the timing of approval between the US and the EU, 103 days (39 %) were due to the late submission of applications by the sponsor to the EMA, and 164 days (61 %) due to a longer regulatory review duration in the EU. The EU process recorded the highest difference in terms of regulatory review duration, +189 (SD 44) days, which corresponds to 86 % of the whole differential timing in approval (Fig. 2, Table S2).

In summation, the EU process is currently 1.8 times lengthier than that of the US; without clock stops the gap would be reduced to 1.6 times (−12.6 %) longer. The time reduction for first approvals would be from the current 2.1 to 1.6 times (−21.7 %) without clock stops and for variation of indications from 1.8 to 1.6 times (−12.3 %) longer. For all the 18 EMA applications, the CHMP presented a total of 35 lists of questions to the sponsor: 9 (26 %) regarded initial marketing authorizations, and 26 (74 %) variations of indications. The median duration

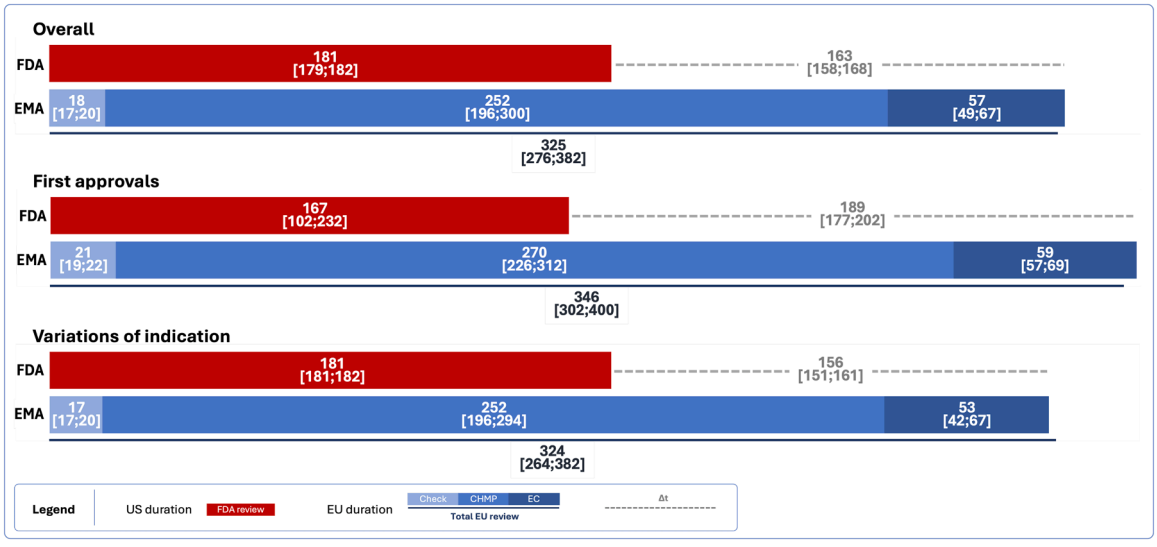

Fig. 2. Regulatory review duration and difference of CFTR modulators in the United States (US) and the European Union (EU). While in the US the regulatory review process is a continuum from the submission of the application to the final decision entirely administered by the US Food and Drug Administration (FDA), in the EU the process is divided into three steps: 1) administrative check of the application (Check); 2) scientific review (CHMP); 3) formal marketing authorization granted by the European Commission (EC). Δt is the time elapsed between the US and the EU approval.

Table 1
Scientific review duration at the US Food and Drug Administration and the European Medicines Agency.

	Overall			ivacaftor			lumacaftor/ivacaftor			tezacaftor/ivacaftor			elexacaftor/tezacaftor/ivacaftor		
	N	Median and Interquartile Range	p-value	N	Median and Interquartile Range	p-value	N	Median and Interquartile Range	p-value	N	Median and Interquartile Range	p-value	N	Median and Interquartile Range	p-value
Overall (all indications)			<0.001			0.038			0.059			0.333			0.110
FDA	19	181 [179 - 182]		9	181 [178 - 182]		4	182 [182 - 196]		2	206 [194 - 217]		4	137 [94 - 181]	
EMA	18	252 [196 - 300]		8	223 [188 - 302]		4	281 [252 - 305]		2	319 [306 - 331]		4	216 [188 - 244]	
First approvals			0.200			–			–			–			–
FDA	4	167 [102 - 232]		1	105 [-]		1	239 [-]		1	229 [-]		1	94 [-]	
EMA	4	270 [226 - 312]		1	190 [-]		1	302 [-]		1	343 [-]		1	238 [-]	
Variations of indication			0.004			0.116			0.077			–			0.400
FDA	15	181 [181 - 182]		8	181 [180 - 182]		3	182 [182 - 182]		1	182 [-]		3	180 [137 - 181]	
EMA	14	252 [196 - 294]		7	244 [191 - 312]		3	259 [245 - 287]		1	294 [-]		3	194 [182 - 227]	
non F508del genotype			0.038			0.038									
FDA	9	181 [178 - 182]		9	181 [178 - 182]										
EMA	9	223 [188 - 302]		9	223 [188 - 302]										
F508del homozygous genotype		0.004						0.059			0.333			0.110	
FDA	10	182 [180 - 182]					4	182 [182 - 196]		2	206 [194 - 217]		4	137 [94 - 181]	
EMA	10	260 [233 - 300]					4	281 [252 - 305]		2	319 [306 - 331]		4	216 [188 - 244]	
F508del heterozygous genotype		0.045									0.333			0.110	
FDA	6	181 [116 - 182]								2	206 [194 - 217]		4	137 [94 - 181]	
EMA	6	249 [205 - 286]								2	319 [306 - 331]		4	216 [188 - 244]	
All indications > 12 years			0.191						–			–			0.221
FDA	4	162 [94 - 232]					1	239 [-]		1	229 [-]		2	94 [94 - 94]	
EMA	4	270 [227 - 312]					1	302 [-]		1	343 [-]		2	216 [205 - 227]	
All indications 6–11 years			0.028			0.100			–			–			–
FDA	6	182 [156 - 182]		3	147 [126 - 165]		1	182 [-]		1	182 [-]		1	182 [-]	
EMA	6	238 [200 - 282]		3	244 [217 - 335]		1	231 [-]		1	294 [-]		1	170 [-]	
All indications < 6 years			0.065			0.518			0.333						–
FDA	9	181 [181 - 182]		6	181 [181 - 182]		2	182 [181 - 182]					1	180 [-]	
EMA	9	260 [196 - 298]		6	201 [180 - 293]		2	287 [273 - 300]					1	260 [-]	

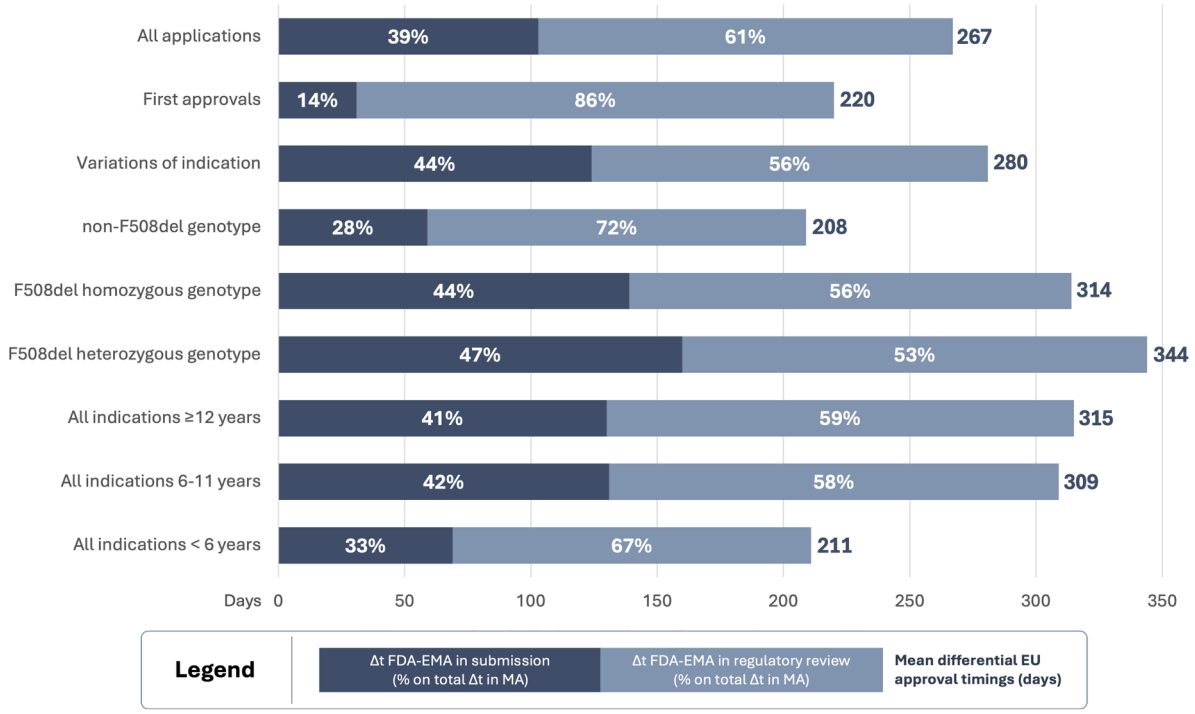

Fig. 3. Mean differential EU approval timings (days) for CFTR modulators compared to the US, and the impact of submission times and regulatory review durations. Differential submission times account for the days elapsed between the submission of applications in the EU and the US, whereas differential regulatory reviews the different times employed by the EU to review and approve an application when compared with the US. Percentages refer to the rate of submission times and regulatory review durations to the overall Differential EU approval timings.

was 60 days (IQR, 37–81). The combinations lumacaftor/ivacaftor and tezacaftor/ivacaftor were associated with a longer clock stop interval, accounting for 70 days (IQR 52–88) and 81 days respectively. Issues raised regarding clinical efficacy were included in the majority of clock stops (17; 49 %). Other clinical-related questions regarded pharmacodynamics or pharmacokinetics (14; 40 %), safety (13; 37 %), and benefit-risk assessment (8; 23 %). However, CHMP also raised issues on non-clinical aspects, i.e., the quality of product (5; 14 %) and pre-clinical efficacy data (2; 6 %). Most of the efficacy issues raised by the CHMP were related to long-term and individual variability in response, also to identify non-responders early and develop robust treatment-stopping criteria (Tab S3 and S4).

4. Discussion

In this analysis, we showed that applications for initial marketing authorizations and supplemental indication approvals of CFTR modulators were generally first submitted in the US, before the EU, and the regulatory review process was faster in the US, where CFTR modulators were ultimately approved 267 days earlier than in the EU. Although such trends are consistent with previous analyses carried out in other therapeutic areas, which described earlier submission, review, and approval in the US [2,9,10], some specific differences in the field of CF deserve further discussion given the clinical implications of delayed initiation of CFTR modulators [4].

It has long been established that early intervention with standard-of-care treatments improves outcomes in CF [14]. Thus, it was hypothesized that early initiation of CFTR modulators, which increase lung function and prevent pulmonary exacerbations would further contribute to the improved long-term health of pwCF 5. Stanojevic et al. applied microsimulation modelling to data from the Canadian CF registry to predict the results of delayed initiation of CFTR modulators for pwCF. Their study showed that over the next 10 years, delaying initiation of modulators by 4 years would increase deaths for pwCF by 15 % and shorten survival by approximately 9 years. Thus, the differences in time of approval in the US versus other countries have real-world health consequences for people with CF [4].

Previous research in oncology showed a decrease in differences between FDA and EMA submission times over the past two decades [10, 15]. However, in the case of CFTR modulators, we found that the differential in submission times was substantial, representing on average 39 % of the final differential times of approval. As also observed in other rare disease areas, these findings reflect the tendency of pharmaceutical companies to seek approval in the US market first, as it is the most remunerative and thus most attractive market in the world [16,17]. The fact that the initial development of CFTR modulators was also substantially supported by the US CF Foundation (CFF), which may also have played a role [6]. Furthermore, the marked delay observed in the applications of more recently developed modulators tezacaftor/-ivacaftor and elexacaftor/tezacaftor/ivacaftor may reflect FDA's willingness to accept data from in-vitro models to expand the panel of eligible variants in comparison with the EMA [6].

Nevertheless, if differential submission time were removed, consistent with other therapeutic areas, the FDA regulatory review duration of CFTR modulators would still perform better timewise [2,9,10]. While in the US all CFTR modulators were enrolled in expedited programs that shortened their review timeframe, in the EU, major objections raised during the scientific review prevented the EMA from granting or completing the initially arranged accelerated assessment to all CFTR modulators. Indeed, the differential timing of approval is ultimately a result of the different approaches to reviewing and accepting evidence by the two regulators [6,18]. Although the US and the EU differential approval interval decreased if clock stops are removed (mainly for initial marketing authorizations) for CFTR modulators, it did not drop to the extent found in other therapeutic areas [2]. Thus, understanding and explaining such differences are determined by the application strategy of a globally operating pharmaceutical company, differences in legal and regulatory systems, and the processing time needed to complete a

regulatory review and decision. Can this gap be reduced to harmonize timely access to CFTR modulators in the EU?

4.1. Revising the EU regulatory system

In April 2023, the European Commission adopted a proposal for a new EU pharmaceutical legislation [19]. Resembling the FDA model, the reform aimed to improve early interactions between the EMA and applicants. This change is expected to enhance the quality of applications and provide tailored scientific support, which should ultimately reduce the clock stop durations. Our findings showed that without clock stops the regulatory review time would decrease by 13 %.While this change alone would not completely align the timing of EU and US approvals, it would streamline the whole process by improving its single components (quality of applications, review duration, and Commission adoption) which may increase the trust in the EU process and trigger earlier submissions by sponsors.

Although legal improvements may streamline the review and approval of medicines in the EU, in the framework we analysed, the main issue remains the policy of EMA to request clinical data also for variations of indications, clearly affecting the timing of the review. Some limitations in the translatability of the current pre-clinical and in vitro models led the EMA to require confirmatory clinical data. As we reported, although price and reimbursement are out of the FDA and EMA's scope, in the EU, the need for data on durable efficacy and criteria for identifying the best responders at the time of marketing authorization has increasingly been claimed by Health-Technology Assessment (HTA) bodies [6].

This requirement is a distinctive character of the European system, whereby assessment is carried out by independent committees representing all the member states. Unlike the US approach, in Europe, regulation has also increasingly strengthened close interactions with HTA bodies, and payers over the past few years, with the ultimate goal of facilitating sequential decision-making, from regulatory approval to pricing and reimbursement (P&R) [19]. In fact, although the EMA centralised procedure provides a single marketing authorization valid in all the EU member states, P&R is set at a Member State level. In the case of new expensive medicines, cost-effectiveness negotiations can take years, delaying access even more than the differential time in approval observed between the FDA and the EMA [20]. From EMA approval to national reimbursement, pwCF have little or no access to CFTR modulators during this period. A paradigmatic example was the combination lumacaftor/ivacaftor in the UK. Initially proposed at a not cost-effective price, the negotiation took from 2015 to 2019, and during this period nearly 8000 packets were destroyed by the company instead of being supplied to patients. A new EU Regulation on HTA [Regulation (EU) 2021/228] intends to harmonize common pathways at the EU level to steer subsequent cost-effectiveness evaluations at the Member State level.

Although the present analysis focuses on the US and the EU regulatory framework, CFTR modulators are also approved in other regions where the disease is prevalent (e.g., Australia, and Canada). But CF has increasingly been reported in middle and low-income countries, in which the disease's diagnosis and treatment has progressively improved in some regions. Therefore, the international community should adopt a global strategy to make such treatments accessible worldwide to reduce health inequalities in pwCF [6,21].

There are some limitations in our analysis to consider. Analyses were underpowered due to small sample sizes. Also, we did not adjust the analyses for multiple testing hypotheses, and the CIs should be interpreted accordingly. Finally, we do not consider the content of early dialogues and interactions (e.g., protocol assistance) as such information is not always publicly available. This exclusion may lead to a bias in some interpretations of the findings.

5. Conclusions

Applications for initial marketing authorizations and supplemental indication approvals of CFTR modulators were generally first submitted in the US, before the EU, and the regulatory review process was faster in the US, where CFTR modulators were ultimately approved 267 days earlier than in the EU. Although the current revision of the pharmaceutical legislation in Europe is expected to reduce such gap in the future, marked differences remain in the way regulators accept and approach supportive evidence. However, negotiations over cost-effectiveness and pricing could be a more important driver of delayed access to new treatments than regulatory procedures. Because of the profound health implications for delayed treatment and the resultant increase in health disparities, continued efforts are needed to facilitate broader access to CFTR modulators.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Please contact the author for data requests.

CRediT authorship contribution statement

Enrico Costa: Conceptualization, Methodology, Data curation, Visualization, Writing – original draft. **Silvia Girotti:** Conceptualization, Methodology, Data curation, Visualization, Writing – review & editing. **Clément Mathieu:** Formal analysis, Writing – review & editing. **Carlo Castellani:** Writing – review & editing. **Joseph S. Ross:** Methodology, Writing – review & editing. **Jennifer L. Taylor-Cousar:** Writing – review & editing. **Hubert G.M. Leufkens:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

Enrico Costa - Member of the Committee for Orphan Medicinal Products (COMP) at the EMA. The views expressed in this article are personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA.

Silvia Girotti - None.

Clément Mathieu - None.

Carlo Castellani – Dr. Castellani has received payment or honoraria for lectures, presentations, speakers or educational events from Vertex Pharmaaceuticals and Chiesi, and he has participated on a Data Safety Monitoring Board or Advisory Board of Vertex Pharmaaceuticals and Chiesi.

Joseph S. Ross - Dr. Ross currently receives research support through Yale University from Johnson and Johnson to develop methods of clinical trial data sharing, from the Food and Drug Administration for the Yale-Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI) program (U01FD005938), from the Agency for Healthcare Research and Quality (R01HS022882), and from Arnold Ventures; formerly received research support from the Medical Device Innovation Consortium as part of the National Evaluation System for Health Technology (NEST) and from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) (R01HS025164, R01HL144644); and in addition, Dr. Ross was an expert witness at the request of Relator's attorneys, the Greene Law Firm, in a qui tam suit alleging violations of the False Claims Act and Anti-Kickback Statute against Biogen Inc. that was settled September 2022.

Jennifer L. Taylor-Cousar - In the last 36 months, unrelated to this work, she has received grants to her institution from the Cystic Fibrosis Foundation, the National Institutes of Health, Vertex Pharmaceuticals Incorporated, Eloxx, and 4DMT; has received fees from Vertex Pharmaceuticals Incorporated related to consultation on clinical research design and participation on advisory boards; and has provided clinical trial design consultation for 4DMT. She served on a DMC for AbbVie. She serves as the adult patient care representative to the CFF Board of Trustees, and on the CF Foundation's Clinical Research Executive Committee, Clinical Research Advisory Board, and as immediate past chair of the CF TDN's Sexual Health, Reproduction and Gender Research Working Group, on the scientific advisory board for Emily's Entourage, and on the ATS Respiratory Health Awards Committee and is the ICC Chair-elect and served previously on the ATS Scientific Grant Review and Clinical Problems Assembly Programming Committees. She is also a member of the International Advisory Board for Lancet Respiratory Medicine and the Editorial Board for the Journal of Cystic Fibrosis.

Hubert G. M. Leufkens - None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.08.002.

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