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To what degree are review outcomes aligned for new active substances (NASs) between the European Medicines Agency and the US Food and Drug Administration? A comparison based on publicly available information for NASs initially approved in the time period 2014 to 2016

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ABSTRACT

Objective To compare review outcome alignment between European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for medicines approved by both agencies in the time period 2014–2016.

Design Using publicly available information from FDA and EMA websites, new active substances (NASs) approved by each agency from 2014 to 2016 were identified and their characteristics assessed. Divergences in regulatory outcomes for simultaneous (within 91 days) submissions to both agencies were identified and then examined for use of facilitated regulatory pathways and orphan designations; submitted versus approved indications; and approval times.

Results In 2014–2016, 115 NASs were approved by EMA or FDA or both; 74/115 were new chemical entities and 41 new biological/biotechnology entities; 82/115 were approved by both agencies, 24 only by FDA and nine only by EMA. Simultaneous submission occurred for 52/115; 13/52 received expedited review by both agencies and 18 only by FDA; 8/52 received conditional approval from both agencies, 2/52 only from FDA and 1/52 only from EMA; 17/52 were designated as orphans by both agencies and 10/52 by FDA only; 31/52 indications were approved as submitted and 21 changed by EMA and 29/46 were approved as submitted (six not assessed) and 17/46 changed by FDA. Median FDA review timelines were 319 days compared with 409 days for EMA.

Conclusions There was general agreement in EMA / FDA conditional approvals. FDA used expedited pathways and orphan designation more often than EMA, suggesting stricter EMA criteria or definitions for these designations or less flexible processes. Despite consistency in submitted indications, there was lack of concordance in approved indications, which should be further investigated. FDA review times are faster because of a wider range of expedited pathways and the two-step EMA process; this may change with recent revisions to EMA accelerated assessment guidelines and the launch of Priority Medicines.

Strengths and limitations of this study

- A 91-day time window was applied to identify 'similar dossiers' being submitted to the European Medicines Agency (EMA) and the Food and Drug Administration (FDA); some uncertainty regarding the identical content could arise but it is unlikely that significant new data would be included in this short time frame.
- Extraction of publicly available data was performed using a predetermined algorithm for each variable; an independent data review was performed by each author, and discrepancies were addressed by consensus.
- Specific inclusion and exclusion criteria were used in the selection of New Active Substances allowing for a consistent cohort for comparisons across agencies.
- Redactions by the FDA in indication information necessitated the exclusion of a few compounds from comparison of submitted and approved indications.
- The lack of concordance between EMA and FDA approved indications compared with submitted indications was not studied but requires further investigation.

INTRODUCTION

The plethora of regulations that govern modern drug development and life cycle management activities across different regulatory jurisdictions has been suggested to contribute to the barriers to the delivery of

safe, innovative and effective treatments to patients in a timely fashion and it was hypothesised that the number and variety of requirements constitute the problem, rather than the requirements themselves.[1]

Efforts to pursue harmonisation of drug regulation have been ongoing but differences in the approval characteristics of drugs by different agencies still persist.[2] The speed of the regulatory review and approval processes between the major regulators, primarily the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have been analysed as a measure of the (dis)alignment of the agencies' various approval models.[3–10]

Approval timelines may not be a comprehensive proxy for the extent of harmonisation; therefore, some investigations have explored differences in indications, in the restrictions of use, or in the limitations of use.[2 4 11 12] Such differences can have considerable implications at the patient level. The same drug can be available without restrictions in one regulatory jurisdiction but with restrictions in another—or not approved and available at all. This is of special concern when a drug is novel and first in class with no comparable therapeutic alternatives available.

Some studies have assessed situations when different regulators have arrived at divergent evaluations of the same drug,[13–17] which is often a result of different interpretations of the same dataset in the benefit-risk evaluation.[18] Instances when regulators reach opposing opinions may erode public trust, especially to those not closely involved in the drug development and assessment processes. With their unique expertise, the regulatory agencies have been entrusted with the goal to protect the health and the well-being of the public they serve.[19 20] Consequently, a reasonable expectation is that regulatory actions and outcomes should not differ significantly between, for instance, the FDA and EMA, given that both regulatory bodies evaluate very similar, if not identical, data packages and regulate for similar types of populations. In order to align their activities and goals, the two agencies have implemented several collaborative approaches such as sharing inspection reports and product safety information and offering parallel scientific advice.

Nevertheless, further research to compare the outcomes could identify specific reasons for divergent regulatory recommendations between the FDA and EMA. This could be done by analysing the products submitted to the two agencies and by determining which were approved by each agency and to what extent the final indications were similar.

This study, therefore, investigated regulatory review outcomes for new active substances (NASs) approved by the FDA and the EMA from 2014 through 2016, with outcomes status tracked into 2017. It assessed to what extent the regulatory outcomes between the two agencies were aligned or identical for medicines submitted for evaluation simultaneously to EMA and FDA—defined as the submissions occurring within 3 months of each other—by investigating the use of facilitated regulatory pathways (FRPs) and orphan designations; submitted versus approved indications; and approval times.

METHODS

General

The drug selection, filtering and work-up process followed the procedure depicted in figure 1. After establishing the initial data-set it was filtered by applying several criteria to focus on the drugs of interest. For the remaining cohort select qualifiers were collected allowing us to conduct the desired analysis and report on findings as detailed below.

Data sources

Using publicly available information from the FDA and the EMA websites we identified NASs (available in online supplementary table 1) approved by each agency. NASs meeting the criteria for the study included:

- A chemical, biological, biotechnology, or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription-only medicine', to be used for the cure, alleviation, treatment, prevention, or in vivo diagnosis of diseases in humans.
- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available.
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure through changes to the nature of source

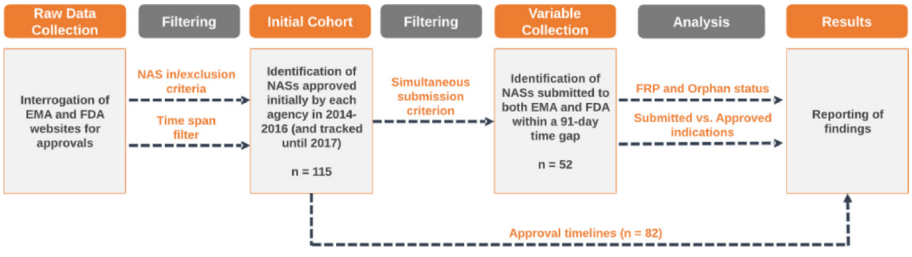

Figure 1 The initial data-set was refined in several steps to arrive at different subsets of interest furnishing cohorts n=115, 82 and 52, respectively. For the n=52 cohort additional variables were collected to broaden and deepen the analysis. EMA, European Medicines Agency; FDA, Food and Drug Administration; NASs, new active substances.

material or manufacturing process and requiring clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product—alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available

The following entities were excluded:
- Vaccines.
- Biosimilars.
- Any other application, where new clinical data were submitted.
- Generic applications.
- Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company.
- Applications for a new or additional name, or a change of name, for an existing compound, that is, a 'cloned' application

The study included NAS applications approved by EMA (through the centralised procedure) or FDA or both between 1 January 2014 and 31 December 2016. Applications were included in the study when dossiers were filed before 1 January 2014, but a regulatory decision was not made until within the study time period. Similarly, although the inclusion criterion was approval by one or both agencies by 31 December 2016, outcomes were tracked for another 12 months to account for a time lag, that is, until 31 December 2017. A 3-year time study period was selected for its ability to provide a sufficiently robust data set. At the time the study was conducted, 2014–2016 was the most current 3-year span for which a full data set was available. Finally, to determine the rationale for non-approval of certain NASs in one agency but not the other, we searched the public domain in June 2018. The public domain websites included clinicaltrials.gov and agency and pharmaceutical company sponsor websites.

Characteristics of the NASs

We collected selected variables for each approved NAS from agency public assessment reports including approval milestone data, indication, FRPs[21] and orphan status (table 1).

In addition, for NASs not approved by either the EMA or FDA, we searched the rationale for this using the agency and company websites to determine if this was due to non-submission by the sponsor; the NAS being currently reviewed or approved in 2018; approval through the decentralised procedure in Europe; rejection by the agency, or withdrawal by the company.

Data extraction was performed by two researchers, MB and NM, where MB extracted the data using predetermined values for each variable and NM verified the data through an independent review; discrepancies were discussed until consensus was reached.

Based on the agency's assessment of the dossier, the indications in the final approved labelling may not reflect the indications requested by the sponsor in the submission. Therefore, a comparison of submitted versus approved indication(s) for each product by each agency was performed independently by two reviewers, MB and Sophie Miet-Eseverri. A difference in indication was defined as a restriction or expansion of the treated population. For NASs where the same indication was submitted to EMA and FDA, we compared the final EMA and FDA labelling for each product to determine the degree of divergence between the agencies. The analyses were compared between researchers and discrepancies were

Table 1 Variables collected for each new active substance extracted from public assessment reports

Variable	Data point	Note on definition
Compound type	New biological/biotechnology entity	A substance isolated from animal tissues or product produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants for therapeutic, prophylactic or in vivo diagnostic use in humans
	New chemical entity	An entity produced by chemical synthesis
Therapy area	Anatomical therapeutic chemical code	As defined by the WHO
Approval milestone dates	Sponsor submission date	Defined as date of receipt of dossier by the agency
	Regulatory approval date	Defined as the date of marketing authorisation; for EMA this refers to European Commission decision date
Indication	Indication submitted by the sponsor	A difference in indication was defined as a restriction or expansion of the treated population.
	Indication approved by the agency	
Facilitated regulatory pathways to facilitate availability, review and/or approval of medicines where there is an unmet medical need	Expedited review resulting in shorter review timelines	Defined as EMA 'Accelerated Assessment' and FDA 'Priority Review'
	Conditional review resulting in early approval based on preliminary data	Defined as EMA 'Conditional Review' and FDA 'Accelerated approval'
	Other non-standard pathways	FDA Breakthrough Designation; FDA Fast Track
Orphan status	Orphan designation	

EMA, European Medicines Agency; FDA, Food and Drug Administration.

discussed with the other authors until consensus. If part of the indication was redacted (as was the case for FDA), those NASs were excluded from this specific analysis.

Time periods

The following time periods were defined: *Approval Time:* Time calculated from sponsor submission date to regulatory approval date. This time includes agency and company time. The EMA time includes European Commission time. *Submission gap:* Date of submission at the first regulatory agency to the date of regulatory submission to the subsequent regulatory agency. *Simultaneous submission:* For the purpose of this study, regulatory submission occurring within a 91-day (3-month) submission gap.

Patient and public involvement

The view of patients or members of the public was not solicited when developing the research questions or the design of the current investigation, nor were they involved in the conduct of the study. The findings and the results of this writing may be further discussed and debated at scientific meetings and other venues open to the public.

RESULTS

Characteristics of the study cohort

In total, 115 NASs were approved by at least one of the agencies, that is, by EMA or FDA or both in 2014–2016, with status tracked until the end of 2017 (See online supplementary table 1). Of the 115, 74 (64%) were classified as new chemical entities and 41 (36%) as new biological/biotechnology entities. The therapy area representing the largest proportion of NASs (36 compounds (31%) according to the Anatomical Therapeutic Chemical classification system) comprised 'antineoplastic and immunomodulating agents'. The next four major therapy groups were anti-infectives for systemic use (17 NASs), alimentary tract and metabolism products (15 NASs), nervous system products (11 NASs) and blood and blood forming organs (11 NASs).

Of the 115 NASs, 82 (71%) were approved by both EMA and FDA, 24 (21%) approved by FDA and not EMA and nine (8%) approved by EMA and not FDA (figure 2A).

In general, the submission to both EMA and FDA occurred within 3 months and almost all within 1 year. The absolute difference in submission gap (ie, irrespective of whether submission occurred first to EMA or FDA) was 0 days for seven NASs, 1–30 days for 30 NASs, 31–91 days for 15 NASs, 92–183 days for 13 NASs, 184–365 days for 10 NASs and >365 days for seven NASs (figure 2B).

For the 82 NASs that were approved by both agencies, the submission to FDA occurred a median of 16 days before EMA (50th percentile in figure 3). In terms of the variance, the 25th percentile for the gap was that submission to FDA occurred 1 day after EMA and the 75th percentile that submission to FDA occurred a median 75 days before EMA.

Types of divergent outcomes by EMA and FDA

NASs submitted or approved only by one of the agencies

Of the 115 NASs, more compounds were approved only by FDA (and not EMA), with 24 NASs (21%), compared with nine NASs (8%) approved only by EMA and not FDA (figure 2A). The type of non-approval was subsequently explored for those NASs. Importantly, the non-approval was never a result of rejection by EMA or FDA and the most common reasons for divergence being a lack of submission by the sponsor; the submission or approval occurring outside the study time range; or the review process not meeting criteria for inclusion in this study.

More specifically, 10 of the 24 NASs approved by FDA but not EMA have undergone a regulatory review in Europe, either having been submitted or approved by EMA in 2018 (five NASs), which is outside the study time range, or via the European decentralised procedure (four NASs) or as a managed entry programme (one NAS), which are outside the study scope. For nine out of the 24 NASs there has been some activity in Europe, with four NASs having had a paediatric investigation plan waivered or agreed

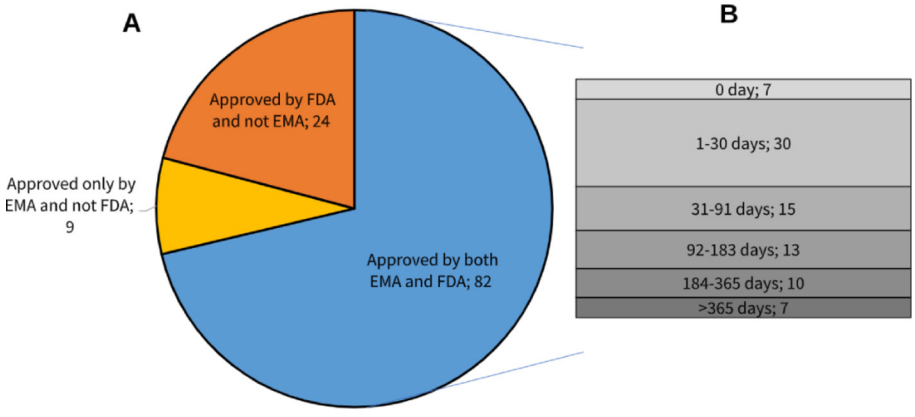

Figure 2 (A) Number and approval status for 115 NASs approved initially by EMA or FDA in 2014–2016, with approval status tracked for the other agency until the end of 2017; and (B) absolute difference in submission gap between EMA and FDA for 82 NASs approved by both agencies. EMA, European Medicines Agency; FDA, Food and Drug Administration; NASs, new active substances.

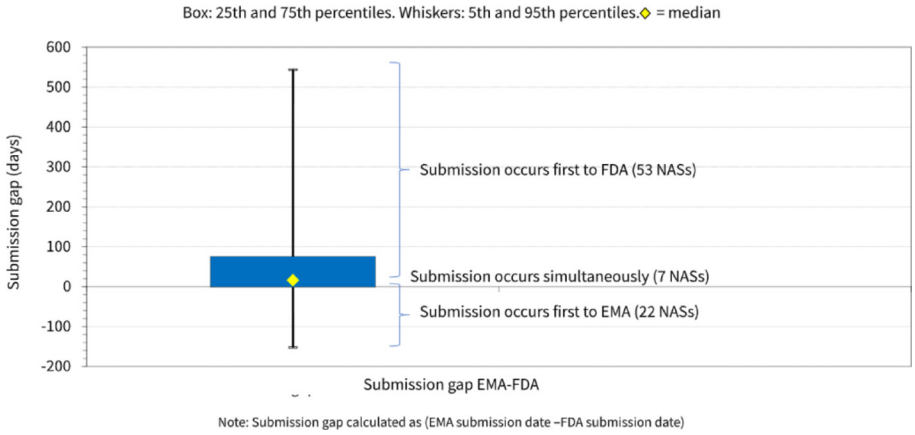

Figure 3 Submission gap between EMA and FDA (relative to FDA) for 82 NASs approved by both agencies. EMA, European Medicines Agency; FDA, Food and Drug Administration; NASs, new active substances

by EMA, whereas four NASs are currently undergoing clinical trials in Europe, which suggests that they may be submitted to the European market in the future. For four of the 24 NASs, there was no published activity in Europe by regulatory agencies or the sponsor.

For five of the nine NASs that were approved by EMA and not FDA, there was no published activity in the USA by the agency or the sponsor. Two of the nine NASs were submitted to FDA, with expected decisions due in 2018 and one NAS has been made available in USA under expanded access (compassionate use). For one NAS, the sponsor indicated plans to submit the application in 2019.

NASs submitted simultaneously to EMA and FDA

In order to analyse the extent to which the regulatory outcomes between the two agencies were aligned, this analysis assessed the cohort of submissions made within a similar time period; the underlying assumption was that the same evidence package was therefore submitted to each agency. A regulatory submission occurring to both agencies within a 91-day (3-month) gap was selected as a marker of a simultaneous submission; 52 of the 115 NASs met this timeframe.

For these 52 NASs, three types of regulatory characteristics were analysed to assess divergence: (a) use of FRPs and orphan designations; (b) submitted and approved indications and (c) approval times (figure 4).

Use of FRPs and orphan designations

FRPs were defined as regulatory pathways designed to facilitate availability, review or approval of medicines where there is an unmet medical need by providing alternatives to standard regulatory review routes. As some of the FRPs offered by the agencies have common characteristics, their use was compared across the 52 NASs (figure 4A).

Both agencies have in place an expedited FRP review system for promising NASs, namely the EMA 'Accelerated Assessment' and FDA 'Priority Review'. For 34 out of the 52 NASs (65%), there was agreement regarding the review type: 13 NASs were reviewed as expedited by both EMA and FDA and 21 NASs were reviewed under the standard timelines by both agencies. For 18 of the 52 NASs (35%) there was no agreement (eg, only one of the agencies used the expedited FRP); in all these cases the expedited FRP was used by FDA but not EMA.

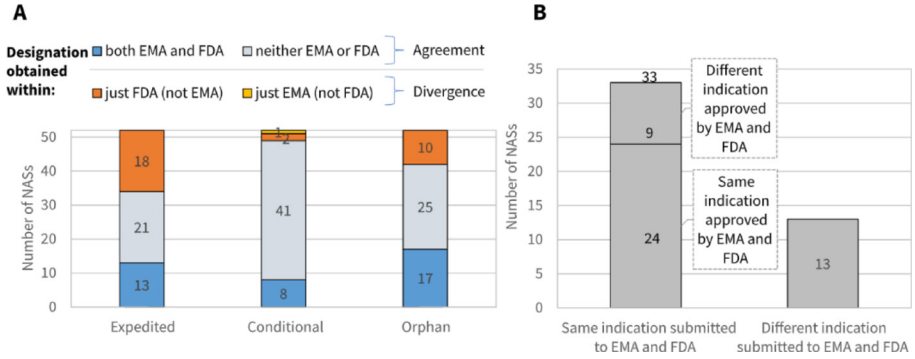

Figure 4 Divergence in outcomes for 52 NASs approved initially by EMA or FDA in 2014–2016, with approval status tracked for the other agency until the end of 2017. (A) Number of NASs which were reviewed through facilitated regulatory pathways, expedited (EMA 'accelerated assessment'; FDA 'priority review') and conditional (EMA 'conditional approval'; FDA 'accelerated approval'); as well as orphan designations; (B) number of NASs for which the indication submitted to EMA was the same or different; as well as number of NASs which received the same or different approved indication where the same indication was initially submitted. EMA, European Medicines Agency; FDA, Food and Drug Administration; NASs, new active substances.

The second type of FRP reviewed was the 'conditional review' resulting in an early approval based on preliminary data, referred to by EMA as 'Conditional Review' and FDA 'Accelerated Approval'. Agreement was reached for 49 of the 52 NASs (94%): eight of the NASs received conditional approval from both agencies, whereas 41 were non-conditional at both EMA and FDA. Of the 52, two NASs received conditional approval within FDA and not EMA, whereas one NAS received conditional approval from EMA and not FDA.

Both agencies offer orphan designations on request of a sponsor for NASs meant to treat a rare disease or condition. Of the 52 NASs, 17 were designated as orphan by both EMA and FDA, whereas 25 did not receive the designation from either agency, reflecting an agreement for 42 of 52 NASs (81%). For 10 NASs, the designation was obtained only with the FDA but not with the EMA.

In all cases, differences in the use of FRPs and orphans could be either as a result of the company not requesting this type of review or the agency not granting it as a result of different criteria. The current analysis could not determine causes for the divergences.

Submitted and approved indications

The submitted and approved indication(s) were compared within each agency and across EMA and FDA. Of the 52 NASs, EMA approved the indication submitted by the sponsor for 31 NASs (60%), whereas for 21 NASs (40%), a change was made to the submitted indication to restrict or expand the treated population for the approved NAS.

Conversely, FDA approved the submitted indication for 29 out of 46 NASs (63%; six NASs not assessed due to redaction of the indication in the publicly available assessment report), whereas a different indication was approved for 17 (37%) out of 46 NASs compared with what was submitted.

A direct comparison was also carried out of the submitted and approved indication across the two agencies (figure 4B). Of the 46 NASs, the same indication was submitted to EMA and FDA for 33 NASs (72%). The remaining 13 NASs (28%) were submitted by the sponsors pursuing different indications. For those 33 NASs where the same indication was submitted, the same was approved by EMA and FDA for 24 (73%).

Approval time

The regulatory review timelines were compared for the 52 NASs at the two agencies (figure 5). The EMA median approval time was 409 days, whereas the FDA timelines were 90 days faster, with a median of 319 days. The variance around the median was similar for both agencies, with a range between the 25th and 75th percentile for median approval of 139 days for EMA (25th percentile=320 days; 75th=459 days) and 128 days for FDA (25th percentile=237 days; 75th=365 days).

DISCUSSION

Medicine development is an increasingly global activity, with the aspiration to develop a common data set to address the scientific needs of regulatory agencies around the world. A consolidated data package in a standardised format does conserve resources—on both sides of the table—and its availability does support the approach of simultaneous submissions of the dossier to two or more regulatory agencies—which in turn would lend itself to work sharing among regulatory agencies and stimulate the uptake of reliance models.[22–24]

The findings described in this paper contribute to the study of regulatory harmonisation by providing an analysis of the extent to which the regulatory outcomes between EMA and FDA were aligned, identical, or different for new medicines submitted for evaluation simultaneously to the two agencies. Our study demonstrates that there generally is alignment between NAS approval status for EMA and FDA and that drug applications were mostly approved by both agencies. Our analysis showed that lack of alignment was due to the applicant delaying submission (to outside the study range), alternatively the sponsor deciding not

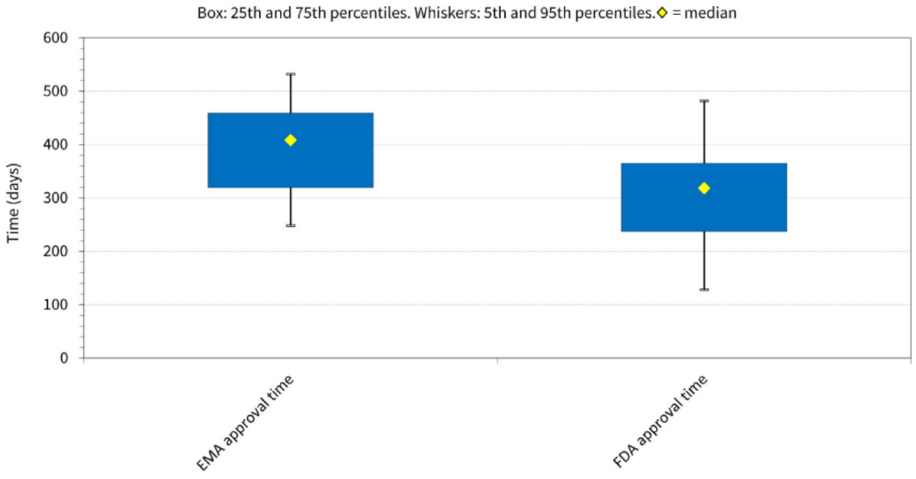

Figure 5 Approval times for EMA and FDA for 52 NASs submitted simultaneously to the two agencies. EMA, European Medicines Agency; FDA, Food and Drug Administration; NASs, new active substances.

to file or opting for a regulatory assessment procedure other than the Centralised Procedure in the EU.

There is a general agreement between the designations for the 52 NASs that were submitted simultaneously to both agencies in terms of conditional approvals, which comprise EMA's Conditional Approval and FDA's Accelerated Approval. A difference was observed for products that benefitted from the use of an expedited pathway, where more NASs were reviewed using this facilitated regulatory pathway by FDA compared with EMA. Similarly, more products were designated as orphan products by FDA than EMA. This suggests that either the criteria or definitions for expedited review or orphan designation are stricter for EMA than FDA or that aspects of the process provide less flexibility in the use of these designations by companies or its designation by the EMA.

It is not certain, but reasonable to assume that slight differences in dossier submission timing (within 91 days) to the two agencies are not owing to differences in dossier content but rather to sponsor project management concerns. Such sequential filing ensures availability of the necessary sponsor resources to promptly respond to regulatory clarification questions.

While the regulatory decision-making process overall seems similar, differences in approval timelines persist. The FDA is considerably quicker than EMA since EMA timelines formally require two steps, namely (1) an opinion from the Committee for Medicinal Products for Human use followed by (2) a European Commission decision. FDA also offers a wider range of expedited pathways that can be applied in different situations, which jointly contribute to a lower median review time. Recently, EMA revised its accelerated assessment guideline and launched the Priority Medicines (PRIME) scheme to stimulate the support for the development of medicines.[25] We find this an important step toward offering additional regulatory filing options in the EU, with the goal of providing for timely patient access to novel therapeutic principles, that are on par with other leading regulators such as the US FDA or the Japanese Pharmaceuticals and Medical Devices Agency.[10]

Although the submitted indications were generally consistent for both FDA and EMA across the cohort, there was less concordance between the agencies for the approved indications. This is something that needs to be explored further by, for instance, examining postapproval commitments as well as benefit-risk profiles. Further studies on this may focus on identifying such characteristics and using them to determine the rationale for divergent outcomes, particularly where the same indication was submitted and different indications were approved. This could illuminate the differences in significance the two agencies attach to the various components in their respective benefit-risk analyses. Bearing in mind that the two agencies have had a close collaboration for many years, and that regulatory decision making should be based on science and evidence, there may be important learnings for drug developers to uncover, helping them to avoid future situations in which the same data set would render different outcomes.

While not evidenced by the current cohort of drugs investigated, the two agencies on occasion have reached divergent authorisation conclusions on drug applications.[13–17] These divergences have been critiqued by third parties such as academia and patient organisations and Regulators have responded with increased transparency on their decision making process by, for instance, the publication of assessment reports or clinical study reports.

Although this study does not delve into the time and effort that sponsors are spending on reconciling divergent requirements before submission it is recognised that this sometimes is a protracted process that can take years to accomplish. Indeed, the significance sponsors put on soliciting input on their development projects from regulators is illustrated by the steadily growing number of Scientific Advice procedures given by EMA and FDA, individually[26 27] or in parallel. Some challenges remain in the applicant uptake of the latter scheme and is presently being reviewed.[28]

When scientific advice or guidance cannot bridge differences in regulatory requirements, sponsors have the choice to develop separate data packages. This has been observed for mainstream therapeutic areas, special populations, or niche indications (including orphan drugs). In view of the considerable attention sponsors at large pay to meeting specific requirements requested by (different) regulators, one would expect that regulatory outcomes would be rather more aligned than not, a notion that is evidenced by the findings in the present study.

As the regulatory environment evolves with increased convergence in regards to good regulatory practices and standards along with an increasing regulatory workload and greater complexity of new drugs coming through the pipeline, the sector will need to transform. This might be driven by increased flexibility being built into the review and approval processes of new medicines such as the adoption of FRPs or iterative decision making (rolling reviews). This may be a result of agencies adopting and applying digital technology to enhance not just compliance and safety surveillance, but also improved regulatory decision making.[29 30] For example, data supporting regulatory decision making could reside in a single (cloud-based) location and be accessed and evaluated on line, simultaneously by different regulators. This could provide the means of stimulating concerted decision-making processes based on the same data set, which could minimise divergences that are not scientifically justified as well as saving time and efforts for the benefit of all stakeholders involved—whether it is society as a whole, individual patients, regulators, payers, or industry.

CONCLUSIONS

Overall this study found that there was general agreement in EMA/FDA conditional approvals. FDA used expedited pathways and orphan designation more often

than EMA, suggesting stricter EMA criteria/definitions for these designations or less flexible processes. Despite consistency in submitted indications, there was still a lack of concordance in approved indications, which requires further investigation beyond this study. FDA review times are faster because of a wider range of expedited pathways vis-à-vis the two-step EMA process. This may change with recent revisions to EMA's accelerated assessment guidelines and the launch of PRIME.

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Contributors TCK and LL designed the study, analysed the data and wrote the manuscript; MB and NM designed the study, collected and analysed the data and wrote the manuscript.

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