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Transparency in European Medicines Agency and US Food and Drug Administration Decision Making: Is It Possible to Identify the Rationale for Divergences in Approved Indication From Public Assessment Reports?

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ABSTRACT

Although it cannot be expected that different medicines' regulatory agencies always reach the same review outcome, it is important that decision making is documented and communicated to ensure transparency. This study examines whether justification for divergences between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) regarding approved indications could be identified from the agencies' public assessment reports (PARs). We focused on 9 products previously identified to have been submitted simultaneously to both agencies with the same indication but had a different indication approved; there were 15 differences in indications. Our analysis confirms that the rationale for observed divergent indication decisions was predominantly found in the benefit-risk section of the PAR (9 of 15 cases for the FDA and 10 of 15 for the EMA). If not found in the benefit-risk section, the rationale for these decisions was found in other PAR sections (eg, labeling or clinical efficacy section) or not at all. Our study found a small number of inconsistencies or gaps in how, where, and whether regulatory decision making on approved indications are documented by the FDA and the EMA. We believe it is important for regulators to standardize their approach and systematically and transparently document their rationale for the approved indication, using a structured benefit-risk assessment format within the PAR. This process is especially important for innovative products for which experience in evaluating similar products worldwide is limited, particularly as agencies are striving to build effective regulatory processes by leveraging assessments by trusted reference agencies through approaches such as reliance. Clear and systematic communication and documentation of the decisions in the PAR are central and should continue to evolve as a best practice; an enabling step toward this would be a harmonized PAR template for use by agencies globally. (*Clin Ther.* 2021;000:1–18.)

Key words: decision making, EMA, FDA, transparency.

INTRODUCTION

The field of regulatory science seeks to align regulatory activities to increase efficiencies and reduce outcome uncertainties. Aligned practices are promulgated by organizations, such as the World Health Organization,[1] the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use),[2] and the Council for International Organizations of Medical Sciences[3] among others, to

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build predictability and consistency into the regulatory assessment and decision-making processes.

Consequently, a reasonable expectation based on the use of the same technical standards is that regulatory actions and outcomes should be consistent, for instance, between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), given that both agencies regulate for similar types of populations. Previous studies[4,5] have found a high concordance in the decision making between the EMA and the FDA. Nevertheless, for a relatively small number of products authorized each year by these agencies, divergences in the outcome of the authorization continue to be observed. It is therefore important that divergences, such as differences in approved indication when the same indication is submitted to each agency, are communicated to ensure transparency in the decision-making processes for other stakeholders, such as patients and other regulators.

Divergent outcomes may result from the submission of a data package that may be more updated than for the first-in-world application.[4–6] Instances in which the same indication is proposed, yet approved indications differ from those proposed or differ across agencies may be the result of complexities and uncertainties in assessing pharmacology, tolerability, and efficacy parameters associated with new medicinal products or therapeutic principles or regional differences in medical practice. In addition, such differences in risk tolerance could be attributable to subjective influences on the process as well as varying agency decision-making practices.

In a recent study,[4] we examined in detail the characteristics of submissions between 2014 and 2016. Of 115 new active substances (NASs; as defined below) that were approved by the EMA or the FDA, 82 were approved by both agencies, and for 33 of those, the same indication was submitted to the EMA and the FDA through a simultaneous submission (defined as a submission occurring within 3 months of each other). Despite consistency in submitted indications, we were intrigued by the lack of concordance in approved indications for several products. The same indication was approved by the EMA and the FDA for 24 of the 33 NASs, leaving 9 NASs for which different indications were approved by the 2 agencies for each product.

Some divergences in regulatory outcomes across agencies are not unexpected, but it is important that these are documented. Indeed, if the rationale for the divergent decision cannot be identified, this may raise questions of consistency and trust. Such transparency is important for informing a number of stakeholders, such as researchers, patients, or clinicians, and clarifying the regulatory pathway for future products as well as informing other stakeholders downstream of the process, such as health technology assessment (HTA) bodies. It is also important as regulatory agencies more widely apply reliance reviews, during which their decisions are informed by reference agencies[7–9] or when agencies conserve resources by collaborating on the review to share the workload.[10,11] The initial decision rationale, particularly when there are divergences across reference agencies, need to be understood in the context of the benefit-risk assessment. We believe that such documentation should be achievable through the use of public assessment reports (PARs) and specifically in the benefit-risk assessment section of the PAR compared with other sections (eg, efficacy or labeling) to ensure consistency in documentation.

Indeed, with the use of information from the PAR, it should be possible to understand the rationale and justification for the regulatory decision (eg, based on risk tolerance and ability to mitigate tolerability issues) and the implications for clinical practice or patient access. If a difference in the approved indication is factually based on the assessment of the product's benefits and risks, the underlying decision evidence should, therefore, be systematically documented in the PARs (ie, in the standardised benefit-risk section of the PAR).[12]

This study examines whether the justification for divergent decisions regarding approved indications between the FDA and the EMA could be identified based on the information provided by each agency in their respective PARs. This work was performed for the 9 products with a different indication approved that we identified in our original study on NASs with a simultaneous submission and same indication.[4] We sought to determine to what extent it may be possible to identify the decision rationale based on data in the PARs, in which section of the PAR this was described, and whether we could determine the product characteristics that pointed toward a divergent decision.

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METHODS

Scope and Limitations

The 9 NASs identified in a previous study[4] were the focus of this analysis. The characteristics of the 9 NASs are as follows: simultaneously submitted to EMA and FDA, defined as a submission occurring within 3 months of each other; initially approved by the EMA or FDA between 2014 and 2016, with outcome at second agency tracked until end of 2017; had the same indication submitted to EMA and FDA; and had a different indication approved by the EMA and FDA (this was defined as treating a different population or conditions of use, such as type of therapy or use with other products).

Data Analysis

The verbatim submitted indication and approved indication (Table I) were compared, and an analysis of rationale for differences in approved indication for the EMA and the FDA was undertaken as well as a search of the divergence documentation in the respective agencies' PARs. A difference in approved indication was considered significant and was noted (steps 1–4 in Figure 1) independently by 2 research groups (group 1: M.B., L.L., and N.M.; group 2: T.K. and S.F.). The results from the 2 groups were compared and any differences adjudicated through discussion to reach consensus. The results were subsequently tabulated by one of the research groups and peer-reviewed by the other group.

Data Sources

Information was collected from the FDA and EMA websites, specifically the agencies' PARs. The following variables were collected as defined in the initial study[4]: compound type; therapy area; approval milestone dates; indication; facilitated regulatory pathways to facilitate availability, review, and/or approval of medicine where there is an unmet medical need, and orphan status.

Definitions

A NAS was defined as follows: 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 tolerability and efficacy from that substance previously available; a biological or biotechnological substance previously available as a medicinal product but differing in molecular structure through changes to the nature of source material or manufacturing process and requiring clinical investigation; or 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, applications on which a completely new dossier was submitted from a new company for the same indications as already approved for another company, and applications for a new or additional name or a change of name for an existing compound, that is, a cloned application.

RESULTS

Part 1: Documentation of Differences in EMA and FDA PARs

The approved indications of each of the 9 identified NASs were analyzed to examine whether it was possible to determine and characterize the nature of the divergence (in approved indications) between the 2 agencies and whether the underlying rationale was (clearly) documented in the associated PARs (Table II). For each NAS, the change in approved indication for each agency was noted and what type of change (eg, addition or deletion) was made by the EMA or the FDA. The documentation for the rationale for the change was noted and whether this was documented in the benefit-risk section of the PAR or elsewhere, such as the clinical efficacy section for the EMA or the labeling section for the FDA. In some instances, the justification was not documented in the PAR but could be found in other documents, such as the FDA Advisory Committee meeting minutes.

The number of divergences (those that were documented in the PAR and those that were not) were tallied for each agency (Figure 2). In general, the rationale for divergence was documented in the benefit-risk section (ie, across the 15 observed divergences for the 9 NASs, 10 of 15 were documented in the benefit-

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Table I. Nine compounds first approved by the EMA or the FDA in 2014-2016 (and approved by the other agency by the end of 2017) for which the same indication was submitted but a different one was approved by each agency (defined as treating a different population or conditions of use, such as type of therapy or use with other products).

Compound	Agency	Submission Date	Approval Date	Submitted Indication Text	Approved Indication Text
Alectinib hydrochloride	EMA	9/8/2015	2/16/2017*	Alectinib is indicated for the treatment of adult patients with anaplastic lymphoma kinase–positive, locally advanced, or metastatic non–small cell lung cancer who have progressed with or are intolerant of crizotinib	Alectinib as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase–positive advanced non–small cell lung cancer previously treated with crizotinib.
	FDA	7/6/2015	12/11/2015*,†,‡	Alectinib is indicated for the treatment of patients with anaplastic lymphoma–positive, locally advanced or metastatic non–small cell lung cancer who have progressed with or are intolerant of crizotinib	Alectinib is indicated for the treatment of patients with anaplastic lymphoma kinase–positive, metastatic non–small cell lung cancer who have progressed with or are intolerant of crizotinib.
Alirocumab	EMA	12/2/2014	9/23/2015	Alirocumab is indicated, as adjunct therapy to diet, for long-term use in adult patients with primary hypercholesterolemia (nonfamilial and heterozygous familial) or mixed dyslipidemia to reduce LDL-C. Alirocumab also decreases other atherogenic lipid parameters, such as total cholesterol, non–HDL-C), triglycerides, and lipoprotein(a). Alirocumab also increases HDL-C. Alirocumab is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy, in patients whose conditions are not appropriately controlled with a statin. Alirocumab is indicated as monotherapy or as add-on to other nonstatin lipid-modifying therapy, in patients who cannot tolerate statins. The effect of alirocumab on cardiovascular morbidity and mortality has not been determined.	Alirocumab is indicated in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated. The effect of praluent on cardiovascular morbidity and mortality has not yet been determined.

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Table I. (*continued*)

Compound	Agency	Submission Date	Approval Date	Submitted Indication Text	Approved Indication Text
	FDA	11/24/2014	7/24/2015[†]	Alirocumab is indicated for long-term treatment of adult patients with primary hypercholesterolemia (nonfamilial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce LDL-C, total cholesterol, non–HDL-C, apolipoprotein B, triglycerides, and lipoprotein(a) and to increase HDL-C and apolipoprotein A1. Alirocumab is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy. Alirocumab is indicated as monotherapy or as add-on to other nonstatin lipid-modifying therapy, including in patients who cannot tolerate statins.	Alirocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
Cangrelor	EMA	4/30/2013	3/23/2015	Cangrelor is a P2Y12 platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in adult patients with coronary artery disease undergoing percutaneous coronary intervention. During the preoperative period when oral P2Y12 therapy is interrupted because of surgery (bridging), Dangrelor is also indicated to maintain P2Y12 inhibition in adult patients with acute coronary syndromes or in patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted because of surgery (bridging).	Cangrelor, coadministered with acetylsalicylic acid, is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention who have not received an oral P2Y12 inhibitor before the percutaneous coronary intervention procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

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Table I. (*continued*)

Compound	Agency	Submission Date	Approval Date	Submitted Indication Text	Approved Indication Text
	FDA	4/30/2013	6/22/2015	Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention B. Maintain P2Y12 inhibition in patients with acute coronary syndrome or patients with stents who are at increased risk for thrombotic events when oral P2Y12 therapy is interrupted because of surgery.	An adjunct to percutaneous coronary intervention to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.
Evolocumab	EMA	8/29/2014	7/17/2015	The applicant applied for the following indications: hypercholesterolamia and mixed dyslipidemia. evolocumab is indicated in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce LDL-C, TC, apolipoprotein B, non–HDL-C), total cholesterol/HDL-C, apolipoprotein B/apolipoprotein A1, VLDL-C, triglycerides, and lipoprotein(a) and to increase HDL-C and apolipoprotein A1: in combination with a statin or statin with other lipid-lowering therapies or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. Homozygous familial hypercholesterolemia: evolocumab is indicated in adults and adolescents 12 years and older with homozygous familial hypercholesterolemia to reduce LDL-C, total cholesterol, apolipoprotein B, and non–HDL-C in combination with other lipid-lowering therapies.	Hypercholesterolemia and mixed dyslipidemia. Evolocumab is indicated in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated. Homozygous familial hypercholesterolemia. Evolocumab is indicated in adults and adolescents 12 years and older with homozygous familial hypercholesterolemia in combination with other lipid-lowering therapies. The effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.

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Table I. (*continued*)

Compound	Agency	Submission Date	Approval Date	Submitted Indication Text	Approved Indication Text
	FDA	8/27/2014	8/27/2015‡	Primary hyperlipidemia and mixed dyslipidemia: Evolocumab is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce LDL-C, total cholesterol, apolipoprotein B, non–HDL-C, total cholesterol/HDL-C, apolipoprotein B/apolipoprotein A1, VLDL-C, triglycerides, and lipoprotein(a) and to increase HDL-C and apolipoprotein A1: in combination with a statin or statin with other lipid-lowering therapies (eg, ezetimibe) or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. Homozygous familial hypercholesterolemia; Evolocumab is indicated in adults and adolescents 12 years and older with homozygous familial hypercholesterolemia to reduce LDL-C, total cholesterol, apolipoprotein B, and non–HDL-C in combination with other lipid-lowering therapies (eg, statins, LDL apheresis).	BLA 125522/original 1: Evolocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C. This application only includes a 420 mg once monthly dosing regimen for the homozygous familial hypercholesterolemia indication.
Isavuconazole	EMA	7/16/2014	10/15/2015‡	The applicant applied for the following indication in adults for treatment of invasive aspergillosis and treatment of mucormycosis.	Isavuconazonium is indicated in adults for the treatment of invasive aspergillosis and mucormycosis in patients for whom amphotericin B is inappropriate. Consideration should be given to official guidance on the appropriate use of antifungal agents.
	FDA	7/8/2014	3/6/2015†,‡	For the treatment of patients 18 years or older: invasive aspergillosis and invasive mucormycosis	For the treatment of invasive aspergillosis and invasive mucormycosis

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Table I. (*continued*)

Compound	Agency	Submission Date	Approval Date	Submitted Indication Text	Approved Indication Text
Olaratumab	EMA	1/29/2016	11/9/2016*,†,‡	Olaratumab is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.	Olaratumab is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin (see section 5.1).
	FDA	2/24/2016	10/19/2016*,†,‡	Indicated in combination with doxorubicin for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery.	Olaratumab is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and that is not amenable to curative treatment with radiotherapy or surgery
Ramucirumab	EMA	8/23/2013	12/19/2014‡	Ramucirumab as a single agent is indicated for the treatment of patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma after prior chemotherapy.	Ramucirumab in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. Ramucirumab monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy for whom treatment in combination with paclitaxel is not appropriate.

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Table I. (*continued*)

Compound	Agency	Submission Date	Approval Date	Submitted Indication Text	Approved Indication Text
	FDA	8/23/2013	4/21/2014†,‡	Ramucirumab is for the treatment of patients with gastric or gastroesophageal junction previously treated with a cisplatin-containing regimen.	Ramucirumab is indicated for the treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma as a single agent after prior fluoropyrimidine- or platinum-containing therapy
Sofosbuvir-velpatasvir	EMA	11/14/2015	7/6/2016†	Treatment of chronic hepatitis C virus infection in adults.	Sofosbuvir-velpatasvir is indicated for the treatment of chronic hepatitis C virus infection in adults.
	FDA	10/28/2015	6/28/2016†	Treatment of adult patients with chronic hepatitis C virus infection	For the treatment of adult patients with chronic hepatitis C virus genotypes 1, 2, 3, 4, 5, or6 infection: without cirrhosis or with compensated cirrhosis and with decompensated cirrhosis for use in combination with ribavirin.
Talimogene laherparepvec	EMA	8/28/2014	12/16/2015	Treatment of adults with melanoma that is regionally or distantly metastatic	Talimogene laherparepvec is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease.
	FDA	7/28/2014	10/27/2015‡	Treatment of injectable regionally or distantly metastatic melanoma. (The indication is currently under discussion between the applicant and the FDA and as a result may be revised.)	Talimogene laherparepvec is indicated for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery,

EMA = European Medicines Agency; FDA = US Food and Drug Administration.
* EMA conditional/FDA accelerated approval.
† EMA accelerated/FDA priority.
‡ Orphan designation.

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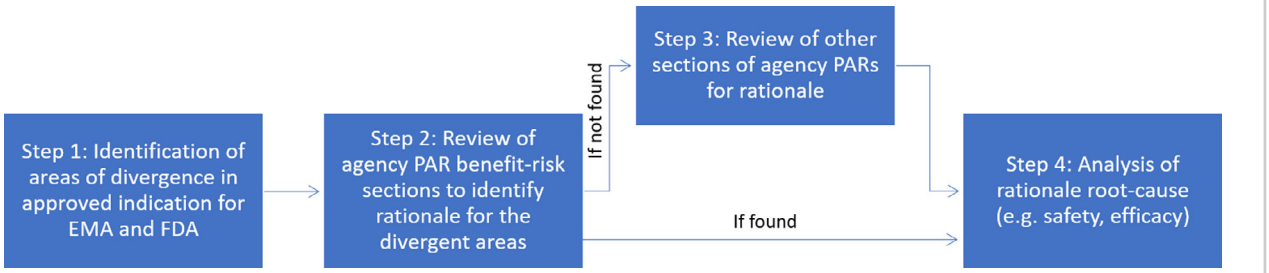

Figure 1. Data analysis process. EMA = European Medicines Agency; FDA = US Food and Drug Administration; PAR = public assessment report.

risk section by the EMA and 9 of 15 by the FDA). For the other divergences, the FDA had documented 4 in another section of the PAR, such as the labeling section or the advisory committee meeting section, whereas for the EMA, 2 were documented elsewhere in the PAR, namely, the clinical efficacy section, and the remainder were not found in the PAR. Three differences were found for the EMA and 2 for the FDA that were not documented at all in the PAR (different products for each agency).

Two compounds had no documentation in the benefit-risk section for both the EMA and the FDA: cangrelor (documented elsewhere in the clinical efficacy section by the EMA and not documented by the FDA) and alectinib hydrochloride (not documented by the EMA and documented elsewhere by the FDA). For these 2 products, alectinib hydrochloride was approved by the EMA as conditional and received accelerated approval from the FDA as well as an orphan designation, whereas cangrelor initially received a complete response letter from the FDA because of lack of clinical relevance perceived by the FDA for one of the studies included.

Part 2: Rationale for Differences in EMA and FDA Approved Indications

Finally, the rationale for a different indication approved for each NAS was analyzed for the 9 NASs approved by the EMA and the FDA based on the total number of 12 divergences noted for the EMA for submitted versus approved indications that were documented in the PAR and 13 for the FDA. We observed that the difference between the 2 agencies was largely attributable to differences related to the efficacy assessment and hence the perceived benefits of the medicine (Figure 3). For the EMA, the efficacy was the rationale for a difference in 10 of 12 cases, whereas it was tolerability for only 2 of 12 cases for which there was documentation. For the FDA, efficacy or efficacy and tolerability were the rationales for a divergence in 10 of 13 cases in which there was documentation, whereas only 3 of 13 were related to tolerability alone.

DISCUSSION

We found a high concordance in the decision making between the EMA and the FDA in a recent study[4] in which we examined in detail the characteristics of a 3-year cohort of submissions. Divergent authorization decisions can occur particularly for compounds with early or limited clinical data and for relatively hard-to-treat medical conditions (eg, for orphan drugs) as well as for complex medicines such as biologics. In our prior study, we found that nonapproval of a NAS by one of the agencies, in general, was not a result of rejection by the other; rather, the most common reason for divergence was that the product had not been submitted to both agencies. This observation is consistent with other recent studies that compared EMA and FDA decision making[5] and indicates an evolution compared with a previous analysis[13] that found that between 1995 and 2009, the European Union rejected 31 applications that the United States approved, whereas the United States rejected 24 applications that the European Union approved. We propose that the increased observed level of alignment in recent years between the 2 regulators suggests that engagement processes (eg, providing parallel scientific advice[14–16]), formalization and standardization of benefit risk frameworks, and collaboration on regulatory science have had a positive

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Table II. Differences in approved indication between the EMA and the FDA (based on same indication submitted to each agency), the rationale for the change(s) made by each agency, and the location of the documentation in agency documents.

NAS	Difference in indication approved by EMA vs FDA	EMA			FDA		
		Change made by agency for approved indication compared with submitted	Rationale documented (yes/no) and type of rationale	Where found in PAR*	Change made by agency for approved indication compared with submitted	Rationale documented (yes/no) and type of criteria	Location in PAR
Alectinib hydrochloride	Locally advanced	Partially deleted (locally)	Not found	Not found	Deleted	Yes - tolerability and (lack of) efficacy	BR section (CR section)
	Metastatic	Deleted	Not found	Not found	No change - phrase retained	Yes - efficacy	BR section (SR section)
	Who have progressed with or are intolerant of crizotinib	Modified to previously treated with crizotinib	Yes - efficacy	BR section	No change - phrase retained	Yes - efficacy	Labeling (SR section)
Alirocumab	Nonfamilial or mixed dyslipidemia	No change - phrase retained	Yes - efficacy	BR section	Deleted	Yes - efficacy	Advisory committee meeting (CR section)
	In patients who are statin intolerant or for whom a statin is contraindicated	No change - phrase retained	Yes - efficacy	BR section	Deleted	Yes - tolerability and efficacy	BR section (CR section)

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Table II. (*continued*)

NAS	Difference in indication approved by EMA vs FDA	EMA			FDA		
		Change made by agency for approved indication compared with submitted	Rationale documented (yes/no) and type of rationale	Where found in PAR*	Change made by agency for approved indication compared with submitted	Rationale documented (yes/no) and type of criteria	Location in PAR
Cangrelor	Coadministered with acetylsalicylic acid	No change - phrase retained	Yes - Efficacy	Clinical efficacy section	Deleted	Not found	Not found
	Reduction of thrombotic cardiovascular events	No change - phrase retained	Yes - Efficacy	BR section	Deleted	Not found	Not found
	And are not being given a glycoprotein IIb/IIIa inhibitor	Not added	Yes - Efficacy	Clinical efficacy section	Added	Y - Efficacy	Labeling (SR section)
Evolocumab	Atherosclerotic cardiovascular disease	Not added	Yes - tolerability and efficacy	BR section	Added	Yes - tolerability and efficacy	BR section (CR section)
	This application only includes a 420-mg once monthly dosing regimen for the homozygous familial hypercholesterolemia indication	Not added	Yes - efficacy	BR section	Added	Yes - tolerability	BR section (CR and SR sections)
Isavuconazole	For whom amphotericin B is inappropriate	Added	Yes - efficacy	BR section	Not added	Yes - (lack of) efficacy	Review of efficacy section (CR section)

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Table II. (*continued*)

NAS	Difference in indication approved by EMA vs FDA	EMA			FDA		
		Change made by agency for approved indication compared with submitted	Rationale documented (yes/no) and type of rationale	Where found in PAR*	Change made by agency for approved indication compared with submitted	Rationale documented (yes/no) and type of criteria	Location in PAR
Olaratumab	Histologic subtype for which an anthracycline-containing regimen is appropriate	Not added	Yes - tolerability and efficacy	BR section	Added	Yes - tolerability	BR section (CR section)
Ramucirumab	Combination with paclitaxel	Added	Yes - efficacy	BR section	Not added	Yes - (lack of) efficacy	BR section (CR section)
Sofosbuvir-velpatasvir	Genotypes 1, 2, 3, 4, 5, or 6: without cirrhosis or with compensated cirrhosis and with decompensated cirrhosis for use in combination with ribavirin	Not added	Not found	Not found	Added	Yes - tolerability	BR section (CR section)
Talimogene laher-parepvec	Regionally or distantly metastatic	Modified to regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung, or other visceral disease	Yes - efficacy	BR section	Deleted	Yes - efficacy	BR section (CR section)

BR = benefit-risk; CR = clinical review; EMA = European Medicines Agency; FDA = US Food and Drug Administration; NAS = new active substance; PAR = public assessment report; SR = summary review.

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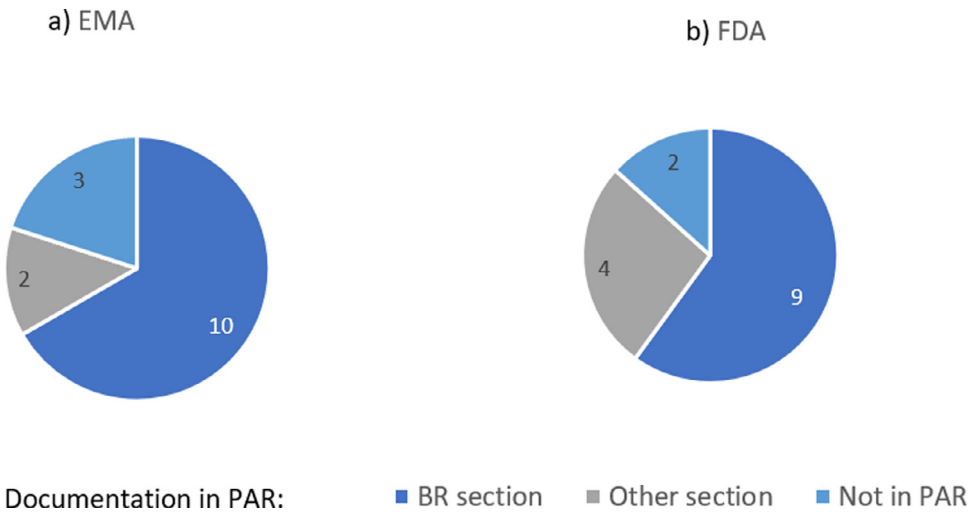

Figure 2. Number of differences in indication for the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) and the proportion documented in the agency public assessment reports (PARs). BR = benefit-risk.

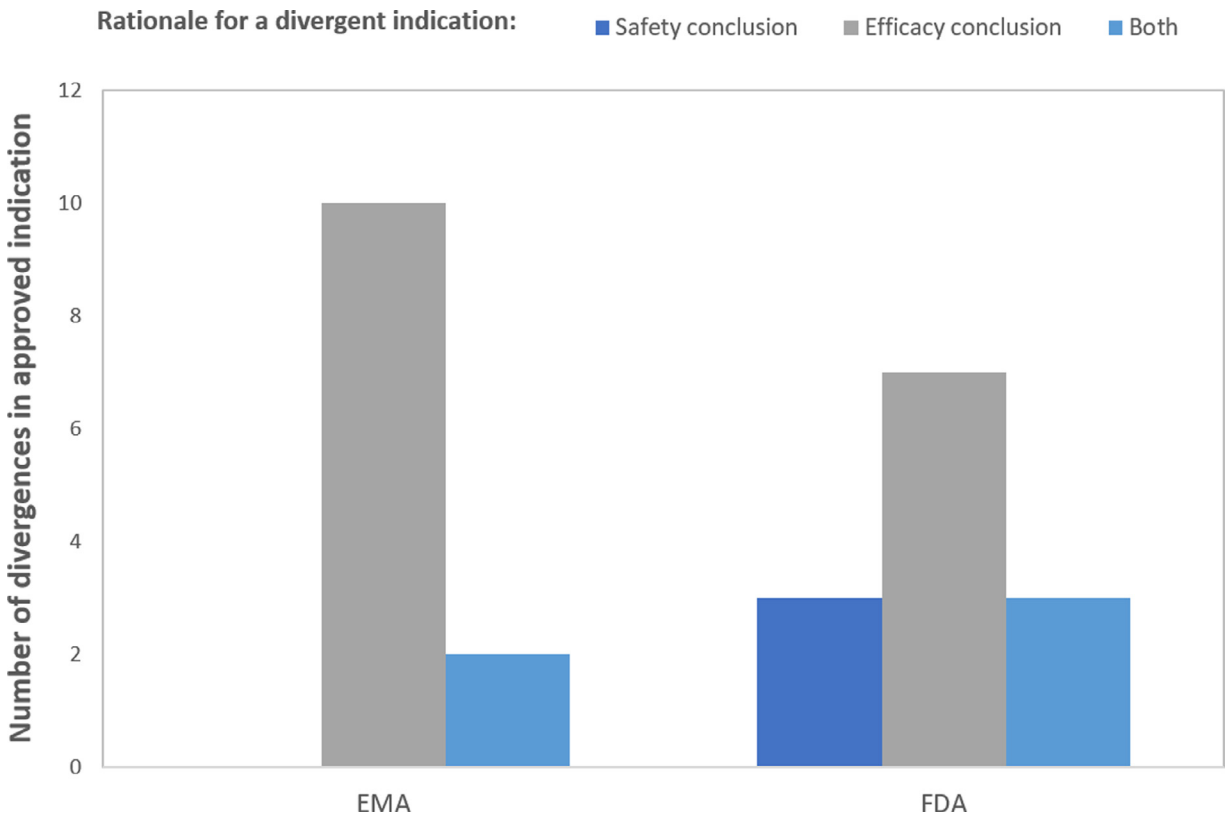

Figure 3. Classification of rationale for a different indication approved compared with submitted for new active substances approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) based on documentation in public assessment reports.

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impact on the regulatory decision-making process, and we hope that further improvements in these areas will facilitate even greater transparency and consistency in decision making.

This alignment is reflected in our prior study[4] in which we found a 73% concordance for decisions on indication where the same indication was submitted by the sponsor to both agencies. In that study, we noted that differences in regulatory decision making remain, as reflected in the approved indication; we identified 9 NASs (27%) in which divergent indications were approved despite the same indication being submitted by the sponsor to both the EMA and the FDA. The divergencies centred more on efficacy issues than tolerability concerns. We had not expected this finding at the onset of the study because tolerability issues often are scrutinized deeply by regulators and receive the greater attention in the public debate, but the finding is actually aligned with what has been observed by others.[17] Huckle[17] concluded that the causes for divergent opinions for marketing authorizations from the European Medicines Evaluation Agency (now the EMA) and the FDA included differences in opinion regarding the suitability of the development plan, encompassing such issues as the number of required pivotal studies, the use of placebo versus comparator studies, and the acceptability and applicability of foreign data as a key component of the submission. A number of reasons may exist for a difference in approved indication between the EMA and the FDA, particularly for drugs that are new in class or offer a new mechanism of action. Other factors may also contribute, such as differences in decision-making processes for the EMA vs the FDA, different criteria and frameworks for assessing benefits and risks, and evaluation of uncertainties.[18–20]

Different indications for the same drug suggest that each agency identified a population for which they believed the benefit-risk balance was most appropriate. Indeed, we found that the labels for 2 NASs (of 9) targeted different treatment-eligible patient groups. Even with off-label prescription being legally accepted in many jurisdictions, this may question why a drug for one indication should be made available on one side of a border and for a different indication on the other, especially in the situation of the European Union and the United States, where the agencies regulate for similar populations.

The present study is the first one undertaken to understand whether the justification for observed divergencies in approved indications could be found in the information provided by the EMA and the FDA in their respective PARs. Our analysis confirms that the rationale for the indication decisions (resulting in our observed divergences) was predominantly found in the benefit-risk section of the PAR (9 of 15 cases for the FDA and 10 of 15 for the EMA), as one would expect. If not found in the benefit-risk section, the rationale for these decisions was found in other PAR sections (2 of 15 for the EMA and 4 of 15 for the FDA), which complicates interpretation of the assessment if the PARs are being used by other agencies to inform their own regulatory decisions. In addition, in 2 instances for the FDA and 3 for the EMA, we found no information to justify the indication decision. Although this is a small number and constitutes only a few instances, it poses a problem regarding decision-making transparency and documentation that informs institutional memory.

Transparency is important from a public trust and confidence perspective, whereas robust documentation supporting institutional memory is key to an internal agency audit trail. In addition, the premise of regulatory reliance is that those removed from the initial decision-making process should be able to understand the underlying rationale for the regulatory outcome, especially when 2 stringent regulatory agencies, such as the EMA and the FDA, do not arrive at the same conclusion. For some reason(s), the various elements in the benefit-risk matrix have seemingly received different emphasis by different review teams.[21] That the public and other regulators are privy only to the end result without visibility or knowledge about the deliberations regarding the benefit-risk evaluation that leads up to the final result is unsatisfactory from a transparency and confidence perspective. This is particularly important for products for which decision making is a challenge,[22] as in this study in which alectinib hydrochloride was approved as conditional by the EMA but given accelerated approval by the FDA and cangrelor initially received a complete response letter from the FDA. Transparency on the factors behind the decision may become a challenge in cases in which the application of formal weightings to the various components of the benefit-risk matrix is not clearly documented.[23]

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We believe it is important for regulators to transparently and systematically document their decision-making processes and that there needs to be clarity particularly about how the benefit-risk balance was interpreted. These factors are especially important for innovative or technologically challenging products for which experience in evaluating similar products worldwide is limited.[22] This transparency is becoming increasingly important as agencies are striving to build effective and efficient regulatory processes by leveraging assessments by trusted reference agencies through approaches such as work sharing and reliance pathways. Transparent communication and documentation of the decisions in the PAR are central and should continue to evolve as a best practice that should be adopted by agencies worldwide.[7,23–25]

An enabling step toward this goal would be a harmonized PAR template, which in a structured fashion could help agencies communicate the rationale behind their benefit-risk and related decisions. Indeed, a standardized PAR template was among the top recommendations identified in a recent workshop hosted by the Centre for Innovation in Regulatory Science.[25] Clearly documenting the inclusion or exclusion criteria, and the weight assigned to the individual components in the benefit-risk matrix would promote the understanding for the basis of the regulatory decision making and hence build trust in the process and increase the scientific rigor of the decision-making process while minimizing biases and hence serve as clear documentation to inform institutional memory. To this end, Leong et al[24] and more recently Keyter et al,[23] building on the development of the Unified Methodologies for Benefit-Risk Assessment benefit-risk documentation framework,[26] proposed a standardized PAR template that encompassed key aspects of the decision-making process that document the benefit-risk outcome. A standardized PAR would be conducive to help stakeholders, such as maturing agencies, HTA bodies, and patients, to readily access and understand the benefits and risks associated with a medication and guide health care professionals to identify the most appropriate treatment for their patients.

Our analysis comprises 9 NASs and relies on data for first worldwide submissions that were collected through the end of 2017. Although almost 3 years from their first approvals, this cohort is important because many of these products are currently being submitted to agencies in maturing markets. Our observations are, therefore, of particular relevance to those agencies currently assessing these marketing authorization applications. Using this cohort, we found that there is room for improvement of the format and content of the PAR, the PAR was not used in all instances to document the rationale for modification in the approved indication, and the information that supported the decision about including or modifying an indication was not consistently documented in the same place in the PAR. Although both the EMA and the FDA have been working to enhance transparency and consistency in their decision-making processes and make improvements to their respective PAR and benefit-risk section in an effort to increase transparency,[27,28] this study suggests that there remains opportunity for improvement. Whether the recently implemented refinements in the respective approaches to documentation of benefit-risk assessment (eg, EMA effects table and FDA benefit-risk summary introduced by agencies in 2015) has resulted in greater transparency in the communication of agency decisions should be investigated with a recent cohort of approvals.

CONCLUSION

Our study found some inconsistencies in the how, where, and whether regulatory decision making on approved indications is documented by the FDA and the EMA. We believe that a consistent and a more unified, systematic, and standardized approach to benefit-risk evaluation and communication by agencies in their PARs can better explain their regulatory decision making in a transparent fashion, especially when regulators arrive at divergent conclusions on the same dossier. Such consistent approaches to decision documentation would also enhance the agencies' institutional memory. Transparency on the scientific rationale underpinning regulatory decisions is important to all stakeholders, including regulatory agencies, HTA bodies, and the patient for whom the medication is intended.

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manuscript. Thomas C. Kühler designed the study, analyzed the data, and wrote the manuscript; Magda Bujar designed the study, collected and analyzed the data, and wrote the manuscript; Neil McAuslane designed the study, collected and analyzed the data, and wrote the manuscript; Lawrence Liberti designed the study, analyzed the data, and wrote the manuscript; and Sara Ferragu analyzed the data and wrote the manuscript.

CONFLICTS OF INTEREST

Thomas C. Kühler and Sara Ferragu hold positions within the pharmaceutical sector but have not received any grants, honoraria, or other compensations to author this article. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2021.03.010.

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