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Comparative analysis of the information reported on labels of medicinal products containing new active substances between Europe and the USA

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Abstract

Introduction. Although notable efforts have been made to harmonise regulatory processes for the approval of new therapeutic drugs by the competent authorities, some discrepancies concerning risk-benefit assessments and regulatory actions remain.

Methods. This analysis compared the approaches of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in the approval of new active substances and identified potential clinical implications associated with these differences in "Indication", "Contraindications" and "Posology and administration of drugs" sections of drug summary of products characteristics (SmPC).

Results. The overall analysis showed major differences in 63.9% for the indications, in 75% for contraindications and in 13.9% for posology. Considering the more represented therapeutic areas (cancer and haematology/haemostaseology drugs), the percentage of major differences for the indications was 70% in cancer area and 50% in haematology/haemostaseology area. For contraindications major differences were observed in 90% of cancer drugs, and 60% in haematology/haemostaseology drugs.

Discussion. Our findings highlight the need of further efforts on harmonizing decision making driven by scientific data between regulatory authorities in the interest of patients in a public health perspective.

Key words

- drug approval
- drug evaluation
- indications
- contraindications
- posology

INTRODUCTION

The approval process of new therapeutic drugs is complex, and highly regulated. It comprises a series of well-defined and sequential phases, ranging from preclinical and clinical development to registration and marketing authorisation. Drug regulatory authorities, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), are responsible for overseeing both the approval and post-marketing monitoring of medicinal products. They ensure the approval of high-quality, safe, and effective drugs to enable timely patient access to new medicines for the benefit of patients, using a wide range of regulatory mechanisms [1].

Over the past two decades, notable efforts have been made to harmonise regulatory processes, contributing to the globalisation of clinical trials through the adoption of shared standards and the development of common frameworks for evaluating the benefit-risk profile of medicinal products. As a result, the EMA and the FDA now assess largely overlapping datasets in most cases [2-5]. Nevertheless, despite progress toward aligning standards and requirements, some discrepancies concerning risk-benefit assessments and regulatory actions remain [6, 7]. Some studies have investigated these divergences, showing that differences in approved therapeutic indications between authorities of Europe and USA occur in more than 50% of cases [8-10], with clinically relevant discrepancies in about 10% of cases [10]. In assessing approved indications, differences between EMA and FDA, especially in the identified targeted population by age (e.g., inclusion or not of paediatric patients), presence of specific genetic or non-genetic mutations or biomarkers or stage of disease (e.g., first line of therapy, refractory, relapse), were found. Such divergences may have important implications for patients' access to appropriate therapeutic options and for clinical decision-making by healthcare professionals.

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Previous studies focused mainly on differences in the approved indications of use of anti-cancer medicinal products not considering potentially divergences in "Contraindications" and "Posology and administration of drugs" sections of drug labels.

The aims of this study were to compare the approaches of the two drug regulatory authorities (EMA and FDA) in the evaluation and approval of new active substances recommended by EMA in 2024 [11] for a European Union (EU)-wide marketing authorisation and to identify potential clinical implications associated with these differences.

METHODS

In 2024, EMA recommended 114 human medicines for marketing authorization [11]. In our analysis only the active substances (biosimilars and generics were excluded) recommended for marketing authorization in the EU in 2024 [11] and authorized by EMA in the same year and for which a label was available. To collect data about the authorised medicinal products, EMA online resources were checked at the webpage https://www.ema.europa.eu/en/medicines/download-medicine-data. A total of 46 medicinal products has been identified from EMA report [11]; of these, ten products were excluded: three vaccines, two diagnostic agents, and five not approved by FDA. For the remaining 36 products, we retrieved the "Annex I – Summary of Product Characteristics" (SmPC) and FDA Prescribing Information (label). The selection and identification of new active substances included in the analysis are reported in *Figure 1*.

All identified labels were extracted, tabulated, and individually cross-checked with the FDA repository of approved drugs consulting the webpage https://nctr-crs.fda.gov/fdalabel/ui/search. Then, the information reported in the "Annex 1 – SmPC", available from https://www.ema.europa.eu/en/medicines/human/EPAR/, was compared with the information specified in Section 1 (indications and usage) of the FDA label.

Our comparative analysis considered three specific domains: "Indications", "Contraindications", and "Posology". For the indications, Section "4.1 of Therapeutic indications" of the Annex 1 – SmPC and Section "1 Indications and usage" of the FDA label were compared. For the contraindications, Section "4.3 Contraindications" of the Annex 1 – SmPC and Section "4 Contraindications" of the FDA label were compared. Finally, for the posology, Section "4.2 Posology and method of administration" of the Annex 1 – SmPC and Section "2 Dosage and administration" of the FDA label were compared.

To standardise the comparative analysis a set of indicators have been identified for the analysed domain as follows:

- *indications*: treated disease(s) including stage or severity of disease, Type of therapy (e.g., prophylactic *vs* on-demand therapy; monotherapy *vs* combination with other drugs, limitations of use), eligible patients (characteristics of target population);
- *contraindications*: population at risk (e.g., pregnancy and breastfeeding), clinical conditions, comorbidities, and concomitant therapies;
- *posology*: standard dose for the target population, starting and maintenance doses (when provided), dosing frequency and treatment duration (when applicable).

In our analysis, minor and major differences were defined *a priori*. A major difference between EMA and FDA was defined as any relevant divergence involving

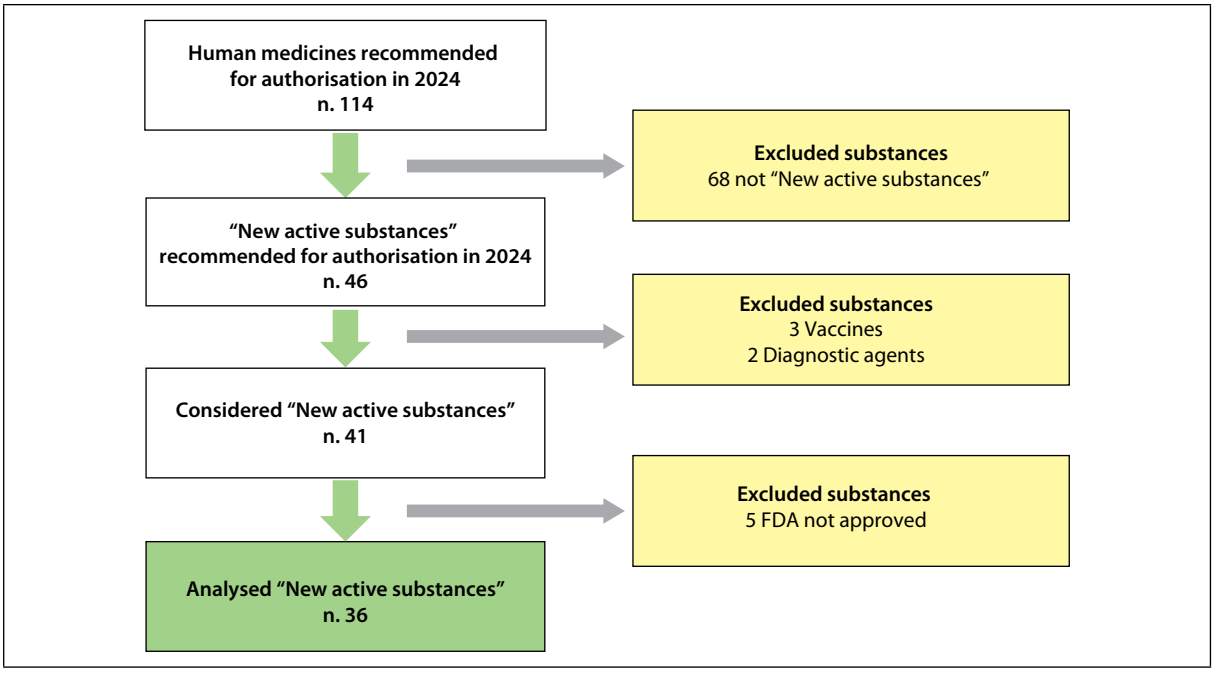

Figure 1
Flowchart of the selection and identification of new active substances.

the target population (e.g., age, gender, weight, etc.) and/or the indications (e.g., type of disease, stage of disease, line of therapy, biomarkers, etc.), contraindications (e.g., reported known *vs* not reported hypersensitivity to the active substance or to any of the excipients) or posology (e.g., differences in dose, frequency or treatment duration). For example, a major difference resulted in the rigorous application of inclusion criteria defined in the pre-registration studies from one agency, while the other restricted/broadened age, gender, or biomarker characteristics. On the other hand, a minor difference was defined as a wording variation that does not alter the meaning of the text or does not introduce any major divergence regarding the indications, contraindications, or posology of the medicinal product.

A panel of three assessors (RDC, II, and GM) independently reviewed the wording and content of the selected sections to determine their consistency, define discrepancies and evaluate the clinical relevance of any differences. In case of disagreement between the assessors, FMI was designated to function as a tiebreaker, although no situation required this intervention. Agreement for "major" and "minor" categories among three assessors was measured by the Fleiss's kappa index with 95% confidence interval (CI). Analysis was performed with the Statistical Software IBM® SPSS® Statistics 29.0.1.0 (https://www.ibm.com/products/spss-statistics).

Given the qualitative nature of the study, we present the results using descriptive statistics.

RESULTS

A total of 36 new drugs recommended for approval by the EMA in 2024 [11] were included in the study. Anti-cancer drugs and haematology/haemostaseology drugs were the dominant therapeutic areas, accounting for 55.5% of the total recommendations for approval (*Table S1 available online as Supplementary Material*). For the above-mentioned medicinal products, indications, contraindications, and posology have been compared between the two agencies.

The overall agreement for all raters on difference grades (major *vs* minor) was strong (κ, 0.889; 95% CI, 0.780-0.998; p<0.001). For "Indications" domain the agreement was high (κ, 0.766; 95% CI, 0.578-0.955; p<0.001) while for "Contraindications" and "Posology" domains was almost perfect (κ, 0.952; 95% CI, 0.763-1.140; p<0.001 and κ, 0.860; 95% CI, 0.672-1.049; p<0.001, respectively) [12].

With regard to the indications, major differences were shown in 23 SmPC. The differences concerned the treated disease in the 52.2%, the eligible patients in 26%, and the type of therapy in 21.8%. For example, we considered as major differences: i) toripalimab-tpzi has been authorised for two clinical conditions by EMA, while for only one by FDA; ii) iptacopan has been authorised for the treatment of subjects with paroxysmal nocturnal haemoglobinuria (PNH) and primary immunoglobulin A nephropathy by FDA and only for PNH by EMA; iii) EMA is more restrictive than FDA in indications for use of lecanemab and mirvetuximab soravtansine excluding apolipoprotein E ε4 (ApoE ε4) homozygotes and non-serous cancers, respectively. Examples of minor differences were: i) lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations; and ii) dasiglucagon for treatment of severe hypoglycaemia in adults, adolescents, and children aged 6 years and over with diabetes mellitus. For more details see *Table S1 available online as Supplementary Material*.

Analysing contraindications, major differences were shown in 75% of drugs (n=27). Among major differences, the most frequent (21 of 27 SmPC) was the presence of a statement in the EMA in section 4.3 of the SmPC about "hypersensitivity to the active substance or to any of the excipients" with respect to the "None" statement reported in FDA SmPC. Other major differences include: i) the contraindication of insulinoma in the FDA SmPC for dasiglucagon; ii) the exclusion of patients who are not currently vaccinated against Neisseria meningitidis in EMA SmPC for crovalimab and danicopan; iii) restriction for lecanemab in EMA SmPC in case of prior haemorrhagic events or ongoing anticoagulant therapy. For more details see *Table S1 available online as Supplementary Material*.

Regarding the reported posology, major differences were shown in 13.9% of drugs (n=5). No specifications regarding the recurrent nasopharyngeal carcinoma were provided for toripalimab-tpzi in the EMA SmPC while in the FDA SmPC is included a recommended dosage for this stage of the disease. For aprocitentan only EMA SmPC reported an increase of dose for patients tolerating the recommended dose and in need of tighter blood pressure control; moreover, a dose limit (30 grams per 2 weeks or 60 grams per month) for delgocitinib is reported only in the FDA SmPC. The FDA indicates that after 18 months of treatment with lecanemab a transition to the maintenance dosing regimen may be considered. For more details see *Table S1 available online as Supplementary Material*.

In *Table 1* the differences by therapeutic area are reported. Considering only the areas with ten drugs (cancer and haematology/haemostaseology drugs), the percentage of major differences for the indications was 70% in cancer area and 50% in haematology/haemostaseology area. For contraindications major differences were observed in 90% of cancer drugs, and 60% in haematology/haemostaseology drugs. Finally, one major difference in the posology was found in cancer drugs and none in haematology/haemostaseology drugs.

DISCUSSION

The decision-making processes within competent authorities (agencies) are designed to ensure that patients receive the greatest possible benefit, balanced against the risks, from the use of medicinal products. In this Policy Review, the divergences between EMA and FDA SmPC of 36 new active substances have been evaluated.

Major differences in the indications were found in 63.9% of the analysed drugs. The differences concerned the treatable disease in more than half of drugs. For example, toripalimab-tpzi (cancer), iptacopan (haematology), and nemolizumab (dermatology) have been authorised for a different number of clinical conditions

Table 1
Comparison between the indications, contraindications, and posology in the European Medicines Agency (EMA) summary of products characteristics and in the US Food and Drug Administration (FDA) labels stratified by therapeutic area

	Number of medicinal products (%)		
	Indications	**Contraindications**	**Posology**
Overall	**36 (100)**	**36 (100)**	**36 (100)**
Minor differences	13 (36.1)	9 (25)	31 (86.1)
Major differences	23 (63.9)	27 (75)	5 (13.9)
Haematology/haemostaseology	**10 (100)**	**10 (100)**	**10 (100)**
Minor differences	5 (50)	4 (40)	10 (100)
Major differences	5 (50)	6 (60)	0
Cancer	**10 (100)**	**9 (100)**	**9 (100)**
Minor differences	3 (30)	1 (10)	9 (90)
Major differences	7 (70)	9 (90)	1 (10)
Cardiovascular	**3 (100)**	**3 (100)**	**3 (100)**
Minor differences	2 (66.7)	0	2 (66.7)
Major differences	1 (33.3)	3 (100)	1 (33.3)
Neurology	**3 (100)**	**3 (100)**	**3 (100)**
Minor differences	1 (33.3)	0	2 (66.7)
Major differences	2 (66.7)	3 (100)	1 (33.3)
Gastroenterology/hepatology	**2 (100)**	**2 (100)**	**2 (100)**
Minor differences	0	0	2 (100)
Major differences	2 (100)	2 (100)	0
Uro-nephrology	**2 (100)**	**2 (100)**	**2 (100)**
Minor differences	0	2 (100)	2 (100)
Major differences	2 (100)	0	0
Dermatology	**2 (100)**	**2 (100)**	**2 (100)**
Minor differences	0	1 (50)	0
Major differences	2 (100)	1 (50)	2 (100)
Infections	**1 (100)**	**1 (100)**	**1 (100)**
Minor differences	0	1 (100)	0
Major differences	1 (100)	0	1 (100)
Endocrinology	**1 (100)**	**1 (100)**	**1 (100)**
Minor differences	1 (100)	0	1 (100)
Major differences	0	1 (100)	0
Pneumology/allergology	**1 (100)**	**1 (100)**	**1 (100)**
Minor differences	0	0	1 (100)
Major differences	1 (100)	1 (100)	0
Immunology/rheumatology/transplantation	**1 (100)**	**1 (100)**	**1 (100)**
Minor differences	1 (100)	0	1 (100)
Major differences	0	1 (100)	0

by the two regulatory agencies excluding a patient's subgroup from the treatment. Moreover, unlike EMA, FDA states clearly that the use of elafibranor and seladelpar – indicated for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA – is not recommended in patients who have

or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

A higher percentage of major differences (75%) was found for the reported contraindications especially due to the presence of a statement in the EMA SmPC about hypersensitivity to the active substance or any of the excipients that was absent in the FDA SmPC. This divergence is related to the FDA recommendations to report only known hazards and not theoretical possibilities [13] and does not have any clinical impact or imply any real risk for patients. On the other hand, some differences on this domain could lead medical decisions. For example, only in the EMA label is clearly specified that treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy. This statement has an impact on patients' management considering that patients with dementia due to Alzheimer's disease are often elderly with concomitant cardiovascular diseases requiring anticoagulation therapy.

As expected, a lower percentage (13.9%) was found for the posology considering that the optimal dose and regimen are defined in the pre-registrative clinical trials and adopted by the authorities for the clinical practice.

A recent article by Pierini *et al*. [8] compared 162 therapeutic indications of 80 medicinal products for solid tumours and blood cancers authorised by EMA between 2015 and 2022, with the corresponding labels approved by FDA. The authors reported clinically relevant discrepancies for about 52% of the evaluated indications [8]. A previous evaluation of oncology drugs approved by EMA between 1995 and 2008 reported 47% discrepancies in therapeutic indications between EMA and FDA that in 10% of the cases were considered clinically relevant [10]. These above-mentioned cases can have an impact on the clinical practice by excluding certain groups of patients (different place in therapy for the same anticancer drug and/or limitation to a specific subgroup).

More recently, a lower percentage difference in indications (about 20%) of new drug marketing applications for a new active substances, chemical entities, or therapeutic biologic products submitted to FDA and EMA in the period 2014-2016 was found [14]. Concerning contraindications, Alshammari TM *et al.* [15] found differences in the drug labels information in almost 70% of 100 drugs approved in the USA, the UK and Canada.

Although our findings are largely consistent with those reported in the literature [8-10, 14, 15], they should be interpreted in light of several limitations. First, we assumed that both agencies received a non-dissimilar Common Technical Document (CTD), which might not be always the case. For instance, the two agencies might have evaluated data at different timelines of the trials, such as different interim or final analyses of the same trial. Moreover, differences may be amplified by a different propensity of the two agencies to adhere to the population included in the pre-registrative studies when drafting the label and by the possibility to withdraw the approved indications in absence of a proven clinical benefit. Finally, the agency that approves the drug after the other one tends to be more restrictive in wording of the indications. Second, for most of the therapeutic areas, it was not possible to derive specific conclusions owing to the low number of analysed medicinal products (three or less products). Third, this is a single-year analysis (year 2024). In light of these limitations, the results may not reflect multi-year patterns particularly considering that product labels may be updated over time in response to emerging scientific evidence. To assess whether the observed differences between the two agencies persist over time, a three-year follow-up analysis could provide additional and valuable insights.

The main differences between the FDA and EMA drug approval processes reflected their health policies, regulatory structure, and review timelines. The FDA handles the US market with a single, faster approval pathway [16]. In contrast, EMA coordinates multiple national agencies for EU market approval, which could slower the authorization process and requires more comprehensive data for standard reviews. The agencies may reach different conclusions about a drug strength of evidence because they emphasize different findings from pre-registrative studies, leading to variations in approved indications or, in rare cases, despite a differing view on the overall benefit-risk assessment. In some cases, such differences could significantly affect patients access to relevant therapeutic options that could raise the uncertainty among patients and healthcare professional about the different statements of regulatory agencies.

In conclusion, a non-negligible number of differences were found in the labels of EMA and FDA licensed products, except for the posology domain. Further efforts on harmonizing decision making driven by scientific data between regulatory systems are needed for the patient benefit and public health.

Authors' contributions

GM, RDC: designed the study; AA, MC: identified and collected the information from EMA and FDA repository; GM, II, RDC: analysed the information from EMA and FDA repository; GM: drafted the first version of the manuscript; RDC, II: reviewed the manuscript and contributed to its content development; GM, FMI, RDC: supervised the overall development of the manuscript. All Authors read and approved the final version of the manuscript.

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