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A COMPARATIVE REVIEW OF DRUG REGISTRATION AND REGULATORY REQUIREMENTS IN NORTH AMERICA AND EUROPE

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ABSTRACT

Regulatory harmonization has improved consistency in pharmaceutical development and global submissions; however, important differences remain between the regulatory systems of the United States and European Union, influencing development strategies, submission requirements, approval pathways, and post-approval management. This study aimed to comparatively evaluate regulatory requirements and strategic considerations for medicinal product registration in the United States and European Union, with emphasis on marketing authorization, expedited pathways, pediatric development, orphan-drug requirements, risk management, post-approval changes, and pharmacovigilance. A qualitative documentary comparison was performed using regulatory guidelines, assessment reports, approval documents, and scientific literature. Lemborexant, Truxima (rituximab), and Luxturna (voretigeneneparvovec) represented small-molecule, biosimilar, and gene-therapy products, respectively. The Common Technical Document and electronic Common Technical Document have facilitated preparation of a common scientific dossier and reduced regulatory duplication; however, significant regional differences remain in administrative procedures, pediatric requirements, risk management, evidentiary expectations, post-approval changes, and pharmacovigilance. Successful global registration

therefore requires a harmonized scientific strategy combined with appropriate regional adaptation. Early regulatory interaction, coordinated pediatric planning, product-specific regulatory strategies, and proactive lifecycle management may improve submission readiness, minimize regulatory duplication, and support efficient medicinal product development and registration across both regions.

KEYWORDS: Drug Registration; Regulatory Harmonization; Pharmaceutical Regulation; Marketing Authorization; Pharmacovigilance; Lifecycle Management.

1. MATERIALS AND METHODS

A qualitative documentary comparative study was conducted to compare medicinal product regulatory requirements in the United States and European Union. Publicly available regulatory documents from the United States Food and Drug Administration (FDA), European Medicines Agency (EMA), International Council for Harmonisation (ICH) guidelines, applicable legislation, clinical-trial information, product-specific regulatory documents, and selected scientific literature were reviewed. The Common Technical Document (CTD) and electronic Common Technical Document (eCTD) frameworks were considered as the principal harmonized structures for regulatory submissions[1–4,13] The comparison focused on major regulatory domains across the medicinal product lifecycle, including clinical-trial authorization, marketing authorization, core regulatory dossiers, expedited pathways, pediatric development, orphan-drug requirements, risk management, post-approval changes, lifecycle management, and pharmacovigilance.[1–4,9–13]

Three medicinal products were purposively selected as representative examples: Lemborexant as a small-molecule medicinal product, Truxima (rituximab) as a biosimilar, and Luxturna (voretigeneneparvovec) as a gene-therapy product. Lemborexant was selected as a representative small-molecule product based on its FDA New Drug Application (NDA) approval documentation.[5] Truxima was selected as a representative biosimilar because it was authorized in the European Union through the biosimilar regulatory pathway, with Mab Thera (rituximab) as the reference medicinal product.[11,12,15] Luxturna was selected as a representative advanced therapy medicinal product and gene-therapy product because of its classification as an advanced therapy medicinal product and its orphan-medicine designation in the European Union. These products were selected to illustrate product-specific regulatory considerations and differences in regulatory requirements and were not intended to represent all approved medicinal products.[6–8,14]

Relevant information was extracted from FDA and EMA regulatory guidelines, assessment reports, approval documents, prescribing information[1–4,13], risk-management materials, clinical-trial databases, product-specific regulatory documents, and scientific literature. The extracted information was organized according to regulatory authority (FDA and EU/EMA), product type (small molecule, biosimilar, and gene therapy), regulatory domain, and lifecycle stage. A predefined comparative framework was used to evaluate regulatory convergence and divergence between the United States and European Union. The CTD structure, including its common Modules 2–5 and region-specific Module 1, was considered when comparing regulatory dossier requirements between the two jurisdictions.[1–4,10]

The comparative assessment included the following regulatory domains: clinical-trial authorization, marketing authorization, regulatory dossier requirements, expedited regulatory pathways, pediatric development, orphan-drug designation and requirements, risk-management strategies, post-approval changes and variations, lifecycle management, and pharmacovigilance. Regulatory terminology, pathway eligibility, and procedural requirements were interpreted according to the applicable jurisdiction, product type, and regulatory framework at the time of assessment. FDA expedited programs and European accelerated/PRIME and conditional authorization mechanisms were considered within their respective regulatory contexts. Similarly, pediatric regulatory requirements were assessed using the FDA's Pediatric Research Equity Act (PREA) framework and the EMA Paediatric Investigation Plan (PIP) framework. Orphan-drug requirements were evaluated using the applicable FDA and EMA frameworks.

Risk-management requirements were compared using the FDA Risk Evaluation and Mitigation Strategies (REMS) framework and the EMA Good Pharmacovigilance Practices (GVP) requirements for risk-management systems. Post-approval regulatory mechanisms were compared using FDA requirements for changes to approved applications and the European Union variation framework.[13,1] Pharmacovigilance systems were assessed using the FDA Adverse Event Reporting System (FAERS) and the European EudraVigilance system.

The same predefined regulatory domains and comparative approach were applied consistently to all three selected products to facilitate qualitative comparison and improve methodological reproducibility. Product-specific regulatory information was additionally assessed using the

FDA approval package for lemborexant and the EMA European Public Assessment Reports (EPARs) for Truxima and Luxturna.[11,12,15]

The study methodology comprised identification of relevant FDA, EMA, and ICH regulatory sources; screening and selection of applicable regulatory documents; purposive selection of representative medicinal products; extraction of information using predefined regulatory domains; organization of the extracted information according to regulatory authority, product type, and lifecycle stage; qualitative FDA–EU comparative assessment; identification of regulatory convergence and divergence; and assessment of implications for global regulatory strategy.[6–8,14]

No human participants, animals, patient-level data, biological specimens, or personally identifiable information were involved in this documentary study. Therefore, ethical approval was not required.

Study methodology flow chart

Identification of FDA, EMA and ICH regulatory sources

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Screening and selection of relevant regulatory documents

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Selection of representative medicinal products

(Lemborexant → Small molecule; Truxima → Biosimilar; Luxturna → Gene therapy)

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Extraction of information using predefined regulatory domains

↓

Organization according to regulatory authority, product type and lifecycle stage

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FDA–EU qualitative comparative assessment

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Identification of regulatory convergence and divergence

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Assessment of implications for global regulatory strategy

Table 1: Regulatory domains compared between the United States and European Union.

Regulatory domain	United States – FDA	European Union – EMA/EU
Clinical-trial authorization	Investigational New Drug application	Clinical Trials Information System
Marketing application	New Drug Application / Biologics License Application	Marketing Authorisation Application
Core regulatory dossier	Common Technical Document / electronic Common Technical Document	Common Technical Document / electronic Common Technical Document
Expedited pathways	Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review	PRIME, Accelerated Assessment, Conditional Marketing Authorisation
Pediatric development	Pediatric Research Equity Act, Pediatric Study Plan, Best Pharmaceuticals for Children Act	Paediatric Investigation Plan, Paediatric Committee
Risk management	Risk Evaluation and Mitigation Strategy	Risk Management Plan
Post-approval changes	Prior Approval Supplement, Changes Being Effected, annual reporting	Type IA, Type IB and Type II variations
Pharmacovigilance	FDA Adverse Event Reporting System	EudraVigilance

The comparative framework was applied consistently across all three selected products and regulatory domains. Regulatory terminology and pathway eligibility were interpreted according to the applicable jurisdiction, product type, and regulatory framework at the time of assessment. The methodology was designed to permit replication through the use of the same regulatory sources, predefined domains, product selection criteria, and qualitative comparison framework.

2. RESULTS

The comparison demonstrated substantial scientific convergence between the United States and European Union through International Council for Harmonisation principles and the Common Technical Document/electronic Common Technical Document framework However, significant procedural differences remained throughout the medicinal product lifecycle. The United States operates through a national regulatory authority, whereas the European Union functions through a regulatory network involving the European Medicines Agency, European Commission, and national competent authorities.[1–4,13]

Clinical development differed in the use of the Investigational New Drug pathway in the United States and Clinical Trials Information System in the European Union. Differences were also observed in chemistry, manufacturing and controls documentation, including the use of Drug Master Files in the United States and Active Substance Master Files in the European Union.

Both jurisdictions use the Common Technical Document and electronic Common Technical Document for regulatory submissions. However, the United States generally uses New Drug Applications or Biologics License Applications, whereas the European Union uses Marketing Authorisation Applications. European applications also include region-specific documents such as the Summary of Product Characteristics, package leaflet, and Risk Management Plan.[1–4,10]

Expedited pathways were available in both jurisdictions but were not directly equivalent. United States pathways include Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval, while European Union pathways include PRIME, Accelerated Assessment, and Conditional Marketing Authorisation. Differences were also identified in pediatric development, orphan-drug regulation, risk management, post-approval changes, and pharmacovigilance.

Table 2: Major regulatory differences between the United States and European Union.

Parameter	**United States – FDA**	**European Union – EMA/EU**
Clinical-trial pathway	Investigational New Drug application[3]	Clinical Trials Information System
Regulatory structure	National regulatory authority	European regulatory network
Marketing application	New Drug Application / Biologics License Application	Marketing Authorisation Application
Scientific assessment	FDA review teams	Committee for Medicinal Products for Human Use
Final authorization	FDA	European Commission
Standard review target	10 months	210 active assessment days
Pediatric framework	Pediatric Research Equity Act / Pediatric Study Plan	Paediatric Investigation Plan / Paediatric Committee
Risk management	Risk Evaluation and Mitigation Strategy	Risk Management Plan
Post-approval changes	Prior Approval Supplement / Changes Being Effected / annual reporting	Type IA / Type IB / Type II variations
Safety database	FDA Adverse Event Reporting[1]System	EudraVigilance

The case assessment showed that regulatory requirements also depend on product characteristics. Lemborexant illustrated considerations related to small-molecule review, labeling, and risk management. Truxima demonstrated the importance of biosimilar comparability and extrapolation, while Luxturna highlighted long-term safety monitoring and post-authorization follow-up.

Table 3: Product-specific regulatory observations.

Product	Product type	Principal regulatory consideration
Lemborexant	Small-molecule medicinal product	Scientific review, labeling, and risk management
Truxima (rituximab)	Biosimilar	Comparability, extrapolation, and interchangeability considerations
Luxturna (voretigeneneparvovec)	Gene therapy	Long-term safety monitoring and post-authorization follow-up

Overall, the findings demonstrate that harmonized technical standards facilitate a common global scientific dossier but do not eliminate region-specific regulatory requirements.

4. DISCUSSION

The findings indicate that International Council for Harmonisation has promoted regulatory convergence but has not produced complete procedural uniformity between the United States and European Union. The Common Technical Document/electronic Common Technical Document framework reduces duplication in scientific documentation, while differences in clinical-trial authorization, pediatric development, risk management, post-approval changes, and pharmacovigilance continue to require regional adaptation.[5]

The differences in clinical-trial and marketing authorization pathways emphasize the importance of early regulatory planning. Although both jurisdictions support multinational development, differences in documentation, regulatory interaction, institutional structure, and review procedures may affect global submission strategies.[11,12,15] Expedited pathways demonstrate similar regulatory objectives but different implementation. Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval in the United States are not directly equivalent to PRIME, Accelerated Assessment, and Conditional Marketing Authorisation in the European Union. Sponsors should therefore assess eligibility and evidence requirements independently in each jurisdiction.

Pediatric, orphan-drug, and risk-management requirements also require coordinated but region-specific planning. Pediatric Research Equity Act and Pediatric Study Plans in the United States differ from the Paediatric Investigation Plan system in the European Union. Similarly, Risk Evaluation and Mitigation Strategies and Risk Management Plans have comparable safety objectives but different structures and implementation requirements.

The case studies demonstrate that product modality is an important determinant of regulatory strategy. Small-molecule products may rely more extensively on a common development program, whereas biosimilars require careful assessment of comparability and extrapolation. Gene therapies may require greater emphasis on long-term safety monitoring and post-authorization evidence. The Luxturna European assessment, for example, includes 15-year follow-up of treated patients and a registry for long-term safety data. European Medicines Agency (EMA).[6–8,14]

Based on these findings, an Adaptive Global Submission Framework (AGSF) is proposed. The framework incorporates early interaction with United States and European regulatory authorities, coordinated pediatric planning, a common clinical, nonclinical, and quality core dossier with regional components, and proactive lifecycle management. This approach may improve submission readiness and reduce unnecessary duplication.

The study was limited by the inclusion of only three purposively selected products and reliance on publicly available regulatory information. Confidential sponsor agency interactions could not be assessed, while pricing, reimbursement, health technology assessment, and broader market-access considerations were outside the scope. Future research should evaluate larger product datasets using quantitative measures such as review timelines, approval outcomes, post-marketing commitments, and submission-related duplication.

5. CONCLUSION

The United States and European Union regulatory systems demonstrate substantial scientific convergence through International Council for Harmonisation principles and the Common Technical Document/electronic Common Technical Document framework, but important procedural differences remain. These differences are evident in clinical-trial authorization, marketing authorization, expedited pathways, pediatric development, risk management, post-approval changes, and pharmacovigilance.

The case studies further demonstrate that regulatory requirements vary according to product characteristics. Small-molecule medicines, biosimilars, and gene therapies may therefore require different approaches to evidence generation, comparability, risk management, and long-term safety monitoring.

Successful global registration requires a harmonized scientific development program combined with appropriate regional adaptation. The proposed Adaptive Global Submission Framework integrates early regulatory interaction, coordinated pediatric planning, a common core dossier, regional requirements, and proactive lifecycle management. This approach may improve regulatory preparedness, reduce unnecessary duplication, and support efficient global development and continued safety monitoring of medicinal products.

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