Evolving Global Regulatory Landscape for Approval of Biosimilars: Current Challenges and Future Considerations

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BACKGROUND AND OBJECTIVE

- Biosimilar development is essential to expand access to quality-assured, safe, and effective biologic medicines. While the latter is a shared objective by healthcare systems across the globe, regulatory challenges resulting from divergent regulatory requirements may complicate the biosimilar development pathway.
- This study aims to assess the degree of convergence or divergence of regulatory frameworks for biosimilar evaluation and licensing between jurisdictions across the world and identify the current regulatory and scientific challenges with regards to biosimilarity demonstration.

METHODOLOGY

- A structured literature review was carried out in scientific databases (PubMed, Embase, and Web of Science) and grey literature up to January 2023.
- Retrieved records were thematically categorized in a data extraction template using Microsoft Excel according to different general principles which are outlined in regulatory guidelines governing biosimilars: analytical, nonclinical, and clinical assessment.

RESULTS

Characteristics of included studies

From the literature search 121 were selected after title and abstract screening. A total of 84 articles were retrieved following the addition of other records through other sources as well (websites, organisations, snowballing).

Key findings

- Although the principle of biosimilarity demonstration is uniform and aligned among jurisdictions, up to date, a large variability exists in data requirements for biosimilar approval across the globe, particularly in minor jurisdictions.
- In this structured literature review, several challenges were identified with regards to the demonstration of biosimilarity and can be broadly categorized into: (i) overarching challenges including, the reference product selection, and analytical and PK/PD bridging studies, and organizational challenges (ii) challenges in analytical assessment, (iii) non-clinical evaluation including in vivo animal studies, and (iv) challenges in clinical evaluation including comparative clinical PK/PD studies, comparative clinical efficacy studies, and local clinical studies.

Reference product (RP) selection

- Difficulties in obtaining access and detailed information on the RP.
- Financial constraints due to the high costs of the RP.
- Lack of clarity in guidelines regarding the necessary number of RP batches required.

Analytican and/or PK/PD bridging studies

- Divergent requirements for the type and number of bridging studies required for the acceptability of a foreign-sourced RP.
- Lack of clarity in guidelines regarding the type and number of bridging studies required.
- Subject to significant development costs and ethical concerns (scientific value).

Organizational challenges

- Lack of capacity and resources of NRAs in understanding state-of-the-art technologies and methods.
- Lack of robust pharmacovigilance systems.
- Unsufficient reciprocal recognition and regulatory reliance among jurisdictions.

Analytical assessment

- Divergence in regulatory requirements regarding determining specifications and analytical methods.
- Limited availability and lack of transparency in reporting analytical data.
- Variability in reporting (critical) quality attributes in public assessment reports.

In vivo animal studies

- Low sensitivity (inter and-intra animal variability).
- Limited immunogenicity predictability.
- Lack of statistical power.
- Divergence in their requirement, with variations in the number of required studies where they are mandated.

Comparative clinical PK/PD studies

- Resource intensive development of PD biomarkers.
- Lack of harmonization across regulatory agencies regarding PK/PD endpoint parameters.

Comparative clinical efficacy (CCE) studies

- Less sensitivity and specificity in detecting or ruling out potential differences.
- Divergence across jurisdictions with regards to a tailored clinical development or waiving of CCE studies.

Local clinical studies

- Divergent requirements for mandating local clinical studies.
- Financial constraints and ethical concerns.

CONCLUSION

While biosimilar development is a global undertaking, this literature study shows that current biosimilar licensing pathways vary a lot, leading to inefficiencies that might complicate the global development of biosimilars. Optimizing and streamlining regulatory frameworks and data requirements, considering the extensive knowledge gained through advancements in analytical sciences and clinical experience with biosimilars, through dialogue and collaboration between regulators across jurisdictions, is crucial for reducing development costs and enhancing patient access to biologic and biosimilar medicines across the globe.