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Pharmacovigilance considerations for biologics and biosimilars

This article explores the various aspects of safety monitoring and risk management for biologics and biosimilar pharmaceutical products. Given the complexity of these products, robust pharmacovigilance (PV) strategies are crucial for ensuring patient safety.

The biopharmaceutical industry plays a crucial role in developing advanced therapies for various diseases. Biologics are derived from living organisms and offer advanced treatment options for various chronic and serious diseases. A biosimilar is highly similar to a corresponding approved reference biologic product. Biologics and biosimilars represent a remarkable innovation in medicine because they can target specific molecules in the body, offering highly targeted and personalized treatments. They often have fewer side effects and can be tailored to match natural substances in body, reducing the risk of rejection while enhancing compatibility. Biologics and biopharmaceuticals provide more effective treatments for a diverse range of diseases like cancer and autoimmune diseases.

This article discusses the unique challenges and regulatory requirements related to biologics and biosimilars, offering insights into the importance of pharmacovigilance for these innovative products. It also sheds light on how the PV strategy is different from generics and provides recommendations to improve patient safety.

What are biologics and biosimilars?

Biologics are therapeutic compounds derived from living organisms including humans, plants, animals and microorganisms. These are very large and complex molecules compared to conventional chemical drugs. While these may be composed of sugars, proteins, nucleic acids or combinations of these substances, they can also be living cells or tissues such as vaccines and blood components.

Top selling biologics as per a CRS Report include Humira (adalimumab), Rituxan (rituximab), Enbrel (etanercept), Herceptin (trastuzumab), Avastin (bevacizumab), Remicade (infliximab).

Biosimilars are highly similar compounds compared to their reference biologic products in structure and function with no clinically meaningful difference. Unlike a generic drug, which is an exact copy of a brand-name drug and once approved automatically interchangeable, biosimilars are not automatically interchangeable with the reference biologics. A biosimilar needs to be specifically approved by regulatory authorities as a substitute for its reference biologic. Biosimilars undergo comparative studies to demonstrate their similarity to their reference biologics.

Some of the FDA-approved biosimilar products include Byooviz (ranibizumab-nuna), Semglee (Insulin glargine-yfgn), Riabni (rituximab-arrx), and Hulio (adalimumab-fkjp).

Given the complexity of these molecules, they have high level of specificity and can interact more precisely with specific protein receptors or genes, with the ability to treat a diverse range of diseases including various malignancies, autoimmune diseases and rare genetic conditions.

Biologics and biosimilars require complex biotechnological manufacturing processes, special handling (such as refrigeration) and processing to avoid contamination by microbes or other unwanted substances. For these reasons, biologics often are referred to as specialty drugs and the cost of these drugs can be extremely high. Biosimilars provides more cost-effective alternative which creates opportunities for a wider range of patients to access innovative therapies, improving overall healthcare outcomes.

Regulatory guidelines for biologics and biosimilars:

While the regulatory guidelines for biologics and biosimilars vary by region, some general principles and key guidance remain the same for all major regulatory authorities. This typically covers various aspects of quality, safety, efficacy and manufacturing standards specific to biologics and biosimilars. For example, the manufacturing processes of biologics require regulatory approval, and any changes to these processes may call for new clinical trials. However, regulatory authorities have developed guidelines to allow companies to report process changes without duplicating clinical trials if they can demonstrate that the change does not impact the safety profile of the product.

Regulatory authorities have also outlined requirements for preclinical and clinical studies, comparability exercises for biosimilars, and safety and risk monitoring for post marketing surveillance.

Pharmacovigilance challenges:

There are unique challenges with safety and efficacy monitoring of biologics and biosimilars due to their complex structure and specifications with respect to manufacturing and administration.

Biologics are often indicated for patients with chronic disorders who are being treated with multiple drugs that can have an impact on accurate causality assessment.

Differences in batches of biologics can occur due to manufacturing variations, impacting the consistency of the biologics' safety profile.

These products trigger immune responses in the patients, which can impact the biologics' efficacy. Therefore, lack of efficacy-related events need to be evaluated carefully for accurate causality assessment.

Biosimilars are approved based on comparative data from their reference biologics, and require careful assessment for safety and efficacy for different indications, population, etc.

The safety profile of biologics will continue to evolve even after the clinical trials conclude and products are in market for approved indications. Long-term monitoring is crucial for assessing safety and efficacy.

Pharmacovigilance strategies for biologics and biosimilars:

Various strategies must be considered during the entire biologic and biosimilar value chain-from development to post-marketing-to address the associated PV challenges:

Thorough preclinical studies to assess potential toxicities, pharmacokinetics and pharmacodynamics.

Phase I to III clinical trials to evaluate safety and efficacy in humans with close monitoring of adverse events and immunogenicity risks and thorough investigation of any safety concerns.

Reporting and analyzing adverse events through **specialized PV programs for post-marketing surveillance**.

Periodic safety updates to regulatory agencies through regular safety reports summarizing adverse events and risk management activities.

Risk management plans, required by regulatory agencies to proactively monitor and mitigate known risks, may include actions such as:

- Restricted distribution of the medications to limited patient population.
- Patient registries to collect consistent data by using observational study models.
- Patient support programs (PSPs) tailored for healthcare benefits to patients as per their needs.
- Training healthcare providers (HCPs) for reporting uniform data about safety and efficacy of the medications.
- Effective risk and benefits communication to HCPs and patients for informed decision-making.

Follow-up studies for long term monitoring to assess rare or delayed adverse events (This may also include biomarker monitoring, which can help identify early signs of adverse events and provide an opportunity for timely intervention.)

Utilizing Data mining techniques and **real-world data for signal detection** to provide valuable insights into the long-term safety of these products in diverse patient populations, given the nature of underlying disorders and indications for these products.

Regular **labelling updates** to include new safety information as it becomes available.

Best practices in pharmacovigilance:

To enhance the effectiveness of pharmacovigilance for biologics and biosimilars, stakeholders should consider the following best practices:

Solicited reporting through patient support programs (PSPs) is an important strategy for comprehensive safety monitoring beyond what may be captured in clinical trials or spontaneous reporting systems.

Analyzing this solicited reporting data enables early detection of potential safety concerns and facilitating timely intervention.

PSPs can also offer educational resources and support services to patients, improving overall safety outcomes.

Additional risk management measures for biosimilars can address risks which may be different from those of the reference product; for example, a specific immunogenicity assessment, extrapolating the indications differently based on their respective evidence and ensuring clear and comprehensive labelling of potential risks.

Collaboration with expert panels arranged by regulatory agencies enable a review of safety data and provide recommendations on risk management strategies.

Information sharing between regulatory agencies, manufacturers, HCPs and patients help ensure ongoing safety.

Continuous education and training help ensure that personnel involved in PV receive ongoing education and training to stay updated on emerging safety concerns and regulatory requirements.

Future perspectives:

It is only a matter of time before AI will be able to create biologic models to create a new kind of therapy. Perhaps at the same time AI can model the projected safety profile, which could be later compared to safety actuals to see how close the AI was to real outcomes.

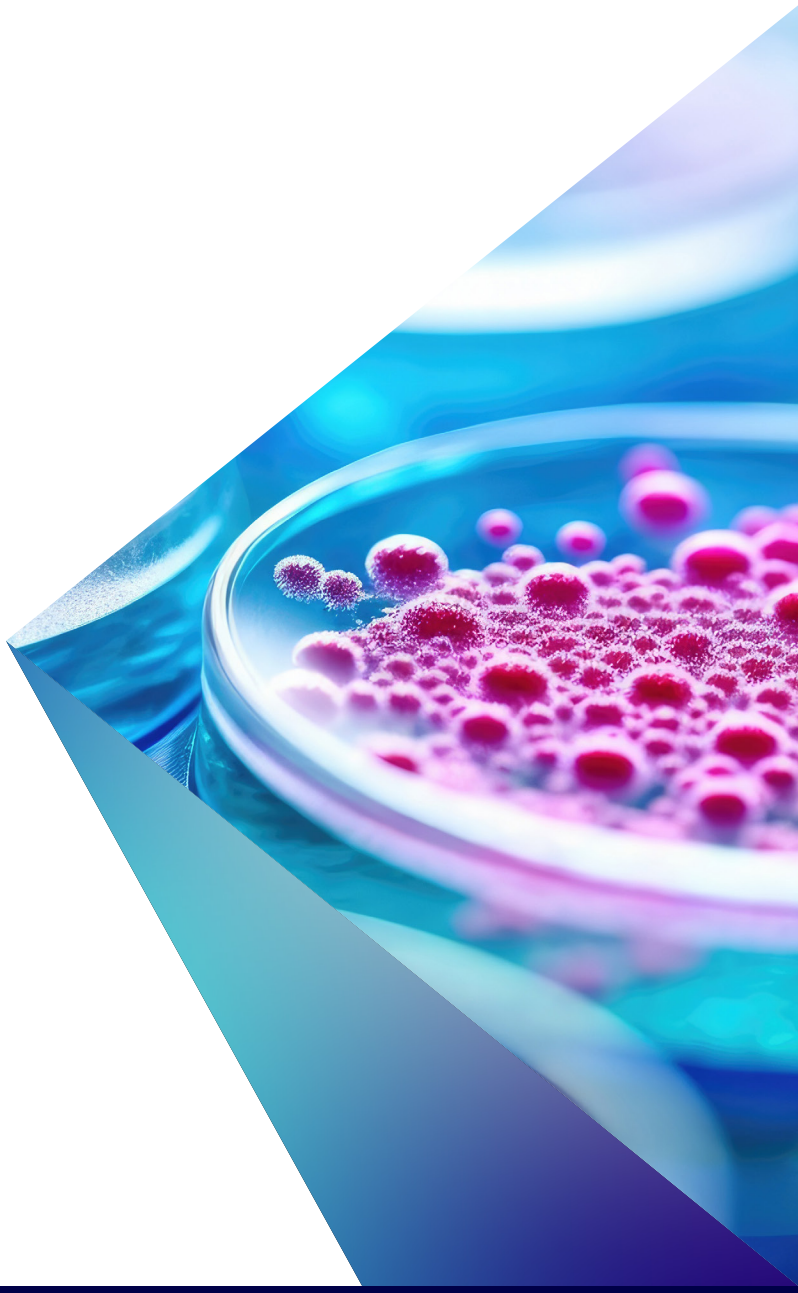
While AI is accelerating drug discovery, development and clinical trials, PV strategies for biologics and biosimilars also need to be constantly evolving. This continuous innovation is primarily driven by technology, changing regulatory requirements and emerging therapeutic innovations, including:

- Advanced surveillance methods leveraging data analytics, artificial intelligence and real-world evidence.
- New opportunities and challenges related to personalized medicine and precision therapies.
- Rapid growth of the biosimilars market with potential benefits of cost saving and expanded access to biologic therapies.
- Ongoing efforts to harmonize regulatory requirements and standards.

Conclusion:

As the landscape of biologic and biosimilar therapies evolves, it is important to be proactive with pharmacovigilance strategies for safeguarding patient health, ensuring regulatory compliance, maintaining public trust and driving continuous improvement in drug safety. Regulatory agencies, HCPs, industry stakeholders and patients all play crucial role in ensuring continued safety and efficacy of biologics and biosimilars.

By adapting emerging technologies and fostering adherence to best PV practices, biopharmaceuticals can ultimately improve the patient outcomes leading to more advancement in these therapies and increasing safety-and possibly even the scope of what these innovative treatment options can be applied to in future.



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