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# A Review on Pharmacovigilance of Biologics and Biosimilars: Emerging Trends and Clinical Research Perspectives (2021–2025)

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**Abstract:** *Substantial growth in biologics and biosimilars is occurring between 2021 and 2025 that has significantly changed the paradigm of therapeutics in the world, especially in oncology, autoimmune disease, and chronic inflammatory disorders. They have increasingly become taken up and have therefore increased the need to have strong pharmacovigilance systems that can handle the unique safety issues that emerge because of these complex biologic entities. In contrast to traditional, small-molecule therapeutics, biologics do not possess fixed molecular structure, production, and immunogenicity, and thus make post-marketing surveillance an essential requirement to provide long-term safety and therapeutic reliability. However, biosimilars, though showing a high level of similarity with the reference biologics, require extra care under the fear of interchangeability, traceability, and minute differences that can affect clinical outcomes.*

*In 2021-2025, pharmacovigilance practices have changed significantly via incorporation of powerful technologies, real-world evidence, and novel methods of analytical processes. AI, big data analytics, and electronic health solutions have become effective intermediaries in the development of safety signals at an early stage, improved adverse drug reaction reporting, and optimization of risk-management strategies. Regulatory authorities across the globe such as the FDA, EMA, and WHO have strengthened their guidelines to allow harmonized surveillance, to improve biologic traceability and to increase monitoring of immunogenicity. At the same time, the clinical research has progressed through the use of modern trial designs, approved post-marketing safety studies, and patient registries, which create a greater understanding of the long-term safety profiles.*

*Despite such developments, there are still unresolved questions such as under-reporting of adverse events, inconsistent regulatory frameworks in developing countries and the urgent need to have standard methods of immunogenicity assessments. Maintaining quality manufacturing operations and correct product labeling remain to be one of the issues that should be discussed within the pharmacovigilance system..*

**Keywords***:* Pharmacovigilance, Biologics, Biosimilars, Immunogenicity, Real-World Evidence, Signal Detection; Traceability, Artificial Intelligence, Regulatory Science.

## I. INTRODUCTION

An independent category of modern therapeutics, biologics and biosimilars has transformed the paradigm in chronic, life-threatening, and immune-mediated pathology, making a paradigm shift in their management. These agents are complex macromolecular assemblies produced through recombinant expression in a living host, e.g. a mammalian cell culture, yeast, or bacterial host. This complexity of structure, size, and reliance on finely controlled biotechnological mechanisms give biologics unique therapeutic potential; they also come at the cost of unique safety considerations quite independent of those related to traditional small-molecule drugs [1].


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The clinical importance of biologics has grown exponentially over the last ten years, which has solidified itself as the mainstay of therapeutic regimen in oncology, rheumatology, endocrinology, and gastroenterology.

The development of biosimilars, which are regarded as their highly similar counterparts to licensed reference biologics, has become more affordable in terms of cost but with similar effectiveness, quality, and safety profiles [2]. Biosimilars cannot be an exact copy as generic drugs are, because of the nature of biological production systems that varies. Rather, biosimilars are subjected to stringent comparability tests such as physicochemical characterization, preclinical testing and confirmatory clinical trials to illustrate structure, function, pharmacokinetics, pharmacodynamics and clinical performance similarity [3]. With the ever-growing biosimilars types in the world market, they present prospects of patient access and lower cost of healthcare, especially in economically limited nations.

### 1.1 Rising Global Adoption of Biologics and Biosimilars (2021–2025

The adoption of biologics and biosimilars increased at an expedited rate in the world between 2021 and 2025 due to various converging factors. To start with, multiple blockbuster biologics, including adalimumab, bevacizumab, and trastuzumab, had their patents expired, which enormous therapeutic markets to the competition of biosimilars [4]. Second, regulatory authorities, such as the U.S. Food and Drug Administration (FDA), European Medicine Agency (EMA) and emerging economy regulatory authorities - empowered approval processes and new guidance to facilitate the development and integration of biosimilars into clinical practice [5]. Third, the global healthcare system was in search of sustainable ways of dealing with escalating treatment burdens as a result of chronic illnesses, which also increased the need of affordable biosimilars.

The real-world evidence (RWE) was an important factor during this time slot in building clinical confidence. Enhanced post-marketing surveillance systems, study switching and cohort studies were supportive of the safety and efficacy data allowing broader clinical use [6]. Such countries like India, South Korea, and Brazil also became the major players in the sphere of the biosimilar manufacturing, and the international availability is also increased. This led to more accessibility to biologics and biosimilars, and there was higher therapeutic adoption in both developed and developing countries.

### 1.2 **Importance of pharmacovigilance (PV) in safety Monitoring**

Although biologics and biosimilars have significant benefits in terms of their therapeutic use, they also present unique safety issues that need to be monitored constantly. Pharmacovigilance (PV) as the science and the activities surrounding the occurrence, evaluation, interpretation, and avoidance of adverse effects or other drug-related issues are hence necessary towards the guaranteed safety of the people [7]. In the case of biologics, PV is especially an important consideration since these drugs are prone to immunogenicity an immune response to the therapeutic protein, potentially lowering efficacy, changing pharmacokinetics, or inducing severe adverse reactions [8]. The immunogenicity of the protein can be affected by the variety of factors containing protein structure, impurities, formulation, and even administration routes.

Biosimilars, despite having similarity with the biologic originators, can have slight structural differences due to manufacturing processes. These differences, though not being excessive, can be still dangerous to immunogenicity. Contrary to traditional generics, biosimilars necessitate powerful PV systems to watch switching pattern, interchangeability, product traceability, and long-term real life safety information [9].

After-market surveillance is therefore necessary since pre-approval clinical trials might not be adequate to identify some rare or delayed adverse events because of small samples and controlled environments. Innovative PV technologies such as spontaneous reporting systems, active surveillance, electronic health record mining and AI-assisted safety signal identification are now crucial in early detecting safety issues with biologic products [10].

### 1.3 Regulatory and Scientific Challenges

Although there have been immense advances during 2021-2025, the pharmacovigilance of biologics and biosimilars still suffers a number of regulatory and scientific issues. The first issue is the ability to trace products, and it is necessary to identify the specific biologic or biosimilar that caused particular adverse event. It is sometimes challenging

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to separate between biosimilar products and reference biologics in adverse drug reaction (ADR) reports due to naming conventions, prescription practices and pathways of distribution [11].

The other limitation is that there is no standardized method of immunogenicity testing among manufacturers and regulatory jurisdictions. The difference in assay sensitivity, detection limits and methodology can also make it challenging to interpret immunogenicity data and difficult to compare cross products and across studies [12]. Also, the manufacturing alterations can affect product properties (e.g., the alteration of cell lines and purification and formulation) and, after some time, may alter the safety profiles, which force the constant comparability testing.

Another reason which makes global PV a difficult endeavor is regulatory differences between the nations. Although agencies such as the FDA and the EMA have a clear-cut system of evaluating and monitoring biosimilars, most of the low- and middle-income nations lack effective infrastructure, resources, and guidelines on which biologics pharmacovigilance should be applied [13]. These drawbacks prevent the standardized reporting of safety and undermine the creation of a universal dataset on safety.

Furthermore, data collection in the field is associated with such issues as incomplete reporting, differences in healthcare documentation policies, and the lack of awareness in healthcare providers about the significance of reporting suspected adverse events. Besides, the growing complexity of new biologic including gene therapies, CAR-T cell therapies, and next-generation monoclonal antibodies presents new analytical challenges to pharmacovigilance systems, requiring more advanced analytical tools and regulatory frameworks [14].

## II. BIOLOGICS AND BIOSIMILARS: SCIENTIFIC BACKGROUND

### 2.1 Biologics: Structure, Complexity & Mechanism

Biologics are therapeutic products that have been manufactured using highly advanced biotechnological procedures on living cells. They are large, three-dimensional, and highly heterogeneous structures comprising of proteins, monoclonal antibodies (mAbs), nucleic acids, or complex glycoproteins which may have a molecular weight of greater than 150 kDa [15]. Biologics, being of biological nature, have micro-variations that depend on cell lines, culture condition, purification process, as well as post-translational process of glycosylation and folding patterns [16]. These architecture complexities enable biologics to have very specific effects of action, such as receptor blockade, immune modulation, and molecular pathway targeted inhibition. Small molecule drugs, e.g. monoclonal antibodies, can specifically target antigens, induce apoptosis, or trigger antibody-dependent cellular cytotoxicity (ADDC), leading to specific therapeutic effects of few off-target toxicities [17].

But, it is also subjected to high complexity, making it prone to structural instability, immunogenicity, and batch to batch variability. Even small changes in the process of production can affect efficacy or cause immune reactions, which underlines the importance of highly analytical characterization and post-marketing control of safety [18].

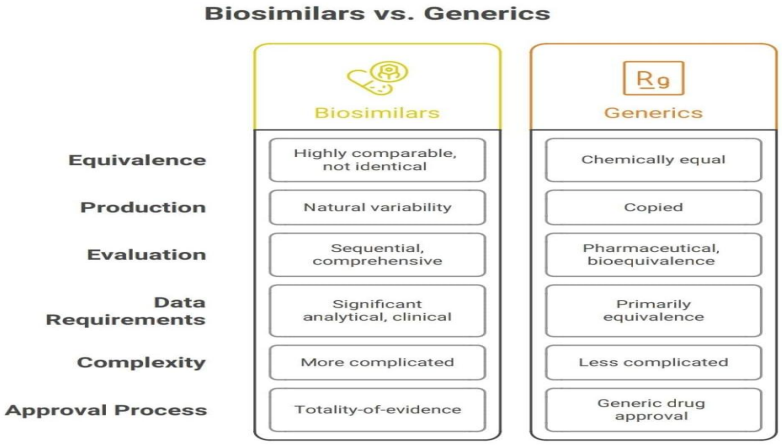


Figure 1 The Difference between Biosimilars & Generics

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### 2.2 Biosimilars vs. Generics: Key Differences

Biosimilars are not replicas of their original biologic counterparts, but highly comparable versions, as a result of the rigorous comparability exercises. Biosimilars, in contrast to generics, which are chemically equal to the small-molecule drugs they represent, cannot be copied because of the natural variability of the systems of biological production [19]. Rather, they are evaluated sequentially involving a comprehensive structural and functional characterization, non-clinical studies, and focused clinical trials to exhibit similarity in pharmacodynamics, pharmacokinetics, efficacy, safety, and immunogenicity [20].

Generics are primarily based on demonstration of pharmaceutical equivalence and bioequivalence, whereas biosimilars need significant analytical and clinical data to demonstrate that there are no clinically significant differences compared to the reference biologic [21]. Also, other topics, including interchangeability, potential immunogenicity, and traceability are more complicated in the case of biosimilars and require greater regulatory control.

The specific biosimilar pathways developed by regulatory bodies like the EMA and FDA have included totality-of-evidence approaches instead of generic drug approval programs, which means that the approval of biosimilars is radically different than the generic drug approval process [22].

### 2.3 Global Market Growth (2021–2025)

**Market Drivers**

The biologics and biosimilars market in the world has expanded significantly in the period between 2021 and 2025 as owing to the expiry of major biologics patents, escalation of chronic diseases, and the growth of health care spending. The blockbuster biologics, e.g., adalimumab and bevacizumab, have lost their patent, and this has opened multi-billion-dollar segments to the onslaught of biosimilars, pushing the market into growth and affordability [23].

Also, the availability was increased by government policies encouraging the use of biosimilars, the evolution of biotechnology, and increased capacity of production in Asia and Europe. The economic sustainability of healthcare systems was a key factor in market development as biosimilars became more and more popular with the aim of treating more people and cutting costs [24].

Major Therapeutic Areas

The biologics and biosimilars have found their niche in the high-burden therapeutic domains such as oncology, autoimmune diseases, diabetes, nephrology, and inflammatory disorders. The biggest segment is oncology, where trastuzumab and rituximab are very popular monoclonal antibodies in the treatment of breast cancer, lymphoma, and gastric cancer [25]. Other autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriasis, inflammatory bowel disease are also big markets since TNF-alpha inhibitors and interleukin-based biologics are effective [26].

With situations where biosimilar products of these products are becoming more acceptable, they are the ones that help in increasing access to treatment and reducing healthcare expenses across the globe.

## III. PHARMACOVIGILANCE FRAMEWORK FOR BIOLOGICS

### 3.1 Need for Specialized Pharmacovigilance for Biologics

**Immunogenicity**

The biologics and biosimilars have found their niche in the high-burden therapeutic domains such as oncology, autoimmune diseases, diabetes, nephrology, and inflammatory disorders. The biggest segment is oncology, where trastuzumab and rituximab are very popular monoclonal antibodies in the treatment of breast cancer, lymphoma, and gastric cancer [25]. Other autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriasis, inflammatory bowel disease are also big markets since TNF-alpha inhibitors and interleukin-based biologics are effective [26].

With situations where biosimilar products of these products are becoming more acceptable, they are the ones that help in increasing access to treatment and reducing healthcare expenses across the globe.

**Manufacturing Variability**

Biologics are grown in living cells and hence their manufacturing processes are complex and highly sensitive to cell line variations, culture condition variations, purification technologies as well as storage practices. Even minor changes

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in the manufacturing process can produce slight alterations in product characteristics (glycosylation patterns, folding structure, charge distribution, etc.), which may change clinical performance or safety profile [29]. These manufacturing changes are closely regulated by regulatory agencies by undertaking comparability tests, but in practical terms, real-life surveillance is necessary to be able to identify any unintended negative consequence of manufacturing drift.

Batch-to-Batch Differences

Biologics are micro-heterogeneous across production batches (where small-molecule drugs are not). The variation between batches can be attributed to either an upstream or downstream process variability that results in a difference in potency, purity, or functional activity [30]. Although manufacturers exercise strict quality controls, such differences can have an impact on immunogenicity or safety in the patient population. Thus, pharmacovigilance systems that are specialized are required to provide early notification of safety signals that may be associated with individual lots or manufacturing shifts or distribution batches.

### 3.2 Post-Marketing Safety Surveillance

Biologics require post-marketing surveillance (PMS) since pre-approval clinical trials usually have small sample sizes, short-term and controlled environments that do not identify rare, delayed, and population-specific adverse events. The regulatory agencies focus on proactive safety surveillance via Phase IV trials, patient registries, switching trials and real-world evidence (RWE) gathered via healthcare databases and pharmacovigilance reporting system [31]. As biologic-specific PMS approaches, immunologic surveillance, extended safety observance, routine reports of safety update (PSUR), and observational cohort trials are included.

Between 2021 and 2025, there was a greater dependence on big data analytics and electronic health records (EHRs) and artificial intelligence (AI) to enhance post-marketing surveillance. These technologies improved signal-detection systems, allowing to detect adverse drug reactions (ADRs) earlier, provide better traceability, and conduct a better analysis of treatment patterns [32]. In many countries, obligatory post-marketing commitments to biosimilars were also broadened so that the safety profiles of the biosimilar would be similar to reference biologics in the long-term use.

### 3.3 Risk Management Plans (RMPs)

Risk Management Plans (RMPs) have taken a decisive role in the pharmacovigilance system of biologic and biosimilars. RMP is a preemptive plan of identifying, characterizing, preventing or reducing risks of a medicinal product during its lifecycle. Biosimilars, and indeed biologic products, are highly risky products that require detailed RMPs set by regulatory bodies, including EMA and FDA [33].

**Key elements of RMPs include:**

- **Safety specification:** Recognition of the risks known and potential including immunogenicity issues.
- **Pharmacovigilance plan:** Description of regular and other PV activities, e.g. Phase IV studies targeted, or patient registries**.**
- **Risk minimization measures (RMMs):** Educational programs, monitoring protocols and controlled switching policies to make sure that it is used safely**.**

It was observed that during the period 2021-2025 RMPs were becoming more focused on the use of real-world data, digital reporting mechanisms, and adaptive plans which reflected changes in manufacturing, or new safety indicators. There were also improved documentations demanded by regulatory authorities to trace products especially biosimilars in cases of automatic substitution or pharmacy-level switching [34].

### 3.4 Adverse Event (AE) Reporting: Challenges and Trends (2021–2025)

Adverse Event (AE) reporting continues to serve as a central mechanism in the safety oversight of biologics, yet multiple barriers limit its effectiveness. Under-reporting remains the most persistent obstacle, especially in low- and middle-income settings where knowledge of biologics-specific risks and reporting pathways is still developing [35]. The inherent complexity of biologics further complicates the process, as identifying the precise product, manufacturer,

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or batch linked to an AE is often difficult. This issue becomes more pronounced in markets where several biosimilars of the same reference molecule are in circulation.

Traceability is also influenced by product naming practices. Although the WHO has proposed unique suffix-based identifiers for biologics, their use has not been uniformly adopted across regulatory systems, leading to inconsistencies within AE databases and reduced clarity during safety evaluations [36]. Confusion among healthcare providers regarding product substitution and switching may also contribute to incomplete AE documentation.

Between 2021 and 2025, several technological innovations reshaped global AE reporting. Tools based on artificial intelligence, automated data-mining, and electronic submission systems improved the accuracy and timeliness of signal detection, allowing quicker response to emerging risks [37]. Regulatory agencies strengthened surveillance strategies by expanding national monitoring networks and introducing real-time dashboards for ongoing safety assessment. Despite these advances, substantial variation in reporting standards across countries continues to challenge the establishment of a unified pharmacovigilance ecosystem for biologics and biosimilars.

## IV. PHARMACOVIGILANCE OF BIOSIMILARS

### 4.1 Regulatory Requirements Across Regions

Regulatory environment in relation to biosimilars exhibits diversity at regional level, but all the major authorities focus on the basic principles of safety, efficacy, and quality of the products. The Food and Drug Administration (FDA) requires in the United States the step and evidence-based demonstration of biosimilarity that involves the extensive characterization of analytics, the non-clinical assessments, and clinical evaluations based on pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity [38]. Moreover, the biosimilar companies must establish extensive post-marketing pharmacovigilance, as well as, they must comply with rigorous adverse event reporting requirements.

The European Medicines Agency (EMA), which happens to be a world leader in biosimilar regulation, uses a totality-of-evidence strategy, where good structural and functional comparability data can be used as a reason to decrease the scope of clinical testing [39]. The EMA guidelines consider product traceability, naming conventions, and constant immunogenicity surveillance to be of great importance in terms of keeping the pharmacovigilance standards of high quality.

The World Health Organization (WHO) offers harmonized guidelines at the global level to facilitate the biosimilar evaluation, especially in areas having underdeveloped regulatory infrastructures. WHO recommends the utilization of standard comparability frameworks, post-approval systematic safety surveillance, and covering into global adverse event reporting systems [40]. Together, these regulatory frameworks help to enhance the global pharmacovigilance practices and guarantee the uniform patient safety in different healthcare facilities.

### 4.2 Post-Approval Comparability/ Traceability

After regulation, Biosimilars receive continuous comparability assessments to ensure that the product remains in line with the reference biologic regarding safety, quality, and performance. Due to the complexity nature to biologic manufacturing, minor changes in glycosylation patterns, protein folding, or even formulation parameters can occur among production cycles. Such differences require strict batch to batch comparability studies in order to maintain consistency on the products and to counteract possible clinical effects [41].

In post-marketing surveillance, traceability is a major requirement to strengthen. Effective adverse event attribution is boosted by proper documentation of product identifiers, batch numbers or lot numbers and producer information coupled with effective electronic reporting systems. Pharmacovigilance activities are effectively protected by effective traceability, which reduces the risks of misclassification and allows identifying safety signals related to certain biosimilar batches in time [42].

### 4.3 Interchangeability and Switching: Safety.

The use of transitioning the patient of a reference biologic into a biosimilar or between biosimilars remains a subject of interest owing to possible issues to do with safety, efficacy, and immunogenicity. In spite of adequate clinical trial and

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real-life evidence that switching does not usually degrade the effects of therapy, there have been isolated reports of immunogenic reaction [43].

Regulatory authorities have come up with certain conditions of giving a product the interchangeability designation, which generally involves data proving that repetitive switching cannot change the safety profile or therapeutic performance of the product [44]. Extensive surveillance, meticulous recording of switch-over incidences and close follow-up are thus critical parts of the post switch pharmacovigilance measures. These measures aid in the early detection of the arising risks and lead to the informed clinical decision-making.

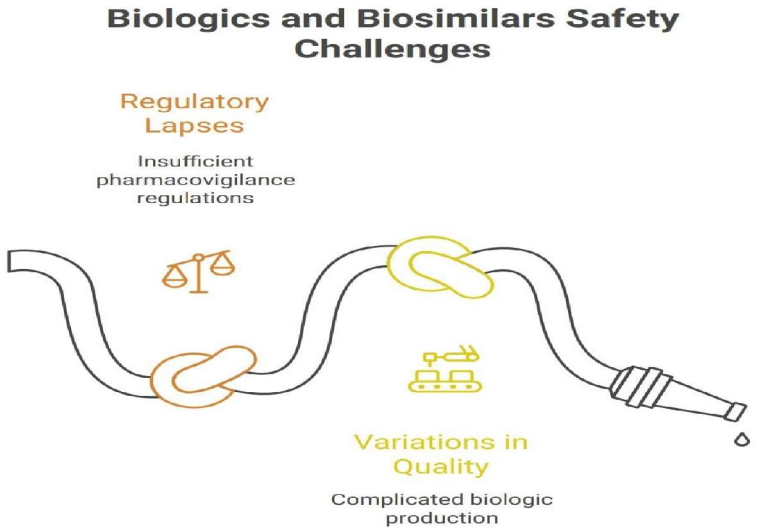


Figure 1 The safety challenge biologics and biosimilar

**4.4 Biosimilars Pharmacovigilance Real-World Evidence (RWE)**

Real-world evidence (RWE) has become a critical part of the post-marketing safety assessment of the biosimilars. The information provided by patient registries, electronic health records, insurance databases and big observational studies can provide up-to-date information on product performance when not in controlled clinical trial environments [45]. Such real-world data sources allow monitoring the immunogenicity continuously, therapeutic outcomes over the long term, and adverse event occurrences.

Notably, RWE is essential in identifying the occurrence of rare or slow safety signals unnoticed in the pre-approval clinical trials. It can also aid the evaluation of the clinical outcomes in patients in case of their transition to reference biologics to biosimilars or between different biosimilar products. The results of RWE have played a significant role in improving the insight of switching patterns, adherence, and comparative safety profiles.

The integration of RWE in regulation reviews became even stronger in the period 20212025, which enhanced the evidence basis of using biosimilars in the global setting. To supplement pre-market information, risk-management strategies, and policy-making, regulatory agencies have increasingly used RWE to inform policy decisions on interchangeability of biosimilar regulated products and wider use [46]. Consequently, RWE has turned out to be a foundation of modern pharmacovigilance systems in biologics and biosimilars.

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## V. EMERGING TRENDS IN PHARMACOVIGILANCE (2021-2025).

### 5.1 Safety Signal Detection by AI.

Recent developments in artificial intelligence (AI) and machine learning have transformed pharmacovigilance with biologics and biosimilars to a great deal. The technologies facilitate the automated extraction and analysis of safety data of large and complex datasets, such as electronic health records (EHRs), spontaneous reporting systems, and clinical trial documents [47]. The AI-based models are able to recognize minor trends, emerging patterns and also correlations which could be missed by traditional manual assessment approaches. This has made the early detection of safety signals more effective to aid prompt responses in regulations. Risk assessment, immunogenicity prediction, and proactive safety-related surveillance involving AI-driven predictive tools have continued to add to the overall pharmacovigilance frameworks of biologic therapies between the years 2021 and 2025.

### 5.2 Machine Learning Applications and Analytics of Big Data.

The addition of big data analytics has also increased the scope of post-marketing surveillance by valuable information sources including insurance claims, genomic data, digital health, social media, and global repositories of pharmacovigilance [48]. All these multidimensional datasets can be processed by machine learning algorithms to identify adverse drug reactions, assess switching-related results, and foresee immune-mediated complications related to biologic. Such analysis methods can also assist regulatory authorities to optimize risk management procedures and enhance precision of benefit risk analysis. This has made big data analytics an essential part of the current pharmacovigilance systems, especially when it comes to biologics of highly complex structural and immunogenic properties.

### 5.3 Digital Health Innovations and E-Pharmacovigilance.

The digital health technologies, including the application of mobile health, electronic adverse event reporting, wearable biosensors, and telemedicine system have improved the speed and accuracy of the pharmacovigilance operations [49]. E-pharmacovigilance supports real-time reporting of safety issues by healthcare workers and patients, minimizes documentation errors, and allows to quickly combine safety data in healthcare networks. The combination with the national and global pharmacovigilance databases has enhanced the real-time monitoring and reporting of safety between regulatory authorities. Together, digital health technologies have increased the efficiency of surveillance and enabled quicker and evidence-based decision-making during the post-marketing of biologics and biosimilars.

### 5.4 Mobile Apps + Patient-Reported Outcomes (PROs).

The mobile applications and patient-reported outcomes allow patients to define the adverse events with an even better degree of granularity and timeliness by enabling them to report the adverse events directly to their healthcare organization [50]. In comparison to the traditional clinician-reported information, the PROs assist to take note of the subjective information, such as infusion reactions, fatigue, or immunogenicity-related symptoms. Mobile health tools increase patient engagement as well as improved reporting of under-reported adverse events in post-marketing surveillance.

### 5.5 Biologics PV Guidelines International Convergence.

The pursuit of the harmonization of the pharmacovigilance guidelines has been on the rise between 2021 and 2025 [51]. The initiatives of the WHO, FDA, EMA and the International Council for Harmonisation (ICH) promote standard adverse events reporting, standard nomenclature that is employed in reporting biologics and standard immunogenicity assessment systems. The harmonization procedure fosters the cross-border safety oversight and comparability of data of multinational biologics and biosimilars.

### 5.6 PV guidelines and Pharmacogenomics

Pharmacogenomics research studies the interaction between drugs and drug safety in different individuals and directs towards developing PV-based therapeutics.

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Through pharmacogenomics, an individual is able to possess his/her own pharmacovigilance; the ability to ascertain the drug-specific genetic factors that can be affected by the specific patient is made possible [52]. The key issue of PV is the encapsulation of the genetic data to forecast the high-risk patients, higher dosing, and to anticipate unfavorable outcomes. Personalized PV is a future strategy particularly in biologics that have unpredictable immunogenicity indexes.

## VI. CLINICAL RESEARCH PERSPECTIVES (2021–2025)

### 6.1 Clinical Trials Design Evolution for Biosimilars

The paradigm of biosimilars clinical trials has shifted toward a situation where therapeutic equivalence, instead of establishing novel efficacy, is used as the main goal, and thus, it hastens the developmental process without compromising the safety oversight [53]. The modern trial designs focus on pharmacodynamic (PD) and pharmacokinetic (PK) comparability, high equivalence margins and the use of smaller patient groups as compared to biologics of origin. Adaptive designs and immunogenicity endpoints have gained mainstream status, allowing to quickly evaluate the potential safety signals, and thus minimizing the exposure of the patients at the same time [54]. Investigations conducted after approval include clinical environments more and more, to ensure relevance to practice.

### 6.2 Methodologies of immunogenicity testing.

Immunogenicity is another critical issue of biologics and its biosimilar analogs, with immunogenicity being able to regulate the efficacy and safety profiles. The standard methods used to evaluate it include enzyme-linked immunosorbent assays (ELISA), electrochemiluminescense assays, and neutralizing antibody assays, which evaluate the existence and practical consequences of anti-drug antibodies [55]. The adoption of harmonized protocols has improved the inter-study comparability and thus provides information to regulatory evaluation and the post-marketing surveillance.

### 6.3 Clinical Monitoring Tools in the Real World.

An inseparable part of pharmacovigilance is real-world evidence (RWE). Longitudinal monitoring of safety, immunogenicity and therapeutic switching effects is supported by electronic health records, patient registries and built in pharmacovigilance databases [56]. Online resources and mobile platforms facilitate effective adverse event reporting and increase patient engagement thus complementing traditional datasets of clinical trials.

### 6.4 Post-Approval Safety Studies (PASS).

Post-authorization safety trials are required to identify infrequent, delayed or population specific adverse events that might not have been identified during pre-approval studies [57]. PASS designs normally entail observational cohort studies, case-control comparisons, and registry studies. These studies have become more organized and incorporated into global pharmacovigilance frameworks between 2021 and 2025 and, therefore, the proactive risk control and timely regulatory responses.

### 6.5 Case Studies (2021–2025): Safety Signals Identified and Regulatory Actions

The effectiveness of advanced pharmacovigilance plans is supported by the recent case studies. As an example, copying of TNF- alpha inhibitor biosimilars has shown adverse events due to immunogenicity, thus triggering changes in labeling, risk-mitigation measures and regulatory advice [58]. The evaluation of the interchange of reference biologics and their biosimilar analogs has been supported with comparative studies on both safety and efficacy, along with highlighting the need to have traceability, robust reporting mechanisms, and real-world monitoring. Government bodies, such as FDA and EMA, have used such results to improve the dialogues of post-marketing surveillance and also provide instructions on the interchangeability of biosimilars [59]

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## VII. CHALLENGES IN PHARMACOVIGILANCE OF BIOLOGICS AND BIOSIMILARS

### 7.1 The under-reporting and traceability problems

Under-reporting of adverse events is one of the endemic problems of pharmacovigilance of biologics and biosimilars. Many medical workers fail to report, claiming that they do not have enough time, awareness, or are not sure that it is a cause [60]. Traceability takes the center stage since subtle changes in the structures between biosimilars and reference counterparts may modify safety profiles. Poor recording of the product identifiers, batch numbers and administration specifics can reduce the proper identification of safety signals and risk evaluation.

### 7.2 The absence of Standard Immunogenicity Biomarkers.

Bio-markers to predict or detect immune responses remain a paramount issue in the field of biologics and biosimilars but no standardized biomarkers are available in the field [61]. The sensitivity of assays, methodology and interpretative criteria vary across numerous studies, making it difficult to compare studies across studies, or detect uncommon immunogenic events. This is because immunogenicity markers are yet to be established on a global scale, thus, making it harder to detect risks and make regulatory decisions.

### 7.3 Naming Conventions, Traceability and Substitution.

Diffusion of naming in different geographical areas hinders the reporting of traceability and pharmacovigilance [62]. Due to the similarity of biosimilars and their reference products in terms of the International Non-Proprietary Name (INN), it is difficult to assign adverse events to the appropriate biosimilars. There are additional practices of substitution such as automatic product
switching that increase the complexity of tracking of the safety outcomes, and it underlines the importance of unique identifiers and strict documentation.

### 7.4 Regulatory Lapses in Low- and Middle-Income Countries.

A large portion of the low- and middle-income states (LMICs) do not have extensive regulations of the pharmacovigilance of biologics and biosimilars [63]. Limited infrastructure and insufficient reporting systems, scarce regulatory guidance, etc., lead to the incomplete adverse-event monitoring. This divides the risk of the late identification of safety and the attempts to harmonize the actions globally.

### 7.5 Variations in quality manufactured.

Biologic production is inherently complicated and prone to variability caused by the change of cell lines, purification procedures, and formulation conditions. The batch-to-batch variability may affect the protein folding, glycosylation forms and immunogenicity [64]. Stability in the quality of batches of production is crucial to maintain health and therapeutic effectiveness, but both monitoring and regulating the changes is difficult.

## VIII. FUTURE DIRECTIONS (BEYOND 2025)

### 8.1 Advanced Biologics (CAR-T, Gene Therapies) Pharmacovigilance.

The new generation of biologics including CAR-T cell therapy and gene therapies is associated with unique safety and surveillance difficulties. They include patient-tailored or genetically designed alterations, thus increasing risks of severe adverse events, including cytokine release syndrome or insertional mutagenesis [65]. Potential pharmacovigilance systems should thus include special monitoring regimes, longitudinal follow-up as well as predictive safety tests to help control these risks.

### 8.2 Digital twin in patient monitoring

This field applies digital twins to improve the quality of care delivered to patients. One of the technologies that promise to transform pharmacovigilance is the digital twin technology: virtual models of separate patients, which can simulate the effects of drugs and predict their adverse reactions [66]. Combining patient-specific data, such as genomics and

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biomarkers, clinical history, digital twins enable the proactive approach to the safety of the patient, optimal approach to dosing, and personalized therapeutic decisions.

### 8.3 Integration of AI with Real word Evidences and clinical Data

The future pharmacovigilance systems will unfold into more and more combinations of AI-based analytics and real-world evidence and clinical trials, thus becoming more prompt about detecting safety signals in a more specific fashion [67]. Machine-learning models have the ability to synthesize heterogeneous data sets and identify subtle patterns and predict adverse event before it presents itself in the clinical picture. The given methodology will improve the early warning mechanisms and strengthen regulatory responsiveness.

### 8.4 Better Global PV Networks and Harmonisation.

International cooperation and synchronization of pharmacovigilance systems will play a key role in the control of new biologics and biosimilars [68]. The enhancement of the international data sharing platforms, harmonization of the adverse event reporting, and the harmonization of the regulatory requirements will help to streamline the multi-jurisdictional safety monitoring. This kind of integration will help identify the safety signals in time and help deal with risk mitigation on a global scale.

## IX. CONCLUSION

Between 2021 and 2025, there has been significant change in the area of pharmacovigilance as it applies to biologics and biosimilars. The key trends include the extensive adoption of biosimilars worldwide, increased post-marketing safety monitoring, the integration of real-world-evidence, and the growing use of digital technologies and artificial-intelligence-driven analytics to provide an opportunity to notice adverse events in time. The regulatory frameworks in different jurisdictions have been updated to adopt safety, traceability and immunogenicity surveillance, post-authorization safety studies (PASS) and risk-management strategies have strengthened the post-marketing surveillance.

Effective pharmacovigilance frameworks are unavoidable to overcome the intrinsic complexity of biologic therapeutics, reduce the risks of immunogenicity, as well as protect patient safety. The future incorporation of advanced monitoring capabilities, such as artificial intelligence, big-data analytics, patient-reported outcome measures as well as digital twin models, is expected to gain an increasingly central role. This type of innovations will enable
proactive identification of safety signals, assist with the individual assessment of risk, and promote the harmonisation of the pharmacovigilance practice worldwide.

Overall, the continuous development of pharmacovigilance methodology, along with technological advances, will continue to play a crucial role in the safe and effective use of biologics and biosimilars, and, at the same time, allow expanding the range of innovative therapies to the clinical sphere.

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