

## CLINICAL STUDY

# Biopharmaceuticals safety perception in Slovakia: considerations and real-life pharmacovigilance data

Lassanova M<sup>1</sup>, Liskova S<sup>1</sup>, Tisonova J<sup>1</sup>, Fundarkova S<sup>2</sup>, Lissan S<sup>3</sup>

*Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Bratislava, Slovakia. lassanstefan@outlook.sk*

**ABSTRACT**

**OBJECTIVES:** Biopharmaceuticals improved the prognosis and quality of life of patients with chronic diseases. The aim of our study was to analyse the total reported suspected adverse drug reactions (ADR) and ADRs of reference biologicals and their biosimilars in Slovakia.

**METHODS:** Using data from the State Institute for Drug Control database, we analysed the trends of suspected ADR submitted between 2001–2017 including the registered biosimilars and their reference biologicals: erythropoietin, filgrastim and infliximab.

**RESULTS:** Severe suspected ADR represented 42.95 % from all the reported cases (n=13,462) over the time period 2006–2017 and 54.98 % over 2015–2017 respectively. Reports from 2015–2017 were further analysed. From 4,364 cases, 27 were associated with infliximab and one with erythropoietin. 75 % of these ADR were severe including one death. The difference between the suspected ADR for infliximab reference biological compared to the biosimilar was not statistically significant (p=0.171) after adjustment to the number of prescribed drug units.

**CONCLUSION:** We did not find any evidence of increased risks associated with biosimilars compared to reference biologics. The spontaneous reporting system represents an inexpensive tool of reporting ADRs and should be utilized more frequently by health professionals, but even more importantly, by patients (*Tab. 3, Fig. 2, Ref. 30*). Text in PDF [www.elis.sk](http://www.elis.sk)

**KEY WORDS:** adverse drug reaction, spontaneous reporting, biopharmaceuticals, biosimilars, infliximab.

**Introduction**

Biological medicinal products, either biologicals or biologics, are important treatment options for a variety of chronic and life-threatening diseases within various specialised fields of medicine, which include (but are not limited to) oncohaematology, gastroenterology, rheumatology, oncology, endocrinology, cardiology, diabetology, pulmonology or dermatology. Biological therapy has been known for more than 35 years, with the pioneering drugs being insulin, growth hormones and heparin. The discovery of biotechnological production of biopharmaceuticals – namely the production of monoclonal antibodies – has been awarded a Nobel Prize in Physiology or Medicine (1). The European Medicines Agency (EMA) defines a biosimilar as “a biological medicine highly similar to another biological medicine already approved

in the EU” (2). Biosimilars are approved based on scientifically tailored data package, which consists of extensive comparability studies between the biosimilar and the reference product (2). Since the introduction of the first biosimilar in clinical use in 2006, an increasing number of biosimilars have been approved and safely used in the European Union (EU).

Biosimilars are introduced into clinical practice after the patent protection of the original biological medicinal product, lasting 10 years, has expired. Moreover, biosimilars are developed to be almost identical with the reference biological medicinal product. However, it must be noted that subtle differences may occur in all biopharmaceuticals – that is, even between different batches of a single reference biological medicinal product. These minor differences are based on the fact that biologically active substances are by nature variable, complex macromolecules produced by living cells (3, 4, 5, 6). The active substances are usually proteins, which are larger and more complex (they have tertiary and quaternary structures) than active ingredients in non-biological medicinal products produced by chemical synthesis (Tab. 1) (7, 8, 9, 10).

Biological medicinal products, just like any other drugs prior to registration, are required to have more benefits than associated risks. Unlike in generic human drugs, the introduction of a biosimilar always requires comparative studies that show the quality, purity, safety, and effectiveness similar to the reference biopharmaceutical. Extensive comparative trials are carried out based on a

<sup>1</sup>Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Bratislava, Slovakia, <sup>2</sup>Section of Clinical Trials of Medicinal Products and Pharmacovigilance, State Institute for Drug Control, Bratislava, Slovakia, and <sup>3</sup>Department of Pneumology and Phthisiology and Functional Diagnostics, Slovak Medical University and University Hospital Bratislava, Bratislava, Slovakia

**Address for correspondence:** S. Lissan, MD, PhD, MPH, Department of Pneumology and Phthisiology and Functional Diagnostics, Slovak Medical University and University Hospital Bratislava, Ružinovská 6, SK-826 06 Bratislava, Slovakia. Phone: +421.2.48234748, Fax: +421.2.48234489

**Tab. 1. Comparison of the characteristics of small chemical molecule pharmaceuticals with biopharmaceuticals (edited from 2, 4, 7, 8, 9, 10)**

Characteristic	Non-biological medicinal product (chemical molecule)	Biological medicinal product (biopharmaceutical)
Mass	100 – 1,000 Daltons	18,000 – 145,000 Daltons
Production	Chemical synthesis	Produced by living organisms, isolated by biotechnological processes and/or genetic engineering
Duration of production	3 weeks	25 – 50 weeks
Structure	Simple, precisely defined	Complex, 3D structure affected by a variety of factors
Stability	Stable	Affected by unstable physical conditions
Route of administration	Enteral, Parenteral	Parenteral
Immunogenicity	Usually, non-immunogenic	Potentially immunogenic
Registration	Variable	Centralised procedure
Price	Lower	Higher
Number of treated patients	Higher	Lower

step-by-step approach. First, detailed pre-clinical studies are conducted in a laboratory, comparing the structure of the biosimilar with its function. Clinical studies usually follow afterwards (studies involving human subjects). The approval of a biosimilar to the pharmaceutical market in the EU is only possible after successfully passing a centralised procedure of registration (compulsory for all biopharmaceuticals). Moreover, a perspective biopharmaceutical needs to be approved by the European committee, based on the recommendation by the EMA (2, 5, 11, 12).

The treatment with both groups of biopharmaceuticals could be associated with adverse drug reactions (ADR) of varying severity and quality. Given the complex nature of biological medicines, they pose a greater potential risk of immunogenicity than non-biological medicines, and hence warrant a special consideration. Therefore, specific ADRs of biopharmaceuticals are based on the immune response in the form of specific antibody production against the biopharmaceutical. This immune response may lead to unsolicited allergic reactions, or even to a decrease in the activity of the biopharmaceutical (neutralising antibodies) (2, 8, 9). Apart from reactions of an immunological nature, most ADRs can be predicted from the pharmacological action, and occur with both the reference medicine and the biosimilar. Despite possible ADRs that differ from small chemical pharmaceuticals, the onset of the era of biopharmaceutical therapy has dramatically changed the prognosis and quality of life of patients with severe, chronic diseases. None of the biosimilars approved in the EU has been withdrawn or suspended for reasons of safety or efficacy (2).

Pharmacovigilance is the cornerstone in monitoring the safety profiles of medicines once they are in clinical use (13). An important goal of the development of biosimilars is safety. For biologicals, as for all drugs, pharmacovigilance plays an important role in the discovery, detection, and characterization of ADRs in the post-marketing setting due to the inherent limitations of clinical trials (e.g., a homogenous population, a relatively low sample size and time window, and limited use of concomitant medication) (14). Developing a biosimilar with a safety profile corresponding to the reference product can be demanding due to the complex molecular structure and complicated manufacturing process involved. In addition, the molecular structure of biologic products is also sensitive to changes in formulation, packaging, and storage. Safety consi-

derations include immunogenicity, hypersensitivity reactions, and an increased risk for other adverse effects (15). Safety monitoring of biosimilars in the EU follows the same requirements that apply to all biological medicines. There is no specific requirement just for biosimilars (16). However, detecting and characterising the long-term ADRs of biological medicines may be difficult using only spontaneous reporting (17). For this reason, additional pharmacovigilance activities (such as including patients in registries) are strongly recommended and biosimilars must not be treated as generic medicines and, as such, require more robust product-specific pharmacovigilance capabilities (3, 18). Moreover, misattribution of ADRs from generics to the branded originator is frequent and has been observed for commonly used drugs (19).

Routine pharmacovigilance becomes particularly important in ensuring the safe and effective use of these products, as rare events such as immune-mediated reactions may be detected only after the products are marketed (13). Because no two biologic medicines are identical, post approval safety monitoring is critical to detect potential differences in safety signals between a biosimilar, its reference product, and other biosimilars. Post approval safety monitoring uses two signal detection systems: spontaneous reporting systems (SRSs) and active surveillance (AS) systems. SRSs are important for the identification of safety signals, including potential rare AEs not identified during clinical trials or premarketing studies. SRSs are considered passive surveillance methods, which rely on voluntary reports from healthcare professionals and patients. For products (such as biologics) that are relatively sensitive to manufacturing conditions, SRSs may be useful for detection of emergent safety signals associated with changes in the product quality throughout the life cycle of the medicine. In this regard, the accurate identification of the biological product in the suspected ADR report is essential, indicating the brand and batch number (8). A limitation of SRS approaches is that they cannot accurately quantify the incidence of identified risks for a given product, because the total number of patients treated with the drug is unknown. AS methods are capable to identify new safety signals and at the same time are better suited to assess the incidence and severity of identified risks (20).

Spontaneous surveillance occurs in Slovakia through reports submitted by physicians, pharmacists, other healthcare providers,

and patients to the State Institute for Drug Control (SIDC). Especially, healthcare professionals are encouraged and legally bound to report appropriately safety signals of biological medicines and biosimilars. Reporting of a suspected adverse reaction must meet the same requirements for biological and non-biological medicines.

## Objective

The objective of the study was to review and analyse the frequency, severity, and character of the suspected adverse drug reaction reports of biosimilars used in Slovakia during a period of 2015–2017 and their corresponding reference biological medicine products to clarify the expected safety of respective biosimilars. Our second aim was to analyse all the reported suspected ADRs submitted to the SIDC over a time period between 2001 and 2017. Our primary aim was to focus on the subcategory of then registered biosimilar drugs - erythropoietin (two biosimilar brand products), filgrastim (five biosimilar brand products) and infliximab (two biosimilar brand products) and their corresponding biological medicinal reference products - erythropoietin (one reference brand product) and infliximab (one reference brand product).

## Materials and methods

According to the current legislation in the Slovak Republic, the SIDC is the appropriate authority to collect and evaluate data on the safety of drugs therefore executing its rightful authority in the process of evaluating any potential risks associated with the pharmaceutical therapy. Therefore, the SIDC operates the only relevant database, from which the only reliable data can be acquired to objectively evaluate the risks associated with the use of biological therapy in clinical practice in the territory of the Slovak Republic (SR).

A safety evaluation study was conducted based on data reported in the Slovak database of SIDC.

For the purpose of this study, we retrieved objective data and analysed trends of all the reported suspected ADRs submitted to the SIDC over a time period between 2001 and 2017. From 2006, the SIDC started to differentiate ADR, thus providing data on the severity of ADRs (according to definition listed above) allowing us to record this data. Prior to data notation, SIDC pharmacovigilance managers evaluated the quality and validity of each suspected ADR report, including the causality assessment.

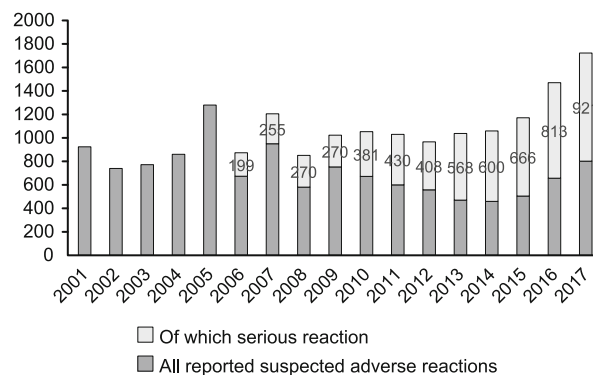
With the help of the database from the Section of Clinical Trials of Medicinal Products and Pharmacovigilance SIDC we analysed the reported cases of ADRs received throughout the period of 2015–2017. We had to consider, that the number of patients treated with reference biological medical products differed considerably from the number of patients treated with biosimilars based on the statistics of sold drug units (21). Therefore, we approximated the number of suspected ADR reports to the market penetration of the corresponding drugs. The extrapolated data was analysed using descriptive statistics. For the construction of the graph, Microsoft Excel (Microsoft Office 2016) was used. Infliximab was statistically analysed using a Student t-test. Specifically, the statistical

significance of the difference between the number of ADRs from originator Infliximab and its corresponding biosimilar was tested. An unpaired, two-tailed type of t-test was selected according to the demands of the data. The threshold of statistical significance was set to 0.05 (thus, the difference would be significant only for  $p < 0.05$ ).

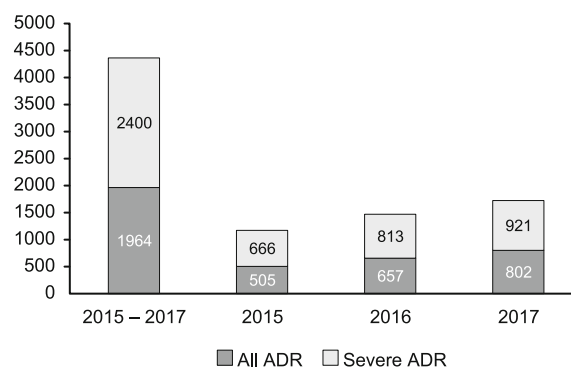
## Results

During the time period of 2001–2017, there were a total number of 18,038 suspected ADR reports registered by the SIDC. Starting from 2006, reporting included in addition the statement about the severity of the ADR. Severe suspected ADRs represented roughly 4/10 ( $n = 5,781$ , 42.95 %) from the number of all reported cases ( $n = 13,462$ ) obtained during the time period 2006–2017 (Figs 1 and 2) (22).

A total of 4,364 have been reported to SIDC between 2015–2017. This reported cases (1,171 cases in 2015; 1,470 in 2016 and 1,723 in 2017, respectively) have been further analysed, since during this time period the aforementioned biologicals have already been used in clinical practice. Of the total sample, the SIDC



**Fig. 1. Total number of reported suspected adverse drug reactions and the ratio of the reported severe adverse drug reactions for the years 2001–2017.**



**Fig. 2. Severe ADR from the total amount of suspected ADR reported in years 2015–2017.**

obtained the suspected ADR reports in 41.47 % from healthcare professionals (n = 1,810), in 37.61 % from marketing authorization holders (n = 1,641), and finally, in 20.92 % from patients or their relatives (n = 913). Severe ADR represented 54.98 % (n = 2,400) from the total amount of suspected ADR (n = 4,364). Figure 1 shows the reported cases for the years 2015–2017 and it is evident that every year the severe ADR reported represented more than 50 % of all the reported ADRs.

From the 4,364 reported cases of suspected ADRs, 28 were considered in context of the monoclonal antibodies use: 27 cases referring to the administration of infliximab and one case to erythropoietin. All these 28 cases were reported by healthcare professionals (Outpatient or Hospital physicians). During the respective period, no registered biological reference of filgrastim was available in Slovak Republic, and no ADR cases for biosimilars of filgrastim were reported. Only one case of suspected ADR associated with erythropoietin was reported in the period of 3 years (2015–2017) and this ADR was of severe nature (Tab. 3).

The number of suspected ADR reported for biological medicinal reference product infliximab, compared to the corresponding biosimilar did numerically fairly differ (Tab. 2). However, after adaptation to the number of prescribed drug units, we did not register a statistically significant difference between biosimilar and its reference biological ( $p = 0.171$ ) (Tab. 2). From the 27 reported cases of suspected ADRs of infliximab three quarters (n =

20; 75 %) were of severe nature, with one case of death registered (Tab. 3). The number of severe ADRs of biological medicinal reference product infliximab reported was 16, which was higher, when compared to the corresponding biosimilars (n = 4) (Tab. 3), but this difference disappeared after adaptation to the number of prescribed drug units.

Regarding the case of death, the ADR was recognized and reported by the attending physician. The affected patient was administered the reference infliximab indicated for the treatment of inflammatory bowel diseases. After 423 days from the onset of the treatment, the patient died due to septic shock as a direct consequence of a perforated peptic ulcer.

## Discussion

In our study we found that ADRs reported to the SIDC tend to increase between the years 2001–2017. After the implementation of the category “severe ADRs” in the year 2006, the reported severe ADRs during the period of 2006–2017 represented almost 43 % of all the reported ADRs. Our study focused to assess the safety of the substance erythropoietin, filgrastim and infliximab, biologics which had biosimilar during the observed period. We found that there were 28 ADRs reported to SIDC, but 21 ADRs were of severe nature, which represents 75 %. All the ADRs related to biosimilars were reported to SIDC by healthcare professionals.

**Tab. 2. Number of reported adverse drug reactions for infliximab, its reference biological and biosimilar medicinal product, for years 2015, 2016 and 2017. The table shows the number of sold drug units for each year (edited from 21).**

Active Ingredient	Products	REFERENCE or BIOSIMILAR	Number of adverse drug reactions for 2015	Number of units sold for 2015	Number of adverse drug reactions for 2016	Number of units sold for 2016	Number of adverse drug reactions for 2017	Number of units sold for 2017
Infliximab	One product	Reference	3	90,249	8	97,842	9	51,515
Infliximab	Two products	Biosimilar	4	6,120	0	7,495	3	8,946

**Tab. 3. Suspected severe drug adverse reaction reports to SIDC obtained over a period of three years (2015, 2016, 2017) for infliximab (both biosimilar and reference biological medicinal product) an erythropoietin (reference biological medicinal product).**

Drug	REFERENCE or BIOSIMILAR	Number (n=21)	Severe adverse drug reaction	Comment
Infliximab	Reference	5	Allergic reaction	Allergic, anaphylactic reactions with the signs of: dyspnoea, palpitation, skin rash, flush, pressure in chest and head, uneasiness
		5	Carcinoma	Basocellular eyelid carcinoma, carcinoma of left kidney, adenocarcinoma of lung, neuroendocrine carcinoma of lung (metastasizing into lymphatic nodes)
		2	Dermatologic reaction	Relapsing eczema, staphylococcal infection of skin
		1	Kidney inflammation	Acute inflammation of kidney and renal pelvis
		1	TBC activation	Infection by mycobacterium tuberculosis, seroconversion of Interferon gamma release assay (IGRA) test
	Biosimilar	1	Infection and ineffectiveness	Infection by clostridium difficile, herpes labialis and ineffectiveness
		1	Death	Septic shock due to peptic ulcer perforation
		3	Allergic reaction	Acute hypersensitive reaction after administration, nausea, dyspnoea, hypotension
		1	Dermatologic reaction	Paradoxical palmoplantar psoriasis
		Erythropoietin	Reference	1

We conducted the first-of-a-kind study in Slovakia aimed at the perception of drug safety covering the group of biopharmaceuticals in the wake of reported suspected ADRs from the official SIDC database. In our study, no ADR was reported as suspected without the identification of the brand name of the biological product. This is in line with the current European regulation on post-marketing biological medicines' traceability that is aimed at the identification and distinction between biological medicines by the trade name and batch number in order to identify any safety signals associated with each biological product. The perception of safety of biological treatment is crucial, as the number of patients treated by this innovative kind of pharmacotherapy is increasing. This is due to the introduction of new biological medicinal reference products, as well as the expiry of the patents for older reference biopharmaceuticals (23). Consequently, the rise in biological treatment has also increased the number of approved biosimilars, which, due to their lower cost, may bring the benefits of treatment to a larger number of patients (at an affordable price) (2, 4). Nonetheless, the safety of the treatment is, besides its effectiveness, a fundamental pillar of rational pharmacotherapy. When registering the reference biological medicinal products or a biosimilar, a pharmacovigilance plan needs to be presented, including a risk management plan. Recently, a new European legislation regarding pharmacovigilance has been introduced – suspected ADR ought to be noted and recorded by all parties involved (16). However, in the post-marketing era, the cheapest and most relevant way of obtaining information about the safety of a treatment are spontaneous reports of a suspected ADR to an authority (SIDC, in this case). Awareness of the need to inform the patient about the safety of treatment, but also the need to report suspected ADRs is lower in the Slovak Republic compared to other countries, which was also confirmed by the study of Varga et al. (24).

Nowadays, we are seeking an increasing trend in the number of suspected ADRs, that are reported. With a rapid increase in the utilization of biosimilars, there is also an increase in reporting ADRs induced by respective agents. In the frame of a recently published Italian real-world data analysis, infliximab biosimilars were shown to have an increased probability of being reported as suspected drugs in infusion reactions along with a decreased probability of being reported as suspected drugs in cases of lack of efficacy or infection (25). We must admit that the perceptiveness of the Slovak healthcare community towards the reported ADR remains still low, especially, when compared to other European countries (26, 27). Like in related Italian and Czech studies dealing with this topic (26, 27), our data consistently show, that the highest number of reports in the analysed three-year period (2015–2017), including all the reports concerning the intended group of biopharmaceuticals, were issued by healthcare professionals, although with a relatively low extent of contribution (41.47 %). More than one half of all the reports described severe ADRs, while in the case of infliximab and erythropoietin, the proportion of reports of suspected severe ADR amounted to three quarters. This can be explained through the fact, that common, well-known, and less significant ADRs are not sufficiently reported to SIDC either by healthcare professionals or by the patients. The most frequent

manifestations of suspected ADR in our data included severe allergic and dermatologic reactions of various types, which is in accordance with the Italian study (26). Moreover, there are reports of outburst of carcinomas (which were not diagnosed prior to the treatment) alongside biopharmaceutical treatment. Specifically, the carcinomas included basocellular eyelid carcinoma, carcinoma of left kidney, adenocarcinoma of lungs, neuroendocrine carcinoma of lungs (metastasizing into lymphatic nodes).

The first biosimilar in the European Union was approved in 2006 (2, 28). Ever since, more than 58 biosimilars have been introduced into clinical practice, without any reports of significant differences in the type, severity, or frequency of ADRs (when compared to reference biological medicinal products). Thus, practical evidence also suggests that the safety of biosimilars is comparable with the reference biopharmaceuticals (2, 29, 30). These conclusions are in accordance with our conducted analysis of the suspected ADR reports for the reference and biosimilar monoclonal antibody infliximab.

Our study is based on the spontaneous reporting system, and it is well known that it is affected by constraints that include under-reporting, lack of clinical data, and improper causality attribution (17). In this regard, a crucial limitation of this study is a relatively low number of reports of suspected ADR to SIDC in Slovakia during a 3-year period. Based on our experience, this might have been caused by several factors, such as: the insufficient perception of the risks associated with the treatment by healthcare professionals; a concern that a healthcare professional might made a mistake; a concern that reporting of suspected ADR can lead to a bureaucratic overload.

## Conclusion

Our study aimed at the perception of the safety of biological treatment did not find a robust evidence of increased risks associated with biosimilars in clinical practice in the Slovak Republic. Compared to the originators, biosimilars did not show an increased probability of being reported as suspected because of ADRs. In the era of biosimilars, there is an unmet need to improve awareness of these agents to facilitate discussions between healthcare professionals, regulatory authorities and patients. In context of such efforts, the concerns about the safety of treatment with biosimilars compared to the reference biologics might not be supported by current level of knowledge. Despite its intrinsic limitations, the spontaneous reporting system still represents a valuable and inexpensive tool, able to detect rare and serious ADRs not identified during premarketing clinical trials. Appropriate pharmacovigilance measures should be put in place to ensure that ADRs are correctly attributed to the responsible medicine at national and regional levels.

## References

1. **The Nobel Prize** in Physiology or Medicine 1984: [www.nobelprize.org/prizes/medicine/1984/summary/](http://www.nobelprize.org/prizes/medicine/1984/summary/) (access 16.1.2021).
2. **EMA: Biosimilars in the EU**. Information guide for healthcare professionals. Prepared jointly by the European Medicines Agency and the Euro-

pean Commission. [www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](http://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf), this guide was last updated on 02/10/2019 (access 16.1.2021)

**3. Felix T, Jordan JB, Akers C, Patel B, Drago D.** Current state of biologic pharmacovigilance in the European Union: improvements are needed. *Expert Opinion on Drug Safety* 2019; 18 (3): 231–240.

**4. Janjigian YY, Bissig M, Curigliano G, Coppola J, Latymer M.** Talking to patients about biosimilars. *Future Oncol* 2018; 14 (23): 2403–2414.

**5. European Commission, 2017.** What I need to know about biosimilar medicines. Information for patients, a consensus document. <https://ec.europa.eu/docsroom/documents/26643> (access 16.1.2021).

**6. NICE | The National Institute for Health and Care Excellence.** Biosimilar medicines, Key therapeutic topic Published: 26 February 2016 [nice.org.uk/guidance/ktt15](http://nice.org.uk/guidance/ktt15) [www.nice.org.uk/advice/ktt15/resources/biosimilar-medicines-58757954414533](http://www.nice.org.uk/advice/ktt15/resources/biosimilar-medicines-58757954414533) (access 16.1.2021).

**7. Mellstedt H.** Clinical considerations for biosimilar antibodies. *EJC* 2013; Suppl 11 (3): 1–11.

**8. Calvo B, Martínez-Gorostiaga J, Echevarria E.** The surge in biosimilars: considerations for effective pharmacovigilance and EU regulation. *Ther Adv Drug Saf* 2018; 9 (10): 601–608.

**9. Tabernero J, Vyas M, Giuliani R, et al.** Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* 2016; 1: e000142.

**10. Nowicki M.** Basic Facts about Biosimilars. *Kidney Blood Press Res* 2007; 30: 267–272.

**11. EMA: EMA/CHMP/437/04 Rev 1, EMA, Committee for Medicinal Products for Human Use: Guideline on similar biological medicinal products.** Date for coming into effect: 30 April 2015 [www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1\\_en.pdf](http://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf) (access 16.1.2021).

**12. EMA: EMA/CHMP/BWP/247713/2012, EMA, Committee for Medicinal Products for Human Use: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1).** Date for coming into effect: 1 December 2014 [www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active\\_en-0.pdf](http://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf), (access 16.1.2021).

**13. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HG.** Pharmacovigilance of biopharmaceuticals: challenges remain. *Drug Saf* 2009; 32: 811–817.

**14. Stricker, B.H., Psaty, B.M.** Detection, verification, and quantification of adverse drug reactions. *Br Med J* 2004; 329: 44–47.

**15. Reinisch W, Smolen J.** Biosimilar safety factors in clinical practice. *Semin Arthritis Rheumatism* 2015; 44: S9–S15.

**16. EMA: Guideline on good pharmacovigilance practices (GVP), Product- or Population-Specific Considerations II: Biological medicinal**

**products: [www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-ii\\_en-0.pdf](http://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-ii_en-0.pdf), (access 16.1.2021).**

**17. Palleria C, Leporini C, Chimirri S, et al.** Limitations and obstacles of the spontaneous adverse drugs Utilization and Safety Profiles of Infliximab Originator Versus Biosimilars in Italy 617 reactions reporting: Two “challenging” case reports. *J Pharmacol Pharmacother* 2013; 4: S66–72.

**18. Oza B, Radhakrishna S, Pipalava P, Jose V.** Pharmacovigilance of biosimilars – Why is it different from generics and innovator biologics? *J Postgrad Med* 2019; 65(4): 227–232.

**19. Lietzan EF, Sim LE, Alexander EA.** Biosimilar naming: how do adverse event reporting data support the need for distinct nonproprietary names for biosimilars? *FDLIs Food Drug Policy Forum* 2013; 3: 1–24.

**20. Grampp G, Felix T.** Pharmacovigilance Considerations for Biosimilars in the USA. *Bio Drugs* 2015; 29: 309–321.

**21. IMS Dataview, Units Year 2015–2017.** <https://ims-dataview.software.informer.com/>

**22. Annual reports of Institute of drug Control in Slovakia covering period 2001–2018.** [www.sukl.sk/hlavna-stranka/slovenska-verzia/o-nas/zakladne-dokumenty/vyročne-spravy?page\\_id=170](http://www.sukl.sk/hlavna-stranka/slovenska-verzia/o-nas/zakladne-dokumenty/vyročne-spravy?page_id=170), (access 16.1.2021).

**23. Declerck P, Danesi R, Petersel D, Jacobs I.** The Language of Biosimilars: Clarification, Definitions, and Regulatory Aspects. *Drugs* 2017; 77: 671–677.

**24. Varga Z, Haiar JM, Oberoi M et al.** Risk perception of NSAIDs in South Dakota in comparison with Slovakia and Greece. *Bratisl Med J* 2020; 121 (11): 771–774. DOI: 10.4149/BLL\_2020\_125.

**25. Scavone C, Sessa M, Clementi E et al.** Real world data on the utilization pattern and safety profile of infliximab originator versus biosimilars in Italy: A multiregional study. *BioDrugs* 2018; 32: 607–617.

**26. Cutroneo PM, Isgrò V, Russo A et al.** Safety Profile of Biological Medicines as Compared with Non-Biologicals: An Analysis of Italian Spontaneous Reporting System Database. *Drug Saf* 2014; 37 (11): 961–970.

**27. Kopečná E, Deščiková V, Vlček J, Mladá J.** Adverse drug reaction reporting in the Czech Republic 2005–2009. *Int J Clin Pharm* 2011; 33: 683.

**28. Schiestl M, Zabransky M, Sörgel F.** Ten years of biosimilars in Europe: development and evolution of the regulatory pathways. *Drug Des Devel Ther* 2017; 11: 1509–1515.

**29. Langhauser K.** Race to the biosimilar space. Pharma navigates unfriendly terrain to reach the next frontier in affordable drugs. Race to the biosimilar space. *Generic / Large Molecule*. Apr 29, 2019: [www.pharmamanufacturing.com/articles/2019/race-to-the-biosimilar-space/](http://www.pharmamanufacturing.com/articles/2019/race-to-the-biosimilar-space/) (access 16.1.2021).

**30. Ingrassiotta Y, Cutroneo PM, Marcianò I, Giezen T, Atzeni F, Trifirò G.** Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction. *Drug Saf* 2018; 41 (11): 1013–1022.

Received February 18, 2021.

Accepted February 21, 2021.