Biosimilar medicines and patient registries – expectations, limitations, and opportunities

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Abstract

Introduction: Biology therapies in a various medical specializations and for a broad spectrum of indications were launched during last two decades. As a new in class the therapies were obliged to provide additional data regarding efficacy and safety after their real medical practice integration. Patient registries, databases collecting various patient data, were introduced to grant data on the treatment effectiveness, safety, and long-term on treatment survival. Satisfactory treatment effect and acceptable safety profile were confirmed after couple of years of careful observation. However, the benefits were usually offered at much higher treatment costs compared to the standard therapies. Biologically similar drugs, so-called biosimilars (B.S), are being launched after original molecule patent protection expiry during recent years. They were expected as an ideal solution to avoid distinct impact on the medical budget: comparable effect for less money. The unsubstantiated doubts about biosimilar efficacy and safety were the reason of the late launch in many markets. Since biosimilars are considered as new therapy entities, the cautiousness to certain extent should be required. Information gained from post-marketing observations and patient registries over several years, confirmed the biosimilar product comparable quality. Healthcare budget savings could secure easier therapy access for more new patients.

Key words: biology therapy registries, biosimilars, biologically similar drugs, HTA (health technology assessment)

BIOSIMILAR MEDICINES

Since the new millennium innovative medicines began to play an important role in the treatment of many diseases in oncology, rheumatology, gastroenterology, dermatovenerology. Drugs generally called "biologics", because they are derived from living organisms or as the products of their metabolism, act at the different levels of the disease process. The everlasting headliners of treatment armamentarium, e.g. in dermatology, were substituted and new books with unusual chapters containing molecular schemes of action were published (1, 2). The manufacturing procedure during which the biologics are obtained is significantly more complex than the one of conventional drugs. The difference in the total cost per unit of purified active substance obtained is even more significant. The negative implications of the new drug introduction with potentially better efficacy and safety were a higher demand on the country´s healthcare system budget.

Terminology

The European Medicines Agency (EMA) defines a biologically similar medicine as a biological medicine that contains the version of the active substance of the already authorized original biological medicine (reference medicine) in the European Union (EU). It must have a similarity with the reference medicinal product determined in terms of quality characteristics, biological activity, safety, and efficacy. The standard generic approach (demonstration

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of bioequivalence with a reference medicine through appropriate bioavailability studies) which is applicable to most chemically derived medicinal products is not, in principle, sufficient to demonstrate the similarity of products derived from biological/biotechnological products due to their complexity (3). A similar definition is also used by the Food and Drug Administration (FDA) and World Health Organization (WHO) (4, 5).

But until now, however, there is no precise definition of biological medicinal products that have the same mechanism of action as the originally authorized biologic, but which contain certain structural modifications that can provide an improvement in the clinical profile compared to the original. In general, these products are called in marketing terminology as biobetters (6).

Another category is a group of medicines called bioquestionables which are declared to be copies of the original molecules, but have not been followed by a standardized procedure of comparative development against the original drug (7).

Biosimilar development

The complexity of the primary, secondary, tertiary, and quaternary structures of the macromolecule makes it impossible to produce a perfect copy. On the other hand, however, it is common for the original drug that two batches differ from each other and do not resemble the originally approved molecule (8). When developing original innovative drugs, the same emphasis is placed on all parameters. While during the development of B.S a biological activity and physico-chemical properties are of major concern. This reduces the likelihood that any of the properties originating from a different structure would result in a failure in subsequent clinical evaluation. Only after this pre-assessment, the efficacy, safety, and one of the most important parameters – immunogenicity is being evaluated in clinical studies (9,10).

Biology therapy actual market situation

Estimated global spending on biological treatment in 2016 was about 210 billion U.S. dollars (USD). It accounts for almost 19 % of all drug spending. 7 of the 10 most expensive medicines (61 billion USD) for 2016 are bio-based or biotechnologically produced. The biology therapy market should grow by almost 11 % per year by 2024. The total estimated expense for these medicines in Slovakia was 151 million EUR, which is approximately 10.5 % of all spending on medicines and medical devices in 2016 (11, 12, 13, 14, 15).

Biotherapeutic development is costly and can last up to 15 years from the discovery of the molecule until the drug is marketed. The median cost level for a pharmaceutical company that has marketed more than 3 drugs is 4.2 billion USD per one drug. Those who launched more than 4 drugs spent on an average 5.3 billion USD (16).

Biosimilar medicines market placement obstacles

Many pharma companies including the original ones also try to reduce their costs by turning their attention to B.S or biobetters to prevent an increased risk of failure in the development of a new innovative drug. Around 700 biosimilars were under development worldwide by the end of 2014. At a typically reduced price of 20–30 %, only the EU alone could bring a cost reduction of up to 33 billion USD to 2022 (17).

It is, therefore, interesting that the EMA does not have a single legislative guide in this respect and that the definition of interchangeability, exchangeability, substitution, or switchability is left to the competent authorities of the Member States. In the case of the Slovak Republic, it is the State Institute for Drug Control (SIDC), with the following rules:

1. No substitution at the pharmacist level is allowed
2. Interchangeability is accepted only based on medical specialist decision since a sufficient amount of information on efficacy and safety is available
3. Pharmacovigilance procedures are similar to those applied in case of reference products while some additional measures might be required based on registration approval conditions.

Not all the Member States support the idea of free interchangeability in this group of medicines (5). B.S were divided into two groups for this purpose by the legislative measures in the United States:

1. Biologically similar drugs for which the same clinical effect as the reference medicine is assumed
2. Interchangeable drugs that can be freely changed for reference medicine at any time.

One of the main reasons for doubts about the ability of prescribing physicians or pharmacists to make a proper decision about the change of treatment is immunogenicity (18). Based on the clinical experience with the use of biological treatment, it is known that the foreign protein components of the drug have the potential to elicit an immune response of the patient's organism in the form of a reduction in the efficacy of the treatment itself or even life-threatening anaphylactic shock (19).

The above mentioned information was backed up by official documents without sufficient explanation; it was speculated that B.S would never be the same as the original drug, and, thus, it will not be possible to achieve the same efficacy and safety. The most frequently cited example is the approval of 12 erythropoietin molecules in Thailand between 1998–2002. The approval procedure was the one usually used for comparing standard generic chemically synthesized drugs, however. Because of the antibodies development, more than 200 patients in advanced stage of renal disease developed a rare diagnosis – anti-erythropoietin antibody-mediated pure red blood cell aplasia (7).

The EMA itself just recently stated in its official online document – Questions and Answers on the topic of B.S - that it is not possible for biologically similar drugs to be identical to the reference drug, without further explanation (20). This misleading information was corrected in the actual version of the document by providing an exact definition as mentioned above.

The results of an interview based research among doctors and patients revealed that both groups perceive the current situation similarly. More than half of the interviewed physicians, among majority of specializations, in the US do not believe that B.S will be as good as original innovative medicines. The little is known that the primary structure of the B.S molecule must always be the same, and the qualitative properties may vary from batch to batch within a strictly defined limit, which is the same for B.S as well as for the original product. Every B.S. manufacturer under the FDA regulation has to include at least one change of treatment from the original to B.S within the clinical trial protocol (21).

Observation in 7 European countries, including Poland, revealed that 90.5 % of the first prescribing decisions were based on the information contained in the Summary of Product Characteristics (SmPC). The problem, however, is that in the case of B.S drugs their SmPC is almost an exact copy of the original product. Physicians would welcome an extension for additional information, e.g. which one comes from the original and which was obtained during the clinical trials with B.S. Since it is not possible to obtain the data on the efficacy and safety in all approved indications of the former original product in the clinical trials, extrapolation is used to overcome this limitation. If the drug yield reliable results during clinical trials in the treatment of Crohn's disease, thus after the totality of evidence analysis, in the direct comparison of all available parameters with the original drug, it can be assumed that it would also successfully treat e.g. rheumatoid arthritis (22). Although this information is missing in SmPC. 70 % of physicians refer to it as helpful or very helpful (23).

The online questionnaire action of the European Federation of National Associations for Crohn's Disease and Ulcerative Colitis (EFCCA) conducted in 2015, asked their members from across the EU for their knowledge and attitude towards B.S. Majority of patients did not know what B.S are and among those who knew, only 31 % of respondents were totally convinced of using B.S. Nearly 50 % expressed uncertainty about safety and 40 % about efficiency (24). The results correspond to the opinions obtained from similar surveys among gastroenterology specialist. Two B.S infliximab molecules were launched in 2013. 90 % of

physicians said that the purpose of this initiative is to save money in the healthcare system. But only half believed it will fulfil the expectations. Most respondents expected guidelines preparation and patient registries establishment by professional societies. Most physicians also refused to accept the extrapolation of data from rheumatology for the treatment of gastroenterology diagnoses. Only 10 % would agree to the interchangeability of the reference drug, if the patient has been already set to treatment and has no medical reason to discontinue (25). The research was repeated two years later. Only 17 % of physicians had no experience with B.S and up to 44.4 % agreed with the interchangeability between the original molecule and its equivalent. It is clear that better awareness and direct personal experience have contributed to a positive outcome (26). Although similar survey was not conducted in the Slovak Republic, the opinion of experts in gastroenterology, rheumatology, and dermatovenerology was similarly conservative based on the official document published in 2013 as a Standard diagnostic and therapeutic procedure – Rational treatment with B.S. Biosimilars were recommended only for biology therapy naive patients and only for the indications that were not approved by extrapolation (27). The generic manufacturer representatives disputed that such materials published under the gestion of the Ministry of Health are in contradiction to the mentioned rational pharmacotherapy idea.

Actual biosimilar market situation

Omnitrope (somatotropine) was the first medicine approved in the EU to be B.S in 2006. The EMA approved 41 B.S as of November 2017 (Tab. 1), including human growth hormone, granulocyte colony stimulating factors, insulin, follicle stimulating hormone, tumor necrosis factor, epidermal growth factor receptor, etc. Three marketing authorizations have been withdrawn at the request of the marketing-authorization holder: two for B.S filgrastim – Filgrastim ratiopharm in April 2011 and Biograstim in December 2016, and one somatotropin – Valtropin in May 2012 (28).

Tab. 1. EMA approved biosimilars

Product name	Active substance	Authorization date	Manufacturer
Abasaglar	insulin glargine	2014	Eli Lilly/Boehringer Ingelheim
Abseamed	epoetin alfa	2007	Medice Arzneimittel Pütter
Accofil	filgrastim	2014	Accord Healthcare
Amgevita	adalimumab	2017	Amgen
Benepali	etanercept	2016	Samsung Bioepis
Bemfola	follitropin alfa	2014	Finox Biotech
Binocrit	epoetin alfa	2007	Sandoz
Biograstim	filgrastim	2008; withdrawn 2016	CT Arzneimittel
Blitzima	rituximab	2017	Celltrion
Cyltezo	adalimumab	CHMP 2017	Boehringer Ingelheim
Epoetin alfa Hexal	epoetin alfa	2007	Hexal
Erelzi	etanercept	2017	Sandoz

Filgrastim Hexal	filgrastim	2009	Hexal
Filgrastim ratiopharm	filgrastim	2008; withdrawn 2011	Ratiopharm
Flixabi	infliximab	2016	Samsung Bioepis
Grastofil	filgrastim	2013	Apotex
Imraldi	adalimumab	2017	Samsung Bioepis
Inflectra	infliximab	2013	Hospira
Inhixa	enoxaparin sodium	2016	Techdow Europe
Insulin lispro Sanofi	Insulin lispro	CHMP 2017	Sanofi-Aventis
Lusduna	insulin glargine	2017	Merck (MSD)
Movymia	teriparatide	2017	Stada Arzneimittel
Nivestim	filgrastim	2010	Hospira
Omnitrope	somatotropine	2006	Sandoz
Ontruzant	trastuzumab	CHMP 2017	Samsung Bioepis
Ovaleap	follitropin alfa	2013	Teva Pharma
Ratiograstim	filgrastim	2008	Ratiopharm
Remsima	infliximab	2013	Celltrion
Retacrit	epoetin zeta	2007	Hospira
Ritemvia	rituximab	2017	Celltrion
Rituzena	rituximab	2017	Celltrion
Rixathon	rituximab	2017	Sandoz
Riximyo	rituximab	CHMP 2017	Sandoz
Silapo	epoetin zeta	2007	Stada Arzneimittel
Solymbic	adalimumab	2017	Amgen
Terrosa	teriparatide	2017	Gedeon Richter
Tevagrastim	filgrastim	2008	Teva Generics
Thorinane	enoxaparin sodium	2016	Pharmathen
Truxima	rituximab	2017	Celltrion
Valtropin	somatotropine	2006; withdrawn 2012	BioPartners
Zarzio	filgrastim	2009	Sandoz

Europe is a pioneer in this respect, as the FDA approved only 8 B.S as of December 2017 (29, 30). Since the first edition of the official Overarching guidelines, it has released its 2nd revised edition in 2012 and has been fine-tuning an approval mechanism that is currently serving as an example for the FDA as well (31). An important role in this process is played by post-marketing monitoring of the efficacy and safety to detect rare side effects. According to the EMA's recommendations, each registered medicinal product should have its own risk management plan and pharmacovigilance system or should connect to the existing solutions (32). Remsima (Celltrion) authorization documentation included also the obligation to undergo patient registry monitoring (33).

One-year clinical trial called NOR-SWITCH comparing two patient groups was conducted in 2015, with the support of the Norwegian Ministry of Health. The treatment efficacy and safety was compared in six possible indications in patients after changing from the original infliximab drug to the biological equivalent of infliximab (CT-P13) to the group of patients who maintained the original treatment. The study demonstrated that B.S was not inferior to the original molecule (34). The results were disputed by Janssen Biotech as the manufacturer of the original Remicade product when it remarked that in the case of a group of patients treated for Crohn's disease with their therapy altered, the proportion of patients who experienced worsening of disease after the change was beyond the permitted interval (35). In spite of this objection, the results of the study and other actual publication sources have become the basis for - Recommendations for the evaluation and use of biosimilars for the treatment of rheumatic diseases, which were consensually endorsed by the international panel of experts on rheumatology (36, 37):

1. B.S must reduce costs and, thus, provide easier access to treatment
2. Approved B.S can be used to treat patients in the same way as a reference medicine
3. Because there were no statistically significant differences in the immunogenicity of B.S and reference drugs. There is no need to monitor the level of antibodies in normal clinical practice
4. Relevant data from preclinical and clinical phase 1 should be available at the time of phase 3 clinical trial data publication
5. The confirmation of the efficacy and safety is sufficient to extrapolate to other diagnoses that had been original product authorized for
6. The available evidence suggests that the change of treatment from the reference medicine to B.S is safe and, therefore, there is no reason to expect that a change in treatment between B.S of the same reference medicinal product would result in another clinical outcome but consideration should be given to the patient's opinion
7. Multiple changes between B.S and the original drug (or between B.S) should be evaluated in patient registers
8. No change should be made without prior notice to the patient and the attending physician.

Consensus also became the subject of further discussions. The financial contribution of B.S from the patient point of view, the value of the data obtained from the patient registries, as well as NOR-SWITCH clinical results significance were questioned (38).

It is likely that similar stylization will be adapted by other specializations within their recommendations as their latest official opinions preceded the publication of NOR-SWITCH and took rather cautious attitudes (39). Danish Registry – Danish database of biological treatment in rheumatology (DANBIO) results could provide necessary support during decision making process. National recommendations were issued in 2015 requiring a change in the treatment of patients treated with the original infliximab medicine without medical reason. All patients, in all three rheumatology indications (rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis) in Denmark, were converted to CT-P13. The activity of the disease was stable after 12 months. The immunogenicity results were the same throughout the follow-up period. B.S was comparable in the monitored parameters. The patient's annual treatment adherence rate was slightly lower in the B.S group (40).

Approximately the same preliminary results were obtained with the biologically similar SB4 (etanercept) (41). Similar results confirming the non-inferiority of B.S versus original molecule were also achieved with GP2013 in oncology (rituximab), although in the biologically naive population of patients with advanced stage of follicular lymphoma only (42, 43).

PATIENT REGISTRIES AS AN IMPORTANT SOURCE OF CLINICAL DATA

General data on oncology diseases prevalence began to be reported for the first time for the statistical purposes in 1904 in Germany. Subsequently, local and regional registries began to appear alongside hospitals. The first national oncology registry was established in Norway and Denmark immediately after the II. world war (44).

Mandatory reporting of malignant tumors was introduced in the former Czechoslovakia in 1952. The National Oncology Registry of the Slovak Socialist Republic was established in 1976. Later it was extended to the whole country and the data was retrospectively completed until 1968 (45). The register was founded and supervised from the very beginning until 2005 by assoc. prof. Ivan Plesko, MD.

The role of the registry is to administer the long-term records of oncological patients from the Slovak Republic. To supplement the data about the patient and the diseases, while respecting the internationally accepted classification systems. Unfortunately, the most recent data available as of December 2017 are for 2010 (46).

The advances in biotechnology brought a significant change in the standards of treatment based on the use of drugs derived from the chemical compounds by the end of 20th century. New approaches using in vitro synthesized protein molecules have been introduced into the portfolio of systemic treatment of autoimmune inflammatory diseases. However, the situation in the treatment of rheumatic diseases, psoriasis, and intestinal bowel disease (IBD) has also brought new challenges from the point of view of short and long-term efficacy and safety data collection. Immunosuppressive therapy is a potential risk factor for the development of lymphoproliferative malignancies and serious life-threatening infections. The first biological drugs were registered for the treatment of rheumatoid arthritis. European countries have introduced patient registries to monitor their proper use. The publications (such as guidelines or clinical resource materials) were issued to answer two questions: WHAT? and HOW? to properly monitor (47, 48). The first registries were initiated in Scandinavian countries and were based on the regional clinical databases of rheumatic patients treated with systemic therapy. The European league against rheumatism proposed an epidemiological surveillance system over the long-term risk of biology therapy in the year 2000. It involved 3 countries: Sweden, the Netherlands, and the United Kingdom, as they had a centralized healthcare system and national mortality and oncology database registries. The project was funded by the pharmaceutical industry, but the outcomes were evaluated by the independent committee for surveillance of data and statistics. The information was obtained by means of patient questionnaires, by checking the patient documentation, and by scanning the links to the mentioned database registries (49, 50, 51).

Not all the European countries had the same need to introduce registries at the time of biology therapy launch. But signals from the initial analyzes in 2003 revealed the importance of security risks monitoring. For example, in DANBIO, where about 90 % of all patients treated by biologics are registered, 20 % increase in the incidence of side effects was recorded compared to the standard data of the Danish medical agency. Subsequent rheumatology registries were introduced throughout the continent in the following decade (52, 53, 54).

The registries have grown through additional patient populations and new groups of parameters monitored that have been added with the increasing number of new biologics and broadening indication portfolio. A better understanding of complex diagnoses such as psoriatic arthritis has required and still requires the collection of substantial amount of

information on the clinical condition, laboratory and radiology values in long-term. The patients are monitored in the rheumatology and dermatology outpatient due to the manifestation of joint and skin symptoms, which requires close mutual co-operation and coordination of procedures. The suggested solution was to extend existing or create separate new registries. There have also been a number of registries administered by pharmaceutical companies as an obligation stated by the regulatory authorities. They start requiring so-called PASS (post registration safety studies) as part of the registration process. However, the scientific value of these databases is low due to limited access for the third parties. Only about 1/3 of post-marketing surveillance studies is being completed and some will not start at all (55, 56, 57, 58, 59, 60, 61).

The greatest benefit of registries compared to observation post-marketing studies under the control of pharmaceutical companies is that patients are monitored in the registries regardless of the medicine they are taking. They are usually included in the registry after drug prescription and follow-up continues even when treatment is terminated or changed (62).

The study of the international incidence of childhood oncology diseases based on population registries is the proof, that not every registry can be a full source of valuable information. Only 1/3 out of 532 oncology registries approached fulfilled the qualitative standards (63). All participants included in the process of creation, approval, management, and evaluation should harmonize the recommendations for evaluating registry data quality in order to avoid any doubts about the value of data extracted (64).

Despite the efforts in rheumatology and dermatovenereology, no biology therapy registry even in oncology and gastroenterology is currently active in Slovakia (65, 66). This status is difficult to accept if we take into consideration that the Czech Republic, with the similar history and actual economic potential, has an active register in each of these specializations (67, 68, 69, 70) (Tab. 2).

Tab. 2. Registries active in Czech Republic

Name	Established	Specialisation	Supervisory body
CNCR	1976	Oncology	Institute of Health Information and Statistics of the Czech Republic
ATTRA	2002	Rheumatology	Czech rheumatological society
BIOREP	2005	Dermatovenereology	Czech dermatovenereology society
CREDIT	2016	Gastroenterology	Czech gastroenterology society

The future of biosimilar medicines in Slovakia

The clear conclusion is that the promotion and enlightenment that accompanied the arrival of original molecules in the first decade of the 21st century proved to create an "aura" of unsurpassed efficiency and safety around the biologics. There is obviously no interest of their manufacturers to promote a comparable quality of B.S. Apparently, current generic manufacturers do not want to take this role either, no matter what their reason is. It is a misinterpretation of their own position. They are not afraid to play a role of almost an original molecule when it comes to the quality. But when it comes to the obligations arising from this position, they defend themselves with the argument that generic drugs have never led a campaign other than price-dumping. Without a massive information campaign, however, no significant progress can be expected in the absence of support and pressure from the regulatory authorities. Most of the available publications and quoted

experts already agree that B.S will allow better access to modern treatment across different specializations: gastroenterology, nephrology, oncology, rheumatology, dermatovenereology, etc. The current market share of B.S versus originator in Slovakia is slightly less than 7 %, three years after the launch (15). For comparison, the significant cost reduction allowed treatment start in more than 1,000 new patients enrolled on the waiting lists compared to the previous year, after the introduction of B.S infliximab into gastroenterology clinical practice in the Czech Republic (31).

Two budget impact analysis of B.S medicine CT-P13 for the treatment of rheumatoid arthritis showed that the introduction of biosimilar infliximab could also bring savings in the Slovak Republic of 20–25 % compared to the original molecule (31). However, the question remains whether the declared price level and the associated better availability of treatment are not promotional claims only. The price difference must be so motivating to be worth of administrative burden and possible, although unlikely, clinical complications (38).

Proactive approach is also expected on the side of regulatory bodies (SIDC and Ministry of Health – MoH SR). The SIDC as a competent authority to which the EMA has transferred the discretionary powers of B.S interchangeability and MoH SR, which has the power to follow the Danish example. Mandatory reduction of B.S market entry price will be adjusted by amending the Act No. 363/2011 Coll. (on the scope and conditions of payments for medicines, medical devices, and dietetic foods from public health insurance and amending certain acts, as amended) in January 2018. Disputable remains the validity of the actual indication limitations. Suggested market entry price reduction of 30 % offers the potential of less restricting prescription limitations e.g. from specialized rheumatology treatment centers to regional rheumatology outpatient offices. More patients, earlier on therapy for the same money, what is perfectly in line with the current strategy of the MoH SR (71). The Health Insurance Company would not need to approve every initiation and continuation of the treatment through written requests, but the revision will rather be directed to more targeted in-depth prescription audits with adequate sanctions for breaking the rules.

CONCLUSION

If the B.S are given the position they deserve while applying proper pharmacovigilance procedures through the system which operates on the principle of shared online databases, either as a sub-unit of government developed eHealth or as a stand-alone software platform, based on the modified original version of the database proposed for rheumatology and dermatology (65). It would contribute to budget savings on the payer side, improving the patient treatment access, better reporting on the treatment benefits and risks, as well as modernizing Slovak healthcare system in general.

REFERENCES

1. Pec J, Chromej I, Martinaskova K, Chribikova I, Danilla T, Adamicova K, Babal P, Fetisovova Z, Frlickova Z, Lidaj J, Masarovicova A, Minarikova E, Musak L, Osusky P, Pec M, Plank L, Vodicka P, Hegyi V. Chronicka loziskova psoriaza: komplexny pohlad na problematiku a biologicka liecba. 1. vydanie. Banská Bystrica: Dali; 2006.
2. Pec J, Urbancek S, Martinaskova K, Simaljakova M, Osusky P, Adamicova K, Adamovicova K, Adamkov M, Babal P, Cerkalova I, Fetisovova Z, Holy B, Chribikova I, Chromy Stefan, Kubatka P, Mensikova J, Mitterova V, Nejdkova A, Pajerchin D, Pec J jr., Pec M, Rasochova E, Stracenska J, Vrtikova E, Zaujec L. Liecba psoriazy acitretinom. 1. vydanie. Bratislava: Univerzita Komenského; 2007.
3. European Medicines Agency, "http://www.ema.europa.eu," [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. [Accessed 28 november 2017].

4. U.S. Food and drug administration, "www.fda.gov," [Online]. Available: https://www.fda.gov/-Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm#biosimilar. [Accessed 29 november 2017].
5. Crommelin D, de Vliger J, Weinstein V, Muhlebach S, Shah V, Schellekens H. Different Pharmaceutical Products Need Similar Terminology. AAPS J 2014; 16(1): 11-14.
6. Biosimilar resource center, "www.biosimilarsresourcecenter.org," [Online]. Available: https://www.-biosimilarsresourcecenter.org/faq/what-is-a-biobetter/. [Accessed 29 november 2017].
7. Halim L, Brinks V, Jiskoot W, Romeijn S, Praditpornsilpa K, Assawamakin A, Schellekens H. How bio-questionable are the different recombinant human erythropoietin copy products in Thailand?. Pharm Res 2014; 31(5): 1210-1218.
8. Schenider C. Biosimilars in rheumatology: the wind of change. Ann Rheum Dis 2013; 72(3): 315-318.
9. Goel N, Chance K. Biosimilars in rheumatology: understanding the rigor of their development. Rheumatology (Oxford) 2017; 56(2): 187-197.
10. Jahnsen J. Clinical experience with infliximab biosimilar Remsima (CT-P13) in inflammatory bowel disease patients. Therap Adv Gastroenterol 2016; 9(3): 322-329.
11. Transparency Market Research, "www.prnewswire.com," [Online]. Available: https://www.prnewswire.com/news-releases/global-biologics-market-will-be-worth-us479-752-million-by-2024-global-industry-analysis-size-share-growth-trends-and-forecast-2016---2024-tmr-596150-181.html. [Accessed 30 november 2017].
12. Reuters, "www.reuters.com," [Online]. Available: https://www.reuters.com/article/us-health-pharmaceuticals-spending/global-prescription-drug-spend-seen-at-1-5-trillion-in-2021-report-idUSKBN13V0CB. [Accessed 30 november 2017].
13. Genetic engineering and Biotechnology news, "www.genengnews.com," [Online]. Available: https://-www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868. [Accessed 30 november 2017].
14. INESS, "www.cenastatu.sk," [Online]. Available: http://www.cenastatu.sk/teachers/vvv_full_-2016.pdf. [Accessed 29 november 2017].
15. IMS health, "IMS data," 2016.
16. Forbes, "www.forbes.com," [Online]. Available: https://www.forbes.com/sites/matthewherper/-2013/08/11/the-cost-of-inventing-a-new-drug-98-companies-ranked/#7b5fb3042f08. [Accessed 30 november 2017].
17. Pharmatimes online, "www.pharmatimes.com," [Online]. Available: http://www.pharmatimes.-com/news/over_700_biosimilars_now_in_development_worldwide_report_1002547. [Accessed 30 november 2017].
18. RAPS - Regulatory affairs professionals society, "www.raps.org," [Online]. Available: http://www.-raps.org/Regulatory-Focus/News/2017/03/31/27240/Are-Biosimilars-Interchangeable-in-the-EU-A-New-Perspective/. [Accessed 1 december 2017].
19. Baker M, Reynolds H, Lumicisi B, Bryson C. Immunogenicity of protein therapeutics. Self Nonself 2010; 1(4): 314-322.
20. Danese S, Fiorino G, Raine T, Ferrante M, Kemp K, Kierkus J, Lakatos P, Mantzaris P, van der Woude J, Panes J, Peyrin-Biroulet L. ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease-An Update. J Crohns Colitis 2017; 11(1): 26-34.
21. Cohen H, Beydoun D, Chien D, Lessor T, McCabe D, Muenzberg M, Popovian R, Uy J. Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians. Adv Ther 2017; 33(12): 2160-2172.
22. Alten R, Cronstein B. Clinical trial development for biosimilars. Semin Arthritis Rheum 2015; 44(6): Suppl S2-8.
23. Hallersten A, Furst W, Mezzasalma R. Physicians prefer greater detail in the biosimilar label (SmPC) - Results of a survey across seven European countries. Regul Toxicol Pharmacol 2016; 77: 275-281.
24. Peyrin-Biroulet L, Lonnfors S, Roblin X, Avedano L. Patient Perspectives on Biosimilars: A Survey

by the European Federation of Crohn's and Ulcerative Colitis Associations. J Crohns Colitis 2017; 11(1): 128-133.
25. Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. J Crohns Colitis 2014; 8(11): 1548-1550.
26. Danese S, Fiorino G, Michetti P. Changes in Biosimilar Knowledge among European Crohn's Colitis Organization [ECCO] Members: An Updated Survey. J Crohns Colitis 2016; 10(11): 1362-1365.
27. Rovensky J, Jurgos L, Pec J. 58. list racionálnej farmakoterapie - Racionálna liečba biologicky podobnými liekmi v indikáciách bioterapeutík. Štandarný diagnostický a terapeutický postup 2013; 16(7): 1-4.
28. Generics and Biosimilars initiative, "http://www.gabionline.net/," [Online]. Available: http://-www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe. [Accessed 29 november 2017].
29. U.S. Food and drug administration, "www.fda.gov," [Online]. Available: https://www.fda.gov/-downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf. [Accessed 1 december 2017].
30. U.S. Food and drug administration, "www.fda.gov," [Online]. Available: https://www.fda.gov/-NewsEvents/Newsroom/PressAnnouncements/ucm587378.htm. [Accessed 1 december 2017].
31. Khraishi M, Stead D, Lukas M, Scotte F, Schmid H. Biosimilars: A Multidisciplinary Perspective. *Clin Ther 2016; 38(5):* 1238-1249.
32. European Medicine Agency, "www.ema.europa.eu," [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. [Accessed 2 december 2017].
33. European Medicine Agency, "www.ema.europa.eu," [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/-WC500151486.pdf. [Accessed 2 december 2017].
34. Jorgensen K, Olsen I, Lorentzen M, Bolstad N, Haavardsholm E, Lundin K, Mork C, Jahnsen J, Kvien T, NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet 2017; 389(10086):* 2304-2316.
35. Healio Gastroenterology, "www.healio.com," [Online]. Available: https://www.healio.com/gastroenterology/inflammatory-bowel-disease/news/online/%7B10599c7d-b5ee-4646-b4c1-59dc1a0b918b%7D/nor-switch-switching-to-remicade-biosimilar-safe-noninferior. [Accessed 3 december 2017].
36. Kay J, Schoels M, Dorner T, Emery P, Kvien T, Smolen J, Breedveld F, Biosimilars to treat rheu diseases task force. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis 2017* , no. pii: annrheumdis-2017-211937. doi: 10.1136/annrheumdis-2017-211937. [Epub ahead of print].
37. PubMed Health, "www.ncbi.nlm.nih.gov," [Online]. Available: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0095881/. [Accessed 3 december 2017].
38. Fleischmann R. Therapy: Biosimilars in rheumatology - why, how and when in 2017. *Nat Rev Rheumatol 2017; 13(12):* 701-703.
39. Moots R, Azevedo V, Coindreau J, Dorner T, Mahqoub E, Mysler E, Scheinberg M, Marshall L. Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician. *Curr Rheumatol Rep 2017; 19(37):* 1-16.
40. Glintborg B, Sorensen I, Loft A, Lindegaard H, Linauskas A, Hendricks O, Hansen I, Jensen D, Manilo N, Espesen J, Klarlund M, Grydehoj J, Dieperink S, Kristensen S, Olsen J, Nordin H, Chrysidis S, Dalsgaard Pedersen D, Sorensen M, Andersen L, Gron K, Krogh N, Pedersen L, Hetland M. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis 2017; 76(8):* 1426-1431.

41. Glintborg B, Sorensen I, Loft A, Heltand M. FRI0190 Clinical outcomes from a nationwide non-medical switch from originator to biosimilar etanercept in patients with inflammatory arthritis after 5 months follow-up. Results from the danbio registry. in *Conference Paper: Annual European Congress of Rheumatology*, 2017.
42. Kim W, Buske C, Oqura M, Jurczak W, Sancho J, Zhavrid E, Kim J, Hernandez-Rivas J, Prokharau A, Vasilica M, Nagarkar R, Osmanov D, Kwak L, Lee S, Lee S, Bae Y, Coiffier B. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. *Lancet Haematol 2017; 4(8):* e362-e373. doi: 10.1016/S2352-3026(17)30120-5. Epub 2017 Jul 14.
43. Jurczak W, Moreira I, Kanakasetty G, Munhoz E, Echeveste M, Giri P, Castro N, Pereira J, Akria L, Alexeev S, Osmanov E, Zhu P, Alexandrova S, Zubel A, Harlin O, Amersdorffer J. Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study. *Lancet Haematol 2017; 4(8):* e350-e361. doi: 10.1016/S2352-3026(17)30106-0. Epub 2017 Jul 14.
44. Missouri State Tumor Registrars Association - MOSTRA, "https://mostra-ctr.org," [Online]. Available: https://mostra-ctr.org/AboutUs/RegistrarsandOurCode/TheOriginoftheCancerRegistry/tabid/145/Default.aspx.[Accessed 3 december 2017].
45. Ondrusova M. Narodny onkologicky register Slovenskej republiky - zakladny zdroj informacii v zdravotnickej politike. *Onkologia (Bratisl.) 2006; 1:* 64-65.
46. NCZI - Narodne centrum zdravotnickych informacii, "http://www.nczisk.sk," [Online]. Available: http://www.nczisk.sk/Publikacie/Pages/Edicia-analytickych-publikacii.aspx. [Accessed 3 december 2017].
47. Pec J, Martinaskova K, Valentova V, Vorcakova K, Adamicova K, Urbancek S, Lipovsky P, Baloghova J, Drotarova K, Fetisovova Z, Hemza M, Chribikova I, Jautova J, Lidaj J, Linkeschova E, Masarovicova A, Osusky P, Palotai T, Pec M, Pecova K, Polak I, Psotova M, Surnakova K, Salkovska J, Svec J, Simaljakova M, Tindirova M, Vojtas I, Zaujec L. Systemova liecba psoriazy u dospelych. 1. vydanie. Bratislava: Univerzita Komenskeho; 2010.
48. Gliklich R, Dreyer N. Registries for evaluating outcomes: User´s guide. 2 ed. Rockville, MD; Agency for Healthcare Research and quality; 2010.
49. Sokka T, Krishnan E, Hakkinen A, Hannonen P. Functional disability in rheumatoid arthritis patients compared with a community population in Finland. *Arthritis Rheum 2003; 48(1):* 59-63.
50. Kvien T, Uhlig T. The Oslo experience with arthritis registries. *Clin Exp Rheumatol 2003; 21*(5 Suppl 31): S118-122.
51. Silman A, Klareskog L, Breedveld F, Bresnihan B, Maini R, Van Riel P, Symmons D. Proposal to establish a register for the long term surveillance of adverse events in patients with rheumatic diseases exposed to biological agents: the EULAR Surveillance Register for Biological Compounds. *Ann Rheum Dis 2000; 59(6):* 419-420.
52. Mariette X, Gottenberg J, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology (Oxford) 2011; 50(1):* 222-229.
53. Hetland M, Unkerskov J, Ravn T, Friis M, Tarp U, Andersen L, Petri A, Khan H, Stenver D, Hansen A, Ostergaard M. Routine database registration of biological therapy increases the reporting of adverse events twentyfold in clinical practice. First results from the Danish Database (DANBIO). *Scand J Rheumatol 2005; 34(1):* 40-44.
54. Elkayam O, Pavelka K. Biologic registries in rheumatology: lessons learned and expectations for the future. *Autoimmun Rev 2012; 12(2):* 329-336
55. Alrubairy L, Rikaby I, Hutchings H, Williams J. Can the inflammatory bowel disease biologics registry lead to improved quality of care?. *Journal of Taibah University Medical Sciences 2015; 10(3):* 373-375.
56. Markman M. Maurie Markman on the Groundbreaking TAPUR Trial. *Oncology (Williston Park) 2017; 31(3):* 158-168.

57. Gladman D, Ritchlin C, Helliwell P. Psoriatic arthritis clinical registries and genomics. *Ann Rheum Dis 2005; 64(*Suppl 2): 103-105.
58. European Medicines Agency, "http://www.ema.europa.eu," [Online]. Available: http://www.ema.-europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000037.jsp&mid=WC0b01ac0580023e7a. [Accessed 3 december 2017].
59. Elder J. Psoriasis clinical registries, genetics, and genomics. *Ann Rheum Dis 2017; 64(*Suppl 2): 106-107.
60. Struve C. The FDA and the tort system: postmarketing surveillance, compensation, and the role of litigation. *Yale J Health Policy Law Ethics 2005; 5(2):* 587-669.
61. Garattini S, Bertele V. How can we regulate medicines better?. *BMJ 2007; 335(7624):* 803-805.
62. Zink A, Askling J, Dixon W, Klareskog L, Silman A, Symmons D. European biologicals registers: methodology, selected results and perspectives. *Ann Rheum Dis 2009; 68(8):* 1240-1246.
63. Steliarova-Foucher E, Colombet M, Ries L, Moreno F, Doyla A, Bray F, Hesseling P, Shin H, Stiller C, IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol 2017; 18(6):* 719-731.
64. Crocetti E, Buzzoni C. Do big numbers assure high-quality of data?. *Lancet Haematol 2017; 4(7):* e309. doi: 10.1016/S2352-3026(17)30107-2.
65. Sutka R, Pec J, Pecova T. Centralised biological therapy registry for moderate to severe plaque psoriasis - overview and methodology. *Acta Medica Martiniana 2016; 16(1):* 36-48.
66. NCZI - Narodne centrum zdravotnickych informacii, "http://www.nczisk.sk," [Online]. Available: http://www.nczisk.sk/Registre/Narodne-zdravotne-registre/Pages/default.aspx. [Accessed 3 december 2017].
67. Pavelka K, Sedova L, Hejduk K, Dusek L. 15 years experience with biological therapy of inflammatory rheumatic diseases in Czech national register ATTRA. *Cas Lek Cesk 2016; 155(6):* 285-293.
68. Kojanova M, Fialova J, Cetkovska P, Gkalpakiotis S, Jircikova J, Dolezal T, Arenberger P, Skupina Biorep. Analýza pacientů se středně těžkou až těžkou psoriázou před zahájením biologické léčby v České republice - údaje z registru BIOREP 2005-2016. *Ces-slov Derm 2016; 91(5):* 223-232.
69. Czech National Cancer Registry (CNCR), "http://www.uzis.cz," [Online]. Available: http://-www.uzis.cz/en/registers/national-health-registers/czech-national-cancer-registry. [Accessed 3 december 2017].
70. CREDIT-Cesky registr IBD pacientu na biologicke lecbe, "http://credit.registry.cz," [Online]. Available: http://credit.registry.cz/index-en.php?pg=participating-centres. [Accessed 3 december 2017].
71. Ministry of Health of Slovak Republic, "http://www.health.gov.sk," [Online]. Available: http://-www.health.gov.sk/?strategia-v-zdravotnictve. [Accessed 12 január 2018].

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