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Biosimilar drugs – automatic substitution regulations review. Polish ISPOR chapter's Therapeutic Programs and Pharmaceutical Care (TPPC) task force report

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ABSTRACT

Objectives: **Review of the EU regulations concerning substitution of biological products with biosimilar products .**

Methods: **The TPPC task force has checked the approach to automatic substitution by WHO, at the EMA level and in countries across European Union. An internet search was performed checking the regulations and direct contact to Regulatory Agencies in all European Union member states.**

Results: **Based on the research we have obtained directly information from 23 EU Member States and Switzerland. Most of the EU countries do not allow for automatic substitution of the reference biological medicinal product by a biosimilar. Currently some EU countries already have local legal regulations towards automatic substitution of medicinal products in place.**

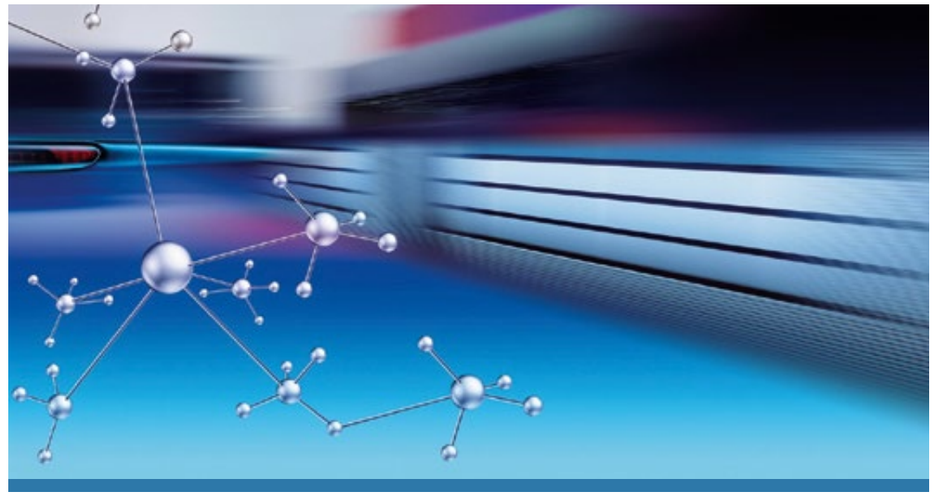
Conclusions: **Due to medicinal product complexity in most of the European Union countries the automatic substitution of a reference biological product by a biosimilar product is not allowed. Local regulations are needed in each of the Member States according to EMA guidance.**

BACKGROUND

Biological medical products, being comprised of proteins, hormones, monoclonal antibodies and gene or cell therapies are produced with advanced technologies. Currently more and more diseases can be treated with targeted therapies. In order to ensure proper safety and efficacy of the final product the manufacturing process of the biologicals is carefully controlled due to its sensitivity and high level of expertise required. The biosimilar products are developed to be as similar as possible to the reference medicinal product in terms of safety and efficacy and in the European Union EMA is the authority responsible for review of the marketing authorisations for the biosimilars. However the final decision on whether to substitute a reference biological medicinal product is the responsibility of the authorities in each of the EU Member States.

Taking into consideration the complexity of the molecules, manufacturing sensitivity, the potential to induce immunologic reactions, it is especially important for clinicians to be involved in the decisions related to the medication choice and possible substitution.

The TPPC task force worked on a review of regulations towards biosimilar drugs reimbursement and definitions in 2011-2012 [1]. As a continuation



of that discussion the automatic substitution regulations are currently in scope of our interest.

METHODOLOGY

In order to prepare the review of the regulations regarding automatic substitution of a reference biological product with a biosimilar product at EMA and in each of the European Union Member States we worked in parallel and; on one hand we performed an internet search and on the other; we contacted directly the Regulatory Bodies in EU Member States. In relation to the internet search there was initially no limitation towards the countries in scope, however due to Poland being an EU member state, the defined scope of countries of interest was specially focused on EU.

Prior to different databases search we have checked for the difference between interchangeability, switching and automatic substitution terms.

Then the databases have been reviewed to identify published regulations concerning reference biologic and biosimilar drugs automatic substitution. The search done by TPPC focused on the following words: "biosimilars", "biological drug", "biological drug substitution", "authomatic substitution", "substitution guidelines" , "substitution regulations" and it was conducted using the Internet.

In parallel, we emailed all European Union Member States' Regulatory Agencies asking for information regarding local regulation towards automatic substitution. The same predefined set of questions was send to the Agencies in order to gather information if the automatic substitution is allowed and if the topic is regulated by legal Acts at country level. In case that such regulation exists we asked for reference documents or website link to access such documents.

FINDINGS

According to European Commission document related to biosimilar products interchangeability is a medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber [2].

Automatic substitution is a practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [2].

The term switching is related to the decision taken by the treating physician to exchange one medicine for another with the same therapeutic intent in patients who are undergoing treatment [2].

WHO has recognized that a number of important issues associated with the use of similar biotherapeutic products (SBPs) need to be defined by the national authorities. They include, but are not limited, to the following: intellectual property issues; interchangeability and substitution of SBP with RBP; and labelling and prescribing information [3].

EMA has only responsibility to review the marketing authorization submission and the decision whether to substitute or not the reference biological product with a biosimilar is on the responsibility of each of the EU Member States competent authorities [4].

Since October 2011, pharmacists in Germany may substitute biotechnologically manufactured products among each other which have been approved with reference to the same reference product and which have been produced by the same manufacturer with the same manufacturing process. The only difference between such substitutable products is their trade name [5]. At the point in time of publication of the European Commission consensus information paper, no country had explicitly authorized the substitution of biological products from different manufacturers, and a number of EU Member States have put legal, regulatory, and political provisions in place that prevent this practice [2].

The Association of British Pharmaceutical Industry (ABPI) working on the biosimilar topic took into consideration EMA guideline on biosimilars from 2006 [6] and the EMA guidance published in 2012 [7] which states that the decision to treat a patient with a reference or a biosimilar medicine is only to be taken following the opinion of a qualified healthcare professional. ABPI recommends that automatic substitution should not apply to any biologic; this includes automatic substitution of a biosimilar for its reference product. Substitution should only ever occur with the knowledge and explicit prior consent of the treating physician [8].

The part of the project based on direct answers from Regulatory Agencies is described in table 1. From 31 countries we contacted we have obtained the answer from 21 countries. Based on the obtained information it is clear that the automatic substitution is not allowed in Austria, Germany, Bulgaria, Czech Republic, Latvia, Luxembourg, Belgium, Denmark, Estonia, Finland, Hungary, Italy, Norway, Portugal, UK, Slovenia, The Netherlands and Switzerland; however most of the countries have no local regulations towards automatic substitution. In Italy the choice is under the decision, control and responsibility of physician. Written criteria for drug substitution are published in Finland and Hungary. In Finland the automatic substitution (generic substitution in pharmacies) of biological products is not allowed. The criteria for substitution of medicines are described in the section 5c of the Medical Act and practically exclude automatic substitution by biosimilars. Based on those criteria a list of substitutable products is prepared 4 times per year. In Finland biosimilar products are not treated as "generic medicinal products", which could be substituted. In Sweden there is no legislation that excludes a biosimilar product from the substitution system, however due to the complexity of the biological products up to now no biosimilar product has been included on the substitution list. In Belgium there is a publicly available report prepared by the Federal Health Care Knowledge Centre (KCE): 'Barriers and opportunities for the uptake of biosimilar medicines in Belgium' and the substitution (the passage of a specialty subject to a prescription to another specialty by the pharmacist, without consulting the doctor) is not all. In France, according to the new legal regulation, since January 2014, substitution is planned to be allowed only in a restrictive way: when initiating a course of treatment, and if the biosimilar belongs to the same grouping as the prescribed product, known as a "similar biologic group" and only when the physician hasn't marked on the prescription that it is a not substitutable product [9]. According to the French law it is clear that patients who have already started treatment on a biological medicine must not have their medicine substituted by a pharmacist [10]. In Czech Republic there is no specific legal regulation towards the automatic substitution problem. However, most of the medical societies in the Czech Republic have official recommendations regarding the suitability of substitution between the reference biological product and biosimilar, not recommending automatic substitution. From Latvia we obtained the information that according to the State Agency of Medicines of the Republic of Latvia there is no automatic substitution of reference biological product by biosimilar product allowed and there are no legal regulations regarding to automatic substitution by biosimilar products in Latvia. In Austria and Germany the automatic substitution is not allowed by law. Mainly due to the differences between the original product and the biosimilar cannot be done at pharmacy and the replacement may only be expressly ordered by a doctor [11].

In Lithuania, automatic substitution of biological product by biosimilar product is allowed only in case, when biosimilar product has the same INN [16]. Despite EMA guidance that the substitution should be regulated at each Member State level still some of the countries don not have local regulations in place. We draw such conclusion based on the internet search we have performed and the answers we have obtained from the regulatory agencies in the EU countries.

Table 1. Automatic substitution – practice and regulations in EU

	Is the automatic substitution of reference biological product by biosimilar product allowed in your country?	Are there any legal regulations in your country in relation to automatic substitution by biosimilar products?
AUSTRIA[12]	No	Yes
BELGIUM[13]	No	Yes
BULGARIA	No	No
THE CZECH REPUBLIC	No	Not regulated by Health Authorities, but medical societies have regulations.
DENMARK	No	No
ESTONIA	No	No
FINLAND[14]	No	Yes
FRANCE[9]	Only for new treatment	The 2014 Social Security Financing Law (SSFL), including Article 47 on biosimilar substitution, was signed and published in the Official Journal on 23 and 24 December 2013 respectively.
GERMANY[11]	No	Yes
HUNGARY[15]	No	Yes
ICELAND	Information not clear	-
IRELAND	Information not clear	-
ITALY	No	-
LATVIA	No	No
LITHUANIA [16]	only in case, when biosimilar product has the same INN	Yes
LIECHTENSTEIN	Information not clear	No
LUXEMBOURG	No	No
THE NETHERLANDS[17]	No	No
NORWAY[18]	No	Yes
PORTUGAL	No	Yes
SLOVENIA	No	No
SWEDEN[19]	Theoretically yes, in practice not	Yes
UNITED KINGDOM[20]	No	No
SWITZERLAND[21]	No	No

SINCE OCTOBER 2011, PHARMACISTS IN GERMANY MAY SUBSTITUTE BIOTECHNOLOGICALLY MANUFACTURED PRODUCTS AMONG EACH OTHER WHICH HAVE BEEN APPROVED WITH REFERENCE TO THE SAME REFERENCE PRODUCT AND WHICH HAVE BEEN PRODUCED BY THE SAME MANUFACTURER WITH THE SAME MANUFACTURING PROCESS.

DISCUSSION

According to our search, Poland has no local regulations towards automatic substitution of reference biological products by biosimilar ones. From most of the countries we obtained an answer to our questions informing that they have no automatic substitution in place, even in case they are not having local regulations. Due to already practical experience with biosimilar products in Australia we also checked the status regarding automatic substitution there. The results were similar to our findings in EU. PBS does not permit automatic substitution of biosimilars with different INN. The pharmacists cannot substitute a glycosylated biosimilar for its comparator drug. Where the drug has the same INN, then the cheapest product can be supplied unless the prescriber stipulates the use of a particular brand [22].

The applicant of the biosimilar marketing authorization must submit a risk-management pharmacovigilance plan and biosimilars are priorities for pharmacovigilance. The approval pathway for a biosimilar is based on the determination of its

similarity to an approved biologic based on fewer patient data than were required for the initial approval of the reference product" and this create a need to collect safety data through effective post-approval safety surveillance systems. Biosimilars are biological medicines too, the molecule active substances of which are highly similar, but are not identical to the reference product [23].

In the US we found that according to the information from September 2013 the legislation regulating substitution was already introduced in several States and it defines that the substitution should occur only when the FDA has designated a biologic product as interchangeable; the physicians when prescribing a medicinal product should be able to prevent substitution and if such occurs then the prescribing physician should be notified of the substitution. The same principle is related to the patient who should be notified of the substitution. The pharmacist and the physician should keep records of the substitution [24].

CONCLUSIONS

Due to the medicinal product complexity in most of the European Union countries the automatic substitution of a reference biological product by a biosimilar product is not allowed. Local regulations are needed in each of the Member States according to EMA guidance.

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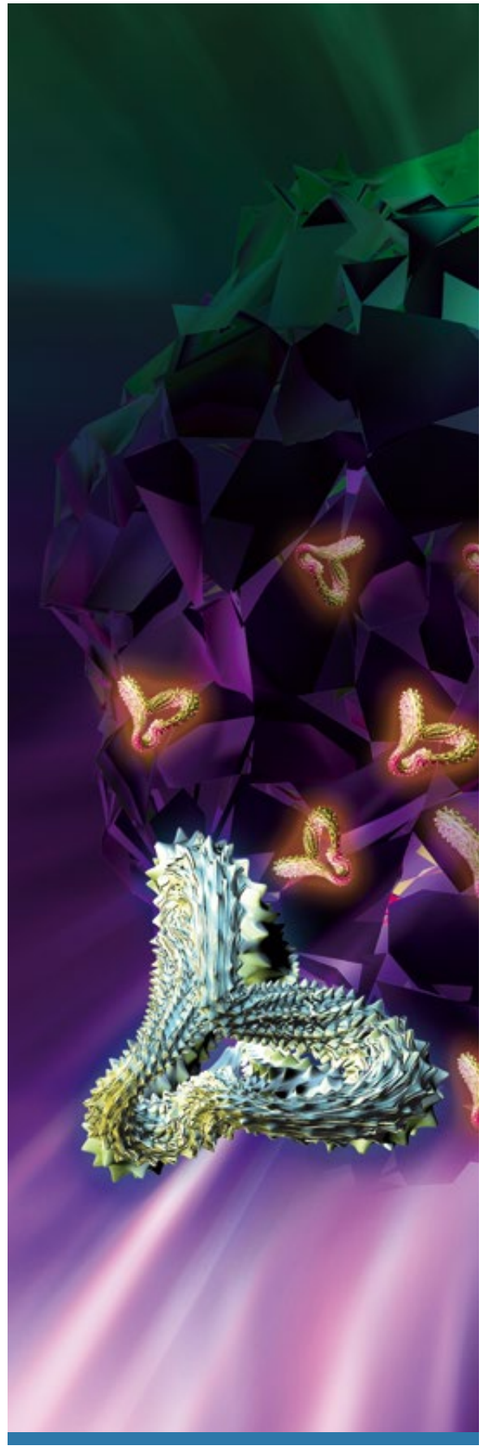

REFERENCES:

1. Drozd M., Szkultecka-Dębek M. Biosimilar drugs-reimbursement regulations. Polish ISPOR chapter's Therapeutic Programs and Pharmaceutical Care (TPPC) task force report. JHPOR 2013, 1, 84-91; DOI: 10.7365/JHPOR.2013.3.1
2. European Commission: What you need to know about biosimilar medical products. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf; [Accessed: 23.01.2014]
3. Expert Committee on Biological Standardization WHO: Guidelines on evaluation of similar biotherapeutic products (SBPs). Geneva 19-23 October 2009. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf; [Accessed: 10.02.2014]
4. European Medicines Agency: EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications. EMA/940451/2011, March 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf; [Accessed: 23.01.2014]
5. Section 129, subsection 1 of the Fifth Book of the German Social Code (SGB V) in connection with the framework agreement between the National Association of Statutory Health Insurance Funds and the German Pharmacists' Association on the supply of medicinal products in the version of 1 February 2011, which is based on section 129, subsection 2 of SGB V.
6. EMA, 2006: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf; [Accessed: 10.12.2013]
7. EMA, 2012: Questions and answers on biosimilar medicines (similar biological medicinal products). Available from: www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf; [Accessed: 10.12.2013]
8. The Association of the British Pharmaceutical Industry (ABPI): ABPI biosimilars position paper. Available from: http://www.abpi.org.uk/our-work/library/industry/Pages/biosimilars-position-paper.aspx; [Accessed: 23.01.2014]
9. Allen & Overy: Biosimilar substitution in France. No way back?. Available from: http://www.allenovery.com/publications/en-gb/Pages/Biosimilar-Substitution-in-France--No-Way-Back-.aspx; [Accessed: 10.02.2014]
10. European Boipharmaceutical Enterprises: French Biosimilar Law – No generics-style substitution policy. Available from: http://www.ebe-biopharma.eu/uploads/Modules/Newsroom/ebe-bs-statement-final_24.01.2014.pdf; [Accessed: 14.02.2014]
11. Die forschenden Pharma-Unternehmen: vfa/vfa bio-Positionspapier "Biosimilars". Available from: http://www.vfa.de/de/wirtschaft-politik/positionen/pos-biosimilars.html; [Accessed: 10.02.2014]
12. Baumgärtel C.: Austria increases dialogue in order to involve physicians more with biosimilars Generics and Biosimilars Initiative Journal (GaBI Journal). 2013; 2(1):8; DOI: 10.5639/gabij.2013.0201.003; [Accessed: 12.02.2014]
13. KCE Belgian Health Care Knowledge Centre: Barriers and opportunities for the uptake of biosimilar medicines in Belgium KCE Reports 199. Available from: http://kce.fgov.be/publication/report/barriers-and-opportunities-for-the-uptake-of-biosimilar-medicines-in-belgium; [Accessed: 12.02.2014]
14. Finnish Medicines Agency: Criteria used in compiling the list. Principles for compiling the list of mutually substitutable medicinal products with marketing authorisation at the Finnish Medicines Agency. Available from: http://www.fimea.fi/medicines/substitutable_medicinal_products/criteria_used_in_compiling_the_list; National laws. Available from: http://www.fimea.fi/national_laws; [Accessed: 27.01.2014]
15. 44/2004. (IV. 28.) ESzCsM rendelet az emberi felhasználásra kerülő gyógyszerek rendeléséről és kiadásáról. Online: http://net.jogtar.hu/jr/gen/getdoc.cgi?docid=A0400044.esc; 52/2005. (XI. 18.) EüM rendelet az emberi alkalmazásra kerülő gyógyszerek forgalomba hozataláról. Available from: http://net.jogtar.hu/jr/gen/getdoc.cgi?docid=A0500052.eum; [Accessed: 27.01.2014]
16. Del Lietuves Respublicos Vyriausybės 2005 m. rugsėjo 13 d. nutarimo Nr. 994 „Dėl Ambulatoriniam gydymui skiriamų vaistinių preparatų ir medicinos pagalbos priemonių, kurių įsigijimo išlaidos kompensuojamos iš Privalomojo sveikatos draudimo fondo biudžeto lėšų, bazinių kainų apskaičiavimo tvarkos aprašo patvirtinimo" pakeitimo. Available from: https://www.e-tar.lt/portal/forms/legalAct.
17. Norwegian Miedicines Agency: Biosimilars: The Norwegian Medicines Agency (NOMA) suggests legislative amendment. Available from: http://www.legemiddelverket.no/Nyheter/Blaa_resept_og_pris/Documents/2012-11%20November/English%20summary.pdf; [Accessed: 5.02.2014]
18. Swedish medical Products Agency: Comments on the List of Substitutable Medicinal Products. Available from:http://www.lakemedelsverket.se/english/product/Medicinal-products/Substitution/; [Accessed: 4.02.2014]
19. Regulating medicines and Medical Devices MHRA: Biosimilar products.Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739; [Accessed: 29.01.2014]
20. Die Bundesbehörden der Schweizerischen Eidgenossenschaft: 832.10 Bundesgesetz über die Krankenversicherung (KVG). Available from:http://www.admin.ch/opc/de/classified-compilation/19940073/index.html;[Accessed: 3.02.2014]
21. Power D.A: Licensing and prescribing biosimilars in Australia; Generics and Biosimilars Initiative Journal (GaBI Journal). 2013;2(3):152-4. DOI: 10.5639/gabij.2013.0203.030. Available from: http://gabi-journal.net/licensing-and-prescribing-biosimilars-in-australia.html; [Accessed: 24.01.2014]
22. Calvo B., Zuniga L. EU's new pharmacovigilance legislation: consideration for biosimilars. Drug Saf. 2014, 37, 9-18. DOI 10.1007/s40264-013-0121-z
23. Karst K.R. The Biosimilars State Legislation Scorecard. Available from: http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/09/biosimilars-state-legislation-scorecard.html;" [Accessed: 13.02.2014]