

LEGITIMACY AND POTENTIAL SAVINGS IN AUTOMATIC SUBSTITUTION OF BIOLOGICAL PRODUCTS IN POLAND, THE EXAMPLE OF INSULIN

KATARZYNA ANNA GRUCHAŁA^{1*}, PIOTR WAŹ² and AGNIESZKA ZIMMERMANN¹

¹Department of Medical and Pharmacy Law, Faculty of Health Sciences with Sub-faculty of Nursing and Institute of Maritime and Tropical Medicine, Medical University of Gdańsk, Tuwima 15, 80-210 Gdańsk, Poland

²Department of Nuclear Medicine, Medical University of Gdańsk, Tuwima 15, 80-210 Gdańsk, Poland

Abstract: Currently in Poland, there is no regulation aiming at framing the complexity of substitution process arising at pharmacy level. In practice, such process exists in variety type of products, both generic and biological scope. Lack of integrity in terms of this process between authorized medical professions who held it might lead to further costs both for the health care system and patients. The aim of the study is to explain, that the economic advantage, which very often is the result of performed substitution process, in some types of products such as biological ones, should be preceded with the decision of the treating physician. Only then, in the cooperation between persons prescribing and dispensing certain medicinal product the process of substitution may fully use its potential of money-saving along with the control over a certain patient. The study brings the yet unknown classification of differences in costs between actually performed automatic substitution of products containing human insulin in the pharmacy setting in Poland in a four-year period in five voivodeships.

Keywords: substitution, biologics, biosimilars

Substitution is the process of changing a prescribed pharmaceutical product into its available equivalent in a pharmacy setting, without consultation with a physician (1). In Poland, such an act is defined in the law of 12 May 2011 on the reimbursement of medicines, food products of a special nutritional purpose and medical devices (2), within which, simultaneously, four necessary conditions must be fulfilled:

1. The same international name (INN).
2. The same dose.
3. Pharmaceutical form which does not give rise to therapeutic differences.
4. The same therapeutic indication.

The above-mentioned conditions apply to both chemical and biological medicinal products. Currently, there is no law which would stipulate a separate proceeding in the substitution of more complex medicinal products: biological ones.

Biological medicinal products are one of the main innovations in the health sector; their active substance is a biological substance, which means they are produced from living organisms, e.g. cells. A biosimilar product is made to be similar to the ref-

erence biological product and therefore cannot be treated as a generic product which has the same chemical structure as the reference one.

The European Medicine Agency (3) does not give recommendations on whether a biological medicinal product can be switched (a decision by the treating physician of changing one medicinal product to another within the same therapeutic area) or substituted with a biosimilar, and entrusts this issue to the individual, internal discussion of each country. Most European Union countries neither ignore nor discount this issue.

In Poland, in terms of pharmacy products, persons authorized to write prescriptions have a possibility to add the notation “NZ”, which indicates the medicine should be dispensed as written, however, the analysis of an undertaken scientific study raises a precariousness of whether, especially concerning biological medicinal products, this activity is adequately undertaken.

Access to biosimilar products should suggest that patients have a higher probability of decreasing the costs of pharmacotherapy. The World Health Organization (4) indicates: *As the patents of some*

* Corresponding author: e-mail: katarzynagruchala@gumed.edu.pl

biotherapeutics have expired, more biosimilars are being produced. Like generic medicines, biosimilars could help to increase access to treatment in lower-resourced countries and provide a solution to escalating health costs in high-income countries. The American Food and Drug Organization (5) stresses: *The approval of biosimilar products can improve access to care for patients by increasing the number of medication options and potentially lowering costs.* The fact of bringing to the market biosimilar products indicated when purchasing a given pharmacotherapy at a lower price, aims at increasing the availability of this pharmacotherapy to patients. The issue, adopted, as a matter of fact, from low-molecule products, reveals that in the case of substitution, most often, the basic criterion is a purely economic one: the price. However, it must be noted that, in terms of biological products, automatic substitution arising at the pharmacy level should be defined more accurately already from the legal basis, as the exemplar of other countries suggests.

In this paper, the authors try to continue the undertaken research field and, after a brief sketch of the existence of automatic substitution of biological products based on the example of insulin, check whether the substitution process, unfortunately as yet not discriminated at the formal level, is firstly driven by the knowledge and the decision of the physician, and secondly, whether it decreases the cost of purchase for patients.

Literature review

In the year 2014, a study was undertaken in which savings arising from moving from biological

medicinal products to biosimilars was estimated. The study took into consideration the public payer perspective; however, considering the fact that medicine is to be cheaper for the public payer, it should also be cheaper for the individual patient. In the study, the estimated savings in fast-acting insulin stand at 11%, and long-acting insulin at 15%, which, in comparison to other products included in the study, ranks as one of the highest (6). In general, savings arising from the switching of biological products (20% – 40%) may not be as high as from substitution between chemical products, which may stand at up to 80% (7, 19). This is the after-effect of the differences in the production process between chemical medicines and biological ones (8); for instance, the chemical generic requires about a \$ 1-2 million investment before approval, whereas bringing the biosimilar drug to the market could oscillate at around \$ 30-\$ 150 million (21).

In the European Union (EU) substitution decisions are the responsibility of the national drug-regulatory agencies in each country (20). In the year 2013, a study was undertaken involving a list of countries with specific measures limiting or prohibiting the substitution of biosimilars. The list, which contains 15 European countries, indicated that in France, from the year 2006, the automatic substitution of biosimilars is prohibited. In Germany, from 2011, only those products that contain the same raw material and undergo the same manufacturing process qualify for substitution. In Greece, from the year 2013, the Greek National Organization for Medicines recommends against the automatic substitution of biological medicinal products.

Table 1. Group of results a; different manufacturer.

	Identified combinations	Approved combinations	%
Short-acting	18	2	66
Long-acting	15	3	54
Biphasic	23	3	51

Source: Own preparation

Table 2. Group of results b; the same manufacturer, different type of pen.

	Identified combinations	Approved combinations	%
Short-acting	6	3	58
Long-acting	4	2	64
Biphasic	6	2	91

Source: Own preparation

Table 3. Numbers of performed substitution in following combinations in groups of results a and b.

Prescribed	Dispensed	2012	2013	2014	2015	p-value
Group of results a; different manufacturer in the following years due to patients' perspective						
Actrapid Penfill®	Gensulin R®	49	99	147	76	0.01329
Gensulin R®	Actrapid Penfill®	13	22	72	22	0.01329
Humulin N®	Gensulin N®	28	20	27	21	0.04597
Gensulin N®	Insulatard Penfill®	33	41	31	17	0.04597
Gensulin N®	Humulin N®	6	18	20	13	0.04597
Humulin M3®	Gensulin m30®	13	13	21	17	0.00088
Gensulin M30®	Mixtard 30 Penfill®	26	28	14	31	0.00088
Mixtard 30 Penfill®	Gensulin M30®	25	11	10	5	0.00088
Group of results b; the same manufacturer but different type of pen in following years due to patients' perspective						
Insuman Rapid®	Insuman Rapid SoloStar®	1	8	19	43	0.00061
Apidra SoloStar®	Apidra OptiPen®	2	13	35	13	0.00061
Apidra OptiPen®	Apidra SoloStar®	3	13	32	49	0.00061
Insuman Basal SoloStar®	Insuman Basal®	14	75	153	169	< 0.000001
Lantus SoloStar®	Lantus OptiPen®	71	183	160	102	< 0.000001
Insuman Comb25 SoloStar®	Insuman Comb25®	1	69	111	140	0.09132
Insuman Comb25®	Insuman Comb25 SoloStar®	6	57	106	103	0.09132

Source: Own preparation

In Italy and Spain, from the year 2007, Slovenia and Slovakia from 2008, Hungary from 2009, UK and Norway from 2010, and Sweden from 2011, biological medicinal products cannot be substituted. In Austria, from 2012, the Austrian Regulatory Authority recommends against pharmacists automatically substituting biological medicinal products (9).

Insulin products are pharmacy products; therefore, apart from them being biological products, and from the pure economic factor of the savings arising from the use of biosimilars, this was the third, decisive reason for choosing them as the example in illustrating the undertaken research field.

The previous work of the authors (10) was based on four-year retrospective data (2012, 2013, 2014, 2015) received from the National Health Fund in Poland (concerning the Masovian, West-pomeranian, Lesser Poland, Silesian and Podlaskie voivodeships) and evaluated whether the automatic substitution of biological medicinal products (based on the example of insulin products) is present in practice and under what circumstances, and tried to assess whether this process will continue; together with outlining the consequences it may bring mainly to the health care system. A group of almost four thousand results (3937) was identified and, regardless of the method of prognosis, it was assessed that the process

of substitution will continue to exist. The authors tried to raise a discussion over the necessity of creating proper regulations concerning the process. It was identified that patients from pediatric to geriatric undergo this process. Insulin products are complex ones, therefore the classic criteria which condition substitution in Poland, aiming at checking whether the prescribed and dispensed product have the same INN, dose and pharmaceutical form, are significantly fuzzy criteria. The paper examines two groups of products: products of different manufacturers and products of the same manufacturer but with a different type of pen, which is a division characteristic for insulin products. Then, within those groups, presents criteria based on the effect period: short-acting insulin products, long-acting insulin products, and biphasic insulin products. The study showed that regardless of the effect period, the substitution rate in the year 2015 increased in comparison to the year 2012 in the products in the group of the same manufacturer but with a different type of pen, and decreased in the group of different manufacturers.

The paper does not, however, assess whether, in terms of biological products, with the example of insulin, the substitution process decreases the purchase costs for patients, which is a necessity in the assessment of the full process.

METHODS

Continuing the previous work (10), the necessity of determining the differences in cost at the moment of purchase was established. The current study takes into consideration the patients' perspec-

tive, continuing to evaluate the process in the most objective way. As in the study from the previous work (10), the calculations were based on retrospective data received from the National Health Fund of Poland. As presented in the previous work (10), they were acquired as prescribed – dispensed, in the form

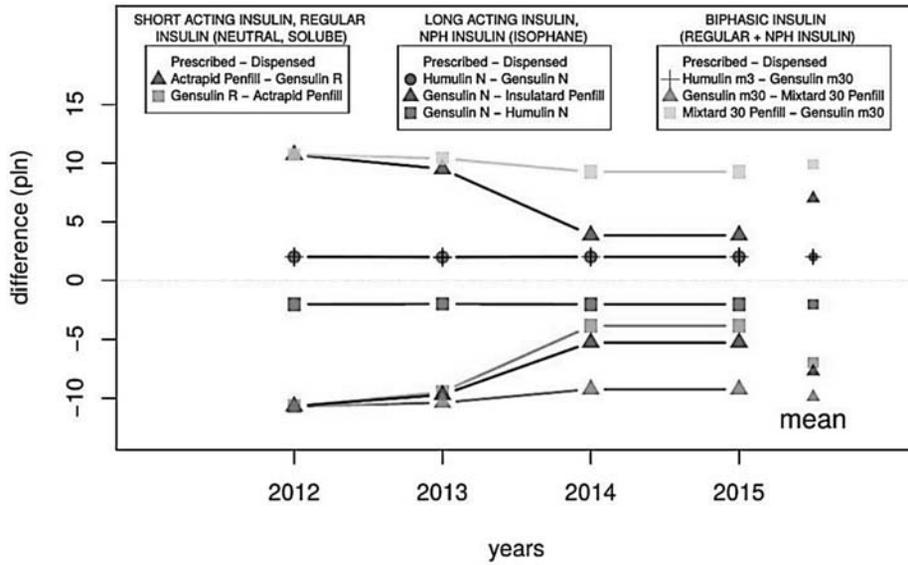


Figure 1. Differences in cost of substitution in a group of results a; different manufacturer in the following years due to patients' perspective

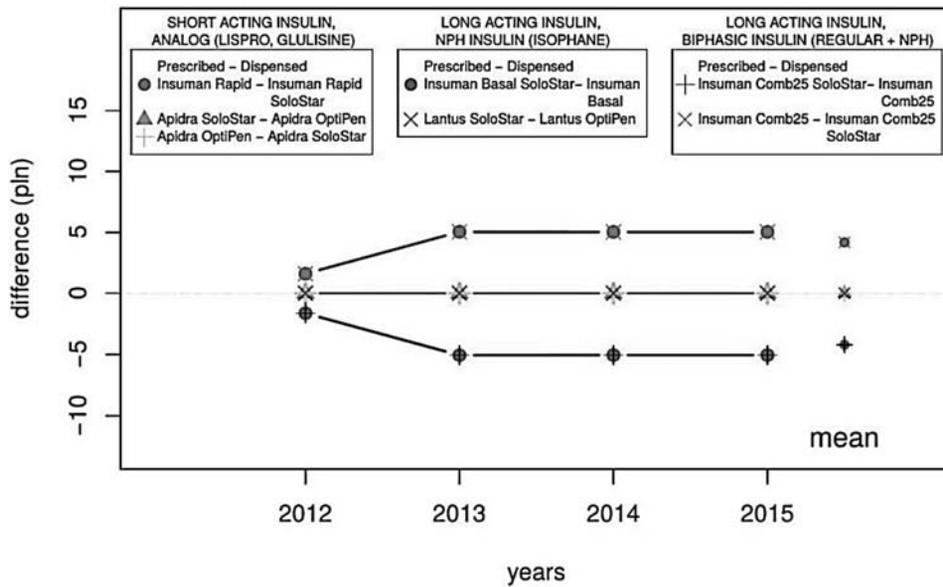


Figure 2. Differences in cost of substitution in a group of results b; the same manufacturer but different type of pen in the following years due to patients' perspective

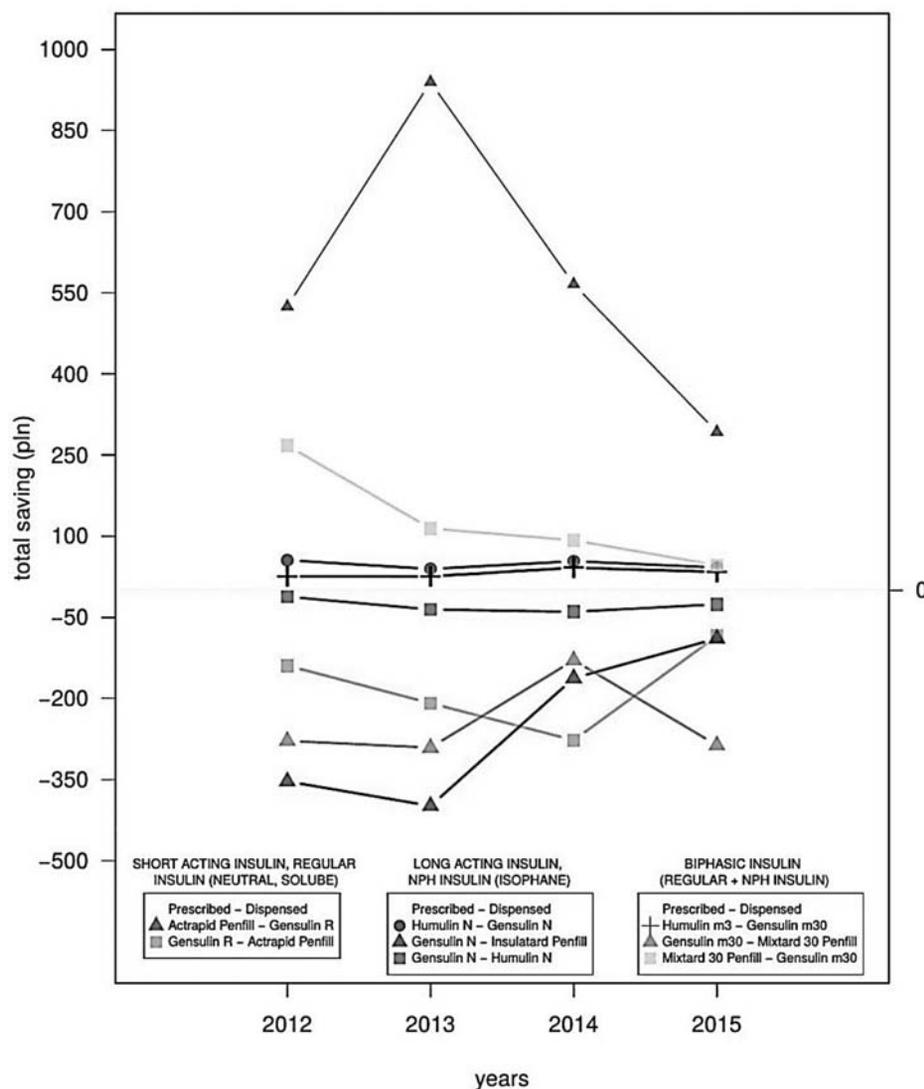


Figure 3. Total saving of substitution in a group of results a; different manufacturer in the following years due to patients' perspective

of EANs, with information from which it was possible to calculate the patient's age. As in the previous study, using the R statistical language (11) and a self-prepared, based on the Office for the Registration of Medicinal Products, Medical Devices and Biocidal Products, Excel template containing the Latin and INN names of active substances, those EANs acquired from the NHF were swapped into active compounds. The base model (n = 3937) was the insulin model. It was then divided into three groups of results: short-acting insulin, long-acting insulin and biphasic insulin. The first group of results considered the substitution rate of the same type of product but a different manufacturer, the sec-

ond – the same type of product of the same manufacturer but with a different type of pen, and the third – substitution between different types of insulin products (10). It was then evaluated whether the process will continue to exist and in what dimension. In this paper, the authors focus on the last element, which is saving money in the patients' perspective. The substitution rate of 3937 between products containing human insulin was accordingly divided into those which took place between products of different manufacturers (group of results a) and ones which took place between products of the same manufacturer but with a different pen for injection (group of results

b). Then, within those groups, the second criterion was established – based on the effect period: short-acting insulin products, long-acting insulin products and biphasic products. Then, within those groups and established sub-groups based on the effect period, the criterion for classifying the differences in the cost of purchase between substituted products was established. This analysis considers products which together amounted to at least 50% of the substitution rate in the sub-groups, and constitute the average of the differences in the cost of purchase in each year (average from the six reimbursement lists which appear in Poland each year). Together, the analysis determines the total

substitution rate of 3937 at 82%. The Chi-square test was used to test the independence of variables presented in Table 3. Using this test, the p-value was determined for each of the subgroups.

RESULTS

The results of the current study take into consideration the patients’ perspective, continuing to evaluate the process in the most objective way. Table 1 presents the substitution rate within the products of a different manufacturer. In total, among the identified combinations, the substitution rate in this group was at the level of 989.

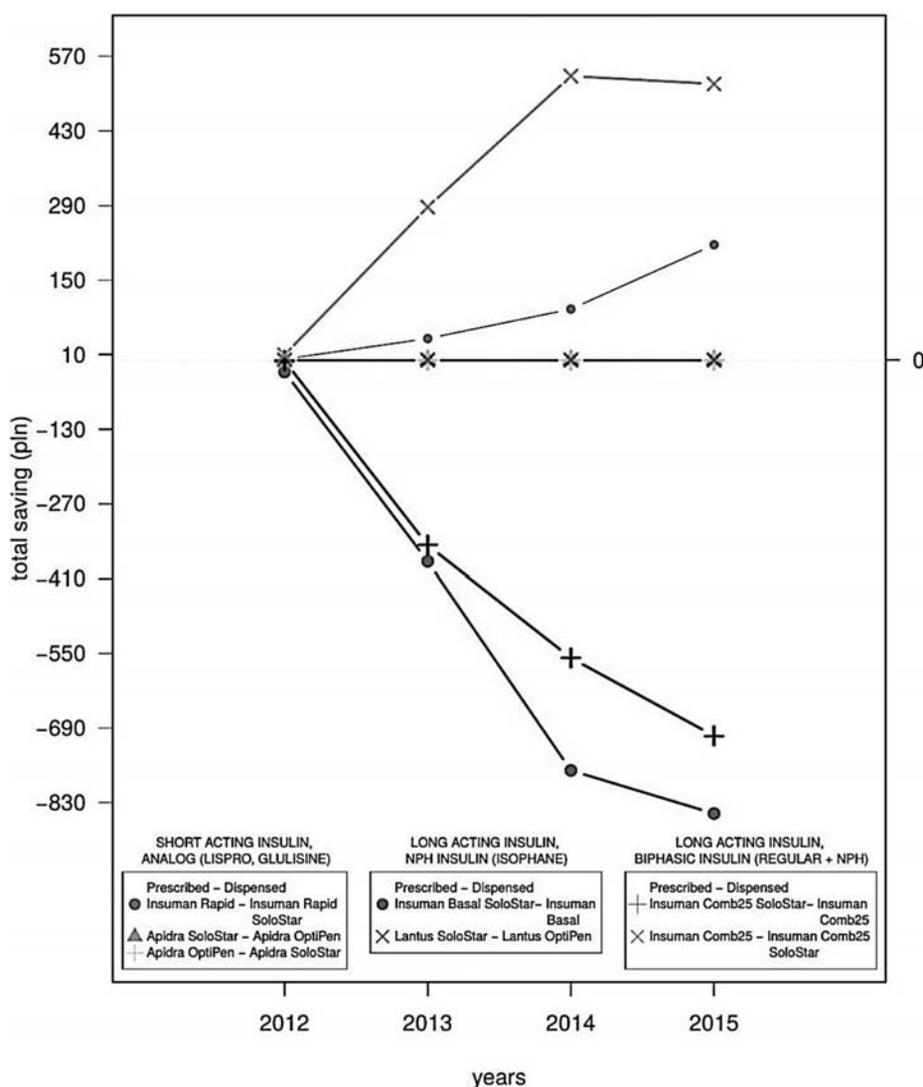


Figure 4. Total saving of substitution in a group of results b; the same manufacturer but different type of pen in the following years due to patients’ perspective

Table 2 presents the substitution rate within the products of the same manufacturer but with a different type of pen for injection. In total, among the identified combinations, the substitution rate in this group was at the level of 2256.

Charts 1 and 2 present the classification of the difference in cost (PLN) of the substitution rate at the moment of purchase. The “y” axis represents the difference in cost in the prescribed-dispensed relation, whereas axis “x” represents the year. On both charts, the symbols on the right side represent the average of differences in the substitution rate over a four-year period, whereas the symbols in each year are the average of differences in the substitution rate from six reimbursement lists of each year. At the top of the charts, there are boxes in which the trade names of products (each combination) occur, divided based on the effect period of insulin products.

Table 3 determines the p-values for the groups of results a and b. It shows the actual number of performed substitutions in the following groups in the following combinations.

For the last subgroup: Insuman Comb25 SoloStar® as prescribed and Insuman Comb25® as dispensed, and the reverse situation, the received p-value is greater than the assumed significance level $\alpha = 0.05$. This is the only case for which the result is not statistically significant. This means that there is no dependence on the variables given in the rows and the columns in this case.

Charts 3 and 4 present total savings in the patients' perspective. The “y” axis represents total savings on each combination performed, taking into consideration the actual number of performed substitutions in each combination. Axis “x” represents the year. All the calculations have been performed using the R statistical language (11).

DISCUSSION

The claim that automatic substitution was, in a way, handed over to market forces seems apposite. For example, chart 1 presents the combinations of substitutions between biological products of different manufacturers, containing human insulin. The products of a manufacturer which were brought to the market as 1st, in the year 1990 (depending on the effect period), have a lower price than the products of a manufacturer which were brought to the market as 3rd, in the year 2002. In general, the prices of medicines from chart 2 are some of the lowest in the European Union. For instance, in a study from China (15), the authors stress that the treatment cost should be considered as an important factor in the

healthcare decision-making process. One has to be aware that there are many medicines with similar clinical efficacies to choose from. Therefore, it is very important to analyze the real world perspective and to provide economic evidence while defining the optimal treatment. In the study mentioned above (15), the differences in the costs resulting from the use of different insulin products have been analyzed. A similar analysis has been performed in a study from a German background (18). Another study from Germany (16) concludes that the final savings in costs resulting from a substitution understood as an exchange of the original with a biosimilar, may be counterbalanced by other factors such as the effort in teaching patients and physicians about the use of other pens for insulin administration, the confusion of patients with the names of medications, a decline in the metabolic control with a change in insulin and, last but not least, potential side effects. The author indicates the need for some careful evaluation of the degree of savings achieved at the end (16). A study from the United Kingdom (17) highlights that in the years 2010/2011 the total annual cost of type 1 diabetes mellitus in the UK was estimated to be £ 1.9 billion. Out of this, £ 1.0 billion stood for direct costs, of which 71% was due to long-term complications.

In this study, the maximum difference in the cost of substitution at the pharmacy was identified around the level of 10 PLN. In 4 out of 8 combinations of substitution from chart 1, patients saved from 1.99 to 9.90 PLN, and in the remaining 4, they had to additionally pay an amount of money from the same frames. In 3 out of 7 combinations of substitution from chart 2, patients saved 0 PLN, in a further 2 out of 7, they had to additionally pay over 4 PLN, and in the remaining 2 out of 7, they saved around 4 PLN.

Looking at charts 3 and 4, it is noticeable that the total saving arising from the performed substitution of insulin products is not enormous from the patients' perspective. For example, in chart 3, the one concerning products of different manufacturers, the highest saving on one product was 939.6 PLN, whereas the highest extra payment for patients was 398.6 PLN. If all the amounts of savings and extra payments were added up in this group of results, the total saving would be at the level of 349.6 PLN, and this concerns a total of 989 performed substitutions of insulin products in five voivodeships in a four-year time period. Chart 4 concerns products of the same manufacturer but with a different type of pen for injection. In this case, the highest saving on one product was 518.4 PLN and the highest extra pay-

ment was 850.6 PLN. If all the amounts of savings and extra payments were added up in this group of results, the total saving would be at the level of -1930.4 PLN, and this concerns a total of 1751 performed substitutions of insulin products in five voivodeships in a four-year time period. If those two groups of results were summed up in terms of the total saving, the result would be -1580.7 PLN.

It is hard, during dispensing, to assess or identify which product is the reference one, and which is a biosimilar (12). It cannot be unequivocally claimed that price is the motivator for automatic substitution. It cannot also be unequivocally claimed that those decisions of substitution are therapeutic ones, because they take place beyond the medical doctor's knowledge; and in terms of biological medicinal products, decisions about changing the medicine should be made by the treating physician.

It can be therefore assumed that automatic substitution is driven by economic factors such as the in-stock situation or marketing actions of pharmaceutical market entities. It seems that the lack of communication between the patient-physician-pharmacist in this matter is an additional inconvenience. It can be assumed that the physician will not discuss with the patient the matter of substitution, due to the assumption that it will not occur in terms of biological products. If it actually occurs, it can be assumed that the patient will not discuss it with the physician, envisaging that (s)he possesses the same state of knowledge of the substitution as the pharmacist. Further studies are to be performed to verify whether in fact medical doctors have any concerns regarding use of the "dispense as written" possibility; also further studies should be performed to verify both how the situation of substitution appears practically at the pharmacy and what the future costs are after the substitution if it occurred where it should not. A study from the US (22) evaluated patients' perception on changing insulin to a cheaper one. Approximately 66% of the respondents reported they would probably or definitely do it, whereas 17% reported that they were unlikely to or would definitely not do it (22). However, the American attitude to substitutions differs from the European one (20).

It must be highlighted that there is currently no database which could connect those medical professions in terms of factual data of substitution; in legal and practical terms it is an unquestionable challenge. Also a question appears whether substitution concerning the type of pen is, in terms of the physician's knowledge, an important criterion.

CONCLUSIONS

Consent for automatic pharmacy substitution, on the example of products containing human insulin, reveals some doubt about the benefits and costs (e.g. further visits at the physician's office, waste of medicines) of this process as well as the integrity of the health care system in Poland. It is necessary to carefully evaluate all the final costs that are the consequence of substitution. This study shows that in terms of substitution performed at the moment of purchase, in terms of insulin products, there is no saving for patients in total, yet extra payments at the level of 1580.7 PLN in total. The study highlights the necessity of planning the process and evaluating current market regulations between subjects in the creation of rational and effective regulations.

REFERENCES

1. Gruchała K.A., Zimmermann A.: *Acta Pol. Pharm.* 74, 1599 (2017)
2. The law of on the reimbursement of medicines, food products of special nutritional purpose and medical devices (consolidated text Journal of Laws from 2016, item 1536 as amended in Polish).
3. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (accessed on 07.01.2018).
4. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDeveloped/Approved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.html> (accessed on 07.01.2018).
5. <http://www.who.int/medicines/access/biotherapeutics/en/> (accessed on 07.01.2018).
6. <https://www.rand.org/pubs/perspectives/PE127.html> (accessed on 07.01.2018).
7. Greene J.A., Riggs K.R.: *N. Engl. J. Med.* 12, 372 (2015).
8. Fuchs D., Świerczyński M., Żarnowiec Ł., Więckowski Z., Łojko N. et al.: *Biologiczne produkty lecznicze. Aspekty prawne* Wolters Kluwer Polska, 2016.
9. Mellstedt H.: *Eur. J. Cancer Supp.* 11, 3 (2013).
10. Gruchała K.A., Wąż P., Kawczak P., Zimmermann A., Wolnik B., Bączek T.: *Acta Pol. Pharm.* 75, 1003 (2018).
11. R Core Team, R: *A Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, Vienna, Austria (2015)

- <https://www.r-project.org/> (accessed on 07.01.2018).
12. Nowakowski A., Obel E.: *Medycyna Rodzinna* 3-4, 120 (2003).
 13. Gruchała K.A.: *Substytucja apteczna produktów biologicznych w Polsce na przykładzie preparatów zawierających insulinę ludzką. Biologiczny produkty lecznicze – aspekty prawne*, Warszawa 4.12.2017.
 14. Gruchała K.A et al.: *Ocena procesu substytucji aptecznej w świetle prawa farmaceutycznego – wyniki wstępne. XXIII Naukowy Zjazd PTFarm*, Kraków 19-22.09.2017.
 15. Gao Y., Wang K., Chen Y., Shen L., Hou J. et al.: *Diabetes Ther.* 9, 673 (2018).
 16. Heinemann L.: *J. Diabetes Sci. Tech.* 10, 457 (2016).
 17. Hellmund R., Weitgasser R., Blissett D.: *Diabetes Res. Clin. Pr.* 138, 193 (2018).
 18. Valentine W.J., Van Brunt K., Boye K.S., Pollock R.F.: *Appl. Health Econ. Health Policy* 16, 357 (2018).
 19. Farfan-Portet M.-I., Gerkens S., Lepage-Nefkens I., Vinck I., Hulstaert F.: *Eur. J. Health Econ.* 15, 223 (2014).
 20. Heinemann L., Khatami H., McKinnon R.: *Diabetes Technol. The.* 7, 510 (2015).
 21. Rotenstein L.S., Ran N., Shivers J.P., Yarchoan M., Close K.L.: *Clin. Diabetes* 30, 138 (2012).
 22. Wilkins A.R., Venkat M.V., Brown A.S., Dong J.P., Ran N.A. et al.: *J. Diabetes Sci. Tech.* 8, 23 (2014).

Received: 21. 01. 2018