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Opinions of Czech general practitioners on generic drugs and substitution

Research Article

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Abstract: The aim of the study was to map and analyze general practitioners` opinions of, attitudes towards and experiences with generic drugs and generic substitution (GS) in the Czech Republic. General practitioners (GPs) who took part in the annual and regional professional conferences of the Society of General Practice in the period from November 2008 until March 2009 were asked to complete the 28-item questionnaire concerning the issue of generic drugs and GS. Questions were organized in 5 sections aimed at assessing the attitude towards GS, understanding the legislation and opinions on statements related to GS. All data were analyzed using descriptive statistics and correlations were tested by selected parametric and non-parametric tests. Total of 263 completed questionnaires were returned (mean age of 52.2 years (SD=13.7), 177 (67.3%) females and 248 (94.3%) GPs having a practice specialization). 99 (37.6%) respondents have considered generic drugs to be bioequivalent to the respective brand name drugs. 121 (46.0%) respondents believed that generic drugs are of lower quality than brand name drugs. None of respondent showed acquaintance with all the legal rules for GS. Awareness of the legislation and attitude towards GS correlated with the age ($p<0.001$). In conclusion, distrust among GPs in generic drugs derives from poor knowledge and personal experiences.

Keywords: *General practitioner • Brand name drug • Generic drug • Generic substitution*

1. Introduction

In developed countries, the cost of health care increases each year, not only because of the aging population, but also due to continuously ongoing innovations in medical technology or demands for early initiation of pharmacotherapy of chronic disease [1,2]. In the Czech Republic, public expenditure on health has risen by 10% each year since 2000 and drugs take up a large part of these costs [3]. In the last decade, drug costs accounted for about 10% of total public spending on health in most European countries. One way to reduce drug costs is to enable generic drugs to enter the market. The competition between generic drug manufacturers lowers their prices, thus reducing overall cost of health care [4-6].

Although the generic substitution (GS) was already in use in the Czech Republic, it was not until December 2007 that it was introduced into the legislation [7,8]. The principle of the GS is that the pharmacist can dispense a drug other than prescribed to the patient without notifying the doctor. Nevertheless, the substituted drug must have the same active ingredient, route of administration, and dosage form with the originally prescribed drug. Furthermore, the patient benefits from the lower price. However, GS cannot be done if the prescriber insists by explicitly stating on the prescription: “No substitution” [8].

The success of the GS policy depends on the attitude of physicians, patients, and pharmacists [9]. Furthermore, health care providers, health care payers, and patients all play an important role in increasing the share of generic drugs on the market and reducing the expenditure of drugs [10-12]. Previously acquired data suggested that changes related to GS were not seen positively by the physicians despite the fact that generic

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drugs could have accounted for a considerable part of their prescriptions [13].

The implementation of generic drugs and GS can be influenced by physicians' poor understanding of the basic principles and legislation governing GS [14]. General practitioners (GPs) are far from rejecting generic drugs but they are concerned with risks associated with GS and generic drugs. Many GPs strongly caution against GS in patients on long-term drug therapy who should use the same drug (either generic or brand name) throughout their treatment [15]. Refusal of GS by patients can be related to the lack of information they have access to or are given by the healthcare professionals. GPs should inform their patients about GS, ask them about their experience with GS, and if needed clarify any misunderstandings [16]. GPs negative attitudes towards GS can be a result of the pressure from the pharmaceutical companies or concerns in the quality and safety of generic drugs due to e.g. their previous negative experience [13,14,17]. According to Slovenian GPs, the prescription of generic drugs could be enhanced by better information by the independent academic institutions or further clinical testing of generic drugs [17].

The study objectives were to record GPs' opinions regarding generic drugs and GS, analyze GPs' experience with GS and assess the level of understanding GS in the Czech Republic. The acquired results should give us an overview of the GPs' approaches to GS and serve as materials for a discussion about wider and safer use of GS.

2. Methods

2.1. Participants

All GPs who took part in the annual conference of the Society of General Practice or in any of the regional professional conferences of the Society of General Practice in the period from November 2008 to March 2009 were addressed. In the Czech Republic, a profession of general practitioner can only be performed by the physician specialized in General practice.

2.2. Methods

Data collection was performed using a questionnaire, which had been distributed along with the instructions for completion. The questionnaire was handed over to all participants of the above-mentioned conferences of the Society of General Practice in the given time period. GPs were asked to complete the questionnaire at the registration of the conference to ensure that only GPs have obtained the questionnaire. Physicians in training under the supervision of General practice specialists were also included in this survey. Completed questionnaires were collected and passed onto the investigators of the study.

The questionnaire consisted of 28 questions divided into five sections. Section 1 was designed to collect demographic data (sex, year of birth, population of work place, and practice specialization upon their graduation). Section 2 was composed of statements related to the use, cost, and safety of brand name versus generic drugs and responses were rated on a five-point Likert scale (1=strongly agree; 2=agree; 3=neutral; 4=disagree; 5=strongly disagree). This section was adopted from two similar questionnaire surveys [18,19] and modified to suit conditions of the Czech Republic. Section 3 focused on understanding the legislation relevant to GS in the Czech Republic (dichotomous questions). In section 4, the attitudes towards GS were examined and rated again on a five-point scale (very positive, positive, neutral, negative, and very negative). Furthermore, checklist questions (multiple choices) were used to examine the most positive outcomes (e.g. cost savings) and the most negative ones (e.g. risk of duplicate drug use) of the implementation of GS as perceived by GPs. The GPs' experience with GS was evaluated using a dichotomous question with the possibility to put a real example in a given field. The last section 5 was designed to test the knowledge of brand names of the drugs commonly used in the clinical practice (closed ended questions). Drugs with four active ingredients (ramipril, atorvastatin, metformin and omeprazole) were presented to the respondents who had to select the correct brand name from a multiple-choice list.

The questionnaire was piloted. The mean administration time was 15 minutes.

2.3. Statistical analysis

Data were transferred to Microsoft Excel. Statistical analysis was performed using the PASW 18.0 software. Descriptive statistics for metric items were given as the mean ± standard deviation (SD), with a 95% confidence interval (CI) in some cases. Pearson's correlation test (r) was used to test for correlations between attitudes towards GS and age, sex, or understanding the legislation for GS with a significance level of 0.05.

One-sample t-test was used to compare the respondents' scores quantifying their understanding of legislation relevant to GS with the hypothetical random guess score. The internal consistency of the questions

regarding understanding of legislation relevant to the GS was tested using Cronbach's alpha reliability scale.

3. Results

3.1. Demographic characteristics

The questionnaire was filled in by 263 GPs (i.e. 14.3% of addressed). The respondents represented 5.0% of all GPs in the Czech Republic [20]. All completed questionnaires were evaluated. Demographic data are summarized in Table 1.

3.2. Opinions of brand name drugs, generic drugs, and generic substitution

GPs' opinions on generic drugs are summarized in Table 2. Respondents were divided into two groups based on answers given to the following questions: therapeutic equivalence, bioequivalence, quality, effectiveness, and adverse effects of generic drugs in comparison with brand name drugs. One group has considered generic drugs equivalent to brand name drugs in the above-mentioned parameters while the other group did not. Both groups had similar number of respondents (Table 2).

Table 1. Demographic characteristics of respondents (N=263)

Sex	
Female	177 (67.3%)
Male	86 (32.7%)
Age (years)	
Mean ± SD	52.2±13.7
44 years or less	44 (16.8%)
45-54 years	110 (41.8%)
55-64 years	74 (28.1%)
65 years or more	24 (9.1%)
Unknown	11 (4.2%)
Mean age by sex (years)	
Female mean age ± SD	49.1±13.6
Male mean age ± SD	52.6±13.6
Population of place where the respondent works	
Under 5,000 population	49 (18.6%)
5,000 - 99,999 population	141 (53.6%)
Above 100,000 population	73 (27.7%)
Practice specialization upon their graduation	
Yes	248 (94.3%)
No*	15 (5.7%)

** in preparation for GP specialization*

3.3. Understanding the legislation for GS

Each respondent has received one point for every correct answer (maximum was nine points). Table 3 summarizes the understanding of legal rules applicable to GS. According to the Czech legislation, all rules listed in Table 3 must be followed with the exception of the prescriber's consent and the same drug strength. None of the respondents was able to achieve the maximum score, i.e. to specify all legal rules applicable for GS.

The number of questions answered correctly by the respondents was 4.7 (SD=2.0) on average, $CI_{95\%}$ = (4.4 – 4.9). For nine questions with two possible answers each, this result is not very different from a random choice of answers and the difference from a coin flip outcome is not significant either (p=0.173). The score achieved corresponds to a probability of knowing the correct answer to 0.33 questions on average, $CI_{95\%}$ = (-0.14-0.81), added with 0.5*(9-0.33) questions answered correctly by accident.

The item-total correlation gained significantly positive values for all items excluding one (the same drug strength) that yielded a strongly negative correlation (r=-0.571, p<0.001), i.e. the question was answered incorrectly by the respondents who showed better knowledge of other items. The reason why the item was answered incorrectly could be due to the author's error (the first choice for explaining the phenomenon) but this possibility was eliminated by comparing with the original wording of the law. Other suggested reasons are the tricky nature of this item or misleading information possibly disseminated e.g. through an information booklet, text book, etc. among the GPs.

3.4. Attitude towards GS

A positive or a rather positive attitude towards GS was reported by 14 (5.3%) and 42 (16.0%) GPs, respectively. By contrast, 95 (36.1%) GPs considered GS as rather negative and 61 (23.2%) as negative. The remaining 51 (19.4%) GPs showed a neutral attitude.

There was a significant dependence (r=-0.135, p=0.033) between the understanding of legal rules for GS and the attitude towards GS. A positive attitude towards GS correlates with a better understanding of GS (see Figure 1). Younger respondents showed a much better familiarity with GS (r=-0.139, p=0.028) and were more positive about GS (r=0.143, p=0.024) than older respondents.

Overall, 202 (76.8%) of GPs reported that none of their patients have encountered any suspected GS-related problem during the last month.

Table 2. GPs' opinions of statements related to the brand name drugs, generic drugs and generic substitution (N=263)

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I got familiar with the issue of generic and brand name drugs during undergraduate studies.	17.5%	20.9%	14.8%	19.8%	27.0%
I got familiar with the issue of generic and brand name drugs during practice specialization.	43.4%	38.0%	7.2%	8.0%	3.4%
Every generic drug is therapeutically equivalent to the respective brand name drug.	3.0%	39.2%	16.7%	30.8%	10.3%
Every generic drug is therapeutically equivalent to any other generic drug.	5.3%	37.3%	25.5%	25.8%	6.1%
Every generic drug is bioequivalent to the respective brand name drug.	5.3%	32.3%	33.8%	20.5%	8.0%
I need more information on results of bioequivalence studies of generic drugs.	33.8%	40.0%	16.0%	6.8%	3.4%
Every generic drug must have the same dosage form (tablets, capsules) as the respective brand name drug.	21.7%	28.9%	16.7%	21.3%	11.4%
Generic drugs are of lower quality than the respective brand name drugs.	8.4 %	37.6 %	25.5 %	21.3 %	7.2 %
Generic drugs are less effective than the respective brand name drugs.	3.0%	36.1%	22.1%	28.9%	9.9%
Generic drugs cause more adverse drug reactions than the respective brand name drugs.	3.0%	34.3%	26.6%	28.5%	7.6%
Generic drugs are less costly than the respective brand name drugs.	37.3%	47.9%	7.2%	5.7%	1.9%
The law imposes the same safety requirements on both generic and brand name drugs.	39.2%	37.6%	12.5%	8.4%	2.3%
The same production quality guarantee is required for both generic and brand name drugs.	27.4%	33.5%	23.1%	12.2%	3.8%
Generic substitution reduces drug costs in patient pharmacotherapy.	30.8%	49.8%	13.4%	4.9%	1.1%

Table 3. Understanding of the legislation for GS (N=263)

Legal rule	Correct answer N (%)
The same active ingredient	216 (82.1%)
Patient's consent	156 (59.3%)
The same total dose	148 (56.3%)
The same route of administration	143 (54.4%)
Prescriber's consent	136 (51.7%)
The same dosage form	123 (46.8%)
The same drug strength	111 (42.2%)
"Branded substitution not permitted" is not indicated on the prescription	108 (41.1%)
Lower patient's co-pay	86 (32.7%)

3.5. Positive and negative outcomes of GS as viewed by GPs

The cost savings for patients and health insurance companies were considered as the most positive outcomes of GS. On the other hand, the most negative outcome was seen in the fact that the prescriber does not know which specific drug the patient uses. A summary of positive and negative outcomes is depicted in Table 4.

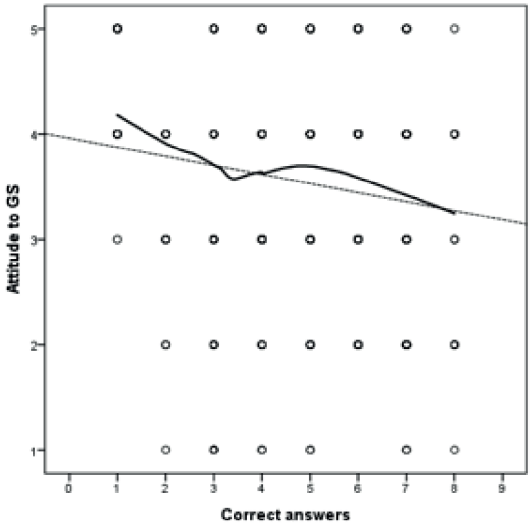

Figure 1. Correlation between the attitude towards GS and understanding of the legislation for GS

Legend: y axis: attitude towards GS (1–very positive, 2–positive, 3–neutral, 4–negative, 5–very negative); x axis: understanding of the legislation for GS (each correct answer scored one point out of maximal nine points); the line is a fitted local regression (loess) curve.

Table 4. Positive and negative outcomes from GP's perspective

Positive outcomes	N (%)
Cost savings for patients.	197 (74.9%)
Potential for cost savings for the health insurance companies.	159 (60.5%)
The prescriber does not have to check for co-pay.	124 (47.1%)
The pressure of the pharmaceutical companies is spread over a higher number of health care providers.	44 (16.7%)
Elevation of the status of pharmacists.	19 (7.2%)
Potential for reduction of range of drugs stocked in the pharmacies.	15 (5.7%)
Other outcomes.	15 (5.7%)
Negative outcomes	
The prescriber does not know which specific drug the patient uses.	195 (74.1%)
The prescriber has not full control over the treatment plan.	167 (63.5%)
Unclear liability for adverse drug reactions.	142 (54.0%)
The risk of duplicate drug use or other drug-related errors caused by patients.	130 (49.4%)
Patient's refusal because of possible higher risk of adverse drug reactions.	98 (37.3%)
Possible formation of "single color" pharmacies.	87 (33.1%)
Other outcomes.	18 (6.8%)
More time required by the pharmacists.	16 (6.1%)

Table 5. Familiarity with brand name drugs (N=263)

	Correct match N (%)	Do not know N (%)
Ramipril	206 (78.3%)	40 (15.2%)
Atorvastatin	196 (74.5%)	40 (15.2%)
Metformin	81 (30.8%)	76 (28.9%)
Omeprazole	61 (23.2%)	50 (19.0%)

3.6. Familiarity with brand name drugs

Less than a quarter of respondents knew the right brand name drugs for ramipril, atorvastatin, metformin, and omeprazole. The most correct matches were for ramipril and the least correct answers for omeprazole (see Table 5).

4. Discussion

Impetuous and often unfounded opinion amongst all physicians after the implementation of GS were the first challenge for conducting this survey. Controversies or negative attitudes often derive from poor knowledge of the principles for the entry of generic drugs on the market and from the lack of understanding the role generic drugs play in drug policy [21].

The GPs' demographic data (sex, age) in this study closely matched those reported by the Institute of Health Information and Statistics of the Czech Republic, i.e. a female to male ratio of 0.636 and the following age distribution: 44 years or less (18.8%), 45-54 years (38.2%), 55-64 years (31.3%), and 65 years or more (11.7%) [20]. In this regard, a representative sample of GPs was available for the present study.

Based on opinions about the therapeutic equivalence and bioequivalence GPs were divided into two groups. 42.2% of the respondents considered generic drugs therapeutically equivalent with the brand name drugs. The bioequivalence of generic and brand named drugs was viewed similarly (37.2%). In comparison with a survey conducted in Australia [19], Czech GPs are more negative about the therapeutic equivalence and bioequivalence of generic drugs. This difference may be explained by the fact that the Australian study was conducted on senior medical students, i.e. on younger respondents who are likely to be more familiar with the issues of generic drugs and bioequivalence than the older cohort in the present study. This assumption is supported by the results of the present study, showing a more positive attitude of younger GPs towards GS as well as their better familiarity with the principles of GS in comparison with their older colleagues. From the results of both studies it seems that the respondents either misunderstood or did not know the principles of bioequivalence studies. The therapeutic equivalence of generic drugs to the respective brand name drugs is derived from the ratio of the pharmacokinetic parameters Cmax and AUC that have to be between 80 and 125% at 90% CI [22]. Therefore, it is surprising that a similar proportion of GPs in the Czech study were not

sure either about the therapeutic equivalence of the generic and brand name drugs or about their bioequivalence. Nevertheless, much more skepticism would be expected about the therapeutic equivalence between generic drugs, as the variability of the above-mentioned pharmacokinetic parameters (Cmax and AUC) could theoretically reach even tens of percent [22]. However, in reality these parameters differ by less than 10% (generic drug vs. brand name drug) and thereby difference between generic drug and another generic drug is also much lower [23].

GPs perceived generic drugs as a cost saving mean, since most GPs agreed with the statement that GS reduces drug costs in patient pharmacotherapy. Moreover, GPs believed that generic drugs are less costly than the brand name drugs. When put on the market, a generic drug should be cheaper than the respective brand name drugs and GS is not feasible without meeting the requirement for lower patient costs. The two prerequisites derive from the Czech legislation [24]. Similar rules apply in other European countries.

It was shown that GPs were aware of the safety and quality regulations for drug production. GPs believed that the law imposes the same safety requirements on both generic and brand name drugs and agreed that adherence to good manufacturing practice is required equally for generic and brand name drugs. On the other hand, despite these facts, GPs considered generic drugs to have lower quality, lower efficacy, and more adverse effects than the respective brand name drugs. This attitude may reflect a fear of failure of an internal or external production control, lack of confidence in drug agencies, or prejudice towards generic drug producers. The lack of confidence in generic drugs may also result from a previous negative experience. The study comparing brand name and generic drugs with clopidogrel pointed out both quality and quantity flaws in some generic drugs tested (e.g. a higher proportion of impurities or a lower content of the active ingredient) [25]. For instance in Norway, the adverse events suspected to be related to generic drugs or GS have been observed [26]. However, at the same time more than three quarters of the study respondents reported not having encountered any problem related to GS or to generic drugs. Underreporting of adverse drug events is currently a problem in the Czech Republic [27]. It implies that the GPs' negative to critical attitude towards generic drugs is based solely on personal experience or myths.

Given the nature of generic drugs (the same active ingredient and different excipients) a higher risk of allergic reactions can be expected. Cases of allergic reactions due to croscarmellose or skin sensitization following the switch from the brand name drug with allopurinol to a generic drug have been reported [28,29]. Australian medical students [19] were more critical about generic drugs than GPs in the Czech Republic. More than 90% of the students believed that generic drugs are less effective or have lower quality and cause more adverse drug reactions than the brand name drugs. Nevertheless, the principles of generic drug studies do not unambiguously imply that generic drugs would be less effective than the brand name drugs and even the opposite may be true. Two recent reviews of Kesselheim et al. have confirmed the therapeutic equivalence of generic and brand name drugs, not suggesting e.g. lower efficacy of the former [30,31].

The quality of bioequivalence studies was addressed in the review of van der Meersch et al. [32]. They have shown that the available studies lack transparency and a body of important information (on the reference drugs, bioequivalence – pharmacokinetic parameters, details on the population tested, methods of testing and evaluation, etc.) that is crucial for the evaluation of the results of a specific test. It is in the interests of both the public and manufacturers of generic drugs to disprove myths about generic drugs [32]. Drug agencies such as Food and Drugs Administration, European Medicines Agency, and other national agencies could contribute to this aim by publishing the results of bioequivalence studies. Accordingly, this could increase the confidence in use of generic drugs and GS.

Nevertheless, we tend to believe that a major problem was the lack of awareness in our respondents and therefore, emphasis is needed on postgraduate training in use of generic drugs and GS. Nearly half of GPs did not get familiar with this issue during their medical studies. Moreover, closer integration between health care professionals and pharmacists should be fostered during their undergraduate studies and further enhanced in every day clinical practice.

Some barriers may also result from the lack of communication and cooperation between GPs and pharmacists. Some problems could be solved by using electronic medical records accessible to health care providers, patients, and pharmacists. Thereby providing the opportunity for the pharmacist to indicate the generic drug he/she dispenses within GS. The GPs' confidence in GS could be enhanced creating a list of substitutable drugs by the national drug agency (State Institute for Drug Control in the Czech Republic). This is similarly to Finland, where such a list is issued by the Finnish Medicines Agency [33]. The pharmacist should consider both the patient and the substitutable drug on an individual basis. A non-compliant patient is not a candidate for GS. When inferring that the patient has not understood GS, the pharmacist should not proceed with it. It is the only

way to prevent drug-related problems due to GS (e.g. duplicate drug use) [34]. More stringent bioequivalence rules apply to drugs with a narrow therapeutic index, or with unpredictable (non-linear) pharmacokinetics and to poorly water-soluble drugs for which the same pharmacokinetic profile (Cmax and AUC) is required [22, 35]. Nevertheless, GS is not recommended for these drugs (immunosuppressants, antiarrhythmic drugs, etc.). Similar problems and risks are posed by some dosage forms (powder inhalers, modified release drugs, transdermal patches, autoinjectors, etc.) and again GS needs to be considered with extreme caution in this context [8,35-37].

Not only poor awareness of the principles and testing of bioequivalence, but also considerable lack of awareness of legal rules for GS were key reasons for the negative attitude towards GS and for concern about GS-related risks (reduced efficacy, adverse events due to generic drugs, etc.). For instance, GPs did not know that the patient's consent is a fundamental prerequisite for GS. More precisely, it is the patient and not the pharmacist who decides whether or not GS will take place. The physician can prevent GS by indicating that substitution for the brand name drugs specified on the prescription form cannot be obtain [7,8]. Poor understanding of GS principles and legal rules for GS was the major reason for concern about the liability for adverse drug reactions.

The critical attitude towards GPs was enhanced by the results shown in Table 5. GPs failed to indicate the correct names of the brand name drugs even for some well-known active ingredients. Therefore, it cannot be excluded that they often unknowingly prescribe generic drugs instead of the brand name ones. Consequently, some of their opinions or experiences might have arisen from incorrect considerations.

The use of a higher proportion of generic drugs and reasonable approach to GS will not only reduce health costs for patients and health care payers but also will increase the availability of health care to general population. Moreover, cost savings can be redirected to the area of rare or costly diseases [38]. Therefore, a major challenge is to raise the GPs' awareness of generic drugs and GS.

5. Limits of the study

Results of the present study could have been flawed by two selection biases: the low questionnaire response rate and selection of respondents. The questionnaire response rate was lower than expected based on similar studies [17,18]. The extent of the questionnaire may have played a role in this regard. It was designed to obtain a comprehensive view of the GPs' opinions about generic drugs and GS. However, such an extensive questionnaire has not yet been used in any of previous surveys. Another limitation to this study may be the selection bias, as only participants of professional conferences were addressed. Nevertheless, the magnitude of this bias is difficult to gauge. It could be assumed that the respondents were primarily GPs actively interested in continuous education.

6. Conclusion

The awareness of generic drugs and GS along with the experiences gained in this area was an important factor involved in the formation of attitudes towards generic drugs and GS in the study cohort. The GPs' relationship to GS was significantly influenced by their awareness of legal rules for GS. Therefore, it would be extremely useful to conduct an information campaign addressing health care professionals. A closer integration of GPs and pharmacists during their university studies could increase mutual confidence between them and thus promote the use of GS. A major prerequisite for GS appears to be sharing electronic medical records between health care professionals and pharmacists in the Czech Republic. Another means to boost the confidence in generic drugs and GS may be publication of results of bioequivalence studies and creation of a list of substitutable drugs.

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Conflict of interest statement

Authors state no conflict of interest.

References

[1] Shrank W.H., Choudhry N.K., Liberman J.N., Brennan T.A., The use of generic drugs in prevention of chronic disease is far more cost-effective than thought, and may save money, Health Aff (Millwood)., 2011, 30, 1351-1357

[2] Pechlivanoglou P., van der Veen W.J., Bos J.H., Postma M.J., Analyzing generic and branded substitution patterns in the Netherlands using prescription data, BMC Health Serv Res., 2011, 11

[3] Institute of Health Information and Statistics of the Czech Republic. Economic information on health care 2010 [online]. 2011 [cited 2012-5-25]. Available from http://www.uzis.cz/en/publications/economic-information-health-care-2010

[4] Aalto-Setälä V., The impact of generic substitution on price competition in Finland, Eur J Health Econ., 2008, 9, 185-191

[5] Posner J., Griffin J.P., Generic substitution, Br J Clin Pharmacol., 2011, 72, 731-732

[6] Dylst P., Simoens S., Generic Medicine Pricing Policies in Europe: Current Status and Impact, Pharmaceuticals., 2010, 3, 471-81

[7] Czech Republic, Act No. 378/2007 on Pharmaceuticals, In: Catch III Registration of pharmaceuticals and steps related to their registration, Article 25, 2008, 115, 22-3, (in Czech)

[8] State Institute for Drug Control, The physician's and pharmacist's roles derived from the new Act on Pharmaceuticals, Pharmacotherapeutic information 2/2008, A monthly for physicians and pharmacists, 2008, 2, 1-4, (in Czech)

[9] Andersson K., Sonesson C., Petzold M., Carlsten A., Lönnroth K., What are the obstacles to generic substitution? An assessment of the behaviour of prescribers, patients and pharmacies during the first year of generic substitution in Sweden, Pharmacoepidemiol Drug Saf., 2005, 14, 341-348

[10] Mott D.A., Cline R.R., Exploring generic drug use behavior: the role of prescribers and pharmacists in the opportunity for generic drug use and generic substitution, Med Care., 2002, 40, 662-674

[11] Suh D.C., Trends of generic substitution in community pharmacies, Pharm World Sci., 1999, 21, 260-265

[12] Shrank W.H., Stedman M., Ettner S.L., DeLapp D., Dirstine J., Brookhart M.A., et al., Patient, physician, pharmacy, and pharmacy benefit design factors related to generic medication use, J Gen Intern Med., 2007, 22, 1298-1304

[13] Andersson K., Jörgensen T., Carlsten A., Physicians' opinions and experiences of the Pharmaceutical Benefits Reform, Scand J Public Health., 2006, 34, 654-659

[14] Heikkilä R., Mäntyselkä P., Hartikainen-Herranen K., Ahonen R., Customers' and physicians' opinions of and experiences with generic substitution during the first year in Finland, Health Policy., 2007, 82, 366-374

[15] Lagarce L., Lusson-Brisset C., Bruhat C., Diquet B., Lainé-Cessac P., How practitioners view generic drugs: an opinion study from general practitioners in Maine-et-Loire (France), Therapie., 2005, 60, 67-74, (in French)

[16] Himmel W., Simmenroth-Nayda A., Niebling W., Ledig T., Jansen R.D., Kochen M.M., et al., What do primary care patients think about generic drugs?, Int J Clin Pharmacol Ther., 2005, 43, 472-479

[17] Kersnik J., Peklar J., Attitudes of Slovene general practitioners towards generic drug prescribing and comparison with international studies, J Clin Pharm Ther., 2006, 31, 577-583

[18] García A.J., Martos F., Leiva F., Sánchez de la Cuesta F., Generic drugs: good or bad? Physician's knowledge of generic drugs and prescribing habits, Gac Sanit., 2003, 17, 144-149, (in Spanish)

[19] Hassali M.A., Stewart K., Kong D.C., A national survey on knowledge and perceptions of senior medical students in Australia about generic medicines, Med J Aust., 2008,188, 123-124

[20] Institute of Health Information and Statistics of the Czech Republic, Physicians, Dentists and Pharmacists 2008 [online]. 2010 [cited 2012-5-25]. Available from www.uzis.cz/system/files/lekfar2008.pdf

[21] Banahan B.F., III, Kolassa E.M., A physician survey on generic drugs and substitution of critical dose medications, Arch Intern Med., 1997, 157, 2080-2088

[22] European Medicines Agency, Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** [online]. 2010 [cited 2012-5-25]. Available from http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

[23] Davit B.M., Nwakama P.E., Buehler G.J., Conner D.P., Haidar S.H., Patel D.T., et al., Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration, Ann Pharmacother., 2009, 43, 1583-1597

[24] Czech Republic, Act No. 48/1997 on public health insurance, In: Part VI Regulation of pricing and reimbursement of drugs and food for special medical purposes, Article 39, 1997, 16, 35-59, (in Czech)
[25] Gomez Y., Adams E., Hoogmartens J., Analysis of purity in 19 drug product tablets containing clopidogrel: 18 copies versus the original brand, J Pharm Biomed Anal., 2004, 34, 341-348
[26] Reppe L.A., Stenberg-Nilsen H., Harg P., Hegge A.B., Lillefloth A.K., Buajordet I., Adverse events related to substitution of generic products in Norway 2005, Tidsskr Nor Laegeforen., 2008, 128, 2696-700, (in Norwegian)
[27] Kopečná E., Deščíková V., Vlček J., Mladá J., Adverse drug reaction reporting in the Czech Republic 2005-2009, Int J Clin Pharm., 2011, 33, 683-689
[28] Chandeclerc M.L., Tréchot P., Martin S., Weber-Muller F., Schmutz J.L., Barbaud A., Cutaneous adverse drug reaction induced by a generic substitute of Zyloric with a residual sensitization to allopurinol, Allergy., 2006, 61, 1492-1493
[29] Mumoli N., Cei M., Luschi R., Carmignani G., Camaiti A., Allergic reaction to Croscarmellose sodium used as excipient of a generic drug, QJM., 2011, 104, 709-710
[30] Kesselheim A.S., Stedman M.R., Bubrick E.J., Gagne J.J., Misono A.S., Lee J.L., et al., Seizure outcomes following the use of generic versus brand name antiepileptic drugs: a systematic review and meta-analysis, Drugs., 2010, 70, 605-621
[31] Kesselheim A.S., Misono A.S., Lee J.L., Stedman M.R., Brookhart M.A., Choudhry N.K., Shrank W.H., Clinical equivalence of generic and brand name drugs used in cardiovascular disease: a systematic review and meta-analysis, JAMA., 2008, 300, 2514-2526
[32] van der Meersch A., Dechartres A., Ravaud P., Quality of reporting of bioequivalence trials comparing generic to brand name drugs: a methodological systematic review, PLoS One., 2011, 6
[33] Timonen J., Bengtström M., Karttunen P., Ahonen R., The impact of generic substitution on the activities of pharmaceutical companies – a survey from the companies' perspective one year and five years after the introduction of generic substitution in Finland, BMC Clin Pharmacol., 2010, 10
[34] Johnston A., Asmar R., Dahlöf B., Hill K., Jones D.A., Jordan J., et al., Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe, Br J Clin Pharmacol., 2011, 72, 727-730
[35] Meredith P., Bioequivalence and other unresolved issues in generic drug substitution, Clin Ther., 2003, 25, 2875-2890
[36] Danish Health and Medicines Authority, Bioequivalence and labeling of medicines with regard to generic substitution [online]. Updated 2012-2 -07 [cited 2012-5-25]. Available from http://laegemiddelstyrelsen.dk/en/topics/authorisation-and-supervision/licensing-of-medicines/marketing-authorisation/application-for-marketing-authorisation/bioequivalence-and-labelling-of-medicine—bstitution.aspx
[37] Duerden M.G., Hughes D.A., Generic and therapeutic substitutions in the UK: are they a good thing?, Br J Clin Pharmacol., 2010, 70, 335-341
[38] Simoens S., Generic and therapeutic substitution: ethics meets health economics, Int J Clin Pharm. 2011, 33, 469-470