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ANALYSIS OF PHARMACISTS' OPINIONS, ATTITUDES AND EXPERIENCES WITH GENERIC DRUGS AND GENERIC SUBSTITUTION IN THE CZECH REPUBLIC

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Abstract: Generic substitution (GS) is an integral part of drug policy in many countries. Similarly to other countries its introduction in the Czech Republic gave rise to a vibrant discussion. The aim of the study was to map and analyze pharmacists` opinions of, attitudes towards and experiences with generic drugs and GS after the first year from its legislative embodiment in the Czech Republic. All 7,665 members of the Czech Chamber of Pharmacists were addressed to participate in a questionnaire survey between November 2008 and March 2009. The questionnaire consisted of 28 questions concerning the issue of generic drugs and GS and was divided into five sections. All collected data were analyzed using descriptive statistics and correlations were tested by selected parametric and non-parametric tests. A total of 615 completed questionnaire forms were returned (a questionnaire return rate of 8.0%). The demographic characteristics of the respondents were as follows: 470 (76.4%) females, mean age of 37.5 years (SD = 10.4) and 429 (69.6%) pharmacists with a practice specialization. Altogether 345 (56.1%) respondents became aware of the issue of brand name and generic drugs during their undergraduate studies. 378 (61.5%) respondents considered generic drugs as bioequivalent and 455 (74.0%) respondents as therapeutically equivalent to the respective brand name drugs. 99 (16.1%) pharmacists believed that generic products are of lower quality than branded drugs and 69 (11.2%) respondents expected generics to cause more adverse drug reactions. GS was perceived as a positive tool by 476 (77.4%) respondents. Only 71 (11.5%) respondents showed acquaintance with all the legal rules for GS. Legislation awareness and attitude towards GS was correlated with age ($p < 0.001$). The use of GS in the routine practice depends on the pharmacists' familiarity with the relevant legislation and attitude towards generic drugs and GS. Approaching patients on an individual basis and pharmacists' awareness can minimize adverse drug events caused by generic drugs and at the same time enhance the professional status of pharmacists.

Keywords: pharmacist, brand name drug, generic drug, generic substitution

The ever increasing drug use and consequent rise in health care costs led to the search for opportunities for cost reduction and savings in most industrialized countries (1). In the Czech Republic from 2000 to 2008, the public expenditure on health increased approximately by 65%. In 2008, the drugs value in total expenditure on health care was 20% (2).

One of the cost saving measures that can be taken without reducing the quality of health care is to increase the share of generic drugs. The expected savings would be beneficial for the whole health care system including patients (1, 3).

Generic drugs are marketed after the patent exclusivity period for the brand name drug expires. The qualitative and quantitative equality of selected parameters between a generic drug and the reference brand name drug is tested in bioequivalence studies (4, 5). The launch of generic drugs on the market brings along, apart from savings, better availability of drugs to a wider range of patients in comparison with the brand name drugs (6).

There are several ways how to support the use of generic drugs in the clinical practice. Since the 1980s, generic substitution (GS) has been used in numerous countries and patient has been provided with the generic drug in the same dosage form, drug strength, route of administration and containing the same active ingredient as the brand name drug indicated by the prescriber but usually available at a lower cost (7, 8). Another policy tool to promote generic drugs is the principle of generic prescription

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applied in some countries. The prescriber indicates the International Non-Proprietary Name (INN) and the pharmacist selects the product best suiting the patient's needs (9).

Despite the general support of GS, particularly for economic reasons, this issue remains controversial and the launch of GS brings along mistrust and confusion among both the general and professional public. Such an attitude towards generic drugs and GS has been adopted even when there is no unambiguous evidence of their negative effects (10).

Although GS has long been available in the Czech Republic, Act No. 378/2007 on pharmaceuticals providing an explicit definition of GS (11) gave rise to a vibrant discussion. Similarly to other countries, in the Czech Republic, it is evident that controversies often arise from the lack of knowledge of the principle of generic drugs entry on the market and from a poor understanding of their role in the drug policy (12).

Objective

The study objectives were to map pharmacists' opinions of and attitudes towards generic drugs and GS, analyze pharmacists' experience with GS and assess the level of knowledge of GS after the first year from its legislative embodiment in the Czech Republic. The present paper is part of a more extensive survey of health care professionals' and patients' opinions, attitudes and experiences with GS in the Czech Republic.

Instrumental

All members of the Czech Chamber of Pharmacists (CCP) were addressed. The membership in the CCP is a compulsory prerequisite for practising as a pharmacist in a pharmacy care service in the Czech Republic. In 2008, the CCP had 7,665 members (13).

The data were collected in a questionnaire survey from November 2008 to March 2009. The questionnaire and instructions for its completion were published in the Journal of Czech Pharmacists and distributed to all CCP members. The questionnaire was also available on the CCP web page. Each questionnaire form was labelled with the respective CCP membership number to ensure that every CCP member could fill in only one questionnaire. The questionnaire consisted of 28 questions divided into five sections.

In section 1 demographic data (sex, year of birth, number of inhabitants in residence location, workplace location and practice specialization upon their graduation) were collected. Section 2 was composed of statements related to use, cost, and safety of brand name and generic drugs and responses were recorded on a five-point Likert scale (1 = strongly agree; 2 = agree; 3 = neutral; 4 = disagree; 5 = strongly disagree). This section was taken from two similar questionnaire surveys (14, 15) and adapted to suit the conditions of the Czech Republic. Section 3 was focused on the understanding the legislation relevant for the GS in the Czech Republic (dichotomous questions). In section 4 attitudes towards GS were examined and rated again on a five-point scale (very positive, positive, neutral, negative, and very negative). Furthermore, list of questions (multiple responses possible) was used to find out the most positive outcomes (e.g., cost savings) and the most negative outcomes (e.g., risk of duplicate drug use) of the implementation of GS as perceived by pharmacists. The last section 5 was designed to test the knowledge of the brand names of the drugs commonly used in the clinical practice (closed ended questions). Drugs with four active ingredients (atorvastatin, ramipril, metformin and omeprazole) were presented to the respondents who had to select the respective brand name from a multiple choice list. The questionnaire was piloted and the mean administration time was 15 min.

Analysis

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) indicated in some cases. Pearson's correlation test (r) was used to test for correlations between attitudes towards GS and age and sex or understanding the legislation for GS. Kendall's tau correlation (τ) test was applied for the analysis of correlation between the drug brand name knowledge and age. A significance level of 0.05 was used.

RESULTS

Demographic characteristics

Six hundred fifteen pharmacists filled in the questionnaire form. This number corresponded to 8.0% of the total of pharmacists in the CCP in 2008 (13). The mean age of respondents was 37.5 years (SD = 10.4). Four hundred seventy (76.4%) respondents were females. The mean age of female pharmacists was 37.8 years (SD = 10.6) and was higher in comparison with male pharmacists (36.4 years, SD = 9.5). Eighty three (13.5%) respondents lived in smaller residence places with less than 5,000 inhabitants, 333 (54.2%) respondents lived in cities with

5,000 to 99,999 inhabitants and 199 (32.4%) were from larger cities with more than 100,000 inhabitants. Four hundred twenty nine (69.6%) respondents have completed a practice specialization upon their graduation. All questionnaires returned were included in the analysis.

Opinions of brand name drugs, generic drugs and generic substitution

Table 1 summarizes pharmacists' opinions of the statements related to the generic and brand name drugs. They became aware of the issue of brand name and generic drugs during their undergraduate studies and got familiar with this issue even more during speciality training while in practice. Altogether, 61.5% of respondents considered generic drugs as bioequivalent to the respective brand name drugs and 74% of respondents as therapeutically equivalent to the respective brand name drugs as well as to one another.

More than 90% of pharmacists perceived generic drugs as cheaper than brand name ones. A similarly large proportion of respondents thought the law requires the same safety measures and the same production quality guarantee (compliance with good manufacturing practice) for generic as for the brand name drugs. Generic drugs were considered by pharmacists as comparable to brand name drugs in terms of the quality, safety and incidence of adverse drug reactions.

Understanding the legislation for GS

Each correct response scored one point (maximum of nine points). Table 2 summarizes understanding the legislation for GS. Apart from the physician's consent and strength equivalence, all legal rules summarized in Table 2 must be followed according to the Czech regulations in force. The mean total score for the correct answers was 7.2 (SD = 1.2), i.e., the respondents gave correct answers to 7.2 ± 1.2 questions on average ($CI_{95\%}$ = 7.1-7.3). This outcome is illustrated in Figure 1. Seventy one (11.5%) respondents knew all legal rules for GS. The pharmacists were sure that generic drugs with the same active ingredient and the same route of administration as the brand name drugs can be dispensed through GS. They were also aware of the need for obtaining the patient's consent to GS and of the fact that the prescriber's consent is always assumed to be granted unless "branded substitution not permitted" is indicated on the prescription.

Attitude towards GS

GS was seen as very positive by 254 (41.3%) and as positive by 222 (36.1%) respondents. Neutral attitude towards GS was reported by 107 (17.4%) pharmacists and 32 (5.2%) considered it as negative. None of the respondents rated GS as very negative.

Statistical analysis revealed a significant correlation between understanding the legislation for GS and attitude towards GS (r = -0.084, p = 0.039). The

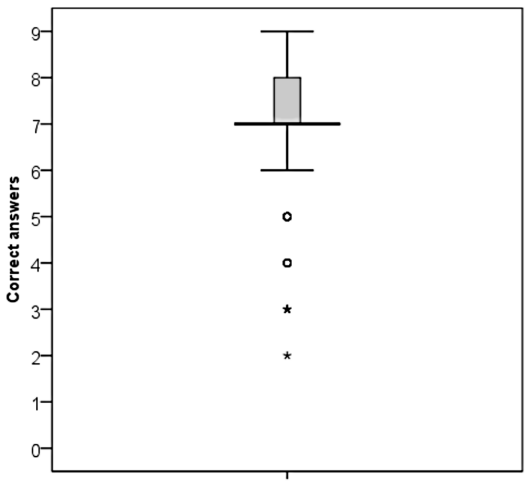

Figure 1. Understanding the legislation for GS. Each correct answer scored one point (maximum of nine points).

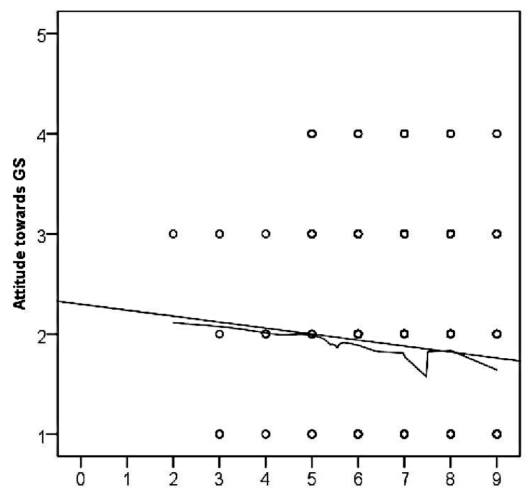

Figure 2. Correlation between attitude towards GS and understanding the legislation for GS y axis: attitude towards GS (1–very positive, 2–positive, 3–neutral, 4–negative, 5 –very negative); x axis: understanding the legislation for GS (each correct answer scored one point, maximum of nine points); the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

Table 1. Pharmacists' opinions of statements related to brand name drugs and generic drugs and generic substitution (n = 615).

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I got familiar with the issue of generic and brand name drugs during undergraduate studies.	19.0%	37.1%	7.5%	23.2%	13.2%
I got familiar with the issue of generic and brand name drugs during practice specialization.	35.4%	42.2%	8.3%	11.2%	2.9%
Every generic drug is therapeutically equivalent to the respective brand name drug.	18.7%	55.3%	6.0%	15.6%	4.4%
Every generic drug is therapeutically equivalent to any other generic drug.	21.0%	53.0%	11.4%	10.9%	3.7%
Every generic drug is bioequivalent to the respective brand name drug.	24.6%	36.9%	21.0%	15.1%	2.4%
I need more information on results of bioequivalence studies of generic drugs.	47.0%	29.4%	13.2%	8.6%	1.8%
Every generic drug must have the same dosage form (tablets, capsules) as the respective brand name drug.	56.1%	26.0%	2.8%	11.0%	4.1%
Generic drugs are of lower quality than the respective brand name drugs.	2.4%	13.7%	14.5%	41.1%	28.3%
Generic drugs are less effective than the respective brand name drugs.	0.3%	6.7%	14.3%	43.4%	35.3%
Generic drugs cause more adverse drug reactions than the respective brand name drugs.	0.6%	10.6%	18.7%	41.8%	28.3%
Generic drugs are less costly than the respective brand name drugs.	59.2%	35.8%	1.9%	2.8%	0.3%
The law imposes the same safety requirements on both generic and brand name drugs.	78.7%	14.6%	3.6%	2.8%	0.3%
The same production quality guarantee is required for both generic and brand name drugs.	72.2%	19.7%	6.2%	1.6%	0.3%
Generic substitution reduces drug costs in patient pharmacotherapy.	56.1%	39.5%	1.8%	2.0%	0.6%

better understanding the legislation the more positive attitude towards GS (see Fig. 2). The significant correlation was also found between understanding the legislation for GS, attitude towards GS and age. Younger pharmacists had better knowledge of GS ($r = -0.163$, $p < 0.001$) and more positive attitude towards the GS ($r = 0.200$, $p < 0.001$). Sex did not appear to be a statistically significant parameter.

Table 2. Understanding the legislation for GS (n = 615).

Legal rule	Correct answer n (%)
Prescriber's consent	605 (98.4%)
The same active ingredient	603 (98.0%)
Patient's consent	601 (97.7%)
The same route of administration	560 (91.1%)
"Branded substitution not permitted" is not indicated on the prescription	557 (90.6%)
The same dosage form	495 (80.5%)
The same total dose	411 (66.8%)
The same drug strength	334 (54.3%)
Lower patient's co-pay	276 (44.9%)

Table 3. Positive and negative outcomes from pharmacist's perspective (n = 615).

	n (%)
Positive outcomes	
Cost savings for patients.	574 (93.3%)
Elevation of the status of pharmacists.	414 (67.3%)
Potential for cost savings for health insurance companies.	402 (65.4%)
The prescriber does not have to check for co-pay.	319 (51.9%)
Potential for reduction of the range of drugs stocked in pharmacies.	179 (29.1%)
The pressure of the pharmaceutical companies is spread over a higher number of health care providers.	173 (28.1%)
Other outcomes.	27 (4.4%)
Negative outcomes	
The risk of duplicate drug use or other drug-related errors caused by patient.	447 (72.7%)
Unclear liability for adverse drug reactions.	305 (49.6%)
Patient's refusal because of possible higher risk of adverse drug reactions.	266 (43.2%)
The prescriber does not know which specific drug the patient uses.	262 (42.6%)
Possible emergence of single colour pharmacies.	167 (27.1%)
The prescriber has not full control over the treatment plan.	98 (15.9%)
Other outcomes.	73 (11.9%)
More time required from pharmacists.	72 (11.7%)

Table 4. Familiarity with brand name drugs (n = 615).

Drug	Correct match n (%)	Do not know n (%)
Atorvastatin	563 (91.5%)	29 (4.7%)
Ramipril	539 (87.6%)	39 (6.3%)
Metformin	431 (70.1%	63 (10.2%)
Omeprazole	311 (50.6%)	48 (7.8%)

Positive and negative outcomes of GS as viewed by pharmacists

The cost savings for patients and health insurance companies were seen as the most positive outcomes of GS. Pharmacists also perceived the potential for raising their professional status as one of the advantages of GS as well as the fact that the physician is no longer required to check for co-pay. Nevertheless, the most negative outcomes were seen in the risk of duplicate drug use or other drug-related errors caused by patients. Summary of positive and negative outcomes is shown in Table 3.

Familiarity with brand name drugs

At least 50% of respondents matched the correct brand name from the provided list with any of the four active ingredients. Acquired outcomes are shown in Table 4. The highest number of correct matches was obtained for atorvastatin and the lowest number of correct matches for omeprazole. The knowledge of the brand names correlated with age: older pharmacists had better outcomes than younger pharmacists. The correlation between age and knowledge was statistically significant ($\tau = 0.136$, $p < 0.001$).

DISCUSSION

The overall questionnaires return rate was below expectations and lower than reported in similar studies (14, 15). This fact could be due to the extent of the questionnaire comprising 28 questions or could be also related to the fear resulting from respondents' knowledge testing.

Demographic data on our respondents were comparable to those provided in the annual report of the CCP or by the Institute of Health Information and Statistics of the Czech Republic (13, 16).

Opinions on brand name drugs, generic drugs and generic substitution

Nearly 62% of pharmacists considered generic drugs bioequivalent to the respective brand name drugs. Furthermore, almost 3/4 of pharmacists found them therapeutically equivalent to the respective brand name drugs. The confidence of Czech pharmacists in the therapeutic equivalence of generic drugs was nearly 25% higher than reported in Malaysian study (17), therefore, Czech respondents seemed to understand the principles of bioequivalence studies. Drug bioequivalence is defined as the ratio of pharmacokinetic parameters (maximum plasma concentration, Cmax, and area under the curve, AUC) ranging from 80 to 125% (90% CI) and it is assumed that the therapeutic equivalence is derived from the concordance of these pharmacokinetic parameters. This was also shown by a similar proportion of responds (79%) considering generic drugs as equally effective as the respective brand name drugs. In practice, the variability of the above mentioned pharmacokinetic parameters is usually less than 10% (5, 18, 19, 20). The respondents probably trusted the regulatory authorities supervising such activities as was also evident from the statement related to the quality guarantees. The difficulty of differentiating between bioequivalence and therapeutic equivalence in this study may reflect either a misunderstanding of the question or of the term "bioequivalence". This assumption could be supported by the large proportion (21%) of the respondents who were not able to answer the statement.

Rather surprisingly, a similar proportion (74%) of respondents considered generic drugs to be equivalent to one another. Nevertheless, the relevant parameters (Cmax and AUC) of two generic drugs may theoretically differ by up to 55% (5).

The confidence of pharmacists in generic drugs would have been enhanced if the results of bioequivalence studies had been available to them.

Altogether, 95% of pharmacists considered generic drugs as less costly drugs and GS as a tool for reducing health care costs incurred in patient pharmacotherapy. The latter statement was referred to the legislation for GS in the Czech Republic (11).

Few pharmacists (1.9%) thought that the good manufacturing practice requirements are not applied to the production of generic drugs and 3.1% of respondents admitted that the regulations do not impose the same safety requirements on generic drugs as on brand name drugs. Close to 15% of respondents believed that generic drugs might be of lower quality than the respective brand name drugs. Furthermore, study from Malaysia (17) has reported an even lower level of confidence in the quality of generic drugs (32.4%).

Generic drugs are sometimes called "carbon copies" of the respective brand name drugs. Such comparison may lead to conclusion that a carbon copy implies poorer quality. Although it is a myth, the critical view on generic drugs of our respondents was in accordance with the study of Gomez et al.. who pointed out discrepancies between the brand name drug containing clopidogrel and its generic drugs with higher amount of impurities, lower content of the active ingredient, etc. (21).

A total of 11% of pharmacists believed that generic drugs cause more adverse drug reactions.

Data on adverse drug reactions caused by generic drugs are lacking in the Czech Republic and the reason may be because of the generally small number of reported cases (22). Adverse drug reactions associated with generic drugs have already been observed by others (23, 24). The nature of generic drugs implies a higher risk of adverse drug reactions associated with excipients, e.g., allergic reactions (25-27). As to the principles of bioequivalence, problems should be expected especially in patients susceptible to drug plasma concentration changes. However, a systematic review comparing the risk in patients with epilepsy treated with generic or brand name drugs did not confirm this assumption (28).

Despite this fact, providing evidence of bioequivalence may not be always enough and more stringent rules are applied to certain generic drugs. These are drugs with a narrow therapeutic index, drugs with unpredictable (non-linear) pharmacokinetics or poorly water soluble drugs (5, 10, 29).

Understanding the legislation for GS

Poor awareness of the legislation for GS may be one of the possible barriers to GS in the Czech Republic. This fact may result in less frequent or incorrect application of GS. Possible consequences may be not only higher health care costs but also negative health effects in patients caused by e.g., use of different dosing or drug form than was prescribed. Moreover, higher costs of medication or co-pay may lead to patient poor adherence to the treatment (30). The system of GS used in the Czech Republic gives a key role to the patient who has the last say whether or not GS takes place. The prescriber can prohibit GS, but has to do so actively by indicating it on the prescription. In addition to GS, the Czech regulations also refer to "drug replacement" or "alternative", which allows the pharmacist to replace the prescribed drug with another one in case of unavailability of the former drug or risk of delay. For either drug replacement or alternative lower co-pay is not insisted on and neither drug alternative requires the same active ingredient. Dispensing drug alternative is then subject to the prescriber's consent. This relatively complicated regulation may have played a role in poorer understanding the legislation for GS. The situation was further complicated by the fact that the rules applicable to drug dispensing and therefore, also to GS, were regulated by several regulations. The short one-year experience with GS may also have played a role. It could explain the less than 50% understanding of one of the legal rules (lower patient's co-pay, Table 2). Better understanding of another legal rule for GS ("same drug strength") was shown. If an alternative drug in the same drug strength is not available it does not pose an obstacle to the application of GS according to the Czech regulations in force. The pharmacist has to adjust the dosage of the generic dispensed to achieve the total dose specified by the prescriber.

Although all pharmacists are involved in continuing education, younger respondents showed statistically significantly better understanding of the relevant legislation. It can be explained by higher interest in obtaining the practice specialization for which active knowledge of the regulations is required. The mean age of the respondents was nearly 38 years and almost 70% of them completed the practice specialization. GS considerably increases the decision-making authority of the pharmacist. As results suggested, understanding the legislation was a statistically significant predictor of positive attitude towards GS. Therefore, younger pharmacists tended to be more positive about GS than their older colleagues.

Confidence in GS and its positive and negative outcomes

Our respondents saw cost savings as the most important benefit from GS. The public cost savings depend on the reference system for retail pricing and insurance coverage. As the system's potential has not been fully put to use in the Czech Republic, it is the patient who can benefit the most from the cost savings. The actual cost savings from GS are closely related to the current cost control policies and that is why the application of GS alone may not result in considerable drug price reduction (31, 32).

The results showed that the positive attitudes of pharmacists towards GS were probably closely related to the fact that GS as a drug policy tool changes the pharmacist's position in the entire health care system. Nevertheless, the respondents were aware of enhancing their status and decision-making authority might bring along some negative consequences such as legal liability for adverse drug reactions or more time-consuming drug dispensing. The level of consent with GS in this study was not as high as reported by a study in France (33). Allenet et al. have given an insight into how large a gap can be between the positive attitude towards GS and the use of GS in routine practice. GS in the pharmacy must be used in accord with the ethical, health care and legal rules approaching each patient on an individual basis. This is the only way towards overcoming possible negative outcomes from GS to all participants of the health care system. Nearly $^{3}/_{4}$ of the

study respondents were worried about drug-related problems associated with GS. Apart from adverse drug reactions mentioned above, the risk of duplicate drug use (i.e., the use of two differently named drugs containing the same active ingredient) needs to be underlined as it can have serious negative impact on patients' health. The pharmacists' fears could be fuelled by their everyday experience with duplicate prescription. The detection of duplicate prescription in the Czech Republic is an accidental event because of the lack of patient medication records and impossibility for pharmacists to share medication or medical records with physicians. Drug-related problems have not yet been documented in the Czech literature but cases of duplicate drug use in outpatient prescription have been reported from other countries (34). To minimize GS-related risks drug characteristics (e.g., a narrow therapeutic index drug), dosage form (e.g., a drug for inhaled delivery, controlled release or otherwise modified delivery or with a different tablet size), patient characteristics (a patient treated on a chronic basis, an elderly patient, or a child) and level of adherence to GS-related recommendations need to be taken into consideration (5, 10, 35). A high-quality education of the patient is one of the preventive measures against GS-related errors. Any doubt about drug misuse should be the reason for avoiding GS (35, 36). The drug agency of the Czech Republic (the State Institute for Drug Control) attempted to define the circumstances under which GS is considered as unsuitable (35). Lists of drugs (un)suitable for GS or other similar recommendations have also been available in some other countries (37, 38). All available tools should be used professionally and therefore, not only patients need to be educated but also health care professionals should be trained accordingly (36). Gaps to be bridged are pharmacovigilance activities of the Czech health care professionals and knowledge of generic drug testing principles.

GS in the Czech Republic is understood as the substitution of a brand name drug with a generic copy or the use of a generic drug alternative to another generic drug. A good knowledge of brand name drugs can be helpful in the pharmacist's decision-making as to the use of GS. Pharmacists showed relatively good knowledge of brand names for atorvastatin and ramipril, however, they were less sure of omeprazole. It is to be reminded that all four drugs from our questionnaire were well known ones. Higher scores of older pharmacists were predictable given their greater opportunity to get familiar with brand name drugs from the very beginning of their patent protection. It means that a given active ingredient was marketed under a single brand name for a certain period of time.

CONCLUSION

In pharmacists' opinion a *lege artis* GS can provide cost savings for patients and health insurance companies and also enhance the status of pharmacists. The use of GS in practice seems to be closely associated with the pharmacist's confidence in generic drugs and GS. The confidence depends, among others, on understanding the legislation for GS. Financial benefit from GS, if any, must not be obtained at the expense of the safety, the guarantor of which is the pharmacist who considers each case on an individual basis.

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