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Antimicrobial drug-nutrition interactions: Consistency of information for generic drugs

Interakcije antimikrobnih lekova i hrane: konzistentnost informacija za generičke lekove

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Abstract

Background/Aim. Antimicrobial drug-nutrition interactions can compromise the efficacy and safety of therapeutic regimen, as well as the nutritional status of a patient. In order to prevent them, health professionals consult the reference information sources. Summary of Product Characteristics (SmPC) is the basis for reliable and objective informing, and in the case of generic products, the content of documents should be consistent. The aim of the study was to compare information on antimicrobial drug-nutrition interactions for generic products, and to consider the influence of relevant factors (the time of the first authorization and the number of generic products) on the outcome of evaluation. **Methods.** SmPCs for all generic antimicrobial products for systemic use were retrieved from the Medicines and Medical Devices Agency of Serbia website, and statements of interest were extracted from different sections and were compared. The comparison was based on classification of statements on interaction into one of five classes: "effect of nutrition status on drug action", "effect of food in general on drug action", "effect of specific nutrient on drug action", "effect of drug on nutrient and metabolic status", or "effect of drug on nutrition status". **Results.** A total of 160 SmPCs were evaluated for 30 antimicrobial drugs corresponding to 46 dosage forms [mean number 3.48, standard deviation (SD) = 1.68; median 3.00, interquartile range (IQR) = 2; range: 2-9]. Nine (30%) antimicrobials (azithromycin, clarithromycin, cefazolin, cefepime, pipemidic acid, ciprofloxacin, levofloxacin, moxifloxacin and gentamicin) had inconsistent information. The inconsistency was related to different classes of interactions, and in some cases it could have clinically important implications (gentamicin, fluoroquinolones). The existence of a larger number of generic products was related to identified differences ($p = 0.003$). **Conclusion.** One third of generic antimicrobial products had inconsistent drug-nutrition interaction statements. Given the potential clinical implications, strategies for further harmonization of this information should be considered.

Key words:
anti-infective agents; drugs, generic; food-drug interactions; databases, factual; serbia.

Apstrakt

Uvod/Cilj. Interakcije antimikrobnih lekova i hrane mogu kompromitovati efikasnost i bezbednost terapijskog režima, kao i nutritivni status bolesnika. Kako bi prevenirali iste, zdravstveni profesionalci konsultuju referentne izvore informacija. Sažetak karakteristika leka (*Summary of Product Characteristics – SmPC*) je osnov pouzdanog i objektivnog informisanja i, u slučaju generičkih proizvoda, sadržaj dokumenata bi trebalo da je konzistentan. Cilj istraživanja je bio da se za generičke antimikrobne proizvode uporede informacije o interakcijama sa hranom, i razmotri uticaj relevantnih faktora (vreme prve autorizacije i broj generičkih proizvoda) na ishod analize. **Metode.** SmPCs za sve generičke antimikrobne proizvode za sistemsku upotrebu su preuzeti sa *web*-sajta Agencije za lekove i medicinska sredstva Srbije i iskazi od značaja su ekstrahovani iz različitih sekcija dokumenta i upoređeni. Komparacija je bila bazirana na klasifikaciji iskaza o interakcijama u jednu od pet klasa: „efekat nutritivnog statusa na dejstvo leka", „efekat hrane kao obroka na dejstvo leka", „efekat specifičnog nutrijenta na dejstvo leka", „efekat leka na status nurijenta" i „efekat leka na nutritivni status". **Rezultati.** Ukupno 160 SmPCs je analizirano za 30 antimikrobnih lekova što je korespondiralo sa 46 doznih oblika [prosečan broj 3,48, standardna devijacija (SD) = 1,68); medijana 3,00, interkvartilni raspon (IKR) = 2); opseg: 2-9). Devet (30%) antimikrobnih lekova (azitromicin, klaritromicin, cefazolin, cefepim, pipemidinska kiselina, ciprofloksacin, levofloksacin, moksifloksacin i gentamicin) je imalo nekonzistentne informacije. Nekonzistent-

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nost je bila u vezi sa različitim klasama interakcija i, u izvesnim slučajevima, mogla je imati klinički važne implikacije (gentamicin, fluorohinoloni). Postojanje većeg broja generičkih proizvoda je bilo povezano sa identifikovanim razlikama (p = 0,003). **Zaključak.** Jedna trećina generičkih antimikrobnih proizvoda je imala nekonzistentne iskaze o interakcijama lek-hrana. S obzirom na potencijalne kliničke implikacije, trebalo bi razmotriti strategije za dalju harmonizaciju ovih informacija.

Ključne reči:
antibiotici; lekovi, generički; hrana-lekovi interakcije; baze podataka, faktografske; srbija.

Introduction

Antimicrobial therapy is highly effective, nevertheless many factors can affect the efficacy and safety of therapeutic regimen as adherence, pharmacokinetic processes (absorption, metabolism, excretion) and drug interactions [1]. Interactions may occur between drugs used specifically for treating the infection as well as drugs used for treating unrelated conditions. Furthermore, interactions can occur between antimicrobial agents and nonprescription drugs, supplements or nutritional substances, such as interactions between saquinavir and herbal preparations containing *Hypericum perforatum* which may lead to loss of virologic response and possible resistance to saquinavir; therefore, simultaneous use is not recommended by the manufacturer of saquinavir with additional warning related to the effects of *Hypericum perforatum* that may persist for at least 2 weeks after discontinuation of the treatment [2]. Lastly, clinically significant interactions can be caused by food-induced changes in the bioavailability of antimicrobials. For example, the bioavailability of ciprofloxacin is reduced by 30% to 36% when it is taken with dairy products (like milk or yogurt); since concentration resulting from standard dosage of ciprofloxacin often only marginally exceeds the minimal inhibitory concentration, the interaction may result in the treatment failure [3]. Therefore, if milk cannot be avoided, milk ingestion and ciprfofloxacin ingestion should be separated by several hours. To prevent drug therapy failures and subsequent bacterial resistance, health professionals consult the reference sources of information. Summary of product characteristics (SmPC) is the basis of reliable and objective informing, and content and format of the document is defined by Standard Operating Procedure [4, 5]. In case of generic products, the SmPC content should be consistent with the reference medicinal product, and any differences should be justified [6]. Despite requirements, certain variations in the composition have been reported. For example, Theuretzbacher [7] compared product information for parenteral colistin in 21 European countries, and highlighted that the posology and pharmacokinetic sections for special patient populations varied substantially requiring careful review and updating. Analyzing SmPCs for the most commonly prescribed antibacterials in the United Kingdom (UK) with respect to dosing guidance for obese patients, Boyd et al. [8] pointed out a lack of advice provided by pharmaceutical companies. Furthermore, Sillo et al. [9] evaluated conformity of prescribing information to regulatory requirements among selected branded and generic antimicrobials (albendazole, ciprofloxacin, amoxicillin, artemether/lumefantrine, metronidazole) on the East African market and revealed the existence of a significant number of medical products without necessary compliance in some parameters (handling and disposal, container package description, excipients used, clinical pharmacology of medicines, and directions regarding overdosage).

Considering antimicrobials as high-risk agents in the context of drug-nutrition interactions (DNIs) [10, 11], so as the fact that all aspects of informing about medicinal products should be accurate, relevant and timely in order to support health professionals in making informed choices about therapy [12], the aim of the present study was to compare information on DNIs for generic antimicrobial products authorized in Serbia. Additionally, it was considered the influence of relevant factors, the time since the first authorization and the number of generic products, on the outcome of evaluation.

Methods

Data collection (sources and extraction)

Information about all nationally authorized antimicrobial drugs for systemic use (n=97) was obtained from Register of Drugs [13]. In the case of generic products, all corresponding SmPCs were retrieved from the Medicines and Medical Devices Agency of Serbia website (https://www.alims.gov.rs). The collecting was conducted between July 2017 and October 2017. A total of 199 SmPCs were identified for 37 antimicrobial drugs. SmPCs of different package size and different content of active substances were combined for appropriate products [5]. Seven drugs were excluded beacuse their SmPCs did not contain a statement in line with DNIs. Different dosage forms (DFs) of antimicrobials were considered separately because formulation can influence on the magnitude of DNI. For example, when two fast-dissolving azithromycin capsules were administered to fed subjects, a decrease of azithromycin bioavailability was great (and probably complete) [14]. However, research with tablets and suspension showed a little effect of a high-fat meal on azithromycin absorption [15]. Finally, 160 SmPCs associated with 30 antimicrobial drugs corresponding to 46 DFs were included in the analyisis.

SmPCs were consulted and statements referring to DNIs were extracted from different sections: “Interaction with other medicinal products and other forms of interactions” (4.5), “Pharmacokinetic properties” (5.2), “Posology and method of administration” (4.2), “Special warnings and precautions for use” (4.4), “Undesirable effects” – “Metabolism and nutrition disorders” sub-section (4.8) and “Contraindications” (4.3).

Data analysis

The extracted statements were assigned to one of five classes (Table 1) [16]. A distinction was made between the effects of nutrition status, foods or specific nutrients on drug action, and conversely, the effects of drug use on determinants of nutrition status. Specifically, class 1 was related to the efffect of overweight or malnutrition on drug action. Class 2 was about impact of food in general to absorption and bioavailability of certain drug. Class 3 was associated with benefit or risk of simultaneously use of certain nutrient or specific food and drug. Class 4 was referred to the effect of drug on the status of specific nutrient (e.g. hypokalaemia, hypocalcaemia, hypomagnesaemia) or metabolic status (e.g. hypertriglyceridaemia, hyperglycaemia). Finally, class 5 was related to the effect of drug on overall nutrition status (e.g. weight gain, weight loss).

Table 1
A classification of statements on antimicrobial drug-nutrition interactions

DNI Class	Classification aspect
Class 1	Effect of nutrition status on drug action
Class 2	Effect of food in general on drug action
Class 3	Effect of specific nutrient or food component on drug action
Class 4	Effect of drug on nutrient and metabolic status
Class 5	Effect of drug on nutrition status

DNI – drug-nutrition interaction.

Classification procedure was repeated two months later and the intrarater agreement was estimated by calculating linear weighted kappa (κ) coefficient. In order to minimize factors (prevalence, bias) that could influence on the magnitude of κ, prevalence-adjusted bias-adjusted kappa (PABAK) coefficient was also calculated [17]. The κ (0.97; 95% confidence interval, 0.94 to 1.00) and the PABAK (0.98; 95% confidence interval, 0.95 to 1.00) values indicated almost perfect degree of agreement. In interpreting of coefficients, guidelines proposed by Landis and Koch (≤ 0 = poor, 0.0–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and 0.81–1.00 = almost perfect) was used [18]. Calculations were performed using software WinPepi version 11.65 (http://www.brixtonhealth.com).

In relation to a practical context, disagreement was resolved by additional considering of statements.

In the case of generic products, classified statements were compared in relation to inconsistency as the outcome of evaluation. A given SmPC was worded in clear and standardized language (e.g. the Medical Dictionary for Regulatory Activities Terminology was being applied in section 4.8) [5], inconsistency was defined as the totally or partially different fact listed under information across paired SmPCs for the same drug, e.g. drug can be given without regard to meals vs. give drug at least 1 hour before or 2 hours after a meal, or e.g. the risk of hypo- or hyperglycemia vs. the risk of hyperglycemia, respectively. In addition, inconsistency was defined as the presence or the absence of particular information in at least one of the paired SmPCs for the same drug, e.g. the risk of a disulfiram-like reaction when drug and alcohol are coingested vs. the risk of a disulfiram-like reaction was not listed.

Statistical analyses

For the purposes of statistical analysis, data were entered into an Excel spreadsheet (Microsoft Excel 2007; Microsoft Redmond, Washington, the United States (US)) and subsequently imported into the Statistical Package for the Social Sciences (SPSS) version 20.0 software (IBM, US). Descriptive statistics was performed to calculate central tendency (mean and median) and dispersion (standard deviation, interquartile range) for quantitative variables, and frequency and proportion for categorial ones. The influence of the time since the first authorization of antimicrobial agents on the Serbian market and the number of generic products on the inconsistency in informing was analysed by the non-parametric (Mann-Whitney) test. Data normality was previously assessed using the Kolmogorov-Smirnov test. The tests were two tailed and p value < 0.05 was regarded as statistically significant.

Results

A total of 160 SmPCs were analyzed for 30 antimicrobials corresponding to 46 DFs; thirteen antimicrobials had more than one authorized DF. The mean number of SmPCs per DF was 3.48 [standard deviation (SD) = 1.68], the median was 3.00 [interquartile range (IQR) = 2), and the range was: 2–9; the mean time since the first authorization per DF was 222.78 months (SD = 133.63), the median was 176.00 (IQR = 201), and the range was: 38-553.

In different sections of SmPCs, 126 individual statements were evaluated and the mean number per DF was 2.74 (SD = 1.53), the median was 2.50 (IQR=2), and the range was: 1–7.

Inconsistency was indentified in 9 (30%) antimicrobials (azithromycin, clarithromycin, cefazolin, cefepime, pipemidic acid, ciprofloxacin, levofloxacin, moxifloxacin and gentamicin) corresponding to four classes of DNIs (Table 2). The examples of inconsistency are presented in Table 3.

The Kolmogorov-Smirnov test revealed that both the number of generic products ($p < 0.001$) and the time since the first authorization were not normally distributed ($p < 0.001$).

In line with inconsistent informing, the number of generic products exerted statistically significant influence (Mann-Whitney $p = 0.003$); oppositely, the time elapsed since the first authorization did not show statistical significance (Mann-Whitney, $p = 0.220$).

Table 2

Inconsistency among antimicrobial generic products in accordance to DNI classes

DNI Class*	Number of drugs		Example of drugs with inconsistent statements
	Consistent statement	Inconsistent statement	
Class 1	1	2	Cefepime powder for solution for injection; Gentamicin solution for injection
Class 2	20	2	Azithromycin tablets and powder for oral suspension; Pipemidic acid capsules
Class 3	17	1	Cefazolin powder for solution for injection
Class 4	12	5	Clarithromycin tablets and film coated tablets with extended releas; Ciprofloxacin tablets and solution for infusion; Levofloxacin tablets and solution for infusion; Moxifloxacin tablets and solution for infusion; Gentamicin solution for injection
Class 5	13	0	-

***See Table 1.**

Note: **Generic products were considered as products which have the same qualitative and quantitative composition in active substance(s), the same pharmaceutical form and the same or very similar bioavailability/bioequivalence, inactive ingredients may not be the same, in accordance to the definition contained in the National Medicines Registry – NRL 2017, The Medicines and Medical Devices Agency of Serbia (https://www.alims.gov.rs). The distinction between generic and reference products was not made. The reference products were available for ≈ 30% (8 of 30) of antimicrobial agents (azithromycin, co-amoxiclav, linezolid, fluconazole, voriconazole, tenofovir, emtricitabine/tenofovir, ribavirin).**

DNI – drug-nutrition interaction.

Table 3

The examples of inconsistent statements in SmPCs of generic antimicrobial products*

Drug and DF	Brand Name: Statement in SmPC
Azithromycin tablets	Azibot , Azitromicin Krka, Hemomycin, Sumamed: Can be given without regard to meals
	Azitromicin Sandoz : Can be taken with food
	Azitromicin Pharma S, Azitromicin Special Product's Line SPA: Give at least 1 hour before or 2 hours after a meal
Cefazolin powder for injection/infusion	Cefazolin, Cefazolin Pharmanova, Primaceph: The possibility of a disulfiram-like reaction in the presence of alcohol
	Cefazolin-MIP: Not reported interaction with alcohol
Ciprofloxacin tablets	Ciprinol, Ciprofloxacin Remedica, Marocen: Decreased appetite, hypo- or hyperglycemia
	Ciprocinal, Citeral: Decreased appetite, hyperglycemia
Gentamicin solution for injection/infusion	Gentamicin HF, Gentamicin Krka: In cases of significant obesity gentamicin serum concentration should be closely monitored and a reduction in dose should be considered
	Gentamicin B.Braun: In obese patients the initial dose should be based on ideal body weight plus 40% of weight excess
	Gentamicin: Not reported dosage regimen in obese patients

***The comment was listed under Table 2.**

SmPC – Summary of Product Characteristics; DF – dosage form.

Discussion

Analyzing different sections of SmPCs in relation to information about DNIs it was found that one-third of generic antimicrobial products had various statements. Similarly, San Miguel et al. [19] assessed quantity and quality of information about food-drug interactions contained in SmPCs of medicinal products authorized in Spain and concluded that SmPCs were a suboptimal source of informing. Namely, interactions were mentioned in only 72.7% of all SmPCs where it should be; and the description and agreement of information with the European recommendations for different sections was between 31.8% and 49.0%.

In the present analysis inconsistency was in line with effects of the nutrition status, food in general or specific nutrient on drug action, as well as effects of drug on the nutrient status. For instance, with respect to the effects of nutrition status on drug action, manufacturers' recommendations for dosage regimen of gentamicin in obese patients were "in obese patients, the initial dose should be based on ideal body weight plus 40% of weight excess" or "in cases of significant obesity gentamicin serum concentration should be closely monitored and a reduction in dose should be considered" or not reported. The absence of information is not only a feature of the Serbian market; namely, as it is above mentioned, analyzing the UK SmPCs, Boyd et al. [8] pointed out a lack of ad-

vice on dosing of commonly prescribed antibacterials in obese patients. From clinical point of view, the exact information is of importance because obesity can significantly alter the tissue distribution and clearence of gentamicin and implicates modification of loading and/or maintenance doses; and dose-adjustment is particularly important due to small difference between therapeutic and toxic dose of this drug [20]. Concordance in findings is not a surprise given that key information included in SmPCs in Serbia is harmonized with the European Union directives and regulations [4].

Statements on food-induced changes in the oral bioavailability of antimicrobials were commonly identified in analyzed SmPCs. Confusion existed regarding the absorption of azithromycin from azitromycin tablets and azithromycin suspension. In keeping with manufacturers' recommendations, "drug can be given without regard to meals" or "drug can be taken with food" or "drug should be administered at least 1 hour before or 2 hours after a meal", however, available data reveals an insignificant effect of food on the bioavailability of azithromycin from tablets and an oral suspension. Thus, in the study of Foulds et al. [15], the mean relative bioavailability of azithromycin after ingestion of standard high-fat breakfast was 96% [90% confidence interval (CI), 82–113%) and 113% (90% CI, 103–124%) for tablets and an oral suspension, respectively; 90% CI has met the limit of 80–125% indicating an insignificant effects of food on the bioavailability. Based on these results, Pfizer (the patent holder in the US) has created recommendations to administration of Zithromax® tablets and oral Zithromax® suspension. On the other hand, Pliva (the patent holder in Yugoslavia and Eastern Europe) has stated differently in the case of administration of oral Summamed® suspension. This unusual case with double patenting for the same active ingredient (azithromycin dihydrate) by two different pharmaceutical companies could contribute to inconsistency. Namely, information contained in generic versions of a drug could be based on it in one or the other reference product.

Disulfiram-like reaction is the most important interaction between antibiotics and alcohol. Thus, metronidazole, thrimethoprim/sulfamethoxazole, chloramphenicol and some cephalosporins decrease alcohol elimination and elevate acetaldehyde concentrations increasing risk of unpleasant but not life-threatening symptoms (nausea, flushing of face, headache, tachycardia, hypotension). In the last compounds, disulfiram like-activity is explained by chemical structure or more precisely by the presence methyltetrazolethiol side-chain at position 3 of the cephem ring (like in cefoperazone, cefamandole, cefotetan). In the case of cefazolin, cephalosporin with 1H-tetrazol group at position 7 of the cephem ring, the study published in 1986 showed that it also had disulfiram-like activity [21]. However, other experimental studies demonstarted that cefazolin did not significantly influence alcohol metabolism [22, 23]. These conflicting findings could contribute inconsistent labeling; namely, in opposite to others, this interaction in the Cefazolin-MIP® SmPC was not reported.

It is well-known that fluoroquinolones upset glucose homeostasis, precipiting both hypoglycemic and hyperglycemic episodes. This adverse effect is rare but may lead to emergency department visits or hospitalizations especially in elderly patients taking sulfonylureas [24–26]. In the present study, evaluating "Metabolism and nutrition disorders" subsection across matched fluoroquinolone SmPCs, certain inconsistencies were identified. Dysglycemia was mainly stated for ciprofloxacin with exception of oral Ciprocinal®, oral and parenteral Citeral® where hyperglycemia was reported as a rare adverse drug reaction, and risk of hypoglycemia was entirely considered during simultaneous administration of ciprofloxacin and glibenclamide in "Interaction with other medicinal products and other forms of interactions" section. Most SmPCs of levofloxacin also reported dysglycemia, whereas oral Leflogal® and parenteral Levoxa® Pharmathen SA only stated the risk of hypoglycemia. The moxifloxacin SmPCs contained statements on hyperglycemia or dysglycemia; furthermore, it is interesting to note that labeling of oral and parenteral Moloxin® was not consistent. In general, inconsistency related to statements in "Undesirable effects" section has also recognized in other studies with a focus on several other pharmacotherapeutic classes [27–29]. This inconsistent medical information is not useful for health professionals who need relevant safety data to make informed risk-benefit decisions across alternative antimicrobial therapies.

A lot of drugs are implicated in electrolyte imbalance. For instance, gentamicin precipitates transient hypomagnesaemia enhancing renal excretion of magnesium that is essential for the normal metabolism of potassium and calcium [30, 31]. In line with mentioned effect, statements for four gentamicin products authorised in Serbia were heterogeneous. So, the Gentamicin HF, Gentamicin Krka, Gentamicin B. Braun and Gentamicin SmPCs stated "hypomagnesaemia", "hypomagnesaemia", "hypokalaemia, hypocalcaemia and hypomagnesaemia" and "hypokalaemia and hypocalcaemia", respectively.

Inconsistency reported in the present study was associated with a number of generic products ($p < 0.003$). The present results confirmed results of Duke's et al. [32] study about a positive correlation between a number of bioequivalent medications and the proportion of different labels ($p < 0.001$), and they may imply lack in collecting, evaluating and/or arbitrating of evidence. Namely, SmPC, as part of the documentation required in procedure of applications for drug authorization, is prepared by a pharmaceutical company and it is ultimately approved by a regulatory agency. In case that an agency considers that information contained is suboptimal, explanation should be requested from a pharmaceutical company.

The lenght of the presence of antimicrobials on the Serbian market was not in line with inconsistent informing ($p = 0.220$). Findings in previous studies are conflicting. San Miguel et al. [19] reported that in SmPCs in Spain, the influence of time of authorization on quality of information on food-drug interactions was close to a statistical significance ($p < 0.0526$), and 1998 was considered as referent year. Namely, the principles of presenting information about food-drug interactions are provided in two European Documents-

Guideline on the investigation of drug interactions (European Medicines Agency, Committee for Human Medicinal Products) and Guideline on Summary of Product Characteristics (European Commission, Enterprise and Industry Directorate-General. Consumer Goods, Pharmaceuticals) that came into force in 1997 and 1999, respectively. Focusing on comparison of statements on adverse drug reactions at international level, Eriksson et al. [27] reported higher consistency of information for drugs approved after 2000 ($p < 0.003$). These results highlight that the quality of safety information included in SmPCs has been improved along the years; nevertheless, there is still room for a further harmonization (e.g. particular aspects of antimicrobial drug-nutrition interactions as effects of nutrition status, foods or specific nutrients on drug action).

The present study was limited to evaluation of information about interactions of antimicrobial drugs only; hence, generalization of findings to other drug groups is restricted. However, other studies also highlighted certain inconsistencies in safety information provided in SmPCs for drugs that were not antimicrobials [27, 28]. Although these studies were focused on adverse drug reactions and hence are not comparable directly to the present study, their findings indicate that differences identified in the present study could be extrapolated to drugs other than those studied. Furthermore, the evaluation was confined to SmPCs of drugs authorized in Serbia; nevertheless, it is expected that the present findings could be of international interest considering the harmonization of Serbian regulations with European ones. Another limitation is associated with the influence of excipients on nutritive and metabolic state, aspect that was not considered in the study; simply, comparison accross generic products was not possible because differences in qualitative and quantitative profile of products related to this subject. Lastly, statements about macro- and micronutrient disturbances contained in "Interference with laboratory tests" subsections were not analysed supposing that they were a consequence of chemical influence on the testing process that is analytical interference [33].

Drug-nutrition interactions are a permanently evolving area of study and interest particularly in high-risk patients as the elderly, obese, those with chronic diseases who use multiple medications as well as those taking high-risk medications (antimicrobials, antiepileptics, warfarin, drugs with narrow therapeutic index); individuals with well-known genetic polymorphism in drug transporters, receptors, or enzymes may also be at higher risk [10]. Data to improve current knowledge about prevention of undesirable effects will continue to emerge in clinical trials and patient care [34, 35], and attention to documentation and relevant statements are of primary importance to produce evidence-based information for those involved in patient care. Lastly, harmonization of safety data is crucial not just for clinical reasons but also for legal ones (e.g. court cases Pliva, Inc. v. Mensing, Mutual Pharmaceutical Co. v. Bartlett, Rafferty v. Merck & Co., Inc.) [36–38]. Therefore, it would be interesting in future work to evaluate if necessary revisions are done.

Conclusion

Analyzing SmPCs of antimicrobials for systemic use authorized at the Serbian market it was found that one third of generic products had inconsistent information about DNIs. Inconsistency was in line with a number of generic products. In some cases, it could have clinically significant implications. Hence, it should be considered strategies for a further harmonization of information on interactions between antimicrobial agents and nutrition.

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