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Review of lists and recommendations for interchangeability of medicines across selected European countries

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Abstract

Generic substitution has been introduced in the healthcare systems of many countries to reduce the costs and ensure the continuity of drug market supply. Common and country-specific strategies on this topic have been presented for several European countries, as well as for the Republic of Serbia. The factors that need to be considered when assessing the interchangeability of medicines may be related to the medicine or the individual patient. Particular caution is required with narrow therapeutic index drugs, drugs with non-linear pharmacokinetics, antiepileptic drugs, medicines with prolonged release formulations, medicines administered in a specific way or with a medical device. Factors such as the different appearance of the medicines, excipients, packaging, indications, but also the patient's condition, age, concomitant diseases, pregnancy, hand function, vision, ability to swallow, and the patient's attitude towards the alternative medicines should also be taken into account. When substituting two generic medicines, it should be noted that those medicines may not be bioequivalent, since bioequivalence is confirmed between a generic medicine and a reference (usually original) medicine, and thus pose an additional risk to the patient's safety. Some countries have opted to form lists of interchangeable medicines and/or detailed guidelines regarding interchangeability to assist healthcare professionals in making decisions on drug substitution.

Key words: generic medicines, interchangeability, lists, recommendations

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Introduction

A generic medicine has the same efficacy and safety, and it is used in the treatment of the same diseases at the same doses as the reference medicine. A generic medicine has been shown to be bioequivalent to the reference medicine and in most cases the generic medicine can be a substitute for the reference medicine. As generic medicines have lower prices compared to reference medicines, generic substitution can significantly reduce costs in the healthcare system while ensuring the continuity of supply of medicines in the market. Therefore, most countries support generic substitution and define drug substitution policies at the national level (1, 2).

The policies regarding generic substitution strategies in several European countries (Ireland, Sweden, the UK, the Netherlands, France, Germany, Spain and Slovenia), as well as the current status of the ongoing generic substitution strategy and policy in the Republic of Serbia (Serbia), were reviewed. In response to the economic crisis, all of these countries have taken steps to tighten their generic policies to encourage cost-efficient use of medicines and generic substitution, or they have introduced prescribing by the International Non-proprietary Name (INN) (2).

Countries have adopted different approaches to generic substitution to support physicians and pharmacists in the decision-making process regarding the interchangeability of medicines. In the Republic of Serbia, a list of interchangeable medicines has recently been established in accordance with the local regulations (3).

Many factors must be taken into account when assessing the interchangeability of medicines (Figure 1). In the selected countries, the criteria for assessing interchangeability are based on the same principles, while the details and scope of the information provided in the recommendations and lists may vary.

The aim of this paper was to review the principles and country-specific strategies regarding generic substitution.

A comprehensive review of the websites of governments and medicines authorities in several European (EU) countries was performed. Websites and documents of professional organizations were also consulted to present the consolidated information on guidelines and recommendations for the implementation of generic substitution in practice. The PubMed MEDLINE and Science Direct databases were also used to find and select the relevant scientific articles.

Among the countries with developed healthcare systems, those that provide the most comprehensive and detailed recommendations on the interchangeability of medicines were selected. The Republic of Serbia was selected for the review as it is a non-EU middle-income country in transition and in the process of harmonizing its regulatory practices with high-income EU countries.

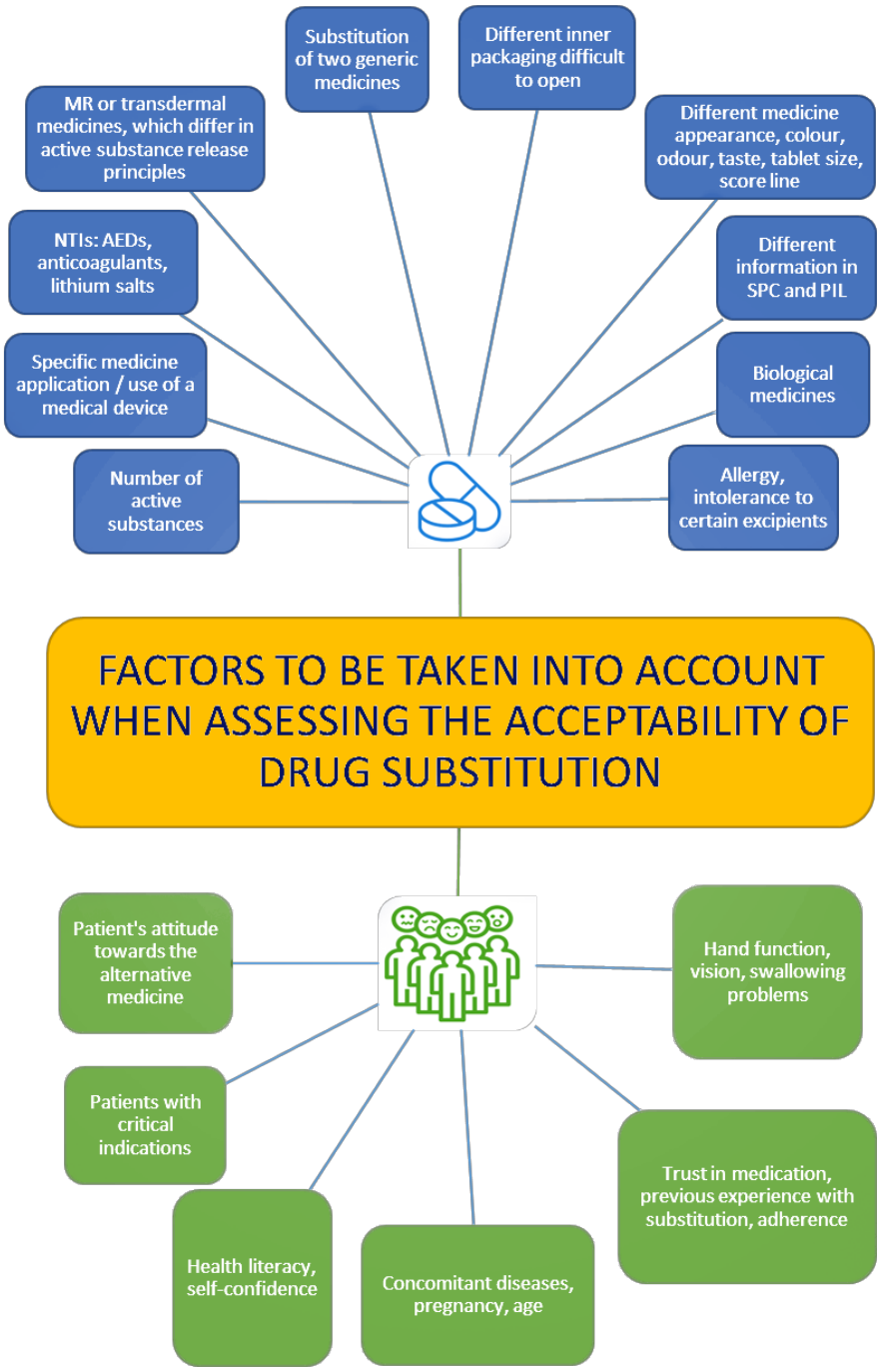

Figure 1. **Important medication-related and patient-related factors to be taken into account when assessing the acceptability of drug substitution. MR: Modified release; NTIs: Narrow therapeutic index drugs; AEDs: Antiepileptic drugs; SPC: Summary of product characteristics; PIL: Patient information leaflet.**

Slika 1. **Značajni faktori u vezi sa lekom i pacijentom koje treba uzeti u obzir pri proceni prihvatljivosti zamenljivosti lekova. MR: modifikovano oslobađanje; NTIs: lekovi uske terapijske širine; AEDs: antiepileptici; SPC: sažetak karakteristika leka; PIL: uputstvo za pacijenta.**

Drug substitution across countries

Drug substitution in Ireland

The establishment of the list of interchangeable medicines in Ireland began in 2013, prioritizing medicines that offer the greatest savings when interchanged (e.g., cholesterol-lowering, antihypertensive and medicines for the treatment of reflux and gastroduodenal ulcers) (4, 5). The criteria used by the Irish Health Products Regulatory Authority (HPRA) to determine interchangeability are listed in Table I (6).

Table I Criteria for establishing interchangeability of medicines proposed by the Irish Health Products Regulatory Authority (HPRA) (6)

Tabela I Kriterijumi za utvrđivanje zamenjivosti lekova prema preporukama Irske agencije za lekove (HPRA) (6)

Criterion	Title	Description
1.	Qualitative and quantitative composition	Must be the same. Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance are considered to be the same active substance, unless there are significant differences in terms of safety and efficacy.
2.	Pharmaceutical form	Must be the same or similar. Different immediate release pharmaceutical forms are considered to be the same pharmaceutical form, e.g., tablets and capsules.
3.	Route of administration	Must be the same.
4.	Bioavailability	The bioequivalence of a generic medicinal product with the corresponding reference medicinal product was demonstrated on the basis of bioavailability data. Waivers to the provision of bioavailability data are permitted under certain circumstances. In cases where there is a difference in bioavailability that is clinically significant in terms of efficacy, medicines are not considered to be interchangeable.
5.	Number of active substances	The concept of interchangeability only applies to medicines containing two or fewer active substances.
6.	Medical device	Products where the medical device for administering the medicine has significantly different instructions for use are not considered interchangeable.
7.	Biological medicines	The concept of interchangeability does not apply to biological medicines.
8.	Safe substitution	Products are not considered interchangeable if they cannot be safely substituted. This is decided on a case-by-case basis (e.g., narrow therapeutic index medicines, some modified-release or transdermal products with different posology).

For medicines that are not on the list and are prescribed under a generic name, the pharmacist can dispense any suitable medicine with the lowest price. This does not apply to narrow therapeutic index (NTI) medicines, certain antiepileptic drugs, anticoagulants, lithium salts and other medicines where small differences in the pharmacokinetic profile may significantly affect efficacy or safety (7).

Drug substitution in Sweden

In Sweden, there is a list of interchangeable medicines (8). When assessing the interchangeability of two medicines, the characteristics of a particular product are evaluated, in addition to efficacy and safety. In certain cases, two medicines that meet the basic criteria for substitutability (given in Table I) may not be interchangeable (9):

- NTI medicines, where relatively small changes in plasma drug concentrations may be of major clinical significance;

- where certain important information in the Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL) is missing or contradictory, which may lead to patient confusion (for example, pregnancy warnings);

- medicines that are administered by a specific route (inhalers, inhalation chambers, medicines in pens, etc.);

- prolonged-release medicines that differ in the principles of active substance release.

In addition to the cases listed above, substitution may be inappropriate if (9):

- there are significant differences in tablet size, particularly if the tablets cannot be divided, crushed or dispersed;

- medicines for children taste different (a banana flavour is not interchangeable with a raspberry flavour, whereas two different raspberry flavours are interchangeable);

- medicines for external use have large differences in excipients.

Some differences between two medicinal products are not considered crucial, but should also be taken into account when assessing interchangeability (9):

- different smell or colour of the medicines may affect the patient's experience with the medicine and adherence. For patients suffering from allergies, this substitution may be unacceptable;

- different inner packaging of the medicine (blister, jar) may be important for patients who have difficulty opening jars or blisters.

Some groups on the list are further subdivided into subgroups: for some NTI medicines, medicines for children that taste different, or medicines with significantly different information in the SPC. Medicines within the same subgroup are considered interchangeable, but not with medicines from other subgroups (9). Biological medicines, including biosimilars, are also included in the list (8).

Drug substitution in the UK

In the United Kingdom (UK), there is no list of interchangeable medicines, but there are detailed recommendations in the form of guidelines for prescribing generic and original medicines (10-12). There is a list of medicines (original or generic) for which it is recommended to prescribe a brand name to avoid substitution when dispensing at the pharmacy (11, 12). This allows the patient to consistently receive the same medication when substitution could pose a risk to the patient. The circumstances in which this applies are specified and explained:

- *NTI medicines* (cyclosporine, tacrolimus, lithium preparations, some antiepileptic drugs, theophylline, aminophylline, etc).

- *Antiepileptic drugs,* as substitution with a generic drug may carry the risk of the occurrence or worsening of side effects and reduced control of seizures. The British Medicines and Healthcare Products Regulatory Agency (MHRA) has categorized antiepileptic drugs into 3 categories to help physicians and pharmacists decide whether it is necessary to continue treating the patient with the drug from the same manufacturer (Table II) (13, 14).

Table II Categories of antiepileptic drugs and prescribing/interchangeability recommendations proposed by the British Medicines and Healthcare Products Regulatory Agency (MHRA) (14)

Tabela II Kategorije antiepileptika i preporuke za propisivanje/zamenjivost koje daje Agencija za lekove Velike Britanije (MHRA) (14)

Category	**Medicines**	**Classification details**	**Prescribing / interchangeability recommendations**
1	Carbamazepine Phenobarbitone Phenytoin Primidone	There is clear evidence that clinically relevant differences can occur between the different products of different manufacturers, even if the dosage forms are identical and bioequivalence between them has been demonstrated.	Substitution is not recommended. The patient should remain on a specific manufacturer's product.
2	Clobazam Clonazepam Eslicarbazepine Lamotrigine Oxcarbazepine Perampanel Retigabine Rufinamide Topiramate Valproate Zonisamide	Drugs that do not fit into category 1 or 3.	The need for continued supply of a particular manufacturer's product is based on clinical judgment and consultation with the patient and/or carer, taking into account factors such as seizure frequency and treatment history, possible negative patient/carer attitudes toward alternative drugs, etc.
3	Brivaracetam Ethosuximide Gabapentin Lacosamide Levetiracetam Pregabalin Tiagabine Vigabatrin	These drugs all have the following characteristics: • High solubility over the relevant pHs range • Essentially complete absorption after oral administration •Dose-response curves for efficacy and safety are not steep • Therapeutic index is not narrow	For these drugs, the potential for clinically relevant differences between the products of the various manufacturers is considered to be extremely low. However, other patient/carer-related factors should also be considered, such as negative perceptions about alternative products and/or other patient-related issues.

In addition to this classification, the recommendations are supplemented by patient-dependent factors:

- the patient's attitude towards the alternative medicine (name, appearance, packaging, taste) (14);

- concomitant diseases (autism, mental illness, impaired learning function);

- for categories 1 and 2, it is safer not to substitute the medicines, especially in stable patients without seizures (12).

- *Certain modified-release medicines*, such as matrix-type fentanyl transdermal patches only, can be cut, while cutting a reservoir-type patch can trigger a more rapid release of the active substance and overdose, which is why substitution is not recommended (10, 12). Modified-release oral preparations of morphine, oxycodone and tramadol are applied for 12 or 24 hours; therefore, prescribing under a brand name is recommended to avoid errors and confusion in dispensing and use (12).

- *Medicines administered with certain medical devices*, as the technique of administration can affect drug delivery. The patient should be given a medicine that they are used to and comfortable with (e.g., inhalation powders, pre-filled syringes for self-injection) (10-12).

- *Medicines with multiple active ingredients;* prescribing under a brand name is recommended as there is no generic name (e.g., emollient creams, antacids with simethicone, macrogols, haemorrhoid preparations, rehydration salts) (10-12).

- *Medicines with different indications,* since in some cases generic medicines do not have all the same indications as the original medicine until the patent expires (this was the case, for example, with pregabalin for the treatment of neuropathic pain) (10-12).

- *Biological medicines, including biosimilars,* as it cannot be claimed that a biological medicine and its biosimilar, or two biosimilars are exactly the same; therefore, their substitution is not recommended (10-12).

- *Medicines that differ in appearance* may cause confusion and anxiety in some patients if they are intended for long-term use (10-12).

- *Different excipients* may be the reason for unacceptable drug substitution if the patient has an intolerance to a particular excipient (10-12, 14).

Drug substitution in the Netherlands

Guidelines for generic substitution in the Netherlands are very detailed (15, 16).

Medicines are divided into 3 categories: red (switching is not allowed unless the medicine is not available); orange (switching is possible if certain conditions are met); green (switching is possible unless prevented by specific patient-related reasons) (15, 16). There is also a list of medicines for which switching is undesirable (17). Substitution of NTI drugs and drugs with non-linear pharmacokinetics is not recommended, as in practice there may be significant changes in bioavailability due to unpredictable patient-related factors and small changes in pharmacokinetics (15, 16, 18).

Substitution is also not recommended for locally acting medicines, as well as for modified-release medicines, where a decision is made on a case-by-case basis. Patient-related factors that prevent drug substitution are intolerance to certain excipients (aspartame in phenylketonuria, wheat starch in celiac disease, sugar, xylitol and honey in diabetes), different appearance, smell and taste of the medicine, but also the differences in side effects or shelf life stated in the PIL, which could in some patients cause aversion and mistrust towards the medicines. Certain excipients could prevent drug substitution, e.g., preservatives in eye drops for patients with contact lenses, propylene glycol in ear drops for open ear canal, propylene glycol in peroral and parenteral preparations for children under 4 years of years, benzyl alcohol for children under 3 years of age. Factors such as concomitant diseases, pregnancy or planned pregnancy, age, hand function, vision, swallowing problems, previous experience with substitution, health literacy, self-confidence, confidence in the medication, and previous treatment adherence are also taken into account when assessing the acceptance of drug substitution. Drug substitution may be unacceptable in patients with critical indications where fluctuations of drug concentrations in the blood should be avoided (epilepsy, Parkinson's disease, prevention of graft rejection, psychosis and manic episodes, cancer), drug substitution may be unacceptable and should be assessed for each individual patient (15, 16).

Drug substitution in France

Generic substitution has been recognized and strongly promoted in France since 1999. The pharmacist can dispense any generic medicine without consulting the doctor, but is obliged to inform the patient, who can refuse substitution. The prescribing physician can prohibit substitution by writing "non-substitutable" on the prescription (19). This is only permitted in three cases: for NTI drugs, for medicines for children under six years of age where the medicine is not available in a suitable dosage form of a generic version, and if patients are allergic to certain excipients that are contained in the generic but not in the branded medicine. In other cases, generic substitution is mandatory, and patients who refuse a generic version of their medication will receive a lower reimbursement (20).

In the list of interchangeable generics, medicines are classified by generic group. Each group includes a reference medicine, labelled with the letter "R", its generics, labelled with the letter "G" and, if applicable, its other substitutable medicines, labelled with the letter "S". Substitutable medicinal products are modified-release oral dosage forms that are different from those of the reference medicinal product, such as esomeprazole gastro resistant capsules versus gastro resistant tablets or tramadol prolonged release tablets with different release principles. Some generics are labelled as G1, indicating the absence of a break line on the tablet, which makes it difficult to achieve smaller doses (e.g., ciprofloxacin tablet 500 mg). Substitution within the same group is allowed between the reference medicinal product and the generic/substitutable medicine, as well as between generic/substitutable medicines. Excipients with a known effect are stated when present in a medicinal product, along with a note/warning when appropriate. Substitution should be performed with caution if a generic group includes a warning

indicating that substitution may pose a particular risk to the health of certain patients; for example, if careful monitoring is required when substituting fentanyl transdermal patches in febrile patients due to accelerated transcutaneous absorption, or in elderly patients and children due to increased sensitivity to the active substance. The list does not include biologicals medicinal products (21).

The list of herbal medicinal products is also given. Each group contains herbal medicinal products that have the same qualitative and quantitative composition of the herbal active substance, the same pharmaceutical form and equivalent therapeutic activity, but there is no reference product. For example, all tablets containing 40 mg of the extract of *Ginkgo biloba*, *folium* are classified within one group, while all oral solutions containing 40 mg/ml of the extract of *Ginkgo biloba*, *folium* are classified in another group. For the substitution of herbal medical products, the same rules apply as for the generics above (21).

Drug substitution in Germany

Pharmacists in Germany are obliged to dispense a medicine that is cheaper than the original, as long as this has not been ruled out by the prescribing physician. The authorized indication, package size and dose strength must be identical, and the pharmaceutical form must be identical or interchangeable (2). There is a so-called substitution exclusion list, which lists drugs that cannot be substituted, above all NTI drugs such as cyclosporine, digoxin, levothyroxine, tacrolimus, some antiepileptic drugs (carbamazepine, valproic acid, phenobarbital, phenytoin, primidone), and some medicines in modified-release dosage forms, e.g., modified-release tablets of hydromorphone or oxycodone with different daily application frequencies (e.g., every 12 or 24 hours), and buprenorphine transdermal patches with different maximum application times (e.g., up to 3 or up to 4 days). The available interchangeable dosage forms are also indicated for each active substance. For some active substances, all the available pharmaceutical forms are considered interchangeable (e.g., lorazepam oral lyophilizate, orodispersible tablets and tablets). For many active substances, however, a distinction is made between some groups of dosage forms. For example, tramadol oral solution is interchangeable with oral drops, but tramadol retard tablets with retard capsules (frequency of use twice daily), retard tablets with retard capsules (frequency of use once daily), and film-coated tablets with hard capsules and tablets. Substitution is permitted not only for the identical pharmaceutical form, but also for the interchangeable pharmaceutical form, as indicated above (22).

Drug substitution in Spain

According to the Spanish legislation, the pharmacist must substitute the prescribed product with a less expensive one (23). An exception is made for medicines which, due to their properties, may not be substituted without the prescribing physician's authorization. These medicines are categorized into 4 groups: biological medicines, NTI drugs, medicines with active ingredients that are subject to special medical supervision

or that require special monitoring measures for safety reasons, and medicines for inhalation (24).

Drug substitution in Slovenia

The list in Slovenia was formed in 2003. At that time, it included about 40 INNs and 230 medicines, mostly solid conventional pharmaceutical forms. Now the list comprises about 600 groups, including 230 INNs, in about 2000 strengths / pharmaceutical forms (out of 5300 authorized strengths / pharmaceutical forms) and 3600 packages (out of 9400 authorized packages). Substitution is not recommended for NTI drugs, modified-release medicines, medicines administered by means of a medical device and medicines for external use (25). The list also includes certain prolonged-release tablets, transdermal patches, inhaled and medicines for external use. Parenteral medicines are not included in the list (25, 26).

As pharmaceutical alternatives are also considered interchangeable (27), it is permitted, for example, to substitute perindopril tablets that contain different salts of perindopril, and therefore have different strengths (tablets containing perindopril arginine 2.5 mg, 5 mg or 10 mg and tablets containing perindopril-tert-butylamine 2 mg, 4 mg or 8 mg) (26). A similar situation with the substitution of perindopril generics exists in France (21), but this is not the case in Ireland, for example, where these preparations are classified into separate groups and are not considered interchangeable (4).

Drug substitution in the Republic of Serbia

In the Republic of Serbia (Serbia), the legal basis for the interchangeability of medicines is contained in the Rulebook on the form and content of a physician's prescription, the mode of dispensing and prescribing medicines (Rulebook) (3). The part of the Rulebook that refers to the list of interchangeable medicines in Serbia is largely based on the information provided on the HPRA website (6), and the criteria defined in the Rulebook for determining the interchangeability of medicinal products are similar to those listed above in Table I. In Serbia, all medicines, including generics, are prescribed under a brand name, and substitution at the pharmacy level is allowed if the prescribed medicine is not available, if it does not cause additional costs for the patient or healthcare system, if it does not jeopardize patient safety and if the patient consents to substitution. When dispensing an interchangeable medicine, the pharmacist should give the patient clear verbal instructions and, if necessary, brief written instructions on how to use the medicine so that the patient is not left with a dilemma or confusion about the medicine being dispensed (6).

The list of interchangeable medicines has recently been established by the Medicines and Medical Agency of Serbia and is available on its website (28). This list is based on the criteria for establishing interchangeability of medicines listed in Annex 3 of the Rulebook (3) and includes only medicines that are authorized in Serbia under the "prescription only" regime. The current version of the list includes 53 INNs and more than 500 individual medicines in various strengths and packages in oral pharmaceutical

forms, but is being further expanded and regularly updated. The list consists of groups of medicines, each group consisting of medicines with the same active substance in the same strength, pharmaceutical form and route of administration. Medicinal products within a group are considered to be substitutable. The list also contains information on excipients with proven pharmacological activity, if these are included in the medicinal product (28). If substitution is not clinically justified for the patient, the prescriber should note "Do not substitute" on the prescription. Medicinal products with special pharmaceutical forms, such as modified-release forms, inhaled medicines, and medicines in pens, cannot be considered interchangeable unless this has been specifically established by the Medicines and Medical Agency of Serbia (3). The interchangeability of NTI drugs, such as antiepileptic drugs, antiarrhythmics, anticoagulants, immunosuppressants, etc., is determined on a case-by-case basis, as their substitution may pose a risk to patient safety. The concept of interchangeability does not apply to biologics and biosimilar medicines (3, 6). This Rulebook represents an important contribution to the regulation of medicinal products in Serbia, as it clarifies and defines, among other things, the procedures related to the substitution of generics. In case of a revision of the Rulebook, we propose a change to the criterion that limits the application of interchangeability to medicinal products with a maximum of two active substances, as there are examples of generic medicinal products with three active substances for which bioequivalence with the reference medicinal product has been demonstrated and which could therefore be considered interchangeable (8).

Substitution of reference and generic medicine vs. substitution of two generic medicines

In the recommendations on generic substitution described above and in the lists of interchangeable medicines, it is assumed that generic medicines are not only interchangeable with the corresponding reference medicinal product, but also with each other. The fact that bioequivalence between two generic medicines is not directly confirmed, but only between each individual generic medicine with a reference medicine, is ignored, probably for practical reasons (29). Therefore, it is possible that two generic medicines are not bioequivalent (29, 30), but this is only briefly mentioned in the Dutch recommendations (16). Against this background, one may ask whether the criterion of bioequivalence between two generic medicines is fulfilled and whether their substitution is safe. This is particularly important for medicines where small changes in bioavailability can lead to significant changes in efficacy and/or safety (31). When considering the substitution of such medicines, additional attention should be given to whether the substitution is between a reference and a generic medicine or between two generic medicines. The substitution of two generic medicines may be seen as an additional risk of reduced efficacy and/or the occurrence of more frequent or more serious side effects.

Conclusion

Generic substitution can significantly reduce healthcare costs and ensure the continuity of supply of certain medicines on the market. Each country established its

national policy on generic substitution and forms a list of interchangeable medicines and/or guidelines and recommendations on the subject.

The list of interchangeable medicines represents an aid for pharmacists, but also for doctors, and makes it possible to maintain uniform professional standards when making decisions on the substitution of medicines. The list is compiled on the basis of the medicine documentation and the interchangeability criteria that should be taken into account when substituting generics. The interchangeability criteria are based on scientific principles and are similar in most countries. Generic substitution should also take into account various factors that may influence the interchangeability of medicines from the perspective of the medicine itself or the individual patient. Thus, particular care should be taken with NTI drugs, drugs with non-linear pharmacokinetics, antiepileptic drugs, medicines with prolonged-release formulations, medicines administered in a specific way or with a medical device. Differences in the approved indications of the individual medicines should be taken into account, as should the differences in packaging, appearance of medicinal products, and excipients. The patient's condition, age, concomitant diseases, pregnancy, hand function, vision, ability to swallow, and the patient's attitude towards alternative medicines are some of the factors that should be taken into account as they can lead to problems when substituting medicines. Attention should also be paid to whether the reference medicine is being replaced by a generic medicine or substitution occurs between two generics, as there is a possibility that the two generics are not bioequivalent. Inappropriate substitution can lead to reduced adherence to therapy, reduced efficacy, an increase in the frequency/intensity of side effects, and an increase in the overall cost of therapy to the healthcare system (more frequent visits to the doctor, more frequent hospitalizations). A list of interchangeable medicines and detailed guidelines on interchangeability can prevent the undesirable consequences of inappropriate substitution, and is also an important aid for pharmacists in their daily work, when they are in contact with a particular patient and his or her needs in relation to the prescribed therapy.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

Conceptualization, B.M. and K.M.V.; methodology, Z.P.; data curation, Z.P.; writing—original draft, Z.P.; writing—review and editing, V.T.V., B.M. and K.M.V.; supervision, B.M. and K.M.V.

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Pregled lista i preporuka za zamenljivost lekova u izabranim evropskim zemljama

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Kratak sadržaj

Generička zamena uvedena je u zdravstvene sisteme mnogih zemalja kako bi se smanjili troškovi i obezbedio kontinuitet snabdevanja tržišta lekovima. U ovom radu predstavljene su zajedničke i specifične strategije za generičku zamenu u nekoliko evropskih zemalja, kao i u Republici Srbiji. Faktori koje treba uzeti u obzir prilikom procene zamenljivosti lekova mogu se odnositi na sam lek ili pojedinačnog pacijenta i njegove specifične potrebe. Poseban oprez je potreban kod lekova sa uskim terapijskom širinom, lekova sa nelinearnom farmakokinetikom, antiepileptika, lekova sa produženim oslobađanjem, lekova koji se primenjuju na specifičan način ili pomoću medicinskog sredstva. Takođe treba obratiti pažnju na faktore kao što su različit izgled lekova, ekscipijensi, pakovanje, indikacija, ali i stanje pacijenta, njegov uzrast, prateće bolesti, trudnoća, funkcija šaka, vid, sposobnost gutanja, odnos pacijenta prema alternativnim lekovima. Pri zameni dva generička leka, treba imati na umu mogućnost da oni nisu međusobno bioekvivalentni, budući da je biološka ekvivalentnost potvrđena između generičkog i referentnog (najćešće originalnog) leka, što predstavlja dodatni rizik po bezbednost pacijenata. Politika generičke zamene specifična je za svaku zemlju. Pojedine zemlje su formirale liste zamenljivih lekova i/ili detaljne smernice u vezi sa zamenljivošću kako bi pomogle zdravstvenim radnicima pri donošenju odluka o zameni lekova.

Ključne reči: generički lekovi, zamenljivost, liste, preporuke