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SOCIOECONOMIC CONSIDERATIONS IN CHOOSING AND EVALUATING CANDIDATES FOR RX-TO-OTC SWITCH

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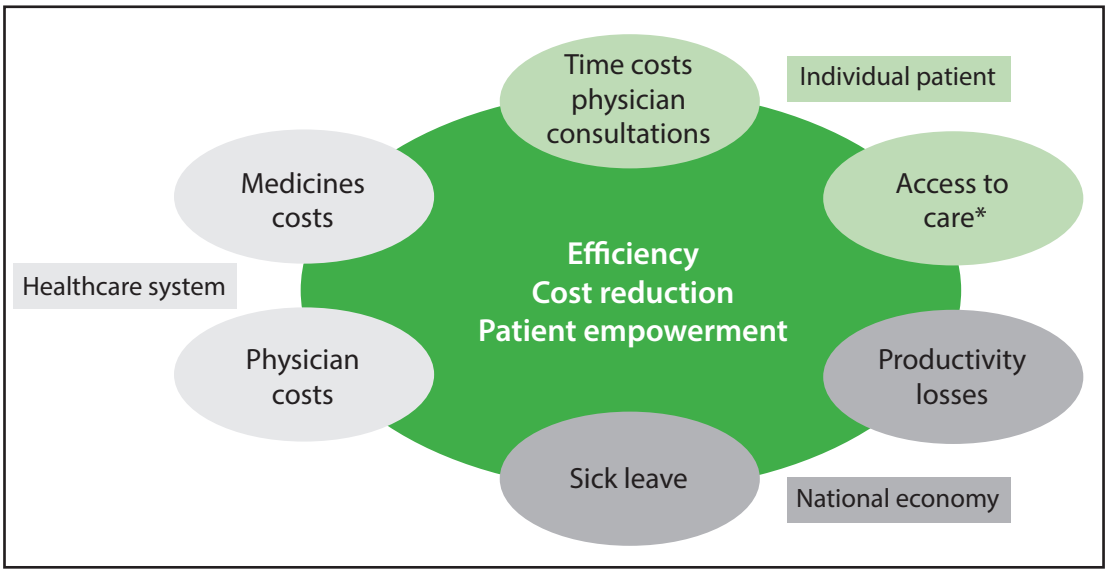
BACKGROUND

Access to over-the-counter (OTC) or non-prescription medicines is an important enabler of self-care. Self-care is a common practice in countries worldwide characterised by patients who take on proactive roles in the management of their own health. OTC medicines can typically be administered without prior medical consultation and thus provide a convenient way for individuals to treat self-diagnosable health problems effectively and safely. Not only can this improve the quality of health outcomes for patients and increase productivity levels, but it is also an approach to alleviate the financial burden on healthcare systems by, for example, reducing unnecessary general practitioner (GP) consultations and avoidable emergency department visits. Valuable financial and GP time resources saved from appropriate self-care and OTC medicines can be re-directed to treat more serious illnesses.

Patient access to suitable OTC medicines can be improved through an increased reclassification of medicines that are initially prescription-only to OTC status. This process is known as a prescription to OTC (Rx-to-OTC) switch or reclassification, and is mostly based on the decision of national authorities. Such switches can generate significant beneficial effects from the perspective of several stakeholders (Figure 1). Through a reduction in the use of prescription-only medicines and unnecessary GP consultations, healthcare systems save financial and time resources in the area of medical and pharmaceutical supply. Similarly, positive effects are generated for national economies as low-threshold access to appropriate treatments results in faster symptom relief and the shortening of disease episodes, and thus potentially leads to fewer sick leave days and productivity losses[1].

Of particular importance is the convenience and faster access to care for individual patients through the availability of non-prescription medicines, including the avoidance of patients' time costs caused by unnecessary GP consultations. These patient-relevant benefits highlight how treatment availability and access, healthcare system costs and economic effects can significantly influence the patients' perspective. Overall, each of the aforementioned perspectives are impacted by an Rx-to-OTC switch decision as illustrated in Figure 1.

Figure 1: Socially relevant effects of switches



*The improved access to care relates to the relief of burden from GP offices in terms of more treatment time for serious cases and shorter waiting times for a GP appointment from the patients' view as well as the low-threshold access to safe and effective OTC medicines as treatment options in pharmacies.

An Rx-to-OTC switch decision is carried out by regulatory authorities based on a risk-benefit assessment of a medicine. This usually involves the consideration of substance-related and application-related risks, which focuses on the possible direct risks that arise, for example, from the undesired effects or incorrect use of a medicine[2,3]. Additionally, indirect risks including those resulting from an incorrect assessment of the health condition, masked deterioration of underlying conditions, or intentional misuse are examined under the European guideline on reclassification[4]. These risks are weighed against certain benefits. Despite the fact that countries have similar assessment approaches to determine the prescription-only or non-prescription status of a substance, switch activity varies from country to country[5].

Regardless of the current number of OTC substances available in individual countries, switch activity over recent years appears to be stagnating worldwide. In the USA, 19 switches took place between 2010 and 2020 compared to the 40 switches that were carried out between 1990 and 2000[6]. Similarly, seven candidates were recently switched in Germany between 2006 and 2015 in comparison to the 36 switches that occurred between 1990 and 2000, as well as the 18 switches between 1971 and 1983[7]. This trend can be attributed to the fact that most obviously suitable and uncomplicated candidates for acute conditions have been switched in previous decades[8].

However, there is still significant potential to increase the availability of non-prescription medicines even though switches in established OTC categories are reaching a point of saturation. Substances considered for OTC classification commonly involve self-diagnosable conditions for minor ailments with: a) minimal consequences from potential misdiagnosis, b) mild adverse-effects, c) minimal potential harm in the case of accidental or intentional misuse and d) are not addictive[9]. Examples of minor ailments include cough and cold, minor pain and gastrointestinal disorders. Recent switch candidates are extending into the area of medicines for the management of long-term conditions, including high cholesterol, migraine, erectile dysfunction and heart conditions[10]. These reclassifications are regarded as innovative or progressive switches. This is because they involve substances selected from indication areas where no satisfactory non-prescription therapy exist, or the switch is considered as a clinically significant improvement compared to current non-prescription therapies in a given country at a particular time[11]. Therefore, 'innovative' switches play an essential role in expanding the existing scope and importance of self-care by increasing the number of safe and effective therapies in new indication areas (i.e. greater therapeutic breadth). Nevertheless, several also require additional conditions linked to their OTC status, such as a prior medical diagnosis, the need for regular check-ups or a certain maximum dosage per pack. Throughout this paper, the innovativeness of a switch is considered from the perspective of individual countries. This means that an innovative switch in this context refers to all substances that have not yet been switched in a given country and, in particular, those that open up a new therapeutic area when switched.

It is clear that innovative switches may be associated with more challenging safety and self-assessment requirements than previous switches commonly accepted to be suitable for OTC classification[12,13,14]. Despite this, commonly applied regulatory switch criteria have not been adjusted to accommodate this evolution in switch activity. In addition to the inherent complexity of switches, future innovative switches may present unique challenges involving aspects that may be substance-specific and have a significant impact on the success of a switch candidate.

To address this issue, in the authors' view, an innovative switch procedure should consist of two key steps[15]. The first step focuses on the identification and prioritisation of potential switch candidates to select substances that are appropriate for reclassification. Following this, the second step involves an evaluation of the selected switch candidates that takes into consideration a comprehensive set of potential medical risks. This two-step approach and adequate criteria for the switch procedure are presented below.

IDENTIFICATION AND PRIORITISATION OF SWITCH CANDIDATES

For the first step three criteria are proposed allowing an international comparison of available OTC substances:

1. The importance of the substance gaps in the international comparison;
2. The relevance for care of the substances that have not been switched; and

3. The market potential linked to the substances.

First, an analysis of the number of substances that are non-prescription across multiple countries can reveal the significance of the substance gap when prioritising switch candidates for a specific country. This means that the number of countries in which a certain substance is available without a prescription should be examined. If a particular substance is non-prescription in almost all other countries under evaluation, then there is a large substance gap and thus a high level of importance can be attributed to this substance gap. On the contrary, a substance gap is of a lower level of importance if the substance is non-prescription in only one or two countries.

Besides determining the size and significance of the substance gap, attention should be given to the relevance for care of the substances that have not been switched. This means that the extent to which patients would benefit from OTC status for a substance should be assessed. Reasons why a switch may not be meaningful in a specific country might include the fact that many substances that have been previously switched in the majority of countries may no longer have any relevance for care today, due to the availability of better substances or the availability of OTC medicines with very similar modes of action (e.g. the switch of another NSAID would be less relevant than the first switch of a triptan for migraine therapy or first cortisone-containing nasal spray for the treatment of allergic rhinitis).

Additionally, the market potential should also be considered when prioritising switch candidates. This can be determined through estimating the burden on national healthcare systems from the turnover and/or sales volume that might be reduced through substitution of prescribed medicines by OTC medicines. In addition, this consideration is of interest to patients in terms of affordability issues. The market potential is therefore also associated with the likelihood of a successful switch.

Completing this first step could ensure that the substance selected for a switch attempt is of a high degree of relevance for care and holds significant potential to generate benefits for the different stakeholders involved. In particular, this methodology could assist in highlighting substances that are innovative switch candidates, which are often indicated for health problems outside of the acute illness paradigm. These switch candidates may exceed the range of established OTC categories. Corresponding treatment indications will henceforth be referred to by the broader term self-treatable conditions. Innovative switch candidates require criteria that are not necessarily completely aligned with or covered by existing risk-benefit frameworks. They require a broader view and thus a more extensive set of criteria for a switch decision. Thus, attention should be directed towards the regulatory assessment approaches and the extent of their current suitability.

EVALUATION OF SUBSTANCES FOR RX-TO-OTC SWITCHES

The national regulatory assessment of substances considered for an Rx-to-OTC switch conventionally takes into consideration a set of criteria that are in line with those defined in the European Commission's guideline on changing the classification for the supply of a medicinal product for human use[16]. This guideline specifies that an application for reclassification must

address the potential for direct and indirect risks associated with the use of the medicinal product without medical supervision in the context of self-assessment. In particular, toxicity, risk of interactions and adverse reactions, masking an underlying condition as well as risk and consequences of incorrect use (i.e. misuse) are examined. These risks are compared against the benefits of a pharmaceutical product and all relevant evidence is weighed and balanced to establish overall levels of quality, efficacy and safety. It appears that besides safety aspects such as substance-related and application-related risks, a broader perspective in the assessment procedure is necessary to address the views, needs and interests of all involved stakeholders. In particular, real-life conditions seem to be underrepresented in the current switch decision process.

The following describes the classical approach to risk-benefit assessment and thereafter presents an extended approach that includes socioeconomic data and considerations on patient behaviour under real-life conditions.

Classical Approach

The classical approach to risk-benefit assessment comprises of substance-related risks, commonly referred to as direct risks, and application-related risks, commonly referred to as indirect risks of potential OTC medicines. This approach focuses on the possible risks that arise from, for example, undesired effects, incorrect use of the medicine and risk of delay or masking of an illness.

Figure 2: Classical approach to the risk-benefit assessment of switches

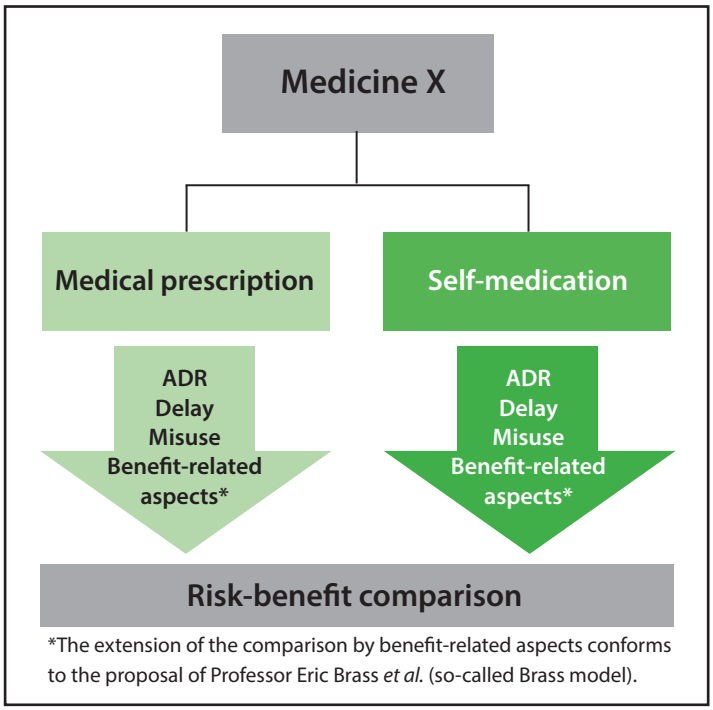


Figure 2 demonstrates that the risks associated with the use of a specific substance as an OTC medicine in self-care are compared against the risks of use under medical supervision to support a switch decision. If the risks of use in self-care outweigh the risks of use under medical supervision,

then a decision against the switch might be made. Within the scope of the so-called Brass model, published in 2011, this approach is extended by benefit-related aspects to provide a better approach to value and measure the incremental risks and benefits of non-prescription medicines. An assessment using the Brass model thus includes aspects such as improved access, enhanced consumer involvement and economic benefits (e.g. reduced physician consultations[17]). From the regulatory perspective, this appears to be suitable as, after a potential switch, two decision options are provided for patients: they can either visit a GP to receive a prescribed medicine or they choose self-medication for treatment and visit a pharmacy. Thus both approaches consider direct and indirect medical risks associated with a successful switch as sufficient for the evaluation. While the Brass model does include socioeconomic considerations as a common domain in the risk-benefit consideration, it does not provide a comprehensive guidance on the types of socioeconomic risks that may arise.

The authors analysed the suitability of these switch frameworks in depth through a comparison of existing approaches to evaluate substances for Rx-to-OTC switches. Resulting from this, the authors concluded that the classical approach and Brass model are not 'fully suitable in the decision-making process on the prescription-only status of individual active substances under real-life conditions'[18] as they do not consider the options to forego treatment or choose alternatives, which may include treatments that have a detrimental effect on patients' health. Therefore, it can be concluded that socioeconomic risks are not yet addressed to their full extent and thus, do not facilitate a multi-dimensional risk comparison. In the authors' view, there is a need to establish an extended socioeconomic approach.

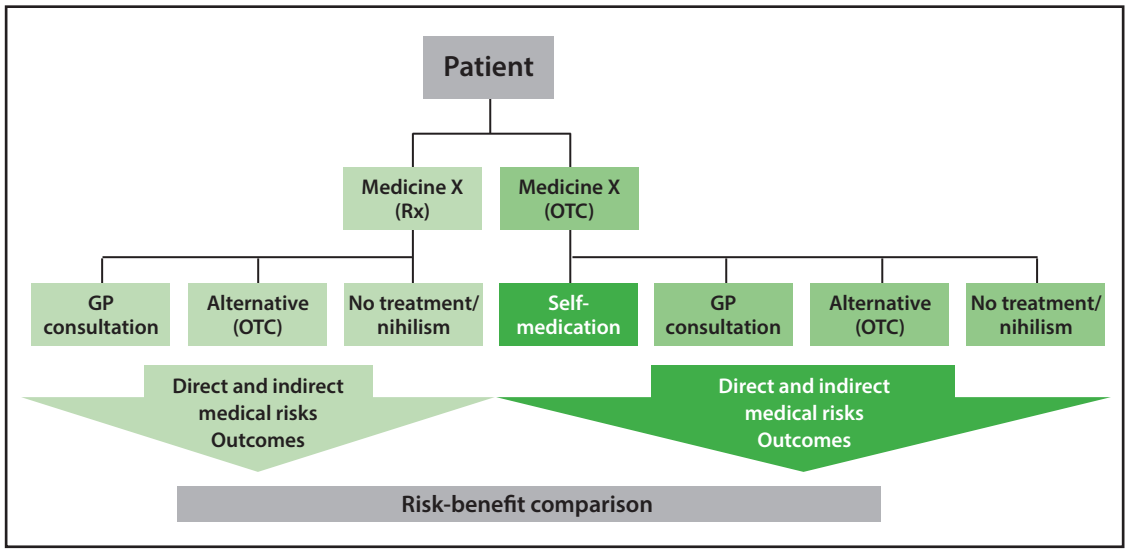
The fundamental rationale behind this approach, is that patients do not necessarily behave rationally or as the authorities expect them to under real-life conditions. Therefore, in addition to making the initial decision to switch, regulatory authorities may also request post-assessment studies to evaluate the safety and benefit-risk profile of the medicinal product in question[19]. This includes observing patient behaviour in the 'real world'. However, these procedures focus on only one aspect of patient decision making, namely the risks and benefits associated with a successful switch. In contrast, the risks and benefits associated with care- and scarcity-related concerns that occur when a medicinal product is not switched are insufficiently considered. Thus, the decision options resulting from the patients' perspective under real-life conditions after a switch may be more multifaceted than only the question of treating their self-treatable condition with a prescribed (via GP) or an OTC (via pharmacy) medicine.

The authors feel that this needs to be considered in the Rx-to-OTC switch decision. Therefore, they developed an extended socioeconomic approach consisting of two main ideas. The first idea aims to adjust the decision options from the decision tree in Figure 2 to the real-life situation. The second idea extends the variety of medical risks by including an additional category of medical risks. Both ideas are explained in detail in the following section.

Extended Socioeconomic Approach

In a specific treatment case, the patient faces two possible situations after regulatory authorities have decided on a switch: a substance that is suitable, safe and effective for the individual treatment case is available without a prescription or as prescription-only medicine. Each of these situations will result in different behavioural options which are affected by the individuals' views towards their personal benefits. From this point on, the patient decides their therapy paths, under real-life conditions. These are illustrated as the first idea of the extended socioeconomic approach in Figure 3 as elements of a multi-dimensional risk-benefit comparison. The authors believe that such an approach is essential for an assessment of individual active substances under real-life conditions.

Figure 3: Decision tree of patients' behaviour when provided options for prescription-only and non-prescription medicines

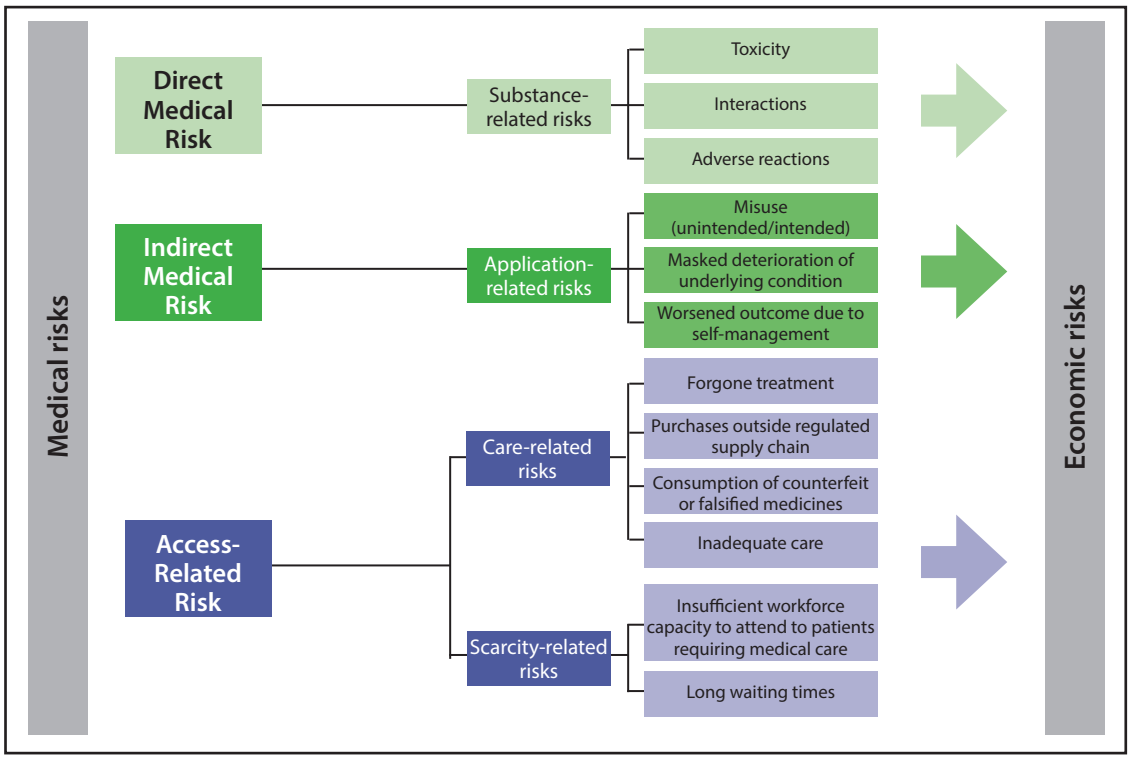


As shown in Figure 3, if a medicine has prescription-only status, the patient does not only have the option to visit a GP, but they can also alternatively choose OTC medicine or forego treatment. If the medicine is available OTC, the patient can either use this for self-medication, consult a GP instead, choose another OTC medicine or forego treatment.

Classic switch approaches focus on both direct and indirect medical risks which can occur after a switch is carried out, and they are clearly considered in all national authorities' switch decision. In contrast, there are risks under real-life conditions that may result if a switch is rejected or not yet realised, including care- and scarcity-related risks. These risks focus on social and supply policy aspects and while they may also be categorised as indirect medical risks, classic switch guidelines do not explicitly and/or sufficiently address them. Consequently, they are generally omitted from current risk-benefit analyses for reclassification in many countries. This shortcoming contributes to the second idea of an extended socioeconomic approach. To highlight the importance of considering care- and scarcity-related risks in a switch process, the authors propose a third

category of risks called 'access-related risks'. The structure of risks according to the extended socioeconomic approach is shown in Figure 4.

Figure 4: Direct, indirect and access-related medical risks



Care-related risks are associated with access to appropriate or required care. Low-threshold access to care may determine whether a minor health problem appropriate for self-care is treated with medicines or not treated at all. If the individual is untreated, although an appropriate, safe and effective treatment is available, then any positive effects on their health-related quality of life that could be expected from treatment are forgone. These 'opportunity cost' risks are relevant from a care perspective and can be linked to work and productivity losses that result directly from the impact of the health problem. Furthermore, risks for patients from non-treatment populations (therapeutic nihilism), which include a lack of treatment or failure of prevention, may lead to further negative effects in the form of worsening or prolongation of a health problem. Moreover, the role of pharmacists as gatekeepers for advanced medical services can only be realised if patients are aware and readily use their services.

Scarcity-related risks encompass risks that arise from a limited availability of healthcare. For instance, patients tend to seek care from hospital or primary care providers when adequate options for self-care are not available for certain indications. This may cause prolonged waiting times for a GP appointment, also for severe cases who need a GP visit, longer waiting times in the GP's office and shorter times for treatment by the GP per patient[20]. Shortened treatment time and delays in treatment impair the quality of care and result in subsequent medical risks if, for these reasons, necessary treatment is delayed or foregone.

Medical risks, in general, can result in economic risks. An example is the restricted access to medicines if an appropriate medicine is not available or patients forego a treatment. This can result in the prolongation of a disease with sick leave days of employees and additional treatment costs associated with disease progression. Thereby, it may cause overall economic costs.

The aforementioned additional aspects that address access-related risks are especially important for the risk-benefit assessment of innovative switches. They provide further guiding principles, alongside the direct and indirect risks assessed in the classical socioeconomic approach, that may increase the likelihood of a switch approval decision for innovative switch candidates. Thus, an individual assessment of the severity of both direct and indirect risks, as well as access-related risks, is first required to determine whether each risk is an enabler or hurdle to switching. Subsequently, an overall comparison should be made to weigh the risks in the direct and indirect category against the risks in the access-related category.

If the direct and indirect risks associated with a switch candidate are considered high, this may result in a low likelihood of switch approval (hurdle), while a low severity of direct and indirect risks may strongly support a decision in favour of OTC status (enabler). For example, if the toxicity profile of a substance is high, this provides a reason not to switch, while a low risk of adverse reactions supports a switch decision. For access-related risks, the assessment is the opposite, as high severity of access-related risks may increase the probability of a switch (enabler), while low severity may hinder a switch (hurdle). This latter effect occurs on the basis that in the absence of a successful switch, appropriate and/or adequate self-treatment may not be possible and the healthcare system may be unnecessarily burdened. This consequently affects patients with severe health conditions. Additionally, there may be an incentive to use illegal substances (including falsified medicines) from sources such as unauthorised websites or the black market, which also entails direct and indirect risks.

Following an assessment of risk severity, the risks identified as direct and indirect risks should be weighed against those in the access-related risk category. This would enable a more complete evaluation of risks alongside the benefits defined by Brass *et al.*[21]. The competing effect between these risks may be especially advantageous when evaluating innovative switch candidates. If the direct and indirect risks are considered to be too high for a switch candidate, this may result directly in a rejection of a switch. However, if the direct and indirect risks are high but are outweighed by a higher risk level of access-related risks, this may lead to a decision in favour of switching. In such cases, innovative candidates that are successfully switched may be subject to certain conditions to minimise any potential risks and ensure the safety of patients. For example, age restrictions, pharmacist involvement in the sale or supply, mandatory blood pressure checks or use of questionnaires. This approach ensures that the risks which may occur due to restricted access (i.e. a decision to reject a switch) are also considered, including how the patient will be affected and effects on the healthcare system.

The authors of this paper advocate a national strategic focus to identifying innovative switch

candidates and a novel socioeconomic approach for Rx-to-OTC switching. From an individual national perspective, potential switch candidates may include first-in-world, early follow-on, or first-in-class switches. These candidates characteristically challenge the established OTC paradigm in which OTC medicines are nationally accepted for the treatment of acute symptoms or temporary health disorders that are of short-term nature. Innovative switch candidates may be indicated for chronic conditions (e.g. triptans for migraines) may influence lifestyle changes (e.g. PDE-5 inhibitors for erectile dysfunction) or support women's health (e.g. daily oral contraceptives). Over the past five years, some countries including Norway[22], Poland[23], the UK[24] and Germany[25] have succeeded in switching these candidates. However, the number of successful switches for innovative candidates remain low worldwide with the rejection of recent switch proposals for sildenafil in Germany[26] and the daily oral contraceptive pill in Australia[27].

For innovative switch candidates, a simple distinction between prescription-only and OTC status cannot be made based on the set of criteria from the classical approach as it creates a key barrier to switch success. Taking sildenafil as an example, it was successfully switched in the UK in 2017, taking into consideration the risks associated with unlicensed and counterfeit medicines, as well as the need to provide men with access to legitimate care within the healthcare system, considered in the consultation process[28]. In 2022, however, the German regulatory authority rejected the sildenafil switch proposal and the outcomes protocol reveals that this decision was centred on the toxicity profile, risk of adverse events, misuse and masking of underlying conditions, without detailing the issue of counterfeit medicines[29]. This country comparison highlights that the inclusion of access-related risks as a standard criterion in the national evaluation process has the potential to be the decisive factor for a positive switch outcome. Therefore, to tackle the complex and heterogeneous nature of innovative switches, the extended socioeconomic approach of a benefit-risk assessment can be used to evaluate these candidates.

CONCLUSION

Rx-to-OTC switches enable the expansion of available safe and effective self-medication options. As a result, they can have a positive impact on patient health and the healthcare system. The examination of current switch activities clearly demonstrated that switch activities vary widely among countries and thus affect the national self-care climate and situation.

The number of switches carried out appears to have stagnated worldwide in recent years. The reason for this is believed to be that suitable und uncomplicated candidates for the treatment of acute minor ailments have already been switched. Therefore, first-in-world, early follow-on, or first-in-class switches within national contexts are the logical step in the world of self-care to expand and enrich self-medication options for the treatment of self-treatable conditions. For their implementation, innovative approaches to switch procedures appear to be necessary.

The authors have defined a two-step process consisting of the identification and prioritisation of switch candidates, as well as an advanced and more holistic evaluation process for substances.

For the first step, it is critical for pharmaceutical companies or national regulatory authorities which are enabled to make switch proposals in certain countries to assess the importance of the substance gap through an international comparison as well as consider the relevance for care of the substance and the expected market potential within their national context. From this, the candidates that are promising as potential switches and how they can be prioritised on this basis can be derived.

As innovative switches are often linked to more challenging safety and self-selection requirements in comparison to substances that are already proven to be safe and effective under real-life conditions, an adjustment of common regulatory switch criteria seems to be necessary. This is addressed in the second step, which is an extended socioeconomic approach of a benefit-risk assessment consisting of two ideas. Thus, the benefit-risk assessments which are carried out so far and the extension of this approach by Brass *et al.* were analysed. It was concluded that considerations regarding healthcare provision in terms of patient behaviour do not go beyond the regulatory switch decision. Although the Brass *et al.* framework extends the classic approach by including certain benefits, the consideration of access-related risks associated with forgoing a switch appears to be critical to the decision-making process regarding innovative switches and should thus be more explicitly defined in future guidelines and frameworks. Thus, the first idea of the extended socioeconomic approach is that patients under real-life conditions do not necessarily decide as rationally as regulatory authorities expect them to do, namely to decide between the prescribed treatment via a physician or the OTC treatment via a pharmacy. They might also forego treatment and cause medical risks through the underutilisation of suitable and effective treatment options. Based on this, an accordingly extended decision tree is provided.

Resulting from this, access-related medical risks, namely care-related risks which arise from the non-availability of OTC treatment options, and scarcity-related risks due to the avoidable use of scarce resources in standard medical care, are included in a holistic switch decision assessment. These additional risks arise in particular if an appropriate treatment for a certain self-treatable condition is not available due to a switch that has not (yet) been implemented in the OTC sector of the respective country. Thus, the innovative approach discussed in this paper extends the already existing approaches. It is also expected to meet the necessity of an evaluation method that enables a comprehensive evaluation of challenging innovative and first-in-country switches for self-medication to support women's health e.g. hormonal contraception or to influence lifestyle changes e.g. erectile dysfunction. The comprehensive approach should therefore be applied accordingly in the national decision-making process for a switch.

In future papers, the authors intend to propose more detailed suggestions for a modified regulatory framework for reclassifications as a stimulus for debate with regulatory authorities and other stakeholders.

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