

RX-TO-OTC SWITCH AND DOUBLE REGISTRATION OCCURRENCE IN POLAND – AN ILLUMINATIVE CASE STUDY

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Abstract: Rx-to-OTC switch is a global occurrence, which aims to promote patients' responsible self-treatment of minor ailments. Many countries could benefit from such self-treatment and reduce their rising health care costs by allowing citizens to avoid the need for a physician's consultations. What must be noted however, is that the inappropriate use of over-the-counter medicines can have also a darker side. Potential problems arising from OTC use might include: increased costs of treating complications resulting from not proper use or abuse, or possible interactions with the other medications, that patients take for chronic diseases. To maintain the desired level of patient safety, relieving one working group (the medical profession) from an existing obligation should be associated with the need for increased involvement and/or authorizations from other working groups. Professional pharmacists are already globally recognized as being trained in the field of health condition assessment. This paper presents an objective case study of current pharmaceutical law and thus, may serve as a starting point for an responsible discussion regarding the institution of a new class of drugs understood as pharmacist-only.

Keywords Rx-to-OTC switch, double registration, OTC medicines, medicinal product, medication, legislation, self-treatment, pharmacist-only

Polish Association of Self Medication Industry (PASMI) reports that the value of Polish pharmaceutical market oscillated around 27 billion PLN for the year 2014. Almost 42% of that value was accounted for by non-prescription drugs, which include over-the-counter (OTC) drugs, supplements, medical articles and dermocosmetics (1). By comparison, the total non-prescription drug market in the U.S. was valued at \$ 41.3 billion for the same year (2). Marwick, almost two decades ago, noted that patients treated themselves back then "4 times as often as they visited a physician's office for a complaint and thus, although 60% of the purchased drugs in the U.S. were OTCs they accounted for less than 2% of the U.S. health care dollar". Marwick concluded that this low cost substitute trend shall continue to grow (3). Moreover, 60% to 90% of ailments were initially managed with some form of self-treatment. In Poland, over-the-counter drug market was valued at over 2.4 billion PLN (for the year 2014) and yet, most popular in terms of sales in pharmacies were the OTC segments of drugs cate-

gorized as treatments for coughs and colds, pain relief, and digestive discomfort (1). What can also be observed is that the OTC drug class is a widely used and media promoted phenomena not only in Poland but also worldwide.

The OTC drug category holds significant potential in terms of time and cost reduction related to patients' visits to physicians' offices. Proper health condition assessment and patient education together with proper labeling can lead to better and more responsible control over self-treatment practices. The result would be more successful disease management processes and outcomes and ultimately, it would provide significant public health benefits (4, 5). OTC drugs are dispensed without a prescription and in accordance with Polish Pharmaceutical Law enacted on 6 September 2001 (JL No. 126, item 1381;) and are available not only at pharmacies and pharmacy dispensaries but also at herbal medicine shops, specialist medical supply shops and various other shops open to the public (art. 71). Certain active ingredients, which can be a

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base of trade in the subjects mentioned above, are defined in the Minister of Health Regulations of 22 October 2010 concerning list of products which can be authorized in non-pharmacy subjects (JL No. 204, item 1353).

Rx-to-OTC switch is a common practice worldwide but is one which must be proceeded by a process which is scientifically rigorous, data driven and highly regulated (6-8). For example, in the U.S., a medicine to be switched from the Rx to the OTC category must have a wide safety margin, be effective and bear understandable labeling to ensure appropriate use (4). The U.S. is also a country, in which pharmacists have more legal authority relative to Poland and where the Food and Drug Administration (FDA) closely and accurately monitors side effects of certain drugs. Furthermore, the FDA effectively shares this information with working groups engaged in developing or studying medications as well as members of the general public. Consequently, the national legal authorities may precede with a category switch for a medication, if legally requested, provided it can be demonstrated that:

- there is sufficient knowledge regarding its usage;
- there is an adequate demonstration that its proper use results in a net benefit to the patient (i.e., the pharmacological effect brings a result as claimed without undue side effects);
- the drug's documentation is factually correct and written in such a way that the average patient is able to independently evaluate his/her particular condition, and apply the appropriate treatment.

In 2013, Poland was classified as the 4th leading nation in the European Union (EU) in terms of medicinal purchases. In 2012, Polish patients made over 2 million purchases of OTC medications (mainly for the relief of pain and common cold symptoms) while spending 870 million PLN for that purpose. While large sums are spent on self medication, it appears that there is insufficient knowledge among the general public in terms of self diagnosis and treatment. It has been claimed that Polish patients do not distinguish pain relief, antipyretic or anti-inflammatory drugs (9). Likewise, the latest American Pharmacists Association (APhA) survey (April 2015) showed, that *"92% of patients who seek their pharmacist's advice are patients requiring assistance in identifying the most appropriate product to treat their condition and 80% of these patients suffer from an acute or chronic disease"* (10). Another issue worth raising is the impact of "the magic of advertising". Pharmaceuticals, as a category, are among the most heavily advertised consumer

products in terms of planned or implemented advertising budgets (11). Since advertising of Rx drugs are banned by law (art. 57 of The Pharmaceutical Law), OTC drugs advertising fills the gap. We might conclude therefore that many Polish patients are not be diligently reading their OTC drug's leaflets and other documentation but rather are simply automatically taking pills in the hope of relieving their symptoms.

LEGAL FRAMEWORKS FOR RX-OTC SWITCHES

According to Poland's Minister of Health Regulation of 14 November 2008 concerning criteria for access to various categories of pharmaceutical products (JL 2008 No. 206, item 1292), "Rp" products are dispensed only by a prescription. These drugs constitute a direct danger to human life even if used properly but without a physician's supervision, or if its inappropriate use can cause direct or indirect danger to human life, if it contains active ingredients for which its therapeutic effect or side effect requires further scientific tests, or if it is designed for a parenteral administration (note: in this paper the term "Rx" has been used in place of "Rp" deliberately as it is understood worldwide as meaning only available by prescription.)

The President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL) has the authority to issue an authorization for medicines, refuse to issue such an authorization, verify the data on which the authorization was issued, renew an authorization, refuse to renew, shorten an authorization's term and also to withdraw an authorization, in accordance to the Pharmaceutical Law of 6 September 2001 (art. 7). Variations or amendments to the supporting data in the authorization and variations to the dossier on which an authorization was issued are also made by the Office of the President (on the request of the marketing authorization holder - art. 31 (12). European Union Regulations attempt to minimize the differences between the member nations in this regard. Each member country must ensure the harmonization of their laws by applying the "draw near" approach which is intended to ease not only the trade of pharmaceuticals between the member countries but also the basis for access to medicines inside the European Union. Each EU country is obliged to respect and comply with community's regulations. Under European law, there are four types of variations to the terms of marketing authorizations for medicinal products for human use.

These are defined in the Commission Regulation No 1234/2008 of 24 November 2008 as (13):

1. minor variation (type IA) for which a variation has only a minimal impact or no impact on the quality, safety or efficacy of the medicinal product concerned; (fully listed in Annex II of the EC No. 1234/2008);
2. major variation (type II) for which a variation is not an extension and may have a significant impact on the quality, safety or efficacy of the medicinal product concerned (fully listed in Annex II of the EC No. 1234/2008);
3. extension of a marketing authorization for which a variation is listed in Annex I of the EC No. 1234/2008. This Annex concerns the changes to the active substance, strength, pharmaceutical form and route of administration;
4. minor variation (type IB) for which a variation is neither a type IA nor a type II nor an extension.

Legally, the Office of the President may specify the date of entry into force of the variations accepted by the URPL following the marketing holder's application (art. 31 of The Pharmaceutical Law). Maximum time is defined as 6 months from the issue date. The Office of the President is legally obliged to, at least once a year publish a register of pharmaceutical products admissible in the Republic of Poland. This register contains the inter alia name of a medicinal product, its pharmaceutical form, dosage, number of admission, the name of the marketing authorization holder and the product category. Under this law there is, however, no statutory obligation to update the current register to include information concerning variations in the product's access category as approved by the above mentioned institution. The authority body gives the public drug related information from the Medicinal Products Commission, which is responsible for taking a switch decision, however it is not dependably updated. Although it provides an online register of medicinal products it does not provide, as a governmental institution, a platform for passing on current information about the most recently performed switches. Such updates should explicitly indicate effective date for each switch – information which is crucial for pharmacists in terms of dispensing.

In accordance with Commission Regulation No 1234/2008 type II variation decisions made concerning marketing authorizations shall be issued within two months following receipt of a decision whether the variation has been accepted or not. The marketing authorization holder is allowed a maximum of 6 months from the entry into force of the

decision to change the labeling of the medication into an acceptable form for medications being dispensed to the public without a prescription. However, it has often been claimed that remaining supplies of the old (Rx) product may be dispensed after the effective date of the category switch. Remaining stocks of these (Rx) format drugs are legally permitted to “stay” in inventory at the pharmacy and at the wholesale level until their expiration date. The marketing authorization holder should however provide certain additional information to supplement the old (Rx) product packaging (e.g., an additional leaflet).

Once duly constituted, the decision becomes valid 14 days after its delivery to the litigant. It should be noted however that marketing authorization holders frequently use this time to launch advertising campaigns for the new OTC product even though the change has not yet legally taken effect. As is often said “time is money” and advertising has always been the driving force behind the marketing of OTC drugs.

IN PRACTICE

Recent category switches performed in Poland have been placed in Table 1.

Looking at the table, with regard to sales and brand awareness, some substances may be perceived to have been good candidates for switching, as they might simply be more lucrative for the marketing authorization holders as OTC products. As an example, analyzing Top 200 Pharmaceutical Products by U.S. Prescription in 2012, *omeprazole* was classified in 28, 29, 45, 46 and 131st position, however its optical isomer *esomeprazole* (S-enantiomer of *omeprazole*) was ranked at number 12 with 2,2286K scripts written. Worth highlighting is the fact that the medication is “by prescription”. However, the Top 200 Pharmaceutical (OTC) Products by U.S. retail sales in 2012 ranks *esomeprazole* as number 1 with \$ 5.989 million in retail sales (14, 15).

The case of *ulipristalum acetate* has been discounted deliberately as it was undertaken (centrally) by an executive decision of the European Commission (7.01.2015).

OTC medicines are used by 60% to 90% of Polish citizens and one in four medicines sold is of the non-prescription variety (16). After their category switch, as reported by IMS Health (2015), sales of medicines with the active ingredients *fenspiridi hydrochloridum* and *inosinum pranobexum* jumped 29% higher.

Table 1. Examples of recent Rx-OTC switches. Based on ref. 20.

No.	Active ingredient	Pharmaceutical form; dosage	Category switch	Type of variation	Year of decision
1.	<i>Acetylcysteinum</i>	Effervescent tablets; 600 mg	Rp-OTC	II (with the indication change and change in dosage)	2013
2.	<i>Acidum tolfenamicum</i>	Tablets; 200 mg	Rp-OTC	II (with the package size change - from 10 to 4)	2014
3.	<i>Calcii dobesilas monohydricum</i>	Tablets; 250 mg	Rp-OTC	II	2014
4.	<i>Ciclopirox olaminum</i>	Fluid on the skin; 10 mg/mL	Rp-OTC	II (with the Product characterization change according to the clarity test)	2013
5.	<i>Choline salicylas</i>	a. Ear drops; 200 mg/g b. Ear drops; 0,2 g/g	Rp-OTC	II	2013, 2014
6.	<i>Desloratadinum</i>	a. Orodispersible tablets; 2.5 mg b. Orodispersible tablets; 5 mg c. Orodispersible tablets; 2.5 mg d. Orodispersible tablets; 5 mg	Rp-OTC	II	2014
7.	<i>Fenspiridi hydrochloridum</i>	a. Syrup; 2 mg/mL b. Oral drops, solution; 25 mg/mL c. Syrup; 2 mg/mL d. Syrup; 2 mg/mL	Rp-OTC	II	2014
8.	<i>Ibuprofenum</i>	a. Film-coated tablets; 200 mg b. Film-coated tablets; 400 mg	Rp-OTC	IB	2014
9.	<i>Inosinum pranobexum</i>	a. Syrup; 250 mg/5 mL b. Tablets; 500 mg c. Tablets; 500 mg d. Syrup; 50 mg/mL	Rp-OTC	II	2014
10.	<i>Levocetirizini dihydrochloridum</i>	Film-coated tablets; 5 mg	Rp-OTC	II	2014
11.	<i>Meloxicamum</i>	a. Tablets; 7.5 mg b. Tablets; 7.5 mg	Rp-OTC	II (with the leaflet change according to the clarity test)	2013, 2014
12.	<i>Omeprazolom</i>	Capsules; 10 mg	Rp-OTC	II	2014 1
13.	<i>Ranitidinum</i>	Film-coated tablets; 150 mg	Rp-OTC	IB/II (affixture of 10 and 20 package sizes; changes in the Product characterization; removal of 20, 30, 40, 60 package sizes)	2013

Beyond the cases of Rx to OTC switches there have been two notable cases of reverse switches effectuated in the year 2011 and 2008 by the Poland's Health Minister. Those are *ketoprofenum* and *ephedrinum*.

Ketoprofenum was the object of such a reverse switch due to the European Commission Decision of

29 November 2010 which was addressed to all the member states. The substance, which is used topically, had been the basis of a European Medicines Agency (EMA) review because of reported allergic reactions following exposure to sunlight. Furthermore, the French Medicines Regulatory

Table 2. Examples of substances doubly registered (possible various pack sizes), where a, b, c... are various pharmaceutical forms and dosages and doubly registered products are bolded. Based on ref. 19.

No.	Active ingredient	Pharmaceutical form; dosage	No. of OTCs registered	No. of Rp's registered	No. of Rp's which are a base of reimbursement
1.	<i>Cetirizini dihydrochloridum</i>	a. Film-coated tablets; 10 mg b. Syrup; 5 mg/5 m c. Oral drops; 10 mg/mL d. Oral solution; 1 mg/mL e. Syrup; 1 mg/mL	a. 9 b. 0 c. 0 d. 0 e. 0	a. 15 b. 1 c. 5 d. 2 e. 2	a. 11 (Category: 30%) b. 1 (Category: 30%) c. 3 (Category: 30%) d. 2 (Category: 30%) e. 1 (Category: 30%)
2.	<i>Dexibuprofenum</i>	a. Film-coated tablets; 200 mg b. Film-coated tablets; 400 mg	a. 1 b. 0	a. 0 b. 2	a. 0 b. 0
3.	<i>Dextromethorphanii hydrobromidum</i>	a. Tablets; 15 mg b. Syrup; 7,5 mg/5 mL c. Syrup; 10 mg/5 mL d. Syrup 5 mg/5 mL	a. 1 b. 2 c. 3 d. 0	a. 0 b. 1 c. 0 d. 1	a. 0 b. 0 c. 0 d. 0
4.	<i>Drotaverinum hydrochloricum</i>	a. Tablets; 40 mg b. Tablets; 80 mg c. Solution for injection; 40 mg/2 mL	a. 6 b. 1 c. 0	a. 0 b. 1 c. 1	a. 0 b. 0 c. 0
5.	<i>Furaginum</i>	a. Tablets; 50 mg	a. 3	a. 2	a. 1 (Category: 50%)
6.	<i>Inosinum pranobexum</i>	a. Tablets; 500 mg b. Tablets; 1000 mg c. Syrup; 50 mg/mL d. Syrup; 250 mg/mL e. Syrup; 500 mg/mL	a. 4 b. 0 c. 1 d. 1 e. 0	a. 1 b. 2 c. 1 d. 0 e. 1	a. 0 b. 0 c. 0 d. 0 e. 0
7.	<i>Levocetirizini dihydrochloridum</i>	a. Film-coated tablets; 5 mg b. Oral solution; 0.5 mg/mL c. Syrup; 0.5 mg/mL	a. 3 b. 0 c. 0	a. 25 b. 2 c. 1	a. 20 (Category: 30%) b. 2 (Category: 30%) c. 0
8.	<i>Omeprazolom</i>	a. Hard gastro-resistant capsules; 10 mg b. Hard gastro-resistant capsules; 20 mg c. Hard gastro-resistant capsules; 40 mg d. Capsules; 10 mg e. Capsules; 20 mg f. Capsules; 40 mg g. Hard capsules; 10 mg h. Hard capsules; 20 mg i. Gastro-resistant capsules; 20 mg j. Solution for solution for infusion; 40 mg k. Powder and solvent for solution for injection; 40 mg	a. 3 b. 6 c. 0 d. 2 e. 0 f. 0 g. 2 h. 0 i. 0 j. 0 k. 0	a. 2 b. 17 c. 6 d. 2 e. 15 f. 2 g. 0 h. 2 i. 6 j. 3 k. 1	a. 0 b. 14 (Category: 50%) c. 5 (Category: 50%) d. 0 e. 15 (Category: 50%) f. 2 (Category: 50%) g. 0 h. 2 (Category: 50%) i. 4 (Category: 50%) j. 0 k. 0
9.	<i>Ranitidinum</i>	a. Film-coated tablets; 75 mg b. Film-coated tablets; 150 mg c. Film-coated tablets; 300 mg d. Effervescent tablets; 150 mg e. Solution for infusion; 50 mg/100 mL	a. 1 b. 5 c. 0 d. 4 e. 0	a. 0 b. 3 c. 1 d. 0 e. 1	a. 0 b. 1 (Category: flat rate) c. 0 d. 0 e. 0

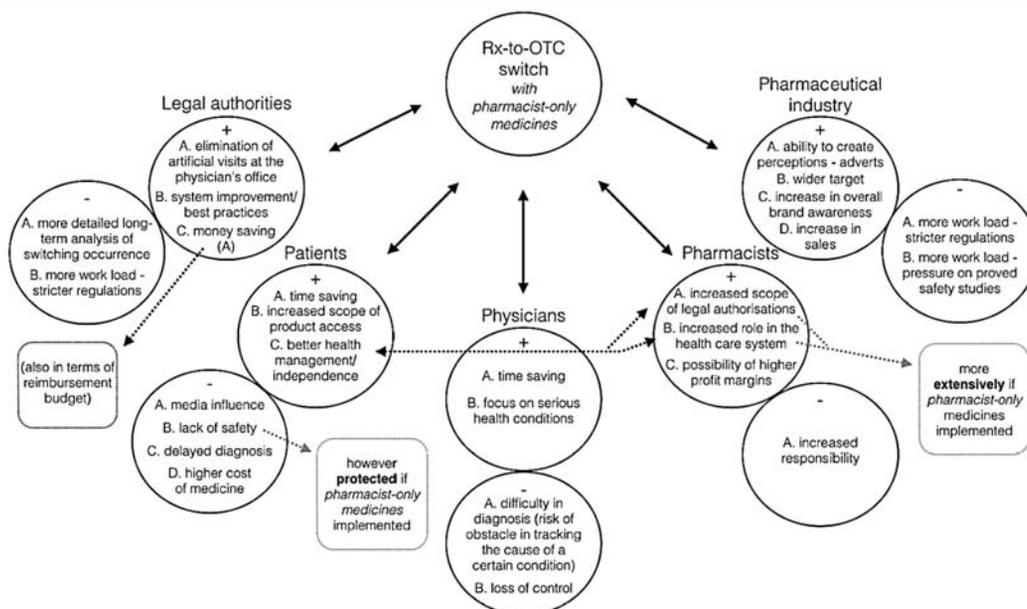


Figure 1. Pro et contra of Rx-OTC switch occurrence with consideration of pharmacist-only medicines

Agency (ANSM) informed EMA about reported reactions with a chemical sunscreen *octocrylene* (used in cosmetics as UV filter) even if not exposed to sunlight. Afterwards, the EMAs' Committee for Medicinal Products for Human Use gave an opinion, in which it reported that despite the fact that the substance causes more benefits than disadvantages, its future risk of possible side effects as reported, should be minimized inter alia by a product category change (to - on only by prescription from a medical doctor) across all the EU member countries (17). The marketing authorization holders were obliged to process changes in product characteristics, leaflets as well as labeling. The Republic of Poland complied with the decision on 1 December 2010.

With respect to the reverse switch of *ephedrinum*, under Regulation 273/2004 of the European Parliament and the Council of 11 February 2004 on drug precursors *ephedrinum* was classified in Category 1. The reverse switch of *ephedrinum* products which were used in respiratory tract treatments was a consequence of national law standardization, the objective of which is to impose law harmonization. This action resulted in a medicinal products documentation adjustment, arising under the Pharmaceutical Law of 6 September 2001. As a result, Poland's Health Minister issued a cate-

gory changing decision based on experts' opinion resulting in a reduction of the risks associated with the use of *ephedrinum* products. (18).

In Poland, side effects of a medicine, if they exist, shall be reported (online or through traditional mail) either to the local (regional) centers or to the URPL. In accordance with the Directive 2010/84 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, such side effects may be reported not only by the specialized medical staff but also by the patients, their legal representatives or supervisors. It has been claimed that all those groups may have different vantage points on a certain issue.

DOUBLE REGISTRATION: WHEN THERE IS THE SAME MEDICINE AVAILABLE WITH AND WITHOUT A PRESCRIPTION

The legal criteria for including certain products in the "Rp" category in Poland may appear to be somewhat vague. There are products which are classified as prescription only, while the same product, under a different trade name, is registered as an OTC drug. Double registration occurs in the case of *furaginum*, *drotaverinum hydrochloricum*, *cetirizini dihy-*

drochloridum, omeprazolom, ranitidinum and *inosinum pranobexum*.

Table 2 presents active ingredients, which are the subject of this double registration phenomena. Certain pharmaceutical forms and dosages of *furaginum, drotaverinum hydrochloricum, levocetirizini dihydrochloridum, omeprazolom* and *inosinum pranobexum* are registered doubly even when they occur in the same pack sizes. *Ranitidinum, omeprazolom, levocetirizini dihydrochloridum, cetirizini dihydrochloridum* and *furaginum* are subject to reimbursement. There are four groups: 50%, 30%, flat rate and free of charge set according to a base substances classified in certain limit groups. One more substance, *ibuprofen* which is mostly registered as an over-the-counter medicine, nevertheless the 200 mg soft capsules and the 200 mg film-coated tablets the 100 mg/5 mL oral suspension and the 200 mg coated tablets are also reimbursed by flat rate and are therefore subjects of a double registration as well (19, 20). Worth mentioning is the fact that once a certain medicine enters the reimbursement list it remains on the list for 2 years and there is no legal avenue available to overturn the decision.

CONCLUSIONS

Rx-to-OTC switch of products authorized in national procedure is controlled in Poland by the URPL. However, in practice the flow of information once a decision is made may not be as effective and complete as it could be. Side effects of certain medicines are to be reported either centrally or regionally, however it is not a common practice. Some substances are the subject of double registration. This can rise doubts as to whether they are safe enough in terms of self-treatment. Patients' safety should be the primary concern in considering a drug for OTC classification. The role of the pharmacist in the switch process should be legally increased in terms of medicine dispensing. That is why, as presented in Figure 1, creation of a new class of drugs described as pharmacist-only should be taken under consideration.

If relieving physicians from duties concerning treatment of small ailments is the goal, the escalation of legal authorizations of pharmacists should rise in terms of selecting and dispensing certain substances to the public which may effect patients' safety. A well-planned and monitored action in this regard could eliminate the inevitable health hazards emerging from the increased ease of access to and possible misuse of OTC pharmaceutical products -

the use of which can often be driven by media influence. In this environment education is critical to success. Pharmacists possess the necessary knowledge and are readily available to protect individual patients from the risk of disorders arising from the use and possible misuse of certain medicinal products.

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Received: 14. 05. 2015