SWITCHING FROM PRESCRIPTION TO OTC STATUS: A REGULATORY BATTLE

Paolo Biffignandi, MD

VI.REL Pharma - Italy

VI.REL Pharma
Regulatory Intelligence and Pharmacovigilance

AN INTRODUCTION TO OTC

- Medicinal products are classified into prescription or non-prescription drug categories based on their inherent toxicity, intended use, dosage form, posology, and safety. The drug's safety information obtained from market experiences plays a significant role in reclassifying the drug in a downward or upward status.

- Also called “over-the-counter” (OTC), these medicines are therapeutic products that can be sold directly to consumers without a medical prescription, in compliance with the regulations posed by each country. OTC medications are historically mainly used as a first-line/initial therapy approach covering many minor and self-limiting illnesses, including but not limited to the common cold, headaches, musculoskeletal pain, heartburn, and allergies.

AN INTRODUCTION TO OTC

- The selection of a product in the OTC category is mainly based on the safety and efficacy of the active ingredient and the intended indications.

- According to World Health Organization (WHO), self-medication has been considered an integral part of the evolving healthcare system, focusing primarily on consumers' awareness, education, and socio-economic status.

AN INTRODUCTION TO OTC

- Self-medication practice with non-prescription drugs [referred to as over-the-counter (OTC) medicines] is increasing worldwide, and the prevalence rate has been assessed to be in-between 11.2 and 93.7%, depending on the target population and country.

- The major driving force behind raising self-medication practices are raising tendency to self-manage symptoms, cost escalation in the health care system, and easy accessibility of health-related information on the internet and social media advertisements and communications of OTC drugs.

AN INTRODUCTION TO OTC

- With an increase in self-care and self-medication practice, the trend towards deregulation of more medicines with well-established safety and efficacy profiles to OTC status is also increasing, and this increase has the support of policymakers, Healthcare Professionals (HCPs), consumers, and pharmaceutical industries. Self-medication utilizing OTC drugs not only provides patients with a higher degree of self-governance in managing minor illnesses but also benefits in economizing the health care cost.

CRITERIA FOR CLASSIFYING A MEDICINAL PRODUCT AS SUBJECT TO A MEDICAL PRESCRIPTION OR NOT

- A new drug application may be submitted for a direct-to-OTC drug product. However, many approved OTC drug products (i.e., OTC products that have an approved license) begin their lifecycle as approved prescription drugs and eventually switch to OTC status under regulatory provisions (e.g., *EC Guideline of January 2006*). This process is commonly referred to as an Rx-to-OTC switch.
- Switching a prescription product, which meets the essential criteria of inherent toxicity, intended use, dosage form, posology, and safety, requires additional criteria to advocate the change of status to non-prescription sale.

CRITERIA FOR CLASSIFYING A MEDICINAL PRODUCT AS SUBJECT TO A MEDICAL PRESCRIPTION OR NOT

First criterion	Second criterion	Third criterion	Fourth criterion
• Direct danger (toxicity, interactions, ADRs) • Indirect Danger (resistance development, «masking») • Patient self assessment • Consequences of incorrect use • Patient information	Frequence of incorrect use	Presence of substances or preparations with activity and/or side-effects that require further investigation	Parenteral use

THE REGULATORY FRAMEWORK

- “Rx-to-OTC switch” should be a strictly regulated, data-driven, and scientifically validated process. Well-documented guidelines and specific regulations have been developed globally to encourage and streamline the process of Rx-to-OTC switch.
- In general, European countries are moving toward the liberalisation of several aspects of the regulatory framework of OTC medicines, such as pricing and distribution modes. A clear example is the lifting of the pricing system of OTCs in Greece in mid-2017, or the deregulation of the distribution modes in Lithuania in 2019, where the Government allowed non-pharmacy retail to sell OTC medicines. Exceptionally, there are a few countries like Poland and Hungary that took the opposite direction, from deregulated systems to a more regulated system, where pharmacies are only owned by pharmacists and retail pharmacy chains are not allowed or limited.

THE REGULATORY FRAMEWORK

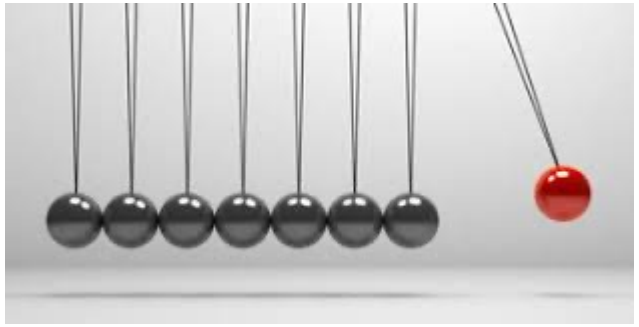
- The so called “switch criteria” were issued 18 years ago: they suffer from the evolutionary change in medical practice and patient’s awareness, often complicated by a compulsory Internet misuse.

- Healthcare needs are a changing…and an “all times” medical supervision is most probably not needed in a more educated and demanding environment.

THE PRICE ISSUE

- A review of the regulatory framework of OTC medicines in European countries shows a clear trend of liberal pricing systems, as most of the countries do not impose any kind of mechanism to set prices. Examples of countries with liberalised pricing systems are Italy since 1995, Germany since 2004, Portugal since 2005, and Greece in mid-2017. Even though, the Greek authorities publish an indicative retail price. There are currently six countries that still regulate prices: Belgium, Bulgaria, Finland, Latvia, Lithuania, and Luxembourg.
- Deregulating the price is one of the most common measures adopted to reduce pharmaceutical expenditure, lower prices, and foster price competition. However, the deregulation of the price of OTC medicines did not lead to lower prices 2 years after the liberalisation in Germany, suggesting that competition was not in prices but rather in services.

THEN WHY AGENCIES ARE SOMETIMES RELUCTANT TO APPROVE AN OTC SWITCH?



A story of regulatory caution…

BioBridges 2024
September 26–27, 2024, Prague, Czech Republic

VI.REL Pharma
Regulatory Intelligence and Pharmacovigilance

CASE STUDY: PRESCRIPTION TO OTC SWITCH FOR VITAMIN D 1.000 UI (ITALY)

Rationale:

- Vitamin D deficiency is widespread worldwide in all age groups, even in Western countries and risk groups are clearly identified
- Supplementation is recommended by Health Authorities' Guidelines
- In the EU, there are already several approved vitamin D products with OTC status (same indications, same strengths)
- Many food supplements are freely available on the retail market (same or higher strengths), but issues in quality have been raised; in addition, these products are not subjected to pharmacovigilance or to any other previous approval
- Efficacy and safety of vitamin D has been proven by decades of use; doses, regimens and target populations have been discussed and recommended by major Health Bodies around the globe
- Costs for the National Healthcare System will be decreased by the OTC status

Therefore, the Applicant is submitting an OTC switch in a prevention setting

CASE STUDY: PRESCRIPTION TO OTC SWITCH FOR VITAMIN D 1.000 UI (ITALY)

First response of the Agency:

- There are no other products containing vitamin D for which the OTC status has been granted in the territory (*sic*…a curious case of regulatory precedence) → ***data from the EU were presented***
- Supplementation is recommended after vitamin D dosing (contradicting a MoH guideline issued a couple of months before….) → ***counter deduction demonstrating the lack of dosing needs in people at risk based on a correct interpretation of the guideline and available literature***
- Although in the EU, there are already several approved vitamin D products with OTC status, this latter is ruled out by National Authorities (national rules still much considered, notwithstanding European guidelines….) → ***tricky comment, we replied acknowledging the role of the Agency…but this was complicated by the fact that in Italy we have two different categories: (a) non-prescription (with free advertising to the public); (b) non-prescription (without free advertising)***

CASE STUDY: PRESCRIPTION TO OTC SWITCH FOR VITAMIN D 1.000 UI (ITALY)

First response of the Agency:

- Many food supplements are freely available on the retail market, but they are not governed by the Agency (true, but public health is just one…) → ***this was discussed in terms offering a non-prescription product to patients, still under the umbrella of pharmacovigilance***
- The risk-benefit analysis should be performed since the granting of the first MA to the date of this request → ***a full safety re-evaluation was filed to the Agency (RWD)***
- Serious ADRs need to be discussed in relation to sales figures → ***this correlation was presented***

The Applicant prepared a reply addressing the above issues

CASE STUDY: PRESCRIPTION TO OTC SWITCH FOR VITAMIN D 1.000 UI (ITALY)

Second response of the Agency:

- Most major objections were solved with the additional data provided by the applicant, including a full set of safety data from the applicant's database, EudraVigilance and VigiAccess, however…
- The switch to OTC status is not approvable because the product does not fulfil the criteria set down in the national guideline dated October 1997…regarding the length of therapy… ***This was solved by addressing the request according to the EU Guideline, while the national legislation concerns only non-prescription with free advertising to the public. In addition, we proposed a daily dose of 500 IU and reminded that risk conditions are easily identifiable by patients (sun exposure, vegetarians, postmenopausal women, night workers, etc.)***

Therefore, the Applicant prepared a second document addressing the above issue

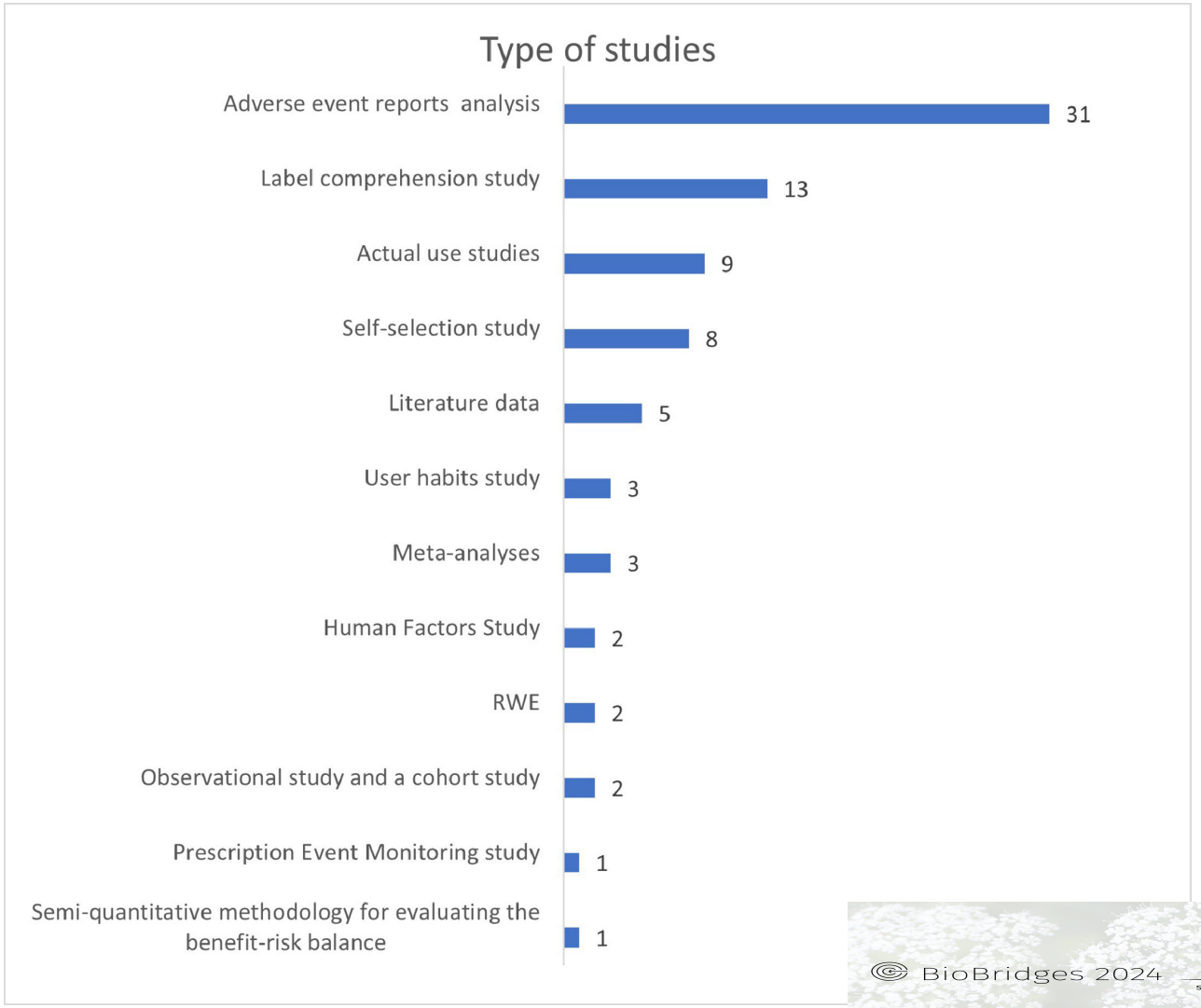
LEARNED LESSONS: KEY POINTS

And the switch was approved…so we have learned a couple of hits:

1. The successful Rx-OTC switch is the result of a multistep process that requires attention to detail at every stage.
2. First, the company should analyse the scientific background and situation in the market and particular countries. Even though the regulatory aspects of OTC switch are clearly defined, it is worth remembering that many other aspects affect the outcome. Do not forget to study the local policies, intended market, competitors, availability of similar medicines classified as OTC and intended for the same target indication, and other factors including pharmacovigilance.
3. Afterwards, the applicant should prepare the arguments and documents to ensure a persuasive Rx to OTC switch request and prepare the necessary clinical documentation.

LEARNED LESSONS: TYPE OF STUDIES NEEDED

(FROM KUHLER TC *ET AL*, 2024)



LEARNED LESSONS: TYPE OF STUDIES NEEDED

(FROM KUHLER TC *ET AL*, 2024)

Rx-to-OTC switching presents complex challenges for both regulators and sponsors but can be appropriately addressed in a regulatory environment with a transparent and standardized regulatory framework with regard to RWD and RWE.

Thank you!

pbiffignandi@virelpharma.it