REVIEW ARTICLE

A Comparative Study of Over-the-Counter Drug Regulations in India and United States of America and European Union

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Abstract

To convert an Rx to an over-the-counter (OTC) version, the drug must have some intrinsic characteristics that make it suitable for self-medication. Although definitions vary by country, the prescription to OTC-switch refers to the conversion of established Rx to OTC classification and done in scenario where the drug must have an extremely high safety limit, it is used in clearly defined circumstances, simple to use, the drug's use potentially hazardous conditions are not be concealed. The pandemic of COVID-19 had a vital effect on the market. India's manufacturers depend largely on Chinese imports of active pharmaceutical ingredients (APIs). The lockdown slowed API output, resulting in less accessibility and more material prices for the products. Due to the huge demand for necessary OTC medications, the government limited the export of some essential medicines. Aside from OTC pain relievers and fever reducer paracetamol, medicines restricted for export include metronidazole and other components containing Vitamin B1 and B12 as well as antibiotics used to treat bacterial and other diseases. On the other side, online purchases of OTC medications have increased. His study focused on a comparative study of OTC drug regulations in India and United States of America and the European Union.

Key words: Division of non-prescription regulation development, medications, non-prescription clinical development, over-the-counter, Rx, switching

INTRODUCTION

Historical background

- In 1860s, the preparations of remedies at home were replaced by purchasing of medicines.
- 1905s the market of patent drugs was at its peak.
- 1920s due to intense economic and political struggle changed preferences and care, resulted in decline in public demand and use of patient medicines.
- The Food, Drug, and Cosmetic Act (FD and C) of 1938 granted the Food and Drug Administration (FDA) some regulatory authority, but it did not specify which medications could only be purchased with a prescription and which could be purchased without one.
- In 1951, FD and C Act was amended to explain the distinction between over-the-counter (OTC) and Rx drugs and to address drug concerns about safety.

OTC medications were required to be both effective and safe, according to a 1962 amendment to the FD and C Act. What works for one person may not work for the other, and any medication may produce unwanted side effects (also called adverse effects, adverse events, or adverse drug reactions). Until 2007, when a new law was enacted requiring companies to report significant adverse events associated with OTC

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drugs, In the United States, there was no formal mechanism in place for reporting OTC medication side effects.[1]

OTC products are regularly available to consumers without the requirement of a doctor's prescription. Most OTC drugs are approved by the regulatory body and contain ingredients that are safe and effective when used without the guidance of a medical professional. Common disorders such as frequent headaches, allergies, the common cold, constipation, backache, acidity, and chronic fatigue can be treated without observation of physician in everyday life.

In general, OTC medications fall into two groups:

i. Since their introduction, the first group of OTC medicines has always been categorized as non-prescription drugs.
ii. The second group of OTC medicines began as Rx medications but was later converted to OTC medications.

WHO states that a product must be sold as a prescription drug for at least 5 years before it can be considered an OTC medicine. Every country has a different time frame for switching from Rx to OTC drugs. Classification of OTC drugs were given in Table 1.

INDIA

- The Drug Consultative Committee of India declared in November 2016 that it was setting up a drug definition that could be dispensed without a prescription. Before this, it was widely assumed that any drug that did not fit into a prescription schedule could be acquired without a prescription. However, by early 2018, the relevant definition had not been passed. Due to the lack of a legal definition for OTC drugs, this $4 billion market segment is unregulated.
- Rural and modern India places a greater emphasis on self-medication in treating minor ailments, whereas Europeans rely on the advice of their local pharmacist, and North Americans rely more on the advice of physicians. Opportunities exist in countries with growing health-care infrastructures and economies to reduce the significant strain on doctors while also assisting governments in reducing their health-care expenditure.

UNITED STATES

- The FDA regulates the manufacture and selling of OTC substances in the United States. Before entering interstate commerce, the FDA requires all "new drugs" to obtain a New Drug Application (NDA), but the act exempts any drugs that are recognized as safe and effective. To deal with the significant number of OTC drugs that were already on the market before the requirement that all drugs acquire an NDA, the FDA established the OTC monograph system to review drug classes and categorize them as GRAS/E after expert panel review. Certain OTC Drug classes would not be required to acquire an NDA and could stay on the market if they followed the monograph guidelines for dosing and labeling.
- To educate consumers about their medications, the FDA mandates OTC products to be labeled with an approved "Drug Facts" label. The labels follow a standard format and are intended to be simple to comprehend for general consumers. The active ingredient(s), indications and purpose, safety warnings, instructions for use, and inactive ingredients are all listed on the Drug Facts label.
- The 2020 Coronavirus Aid, Relief, and Economic Security Act (CARES Act) involves changes to modernize the regulation of certain OTC Drugs in the United States. Numerous OTC monographs need to be modified but doing so necessitates the time-consuming and onerous notice-and-comment rulemaking procedure. The CARES Act contains provisions for OTC monograph reform that replace the rulemaking process with an administrative order process.[2]

DEFINITION OF RX TO OTC SWITCH

To convert an Rx to an OTC version, the drug must have some intrinsic characteristics that make it suitable for self-medication. Although definitions vary by country, the prescription to OTC switch refers to the conversion of established Rx to OTC classification. These are, in general, as follows:

1. The drug must have an extremely high safety limit.
2. The drug must only be used for clearly defined circumstances.
3. The medication must be simple to use.
4. The drug's use potentially hazardous conditions must not be concealed.
    - The USFDA has clearly outlined the regulations for converting the condition of a drug from prescription to nonprescription. The drug's status is modified based on the drug's safety and information on the label detailing the pros and cons of the drug product when used without a prescription from a health professional. The sponsor conducts labeling comprehension tests, with the main study endpoint being self-recognition of the condition. The FDA's division of non-prescription regulation Development and division of non-prescription clinical Development are responsible for updating monographs and handling NDAs regarding OTC drug products, respectively.
    - Finally, OTC has no legal recognition in India drugs that are not part of Rx-only drugs are considered OTC drugs. There is no well-documented procedure or specific regulation in India for switching from Rx to OTC products. Many countries around the world have a formal procedure for transforming Rx to OTC status. Indian authorities will eventually need to formally list the OTC as a category, as switching will be one of the most common strategies used by global players to join OTC.

- A new investigational product's clinical trial period noticed a rise in the number of individuals being evaluated is far lower than the actual population that will be subjected to after marketing begins. Consequently, following a new product's initial registration, whereas Clinical evidence currently available may confirm the product's safety and efficacy, it is always prudent to carefully monitor the drug's usage in the actual patient community. Therefore, regulatory authorities generally prefer to be extra cautious when it comes to making a new product available only by prescription.
- Self-administration of treatment with OTC medications depends on the patient's judgment, including details on the label, for accurate diagnosis of disorder or symptom. An OTC medication may be used because of a false diagnosis even though it is ineffective at addressing the underlying problem. In general, the risks associated with a misdiagnosis include both the possible negative effects of the medication when used inappropriately and the risks related to not treating the true cause of the symptoms.
- Although the pharmaceutical company benefits the most from an OTC transition, independent health insurance providers are also permitted to drive the switch in some countries. Patients are reimbursed for medication costs by private insurers in nations such as the United States. Thus, when a popular, secure, and efficient Rx drug becomes OTC, the insurance is no longer responsible. Therefore, Rx-to-OTC modifications have been supported by several insurers.

GUIDELINES FOR OTC DRUGS IN INDIA

Lack of specific regulations for OTC drugs

- At present, industry lacks a strong regulatory framework due to which numerous OTC medications have been recalled in various markets. According to Indian law, OTC medicines are not covered by the D and C Act of 1940. The CDSCO intends to establish a strong regulatory structure for OTC medications that will support policies.
- The Drug Technical Advisory Board authorized a list of OTC Drugs in January 2022, including analgesics, antifungals, cough syrups, and decongestants, antiseptic that will be sold without a prescription. The current regulations for OTC products in India are given in Table 2.

SWITCHING IN INDIA FROM RX TO OTC

- Numerous Rx goods could be revitalized in India using OTC switches. The emphasis is on NSAIDs, antacids, antipyretics, cough and cold remedies, and vitamins as potential areas for switch in India, according to an analytical interpretation of different data.
- India lacks a clearly defined procedure or law that addresses switches from Rx drugs to OTC Products, despite the fact that these things are urgently needed.
- The "Rx-to-OTC switch" is a formal procedure that many nations use to convert Rx to OTC classification.
- By enhancing the most affordable form of healthcare with OTC medications, the Rx to OTC switching is also viewed as an effective method to lower healthcare costs in these markets.
- In India, regulators should explicitly define OTC as a category to promote market access. In reality, switching will likely become one of new players' most popular methods of entering OTC in future.

SWITCHING PROCESS IN INDIA

The shift in consumer attitudes toward self-medication, product changes, and Pharmaceutical companies' propensity toward OTC drugs from prescription (RX) drugs are the main reasons propelling the growth of the Indian OTC drugs market as shown in Figure 1.

Apart from these regulations, OTC products can be categorized into:

1. True OTC products are released to the market and promoted in the media.
2. Rx drugs changed into OTC drugs that are bought as OTC-OTx drugs.
    - Schedule K of the Drug and Cosmetics Act and its Rules contains potential OTC drugs such as paracetamol, liquid paraffin, eucalyptus oil, tincture iodine, and various formulations for the treatment of cough and cold.
    - For instance, even though topical diclofenac is present in schedule H, it is not a medication in that schedule. Aspirin, which had previously been listed on the Schedule K list of home medicines, was made illegal to purchase without a prescription in Delhi, according to a 2015 state government announcement. This was due to a rise in deaths among dengue patients who purchased aspirin OTC.
    - The Drugs Consultative Committee **(DCC)** has made some suggestions that have led to development. The Central Drugs Standard Control Organization **(CDSCO)** had previously proposed to include a separate schedule for OTC drugs to the D and C Act and D and C Rules to define the scope of the word "OTC".
    - In India, where the doctor-to-patient ratio is pitifully low, designating OTC drugs as a distinct class can increase access to safe medications bring about clarity to regulation framework regulating those medications.

Deliberations by the DCC - 57th meeting of the DCC

On August 20, 2019, at its 57th meeting, the DCC stated that the Ahooja Committee had given the following recommendations:

1. Assist self-care while maintaining patient safety to cut down on treatment expenses.
2. Establish the D and C Rules' description of OTC drugs.
3. Include fundamental aspects of OTC medications.
4. Regulate the switch from Rx to OTC medications.
5. Regulate the approval of new OTC medications.
6. Regulate the advertisement, distribution, and sale of OTC medications.

Initially drafting any amendments to the D and C Rules, the Ahooja Committee must first name the OTC medications. In contrast to the long overdue amendment of the drugs and cosmetic Act, the government has been aggressively amending the D and C Rules.[3]

Labeling criteria

- Labeling is crucial for OTC medicines. It provides consumers with important drug information, and the content should be easy to understand. According to Rule 95 of the D and C Act, labels must adhere to the requirements.
- The most important characteristics of OTC medications will also be modified, and they will be classified as OTC-1 and OTC-2 based on safety, therapeutic index, patient accessibility requirements, availability, non-addictive nature, supply chain mechanism, and sociodemographic conditions of the nation. Along with the definition and rules for advertising, these changes will be made.
- Self-medication is defined by the WHO as either the continuous use of Rx Pharmaceuticals for chronic sickness or the use of medications to treat self-diagnosed disorders. In addition, it covers the administration of family members' drugs, particularly while caring for young children or the elderly.[4]

OTC POLICY – INDIA

1. The Organization of Pharmaceutical Producers (OPPI) of India conducted a study on India. The crucial role of OTC medicines in maintaining viability in the most remote places has long been disregarded in discussions about "access to medicines in India." A Vaidheesh, President-OPPI and MD India and VP – South Asia, Glaxo SmithKline Pharmaceuticals, stated that the already a well-regulated OTC guideline will improve patient access.
2. The 2018 OTC Policy in India is an example of the Pharmaceutical industry's collective endeavor to enable people to make responsible choices and self-manage their health results. This policy emphasized that it was important for fundamental factors such as quality, safety, and efficacy criteria to stay the also for "Prescription" medications.[5]

USFDA GUIDELINES FOR OTC DRUGS

USFDA regulates over-the-counter (OTC) drugs, and there are specific guidelines that manufacturers and marketers of OTC drugs must follow. Some key aspects of these guidelines includes Monograph System, Active Ingredients, Labeling Requirements, Good Manufacturing Practices (GMP), New OTC Drug Approval and Post-Market Surveillance. The increase in usage of OTC drugs in USA was depicted in Figure 2.

SWITCHING IN UNITED STATES FROM RX TO OTC

Rx products can be switched to OTC by the following means:

1. The FDA commissioner started an examination of OTC medications.
2. A sponsor can totally convert the Rx medicines to OTC by submitting an efficacy supplement to the present NDA.
3. By submitting an efficacy supplement to the current NDA, a sponsor can completely switch the Rx products to OTC.
    - FDA requires that a prescription medication satisfy certain requirements before considering reclassifying it as an OTC drug, including the medication intended uses should be consistent with its prescription indications and allow for simple patient diagnosis and surveillance.
    - The drug should have a low potential for abuse and comparatively low toxicity. The prescription drug must demonstrate its safety and have 3–6 years of marketing.
    - In the US, there are primarily two regulatory ways for switching a prescription drug into a non-prescription drug, including,
        1. NDA process – Some medications are authorized under the NDA procedure to be sold OTC, but the majority are first authorized for prescription use. The "Division of Non-Prescription Clinical Development" is primarily responsible for the development of this NDA concerning OTC drugs. The differences between NDA approval and monograph processes were given in Table 3.
        2. OTC drug review (OTC monograph) process – The active drug components, uses (indications), doses, labeling, and testing at which OTC medications are often recognized as safe and effective and sold without regard to NDA and FDA pre-market authorization are all contained in an OTC monograph, which is a "rule book" for each therapeutic category. Non-prescription Pharmaceutical goods distributed in compliance with the OTC Drug Review are known as OTC medications.[6] The switching process of OTC drugs in USA is shown in Figure 3.

CLINICAL TRIALS REQUIRED FOR SWITCH PROCEDURE

- According to the CDER of the FDA, an actual use study of OTC drugs is"a controlled experiment in which subjects use an Rx medication or an unapproved new product under circumstances similar to those of an OTC product".
- OTC research is intended to support a significant change in the drug's labeling. These studies are thought to be the most important for figuring out whether a medication is suitable for switching. The main objectives of a prescription to OTC study can be classified into four types.

SCENARIO WHERE SPONSORS REQUIRED TO SUBMIT ADDITIONAL DATA

The following various types of consumer behavior studies:

Label comprehension studies

These analyses are performed to ascertain whether most people can understand the label on a medicine. OTC label that follows the required format (often known as a "Drug Facts label"). The drug facts were depicted in Figure 4.

Self-selection studies and de-selection studies

These studies are intended to observe if consumers can accurately assess whether and whether they can utilize OTC medications without risk. Based on the information, they obtain from the label and their unique medical background. For example, Actual usage research must be planned, for instance, if the package labels advise that a person consult a doctor before using a product.

Actual use studies

Studies on actual usage are conducted to determine whether the patient uses the medication correctly and securely after making their own choice. These studies also attest to the fact that consumers cannot exploit or misuse the product.

The study's main objectives should be to assess customer self-selection and collect consumer compliance data based on label instructions. It should be carried out in an environment like that of an OTC without the use of a "learned intermediary." Studies on actual use typically comprise between 800 and 5000 people and past 4–12 months. The design must specify a suitable representation of the minority population.

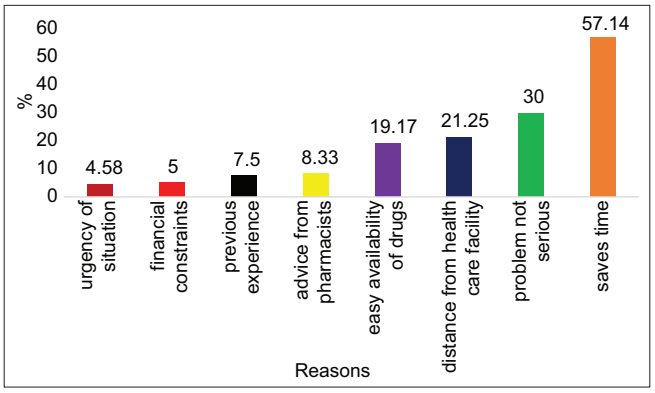

Figure 1: Reason for considering over-the-counter drugs

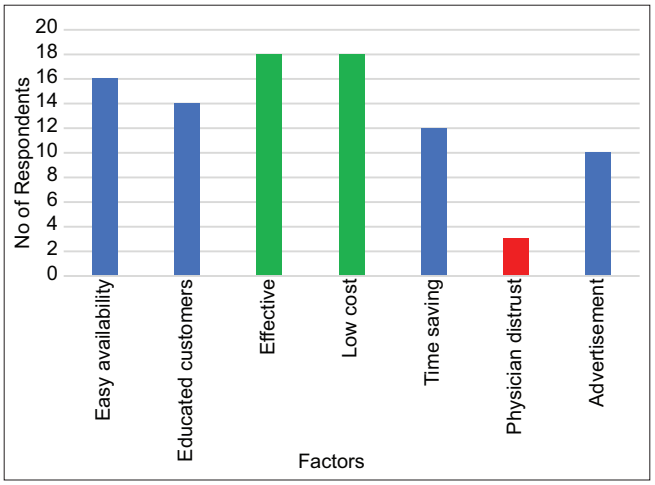

Figure 2: Increased usage of over-the-counter - United States

Short-term compliance

Consumer compliance is frequently evaluated over the course of several weeks or months in an actual use study. Evidence of self-management or lack thereof, becomes crucial in determining whether a medicine is suitable for OTC usage during the compliance stage of the study.

Long-term compliance

Once the new OTC medicine enters the market, the main goal of these studies is to evaluate compliance over time. Information on prescription drug post-marketing surveillance is a crucial addition to the OTC research.

Evaluating risk

The FDA, sponsor, and customer choose the amount of risk they are ready to accept before granting a product OTC status. Unavoidably, there is some risk, but using approved medications also carries some. The baseline for compliance in the OTC scenario should be contrasted with the adherence to the medication and the condition in the Rx setting.[7]

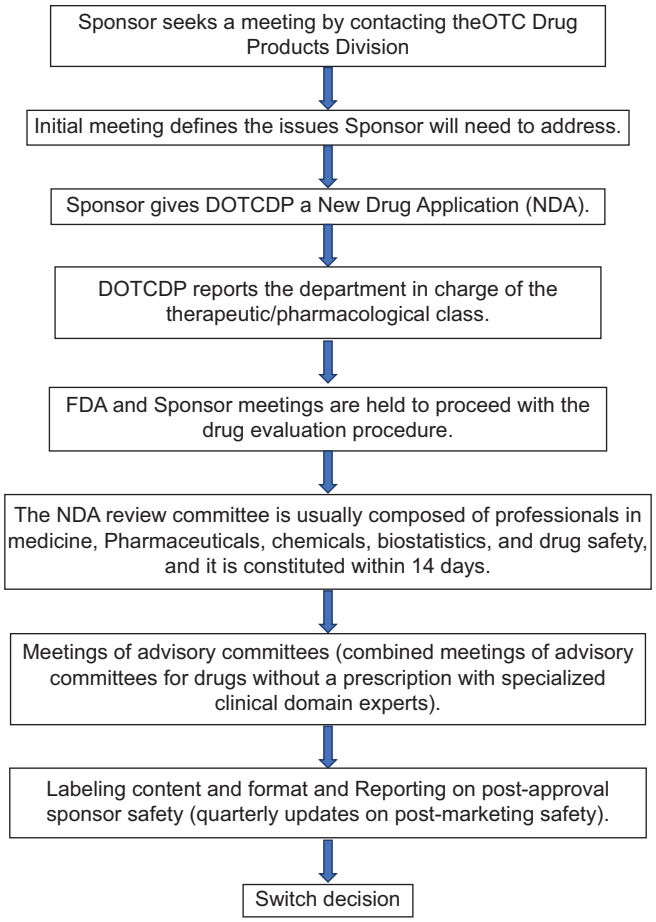

Figure 3: Switching process from Rx to Over the counter in the United States

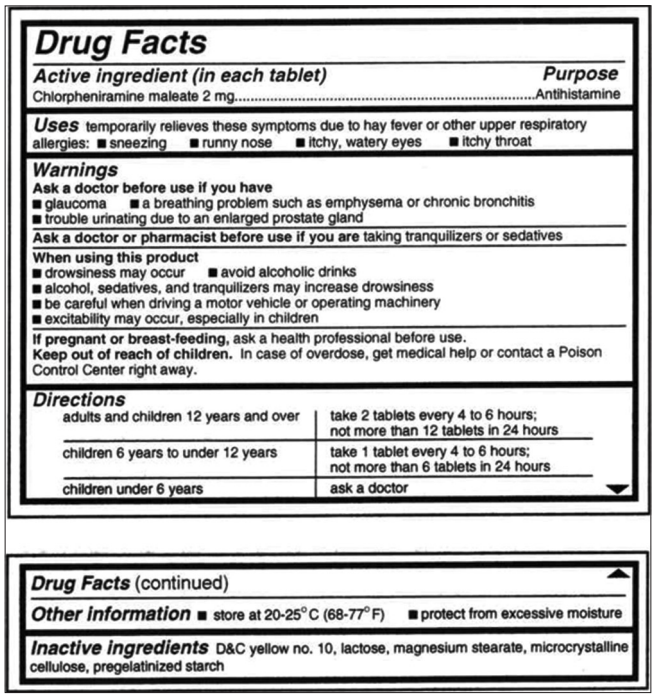

Figure 4: Drug facts

Table 1: Classification of OTC products

OTC drug classes	• Acne medications, analgesics • Bronchodilators and antihistamines • Cold remedies, contraceptives, and vaginal products • Dandruff and athlete's feet, dentifrices and dental products • Emetics and antiemetics • Laxatives • Ophthalmic • Stimulants, sleep aids, sunburn treatments, and sunscreens • Vitamins and minerals

OTC: Over-the-counter

Table 2: Current regulation for OTC products in India

Legal recognition	There is no clear formal recognition. Products listed in schedules H, G, and X, which do not require a prescription but must be labeled as such, and schedule K are regarded as non-prescriptions
Drug registration	Before applying for the transition to OTC, the product must have a valid prescription
Criteria for acceptance	Stability information for the plant's three validation batches that were approved for good manufacturing practices

DATA EXCLUSIVITY IN THE UNITED STATES

"Drug Price Competition and Patent Term Restoration Act" amendment, often known as the "Hatch-Waxman Act," data exclusivity was first implemented in 1984. The FDA Act Section 505 (CFR) of Title 21 of the CFR now has a codification of it.[8]

Levonorgestrel 0.75 mg (Plan B® Duramed Research Pharmaceuticals).

- In line with Section 505(b)(1) of the FF D&C Act, the supplementary (NDA) for Plan B® (levonorgestrel 0.75 mg tablets) was initially submitted to the FDA in April 2003. After this application was rejected by the FDA in May 2004. Following an agreement on certain pledges to be kept by the applicant, Plan B® was eventually successfully reclassified to OTC for women who were 18 years of age or older on August 24th, 2006.
- The hormonal contraceptive Plan B®, also known as the "morning after pill" prevents pregnancy. Although any drug product having several variations of the same active moiety had already gotten approval, this specific version of the active moiety for which the application was made does not comply with Section 505 of the F D and C Act.

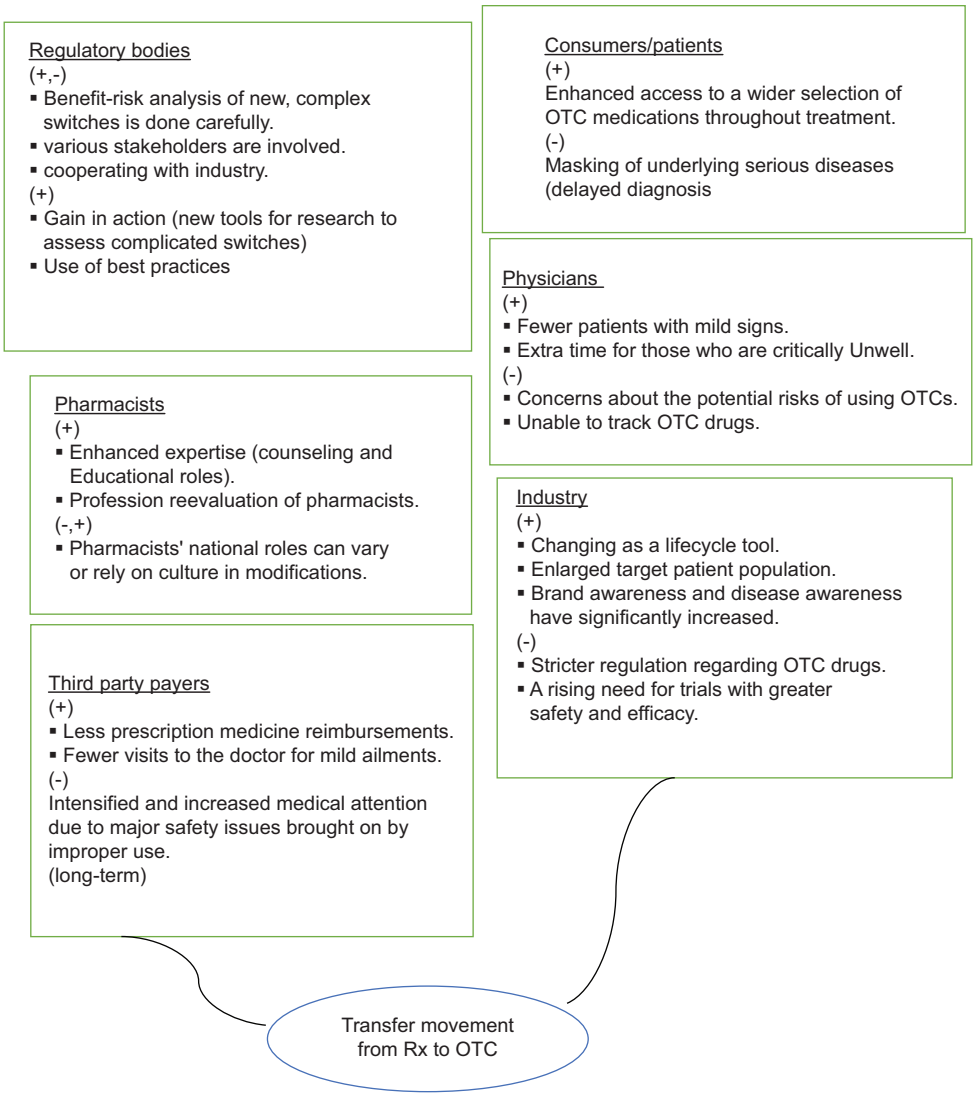

Figure 5: Current switch strategies: Rx-to-OTC

Examples

- Three years of data exclusivity were asserted in the request to alter the drug's legal status. The applicant provided two original clinical data that were considered necessary for approval but had never been employed by the agency previously. In addition, the applicant did not rehash the results of other investigations that the agency had used to exemplify the efficacy of a drug product that had already been given approval.
- Both the actual use trial and the label comprehension study examine consumers' comprehension of the product label. The actual use experiment shows actual use in a simulated OTC context with repeat use, the possibility negative consequences of pregnancy.
- The FDA granted Plan B® (levonorgestrel 0.75 mg tablets) 3 years of exclusive OTC approval based on the standards stated in the CFR.

OTC DRUGS: LABELING REQUIREMENTS

1. The Fair Packaging and Labeling Act (FPLA) and the F D&C Act are two laws that must be followed for the mandated labeling of OTC Pharmaceuticals. According to these requirements, labels must include the dosage strength and the manufacturer's, packer's, or distributor's name and address.
2. To make essential information clear, condensed, and simple to use for OTC labeling, the FDA proposed the establishment of a standard format in 1997. On March 17, 1999, the Federal Register published the revised format as a final rule. A "drug facts" box and other information are required for this. The product's active ingredient, use(s), directions, inactive ingredients, cautions, and other information are listed on the package.[9]

Table 3: Differences between the NDA approval process and the monograph process

NDA approval process	OTC monograph process
Pre-market approval – Before marketing, the FDA examines and authorizes the formulation and labeling	Since the FDA specifies standards for generally regarded as safe and effective, there is no pre-market approval. It outlines the conditions for continued promotion of a developing monograph while awaiting the completion of a final one. Following marketing is monitoring
Confidential application filling for a particular drug product	No confidential application filling
A user fees is necessary	No user fees
Marketing exclusivity	No marketing exclusivity
FDA assesses deadlines	Manufacturers are in control of assuring a compliant product; FDA review is not necessary (either pre-or post-market)
Clinical studies such as label comprehension, self-selection, and actual use are needed.	• Clinical studies are not required • For substances that are already listed in a final or prospective final monograph, investigations on label comprehension and actual use are not required
Approved label for unique of drug	The book defines labeling. After the product has been marketed, the FDA may evaluate the finalized labeling at any time to assess whether it is truthful or misleading
The "licensee" to advertise a Trade name that is assessed before marketing is referred to as NDA approvals	• Open access to the final monograph. • Before marketing, there is no trade name evaluation. After it has been marketed, the FDA has the right to evaluate the trade name at any time

FDA: Food and Drug Administration, OTC: Over-the-counter, NDA: New Drug Application

Table 4: According to 21 CFR 201.66, all OTC must include the details regarding the drug product

S. No	Category	Description
1.	Title (drug facts)	The first panel must have the title Drug Facts, and each successive panel must have the title Drug Facts (continued).
2.	Active ingredient (s)	Any product meant to have pharmacological activity or other direct influence in the diagnosis, treatment, is considered an active ingredient.
3.	Purpose (s)	If a medication has two active components that are used for the same purpose, just one purpose statement is necessary if the purpose clearly refers to both active ingredients.
4.	Use (s)	Involves endorsed applications for the medication. For drug cosmetic products only drug indication is mentioned.
5.	Warning (s)	Subheadings like • "Do not use for/if" • "Ask a doctor or chemist if you have" • "Pregnancy and related warnings" • "Keep out of reach of children" must be displayed.
6.	Directions	• Contains instructions on how to use the product such as "shake well," • "Drink a full glass of liquid with each dose." If the medication is utilized for numerous ages a table is used.
7.	Other information	• Qty of ingredients presents in each dose. • Storage information.
8.	Inactive ingredients	The established names of inactive components in OTC medicine products must be given alphabetically.

FORMATS FOR STANDARD AND MODIFIED LABELS

In accordance with US standards 21 CFR 201.66(d), a modified labeling format is necessary when the required drug facts labeling takes up more than 60% of the entire surface area available for labeling, including other FDA-mandated information for medications or drug-cosmetic products. The details were given in Table 4 and the label guidelines in Table 5.

RX-TO-OTC CHANGES IN THE FUTURE

- Many medications that are exclusively available with an Rx in the United States are already sold

Table 5: Label guidelines

Labeling element	Standard element	Modified element
Drug Facts box	Triggered by a barline.	If color contrast is used to separate it from the rest of the marking, the barline might not be present.
Drug Facts	Font size that is larger than that of the Drug Facts box.	Font size that is larger than that of the Drug fact box.
Drug Facts (continued)	A minimum of 8-point type.	A minimum of 7-point type.
Headings	>8-point type or 2-point type.	>7-point type, or 1-point type.
Leading	0.5-point minimum type.	<0.5 points may be employed
Bullets	A minimum of 5 points Vertical symmetry	Minimum 5-point type No symmetry.

Table 6: A review of Rx to OTC switches in the USA, India, and the EU

S. No.	Key point consideration	USA	India	Europe
1.	Regulatory authorities	US FDA	Drugs and Cosmetic Act (1940)	Article 70 of Directive 2001/83/EC
2.	Monographs	The Division of OTC Regulation Development	NA	NA
3.	Prescription to OTC switching	Drug Review Panel	Lacks such system	Directive 2004/27/EC
4.	Price	Group purchasing organization	DPCO1995	89/105/EC (Transparency directive)
5.	Marketing exclusivity period	3 years	Not defined	1 year
6.	The duration of time before switching that Rx medicines must be marketed	3–5 years	5 years	3 years
7.	Labeling	Drug fact labeling 21 CFR 201.66 days	D&C act rule 95	Articles 54-69 Directive 2001/83/EC
8.	Advertisement	Federal Trade Commission	Magic remedies Act 1954	Article 88 of Directive 2001/83/EC
9.	Dispensing	Supermarket	Independent groceries	Supermarket
10.	Serious adverse events reporting	15 Calendar days	24h to EC within 7 working days	15 Calendar days

OTC: Over-the-counter, FDA: Food and Drug Administration

without a prescription in other nations. Consider topical erythromycin, which is prescribed in the US but sold OTC in Belgium and Poland. In addition, in contrast to several European nations, many indications in the US, such as high cholesterol and irritable bowel syndrome, have limited to no OTC therapeutic alternatives.

- Companies that are concerned about switching from Rx drugs to OTC products should start by maintaining the patient in mind. In this regard, picking the right product ingredients can be quite important.
- Future switchovers now face greater regulatory obstacles than they did a decade ago, in part because the medications and diseases are more complicated. A saturation point is being reached for switches in traditional OTC categories.
- The UK, Poland, and New Zealand are some of the smaller; more open markets that frequently support ground-breaking switches, despite the USA's dominance in the switch industry.

REGULATORY GUIDELINES FOR OTC DRUGS

In European Union

Switching in Europe from Rx to Otc

Two categories are provided for the regulation of Pharmaceuticals for human use in Article 70 of Directive 2001/83/EC, such as

1. Medical prescriptions are not required.
2. Medications that require a prescription from a physician.
    - An Rx medicine must be legally available on the market for 5 years before it can be sold OTC.
    - The switch application for a product is approved by CHMP using the centralized process. In these cases, the sponsor is permitted to promote his products without a prescription and the federal health agencies' key competencies include the classification of medications. Each member state decides whether to classify OTC medications as pharmacy-only or general sale (GSL) drugs.
    - Depending on the initial approval process, there are several regulatory pathways—national procedure, centralized procedure, and decentralized procedure—available for changing legal status.
    - The European "Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use" outlines the major guidelines and the specific information that must be provided by a marketing authorization holder (MAH) in Europe to submit an application to change a Medicinal Product's Classification from prescription to OTC. (2006) (EU) Commission 2006a). It was established by the European Commission in 1998 in an effort to increase transparency and standardize switching conditions across European countries.
    - Granted that the MAH is given a data exclusivity for an year under Article 74a of Directive 2004/27/EC if the switch application includes "signicant pre-clinical tests or clinical trials," the third section of the rule specifically Concerns data exclusivity.[6]

EUROPEAN COUNTRIES HAVE ESTABLISHED DIFFERENT KINDS OF PROCEDURE FOR APPROVALS, NAMELY

1. Procedures for mutual recognition (MRP)
2. Decentralization (DCP), and Centralization (CP).

Mutual recognition procedure (MRP)

A "mutual recognition procedure" must be employed if a Pharmaceutical product already has a marketing authorization in one European member state.

Mutual recognition implies that member states of the EU may approve a decision made by one of them to accredit a medicinal product. Therefore, the system is predicated on the mutual recognition of national marketing permits. (2010) (Medicines Agencies).

Decentralized procedure (DCP), or centralized procedure (CP)

Contrarily, the decentralized process needs to be applied to products that have not yet been authorized in an EU nation (i.e., products that have not previously obtained approval in any member state) (Medicines Agencies 2010).

DATA EXCLUSIVITY FOR PRESCRITION TO OTC DRUGS

For marketing authorizations of Pharmaceutical products in the EU, including a change in classification, the drafting Directive 2004/27/EC updating Directive 2001/83/EC initially called for a 3-year data protection period. However, this was subsequently shortened to 1 year.Pantoprazole 20 mg (Pantoloc Control®, Nycomed)

- The drug pantoprazole is a substituted benzimidazole that belongs to the pharmacological class of proton pump inhibitors. It works by inhibiting the hydrogen/potassium adenosine triphosphatase enzyme permanently system (also known as the "proton pump") of the gastric parietal cell.
- According to the patient health community level, "Heart burn" is the most prevalent symptom among the population. A harmonized OTC pantoprazole product would provide for both consumer protection and community-wide access.
- Accordiing to the (EMA 2009b) "Hybrid application" in reference with previously approved products that were subjected to therapeutic indication revisions supported by the results of relevant non-clinical and/or clinical investigations. It was necessary to provide clinical evidence in support of the proposed change in indication. It was necessary to provide clinical evidence in support of the proposed change in indication.
- The management of symptoms in patients with GERD was the primary or secondary outcome in 17 clinical investigations, with heartburn and acid regurgitation being considered the disease's cardinal symptoms. These studies compared the administration of pantoprazole 20 mg during the first 14 days of addressing GERD symptoms at any stage to a placebo or another PPI/H2-blocker.

Clinical study

- Pantoprazole was replicated as self-medication in one trial that only included patients due to reflux symptoms being present but not endoscopic assessment. No clinical research or study analysis in specific populations was carried out to support the application.
- In response, the CHMP acknowledged and concurred that the 20 mg dose was effective, safe, and

suitable for the intended indication in a nonprescription status.
- Data from the global clinical trial database and post-marketing surveillance were used to determine safety. Pantoprazole 20 mg is not required to be used under a physician's supervision, according to the CHMP, due to the drug's well-established safety profile in Europe since its introduction in 1994.

Examples

- According to Article 74a of Directive 2001/83/EC, as amended, the applicant asked for a year of data exclusivity based on six unpublished studies out of the 17 studies that were submitted. At least once during the first 14 days of treatment, the significance of the new study's data regarding reflux-related symptoms was noted to assess a change in classification.
- The early onset of alleviation from reflux symptoms was seen in (54.0–80.6% after day seven) selected studies suggesting early onset of efficacy in a nonprescription setting.
- The CHMP made the following observations in response to the applicant's claim of data exclusivity: Either the overall study results were comparable to those of previously published studies, thereby not significantly adding value to the proposal, or the study had no efficacy data available after a 2-week period of treatment. If a patient's symptoms do not go away after 14 days, they should see a doctor.
- The CHMP rejected the applicant's request for a year of data exclusivity because it did not find the information provided with reference to Article 74a of Directive 2001/83/EC, as amended, to be significantly more valuable in supporting the change in classification.[10] The comparison of regulations for OTC switch in India, USA and EU was tabulated in Table 6.

CONSEQUENCES FOR RX-TO-OTC TRANSITIONS IN THE FUTURE

- OTC products should be subject to post-marketing surveillance that includes not just the building of a traditional, reliable, and easily accessible pharmacovigilance system that facilitates (spontaneous) reporting of suspected AEs/ADRs, but also monitoring for "upstream" behavior's that could endanger consumers (such as use by inappropriate populations).
- The creation of "test market" notions as a generic sort of behavioral study has been advised to handle case-specific (switch-related) concerns, arm the determined object demographic, and respective possible risk populations.
- For example, – The availability of triptans to treat migraines or emergency hormonal contraception as self-treatment options exemplify the need of accommodating patients' requests for more prompt access as a crucial component of a successful OTC changeover.

UNITED KINGDOM

- Medications may be reclassified in the United Kingdom so long as they meet the criteria for OTCness outlined in Article 71, Title VI of 2001/83/EC.
- The process to be used for a product's reclassification depends on the regulatory path taken during the product's first registration.
- Products whose national procedure approval was obtained in the UK must be reclassified by submitting an ARM, or Application to Reclassify Medicines, and products whose Rx version was approved through the centralized route must be reclassified through the centralized route by submitting a Type II Variation.[4]

DATA REQUIREMENTS MUST MEET FOLLOWING SWITCHING CRITERIA

1. Including clinical and non-clinical
   Along with the dosage and indications and authority should offer a crucial analytical report on the planned availability of the product without a doctor's requirement. This section's format needs to be created in accordance with the Common Technical Document (CTD).
2. Clinical and nonclinical safety data
   This section deals with descriptions of research on human beings or animals that demonstrate low overall toxicity and no impacts on reproduction, genotype, or carcinogenesis relevant to the use of exposure to a medical treatment.
3. Clinical impact
   It is typically not taken into consideration when changing the categorization of a medical item. Unless the substituted product modifies the posology or indicators.
4. Information on the product
   The effectiveness of non-prescription medications in shielding patients from safety risks will be carefully studied for thorough information. According to Article 54 of Directive 2001/83/EEC, the immediate packing must provide usage instructions for non-prescription medications that do not have an outside package or outer carton. The current OTC drugs switch strategies were depicted in Figure 5.

CONCLUSION

As a result, to conclude OTC medication plays a key role in day-to-day life. According to the Report, Cough, and cold remedies occupies half of worldwide Market. Due to COVID-19 era, most of the population is dependent on self-medication instead of visiting hospitals and pharmacy.

There is an increase in demand for e-commerce sites as compared to offline channels. Analgesics are the most used medication for geriatric as well as adult population. The prevalence rate is more in United States, followed by Europe and India. India is under the development phase due to lack of proper OTC regulation. Pharmaceutical companies focus on pricing strategy, target of audience with diseases, safety, and efficacy guidelines. In the OTC drug marketing point of view, consumer and customer are same. The demand for OTC medications is steady and they have the features of everyday commodities. In addition, even though OTC medications are distinguished by high brand loyalty in comparison to other consumer items, merchants have a great sales record and are anticipated to increase the availability of their private labels in markets in the future. Labeling of OTC medication should be clearly visible, easily understandable, and easily accessible for uneducated populations. Cost-effectiveness of OTC medications and self-medication is another significant factor driving market expansion. About 50% of physicians believe that medicare and insurance coverage should be included for OTC medications. For instance, use of antacids (Maalox) instead of pantoprazole for moderate stomach upsets, which improves health satisfaction. It is preferable to use technology to accelerate the expansion of OTC medicinal products.

Rx-to-OTC switchovers have significant potential for economic rewards in addition to benefits for health. To estimate cost reductions from switching from Rx to OTC drugs, policymakers rely on economic models. The switching process helps manufacturers recover lost revenue from prescription sales. It is important to educate the public on drug product labeling, abuse, and misuse of Rx to OTC medications. These initiatives would prevent people from using substandard and fake products to treat minor ailments, which could endanger their health. The government should enforce regulations stating that only licensed people should offer OTC products.

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