

Switching Drugs from Rx to OTC status – A Regulatory Perspective

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ABSTRACT

Initially drugs are available for consumption to the public only after consulting with a healthcare professional and obtaining a prescription for the same. However, to enhance consumer access to a safe and effective drug, it is possible to 'switch' the same to over-the-counter status after the initial prescription marketing if the post-marketing safety data of the prescription version of the medication reiterates the safety, effectiveness and ease of use of the drug. This is known as a 'Prescription-to-OTC Switch'. Prescription to OTC Switches are supported by a large number of driving factors such as increasing consumer awareness, growth of the self-medication movement, pharmaceutical companies' attempts to increase sales and government efforts to curtail public spending on prescription products for minor, self-treatable ailments. It is estimated that nearly 40% of all OTC medication available today in the US was once upon a time marketed as a prescription drug. The therapeutic indications that are considered appropriate for self-treatment are also evolving – from minor afflictions like cough and cold in the past to allergic rhinitis in the present. Rx to OTC switching is

responsible for the availability of several safe and effective drugs for the self-treatment of a multitude of indications like diarrhea, heartburn, nasal congestion etc.

Key words: OTC switch, Regulatory, Prescription.

Key message: Prescription to OTC switching is beneficial for the people for the usage of several safe and effective drugs for the self-medication.

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DOI: 10.5530/jyp.20179.2

INTRODUCTION

In order to switch a prescription version of a drug to OTC, the drug must possess some inherent traits that cause it to be amenable to self-medication. In general, these are as follows:¹

1. The symptom intended to be treated by the drug must be one that can be easily recognizable by an individual of average intelligence
2. The drug must possess a very high safety margin
3. The drug must be used for easily recognizable conditions
4. The drug must be easy to administer
5. The drug must exert its effect rapidly post-administration and the effect must be easily noticeable
6. The drug must not be addictive or narcotic in nature
7. The use of the drug must not mask any underlying potentially dangerous conditions
8. The treatment regimen must be uncomplicated enough for a layman
9. The drug must not be parenterally administered

During the clinical trial phase of a new investigational product, the number of patients on whom the product is tested is far lower compared to the actual population that will be exposed post initiation of marketing. Thus after the initial registration of a new product, although available clinical data may reiterate the safety and efficacy of the product, it is always prudent to closely monitor the usage of the drug in the actual patient population. This is the reason regulatory authorities usually prefer to err on the side of caution by making a new product available by prescription.

In fact, pharmaceutical companies themselves prefer to submit their initial product application under the category of prescription only. The most common reason for this is that these new drugs are always protected by patents and thus the company can recover their initial R&D costs by utilizing a high pricing structure without the fear of generic competition eroding their sales. It is not practical for companies to similarly price new OTC products for reasons further explained below.

Post-termination of the patent regime, innovator companies commonly face a steep decline of sales as a result of the influx of multiple low priced generic products. However, if the product exhibits certain conducive characteristics that make them amendable to OTC use, these innovator companies have yet another opportunity to extend their product life-cycle in the form of a prescription-to-OTC switch. Products with a strong and well recognized brand name can leverage on their identity to continue to ensnare large sections of the consumer market post making their product available as OTC.² Although the resultant sales may never be as high as they were during the patent protected period, they still are significantly more resistant to generic competition.

Although the primary benefit of an OTC switch lies with the pharmaceutical company, in several countries, private health insurance companies also are allowed to drive the switch. In countries like the US, private insurers reimburse patients for their prescriptions. Thus a switch of a popular, safe and effective prescription product to OTC means that the insurer is no longer obligated to bear the cost of the medication. This is the reason several insurers have lobbied for certain Rx to OTC switches. Lastly, in certain instances, regulatory authorities themselves may request sponsors to submit OTC applications if they believe that the availability of a particular product without prescription control may

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benefit the general public. This approach raises a few questions as the authority never conducts clinical studies on its own and is completely dependent on the sponsor to supply adequate clinical data to demonstrate safety and efficacy within the realms of the OTC use of the product.

Advantages of Switching

The path to obtain prescription medication is often long, complicated and costly. The patient needs to take time off work to make an appointment, visit a doctor, obtain a prescription and fill it at a pharmacy. The availability of OTC medication enables a patient to bypass nearly all of these arduous steps. Thus, OTC medicines provide a much more convenient means for patients to self-treat their minor afflictions. In addition to patients, physicians can also benefit in not having to unnecessarily spend their already limited time in diagnosing obvious, self-treatable conditions.

OTC products in general being ineligible for reimbursement schemes are usually paid for by consumers. Thus pharmaceutical companies usually place OTC products at far lower price points than their prescription counterparts in order to ensure larger volumes of sales. Due to the reduced pricing, profits are obviously lower, but this is a small price to pay to continue to capture required market volumes post expiration of the drug patent. Ultimately, the consumer wins due to the reduced prices of the switched product.

Another significant impetus to switching may present itself in the form of exclusivity for the sponsor who submits clinical data that is deemed sufficient to justify the down-regulation of the product. The period of exclusivity varies from 3 years in the US, under the aegis of the Hatch-Waxman Act, to 1 year in the EU, under the aegis of Article 74a of the Directive 2004/27/EC. This further helps the sponsor shield himself from generic erosion in this limited time period.

Mechanism of an Rx-to-OTC switch

Prior to applying for a change in the dispensing class, the sponsor must self-assess his product to ensure that it falls within the realm of OTCness. For example, applying for the OTC switch of an extremely toxic chemotherapeutic drug is certainly an exercise in vain. The WHO has released a guideline that may help sponsors in determining the same. In general the product must have the following characteristics:

1. The sales volume is high enough during the period of marketing to determine that the product is extensively used by the consumer
2. The product has been made available in the previous Rx status for a sufficient number of years. This period varies from country to country.
3. The PMS data shows no particular cause for concern and there are no serious adverse events that have increase unduly in frequency during the marketing period.

The OTCness of a product in any particular country is highly dependent on the literacy rate, consumer awareness, socio-economic background and general environment of the individual country. While approving an Rx-to-OTC switch, regulators may also require certain changes from the previous Rx version such as restrictions in pack sizes, restrictions in the approved indications for the OTC version, changes in the label and insert to a more layman-friendly format etc.

The health authority in general refers to the safety and efficacy data submitted in the original NDA for the Rx version of the product, along with the post-marketing data and additional clinical trials conducted by the sponsor to support the OTC class. There is no 'one-size-fits-all' approach when it comes to the type of safety, efficacy and real use data that can be used to support the switch application. Sponsors are commonly encouraged to hold frequent meeting with the OTC division and corresponding therapeutic class division of the health authority to gain

a clear understanding of the requirements. Sponsors must also lobby to key-opinion leaders, health care professionals, patient organizations and pharmacists whose opinions have great implications on the fate of the switch application.

The following sections give a brief overview of the regulatory procedures and documentation to be followed to switch a prescription product to OTC status in 4 significant countries – US, UK, Singapore and China.

USA

In the USA, Rx and OTC products are regulated by two distinct methods. OTC products can be introduced into the US market without FDA pre-approval if the active ingredient, dose, formulation and indication fall within pre-approved values, which are specified in an 'OTC monograph'.³ Rx products (or innovator OTC products), on the other hand require an NDA.

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

1. By the OTC drug review – this is initiated by the FDA commissioner
2. By submission of an efficacy supplement to the existing NDA – This is the means for a sponsor to switch the Rx products in its entirety to OTC
3. By submission of a new NDA – This is required for a sponsor to partially switch some of the indications to OTC, while retaining others within a prescription status.⁴

The USFDA will approve of the switch application when it is of the opinion that the previous Rx designation is “*not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and . . . the drug is safe and effective for use in self-medication as directed in proposed labeling*”⁵

While evaluating the switch application, the USFDA seeks recommendations from a joint advisory committee made up of members of the FDA's Nonprescription Drugs Advisory Committee and another advisory committee with expertise in the type of drug being considered.

In addition to the already available clinical data from the existing NDA, safety and effectiveness can also be confirmed by means of additional data, whether new clinical trials or post-marketing data submitted by the sponsor. The sponsor should also submit additional clinical data that supports the use of the drug in the OTC setting. These consumer behavior studies are of the following types:

1. Label comprehension studies⁶–LC studies are those where the subjects are not actually administered any drug. Instead they are provided with an OTC label that adheres to a pre-requisite format (called a 'Drug Facts label'). Based on a questionnaire provided to the participant, the ease of a layman comprehending key facts on this OTC label is judged. If the responses of the participants show that certain vital elements of the label are not effectively understood, the label is revised to emphasize the pertinent section and the LC study is repeated till it is proved to be of the most effective wording. LC studies are also vital to determine if new warnings generated (from AEs observed in the PMS data) are effectively communicated to the consumer.
2. Self-selection studies⁷–After the label comprehension studies are performed and the most effective Drug Facts Label is developed, SS studies are carried out. These studies test whether consumers can extrapolate the information acquired from the OTC label to their personal medical history and make correct self-selection decision, i.e. decide whether the OTC drug is safe for them to use.
3. Actual use studies–AU Studies help simulate the OTC use of the product and thus help determine whether the consumer actually

uses the drug safely and effectively after the correct self-selection. They also help confirm that the product cannot be abused or misused by the consumer.

In case the FDA deems that the clinical data submitted along with the application is 'sufficient to justify the OTC switch', the sponsor can avail 3 years of marketing exclusivity under the aegis of the Hatch Waxman Act given that the results of the trials "*have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product*".⁸

The entire process of switching the product can be summarized as follows:

- The sponsor contacts the office of non-prescription products (ONP) and requests a meeting
- The initial meeting identifies all the issues sponsor will need to address
- The sponsor submits the switch application to the ONP
- ONP notifies the Specific Subject Matter Review Division (SSMRD) responsible for the therapeutic/pharmacological class
- The division of non-prescription evaluation (DNCE), which is part of the ONP responsible for review management and oversight of the NDA forms the review team with the SSMRD
- The SSMRD reviews the clinical efficacy and safety from clinical trials. The DNCE reviews the post-marketing data and consumer behavior studies as well as the non-prescription labeling.⁹
- Meetings between review team and sponsor continue during review process
- The NDA review team identifies certain issues to be brought to the notice of an advisory committee. This non-prescription drug advisory committee (NDAC) is composed of individuals selected by the FDA Commissioner from among authorities knowledgeable in the fields of internal medicine, family practice, clinical toxicology, clinical pharmacology, pharmacy, dentistry, and related specialties.
- The sponsor and the FDA review team also provide briefing documents and presentations to the NDAC. These are published on the FDA website
- The NDAC reviews and evaluates available data concerning the safety and effectiveness of the product for over-the-counter use and advises the Commissioner on the approval of the switch application for the drug.¹⁰
- The directors of SSMRD and DNCE write a summary decisional review and come to a final consensus.

United Kingdom

Medicines can be reclassified in the UK as long as they fall within the scope of OTCness as described in Article 71, Title VI of 2001/83/EC. The procedure to be followed for the reclassification of a product is dependent on the regulatory route involved in the initial registration of the same. Products whose Rx version was approved via the centralized route are required to be reclassified by the centralized route by means of submission of a Type II Variation, and those approved by national procedure in the UK are required to be reclassified by submission of an ARM or Application to Reclassify Medicines.

The data requirements for the Switch are as follows:¹¹

1. Non-clinical and/or clinical overview—This must be prepared by an expert and must clearly justify the reason why the product does not

possess any characteristics that require supply only through a prescription. This section should be prepared in CTD format.

2. Evidence of the medicinal product's efficacy—This is not necessary unless the strength or indications are changes from the Rx version, in which case adequate justification must be provided.
3. Draft of the OTC label and Product Insert.
4. The Risk Management Plan.

In case the CHMP approves the switch application for a product by the centralized procedure, the sponsor can market his products without a prescription. However, certain countries have two separate non-prescription categories, i.e. behind-the-counter, where the product can be purchased only in the pharmacy after consultation with a pharmacist or pure over-the-counter, where the sale is not restricted to any particular channel, in effect allowing the product to be accessed in grocery stores as well. It is up to the relevant regulatory authority of each country to determine the exact non-prescription class once the CHMP approves the switch application.

The US is far more conservative compared to the UK in reclassifying products to OTC, as evidenced by the repeated rejection of the switch application for statins by the FDA, which have been granted non-prescription status by the MHRA. The existence of the intermittent behind-the-counter category, where the pharmacist can exert his control on the non-prescription product, probably can attribute to this stance.

On 31st March 2004, a new directive 2004/27/EC was introduced which amends the previous Directive 2001/83/EC. The new directive inserts a new Article 74a that states:

"Where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized"

The article, though strangely worded has the following implication: If a sponsor conducts and submits additional clinical or non-clinical trials to support his reclassification application, he is granted a year of data protection for this information. Thus the MHRA will not allow another applicant to refer to this data for a period of one year from approval of the application. In effect, this will cause the initial applicant to remain the only over-the-counter product authorization holder, unless a subsequent applicant produces other data from separate clinical trials to support his application, which is rarely the case.¹² This one year exclusivity is far lesser compared to the three year period afforded by the Hatch-Waxman Act in the USA. The CHMP and MHRA are also quite restrictive in their definition of appropriateness of the clinical trials. Up to this date, there have been no known examples of products being granted this one-year exclusivity.

Thus although the MHRA is far more liberal in granting switch approvals, the USFDA yet affords a much longer period of exclusivity to the switch application.

Singapore

A differentiating factor between switch applications in countries such as US/UK and those like Singapore/China is that the Singaporean and Chinese Authorities rely heavily on the approval status in 'reference' countries such as the USA, UK, Australia etc. Thus a sponsor usually applies for the switch in these countries post approval from a 'major' health authority.

Reclassification applications in Singapore are considered to be a type of 'variation' application. A variation application may either be major or minor in nature. Minor variations are those affecting quality or admin-

istrative variations. Major variations are those that entail changes in the safety or efficacy of the previously registered product. So it is obvious that a change in the forensic class will fall under a major variation. There are two types of major variation applications in Singapore. MAV-1 applications are those to change the approved dosage, indication, patient groups and to include clinical information outside the approved usage of the product. MAV-2 applications are required to change the forensic classification of the drug.

Thus prescriptions to non-prescription reclassification applications in Singapore are submitted as a MAV-2 variation application. The reclassification application needs to be submitted on on-line via HSA's Pharmaceutical Regulatory and Information System, commonly abbreviated as PRISM.

In general the following documents need to be submitted to support the sponsor's MAV-2 application:¹³

1. Introduction: This section refers to the status of the product in other reference countries, examples of which are USA, UK, Canada and Australia, along with the exact OTC indication, dose and period of OTC sale in the respective country. With this introduction, the sponsor justifies the reason for which the product must be reclassified to OTC in Singapore.
2. Clinical Overview: The clinical overview contains the following information:
 - a. Forensic classification of the product in the UK, US, Canada and Australia with specific information on whether the product is a Prescription-Only, Pharmacy or General Sale List medicine and the duration of sale in that classification;
 - b. Experience in terms of patient exposure to the product (i.e. sales volume, patient-years);
 - c. A summary of the product safety profile based on worldwide spontaneous adverse drug reaction reports, data from post-marketing surveillance studies, clinical trials and published literature;
 - d. Information on local adverse drug reactions;
 - e. A list of potential problems arising from using the product without medical supervision; and
 - f. An analysis of the hazards arising from therapeutic misuse or drug abuse, whether deliberate or accidental e.g. consequence of delay in seeking medical attention

The applicant need not provide any additional information on CMC sections if the OTC product is exactly the same as the prescription version in dose and presentation.

China

In July 1999, as a part of medical insurance reforms, the SFDA began to select and examine different drug types in order the adequately distinguish between prescription and OTC drugs. As a consequence, the SFDA publicized 4,610 types of OTC drugs, which include both traditional Chinese medicines as well as allopathic drugs. The SFDA also formulated detailed regulations regarding the OTC labeling of drugs and mandated that these drugs also have a specific OTC logo on the packaging. They did so in order to encourage patients to purchase OTC medicines for non-serious conditions, as a continuing effort to reduce the number of physician visits and public expenditure on prescription drugs.¹⁴

The data requirements for switching are as follows:¹⁵

(A) Summary dossiers

1. Application form
2. Table of contents

3. Application rationale – Should include the switch criteria, manufacturing information, sales data and an overview of safety and efficacy.
4. OTC draft labeling – Accompanied by the original prescription labeling with a justification of the changes made.
5. Drug sample
6. Other certificates – Should include pharmaceutical production licenses or import registration certificate. Agents should also provide the original manufacturer authorization.

(B) Pharmaceutical Dossier

7. Product formulation - Should include the specification of active ingredients and other ingredients that have been included in the Chinese Pharmacopoeia
8. Quality & stability dossier – Should include drug quality dossier and stability studies.

(C) Safety Dossier

1. Toxicology data – Should include toxicological data of both the active ingredient as well as that of the final product
2. Adverse events report – This should include a summary of the adverse events, and full adverse event reports with a cut-off date of 3 months before the date of submission of the switch application.
3. Drug dependence research data – Should include related clinical trials data and literature review
4. Drug tolerance research data – Should include review of research and related tests and literature.
5. Drug interaction with other drugs or food
6. Patients' self-diagnosis and treatment data – Should include a justification of the applicability of the medicine in a self-medication situation, whether the consumer can self-administer the correct dose without a doctor's intervention.
7. Widely use safety data – should include data which highlights the widespread use in an OTC setting and the extent of harm.
8. *Efficacy Dossier*
9. Pharmacodynamic study data – should include a review of pharmacodynamics and related tests and literature information.
10. Drug clinical efficacy data – should include clinical trials and related literature supporting the effectiveness of the product.

Wherever relevant, domestic and foreign journal articles must be referenced and Chinese translations provided.

The data requirements that are to be submitted for the switch depends on whether the API or the formulation is already present or not in the OTC list published in the SFDA site. Thus the switch applications for both TCMs and Chemical drugs fall under the following three classes:

Traditional Chinese Medicines:

- Class I: The drug is only different in the dosage form or the specification, with the same formulation and delivery route of the published OTC.
- Class II: The drug does not contain any toxic herbs ("Toxic herbs" refers to the herbs' toxicity recorded in the legal standard).
- Class III: The drug is not included in the above two kinds (i.e., a new TCM switch)

Chemical Medicines:

- Class I: The drug is only different in the dosage form or the specification, with the same formulation and delivery route of the published OTC.

- Class II: The drug is the compound preparation of the published OTCs' active ingredients.
- Class III: The drug is not included in the above two kinds. (i.e. a new API switch).

The data requirements for each Class are shown in Table 1.

The efficacy evaluation focuses on whether a majority of the target patient population would benefit from the pharmaceutical product for cure and symptom relief provided sufficient instructions for use and warning. The CFDA's final decision regarding the exact OTC class depends on the safety profile of the drug. Generally, drugs with a lower margin of safety are classified as Class A OTC drugs, which are analogues to behind-the-counter i.e. sold in a pharmacy after consultation with a pharmacist. Class B drugs i.e. pure over-the-counter drugs, requiring no control from the pharmacist for their purchase, are generally those used for minor indications, that have been marketed for more than 10 years as the prescription counterpart and whose ADR report reiterates the safety of the product.

There is no clause within SFDA regulations that permit the first applicant to enjoy data or marketing exclusivity on submission of pertinent clinical trials to support the switch application.

CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATIONS USED

Rx: Prescription; **OTC:** Over the counter; **NDA:** New drug application.

SUMMARY

The definition of drugs amenable to OTCness is constantly evolving. The availability of information at one's fingertips has empowered the consumer, enabling the movement of certain therapeutic indication from the purview of prescription to OTC. Indications like cholesterol management, menorrhagia, incontinence, obesity etc., that were once upon a time considered to be treatable only under physician control, can now be switched to OTC depending upon consumer literacy and awareness in each country.

Considering this rapid evolution of the definition of OTC drugs, it is imperative for the relevant regulatory authority to modify its definition of OTCness to accommodate consumers growing needs, while at the same time, restricting the use of certain products. Before the implementation of any relevant regulations, the feedback of all affected stakeholders must be taken into consideration. Actual use data must be kept at the pinnacle of the switch approval. Pharmaceutical companies that wish to initiate OTC switches must also ensure that consumers are educated to a satisfactory degree to diminish the risk of reduced physician intervention that accompanies self-medication.

It is always beneficial if the authority establishes an intermittent behind-the-counter category so that pharmacists may use their skills to assist consumers in their self-medication choices. In the near future, it is advantageous to use technology to further the growth of OTCness. For

example, the wide availability of reliable and simple methods to measure serum cholesterol levels may help move statins to an over-the-counter class worldwide to help patients manage their cholesterol levels better.

The future thus promises the use of OTC medications for a wider variety of indications. It is the responsibility of the regulatory authority to 'move with the times' and amend its regulations accordingly albeit without compromising patient safety.

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Article History: Submission Date: 08-06-16; Revision Date: 30-07-16; Accepted Date: 07-08-16.

Cite this article: Kartha SS, Kulyadi GP, Bhat K, Sathyanarayana MB. Switching Drugs from Rx to OTC status—A Regulatory Perspective. *J Young Pharm.* 2017;9(1):3-7.