An overview of the US regulatory system for OTC products

Abstract
Over-the-counter medicines (OTCs) are increasingly important to the US healthcare system, where many of today’s OTC products were only available by prescription just a few years ago. By leveraging lower-cost OTCs and the reduced costs associated with fewer physician visits, the OTC segment delivers billions of dollars of value to the US healthcare system annually. OTCs reach the US market via two regulatory pathways: the OTC monograph system and the new drug application (NDA) process. The OTC monograph provides a rapid route to entry for qualifying products, since pre-marketing approval is not required for conforming products. Products marketed via the NDA route require FDA approval prior to marketing, but may be entitled to exclusivity. The “general sales” status of OTCs in the US expands access to important medications that consumers can use to manage their health and wellbeing. By understanding the regulatory framework and requirements for each class of products, regulatory professionals can better lead innovation in this exciting area of healthcare.

Introduction
It is widely recognised that non-prescription medicines (also referred to as over-the-counter drugs or OTCs) play an increasingly vital role in the US healthcare system. The benefits to the individual consumer are well known in terms of increased access and affordability. US census data in 2011 indicated more than 48 million Americans were uninsured, representing a significant population of users who may rely heavily on OTCs to manage their healthcare needs. By leveraging the lower cost of OTC medicines and the reduced costs associated with fewer physician visits (insured), emergency room visits (uninsured), and medical staff, the OTC segment delivers billions of dollars of value to the US healthcare system annually.

The premise of self-medication is that for certain indications it is possible or even preferable for consumers to manage their health through the use of nonprescription medicines; consumers around the world rely on OTCs for the treatment and prevention of a variety of common conditions such as headache, cold and flu, allergy, heartburn and dermatitis.

Because OTCs are used directly by consumers they must have a wide margin of safety; the following are some typical characteristics of OTC products:
- The product can be safely used without a prescription based on a long history of use
- Consumers can appropriately self-select (or de-select) the product based on the OTC label, supported by label user testing
- Potential for misuse or abuse of the product is low
- The benefits of using the product as OTC clearly outweigh the risks.

OTCs in the US
The US subscribes to a two-tier drug class system comprised of prescription and non-prescription drugs (OTCs). The US regulatory system mandates that drugs be available without a prescription unless certain circumstances require dispensing by a licensed practitioner. The two-class distribution system is relatively unique in the global marketplace. Many markets subdivide non-prescription use into different categories depending on the degree of intervention considered necessary for safe use, such as pharmacist-only, pharmacy-only or general sales list (GSL). Additionally, when products are switched from prescription to non-prescription status, many markets will first require pharmacist intervention or location within a pharmacy for a period of time before the product can be considered for direct consumer access. In contrast and with few exceptions, all OTC medicines in the US are available in a variety of retail outlets, such as grocery stores, discount department stores, convenience stores, mass merchandisers and pharmacies. With more than 750,000 retail establishments nationwide, consumers enjoy direct and ready access to important OTC medicines.

How the FDA regulates OTC drugs
In general, regulations applicable to prescription drugs also apply to OTC drugs. Regulations relating to manufacturing, testing, facility registration and inspection, clinical trials, importation, safety monitoring and risk management apply equally to both classifications. There are hundreds of thousands of marketed OTC drug products in the US, representative of approximately 800 active ingredients spanning 80 therapeutic classes of drugs. It would be an impossible and impractical task for the FDA to review each product individually; therefore the FDA has devised two distinct pathways for the development of OTC drugs. The OTC monograph system considers “well-established ingredients” by therapeutic class (eg, analgesic, antacid). Products that fall outside this system are considered “new drugs” and are assessed on an individual basis through the new drug application (NDA) process.

OTC monograph system for well-established ingredients
The OTC monograph system was set up in 1972 with the FDA’s OTC Drug Review, an ongoing process by which the safety and efficacy of OTC ingredients is assessed. An expert advisory panel reviews data relating to claims and active ingredients for different therapeutic ingredients.
Table 1: Required elements of US NDAs to support the OTC label.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirements</th>
<th>Objective</th>
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<tr>
<td>Safety and efficacy data</td>
<td>Pivotal clinical data (may be from Rx drug for switch products); additional studies may be required if proposed OTC dose or indication differ. Adequate patient exposure in both time and extent to address any potential FDA safety concerns.</td>
<td>Support benefit–risk in OTC environment.</td>
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<td>Proposed labelling</td>
<td>Label is directed to the consumer with words that are easily understood. Follows standard format of OTC Drug Facts: active ingredients, purpose, use (indication), specific warnings, directions and inactive ingredients.</td>
<td>Provides information that allows consumers to determine whether the drug is appropriate for their condition, how it should be used, and clearly communicates safety considerations.</td>
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<tr>
<td>Label comprehension</td>
<td>A series of consumer research studies in which individuals are asked to read the label and answer questions to test their ability to read and comprehend the label’s key messages. Requires identification of key communication objectives and prospectively defined endpoints and success rates. No drug is administered.</td>
<td>To assess understanding of major communication objectives by demonstrating that consumers can read and comprehend the information which details the safe and effective use of the OTC product.</td>
</tr>
<tr>
<td>Self-selection</td>
<td>Consumer research studies in which individuals are provided with the label and asked questions to determine whether the drug is appropriate for them to use. Requires identification of key communication objectives and prospectively defined endpoints and success rates. No drug is administered.</td>
<td>To assess the consumer’s likely behaviour by demonstrating appropriate selection and deselection based on labelling which clearly communicates who should or should not use the product.</td>
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<tr>
<td>Actual use trial</td>
<td>An open label study conducted under simulated OTC conditions in which subjects are provided with the drug to determine their ability to follow the label’s directions for use, warnings, etc. In this type of trial, the consumer can purchase the drug, take it home and use it without physician supervision.</td>
<td>To assess safety in a real-world setting by demonstration that consumers can correctly self-select and use the product appropriately in the absence of intervention by a healthcare provider.</td>
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Classes. The panel recommendations become mandated in an official OTC Monograph through a three-step public rule-making process.

**Step 1:** Panel reports are published in the Federal Register as “Advance Notice of Proposed Rulemaking” (ANPR). The ANPR provides preliminary assignments of ingredients in terms of safety and efficacy:
- Category I – Generally recognised as safe and effective (GRASE)
- Category II – Not GRASE
- Category III – Insufficient data to determine safety and/or efficacy.

**Step 2:** Following FDA review and public comment, a tentative final monograph (TFM) is issued by the FDA proposing approved ingredients, uses, doses, required warnings and appropriate claims. TFM are in place for virtually all categories of OTC drugs.

**Step 3:** Publication of a final monograph (FM) setting forth allowable claims, labelling and active ingredients for OTC drugs in each class. The FM will appear in the Federal Register and be reflected within 21 CFR Part 330 which lays out the general conditions by which OTCs are generally recognised as safe, effective and not misbranded.

Drugs marketed in accordance with a final monograph can go directly to market and do not require FDA approval of a marketing application. The OTC monograph system is commercially advantageous as it enables rapid entry of conforming products to the marketplace.

Industry or another interested party can propose changes to the monograph (eg, new ingredient or new indication) through two mechanisms – the “Citizen Petition” (CP) or the “Time and Extent Application” (TEA) process. Both are public processes without statutory timeframes for complete response, so these proceedings can be quite lengthy. OTC monographs can also be amended by the FDA as new information becomes available (eg, emerging safety issues that require new labelling).

OTC drugs which fall outside the scope of a monograph by virtue of ingredient, dose, indications, etc, are considered to be “new drugs” subject to the NDA process.

**NDA process for new drug products**

For those drugs requiring an NDA – either as a direct-to-OTC product or a drug switched from prescription (Rx) to OTC status – the content and format of the application is similar to the requirements for prescription drugs. Companies must submit an NDA to the FDA supporting:
- **Safety and efficacy:**
  - Typically nonclinical (preclinical) safety is well supported for OTC ingredients; however, modified active ingredients or novel excipients may require additional support
  - Clinical data support use of the product in line with labelled use. Clinical trials demonstrating safe use in an OTC environment (“Actual Use Trials”) may be required.
**Benefits outweigh the risks**: Clinical data support use of the product with appropriate label warnings and precautions that can be understood by the consumer, with low potential for severe side effects, misuse or abuse

**Quality of the product**: Data support ingredients, formulation, specifications and test methods, manufacturing process, stability, shelf-life, packaging and production site and certification that the product is made in line with good manufacturing practices (GMPs). The format of the application is consistent eCTD requirements; organised into five modules and submitted electronically in conformance with standards for electronic submissions.

**Labelling and the role of consumer studies**
The labelling is a critical element of the OTC application and the FDA requires specific types of studies to demonstrate that the consumer can use the product safely and effectively in an OTC environment without a doctor’s supervision. Three types of consumer research studies are typically conducted to predict consumer behaviour to an OTC drug: label comprehension, self-selection, and actual use studies (see Table 1).13–16

Label development is an iterative process and the data collected from label comprehension and self-selection studies are used to inform the final proposed labelling. Where required, this final proposed labelling is tested under ‘actual use’ conditions to provide direct evidence of safety in an OTC environment.

In cases where new clinical data are required to support product approval, companies may be entitled to three years of marketing exclusivity.

**PDUFA fees – enabling efficient and effective drug review**
The Prescription Drug User Fee Act of 1992 (PDUFA) has become a cornerstone of modern FDA drug review. PDUFA was enacted to enable the FDA to collect fees from industry to facilitate the drug review process by providing funding for increased FDA staffing to enable shorter review times.17 FDA performance goals provide greater transparency, quality and predictability to the drug review process.

There are three types of user fees applicable to application drug products: fees associated with the review of the application itself, fees associated with the named application product and fees for the establishments where it is manufactured. The specific user fees are established on a yearly basis based on inflation rates and anticipated FDA workload. Figure 1 shows that, over time, the FDA’s user fees – particularly those tied to application review – have increased substantially.18 For example, at its inception in 1992, the user fee for review of a new application requiring clinical data was US$100,000. In fiscal year 2013, this fee is US$1,958,800. Thus OTC drug manufacturers must build filing costs into their innovation pipelines, as new product introductions or line extensions (new claims or indications) may require significant fees.

**Expanding access to OTCs through Rx to OTC switch**
The process of Rx to OTC switch has contributed significantly to the health and wellbeing of consumers, with more than 700 OTC products on the market today using ingredients or dosages available only by prescription less than 30 years ago.19 Table 2 shows a variety of OTC indications made available through this process.20 Historically, OTCs have been geared toward symptomatic relief and short-term use; however, a number of the switches noted in Table 2 have been “paradigm-busters”:

- Approved for long-term use and non-episodic treatment
- Approved with Phase IV commitments such as limited distribution and age verification to manage risk in an OTC environment
- Provided supplemental information beyond the traditional “Drug Facts” label (eg, behavioural programmes, educational materials) to promote safe and effective use in an OTC environment.

When considering the medical needs of today’s ageing population and potential options available to consumers to manage their own health, future switch candidates might include antihypertensive
agents, cholesterol-lowering drugs, oral antidiabetic agents, and treatments for osteoporosis.

It is imperative that we challenge our industry to explore ways to enable these innovative future switches by broadening the assistance and information a consumer receives to use products safely and effectively without a doctor’s supervision. Companies can work with the FDA to define ways to address unique challenges that may be associated with these potential switches. Consideration of appropriate “special conditions of safe use” on a case-by-case basis can enable progress within the current US two-tier regulatory paradigm.

Also, as we consider the possibility of expanding OTC treatment options, it becomes increasingly important to establish rigorous tools for assessing the benefit–risk profile of these products. A systematic, quantitative assessment tool can help identify and evaluate incremental risks and benefits associated with OTC use and provide transparency and consistency to the regulatory decision-making process.21 A comparison of the OTC monograph and NDA process appear in Table 3.

### Specific OTC requirements

Although many of the same regulations apply to OTC and Rx drugs, different rules apply to OTC packaging, labelling, and advertising and promotion.

#### Table 2: Examples of products switched from Rx to OTC status in the US.

<table>
<thead>
<tr>
<th>Approved</th>
<th>Brand name</th>
<th>Active ingredient</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 2002</td>
<td>Commit</td>
<td>nicotine polacrilex</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>November 2002</td>
<td>Claritin</td>
<td>loratidine</td>
<td>Allergy (antihistamine)</td>
</tr>
<tr>
<td>June 2003</td>
<td>Prilosec OTC</td>
<td>omeprazole magnesium</td>
<td>Acid reducer to treat frequent heartburn</td>
</tr>
<tr>
<td>August 2006</td>
<td>Plan B</td>
<td>levonorgestrel</td>
<td>Contraceptive</td>
</tr>
<tr>
<td>October 2006</td>
<td>MiraLAX</td>
<td>polyethylene glycol 3350</td>
<td>Laxative</td>
</tr>
<tr>
<td>February 2007</td>
<td>Alli</td>
<td>orlistat</td>
<td>Weight-loss aid</td>
</tr>
<tr>
<td>January 2013</td>
<td>Oxytrol</td>
<td>oxybutynin</td>
<td>Overactive bladder in women</td>
</tr>
</tbody>
</table>

#### Table 3: Comparison of OTC monograph and NDA processes.

<table>
<thead>
<tr>
<th>OTC monograph</th>
<th>New drug application (NDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-market approval not required</td>
<td>Pre-market approval of NDA</td>
</tr>
<tr>
<td>May require user fee if new clinical studies required</td>
<td>Confidential filing</td>
</tr>
<tr>
<td>Potential marketing exclusivity if new clinical studies required</td>
<td></td>
</tr>
<tr>
<td>Drug product-specific</td>
<td></td>
</tr>
<tr>
<td>May require to support: Safety and efficacy</td>
<td></td>
</tr>
<tr>
<td>May require to support: Safety and efficacy</td>
<td></td>
</tr>
<tr>
<td>Label comprehension</td>
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<td>Label must conform to “Drug Facts” label requirements.</td>
<td></td>
</tr>
<tr>
<td>Label must conform to “Drug Facts” label requirements.</td>
<td></td>
</tr>
<tr>
<td>Content of labelling to be developed and approved by the FDA based on the results of: Clinical studies</td>
<td></td>
</tr>
<tr>
<td>Content of labelling to be developed and approved by the FDA based on the results of: Label comprehension studies</td>
<td></td>
</tr>
<tr>
<td>Content of labelling to be developed and approved by the FDA based on the results of: Self-selection studies</td>
<td></td>
</tr>
<tr>
<td>Content of labelling to be developed and approved by the FDA based on the results of: Actual use studies.</td>
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</tbody>
</table>
Packaging requirements: Regulation is often reactive and driven by tragedy. A series of accidents involving the death or injury of children due to the ingestion of hazardous household substances led to the enactment of the Poison Prevention Packaging Act (PPPA) of 1970, under the authority of the Consumer Product Safety Commission (CPSC). The PPPA requires child-resistant packaging for certain OTCs (eg, aspirin, diphenhydramine, acetaminophen) and oral non-prescription drugs that were previously available by prescription ("switched drugs"). The regulations require that packaging be significantly difficult for a child under five years of age to open or obtain a toxic amount of the substance, while also not impeding a "normal adult" from proper use.

Similarly, tampering incidents involving Tylenol capsules laced with cyanide in the early 1980s led to the implementation of strict tamper-resistant packaging requirements in 1982. All OTCs (except dermatological, dentifrice, insulin or lozenge products) must be packaged in tamper-resistant packaging and be labelled to prominently disclose the tamper-evident features. Additionally, two-piece hard gelatin capsules must be sealed using an acceptable tamper-evident technology.

Labelling requirements: For consumers to safely and effectively use OTC medicines without the assistance of a learned intermediary, the labelling of the product needs to be clear, legible and readily understood by a lay person. In 1999, the FDA established standardised format and content requirements for the labelling of OTC drug products – NDA and monograph drugs alike. Known as "Drug Facts", these requirements were analogous to the "Nutrition Facts" labelling standards implemented in 1992.21 The Drug Facts label required the following elements:

- Use of standardised headings to organise important information such as ingredients, product uses, specific warnings and dosing instructions
- Prescribed order of information to help consumers locate information across OTC products and brands
- Use of plain-speaking terms to promote consumer understanding, particularly in those with low literacy
- Minimum font size and specific layout details (bullets, line spacing, and clearly marked sections) to improve readability.

OTC regulations may also require certain ingredient-specific or class-specific warnings; for example, the warning statement for drug products containing or manufactured with chlorofluorocarbons (CFCs) or other ozone-depleting substances. These warnings may appear in the "Other Information" section of the label.21

Advertising and promotion: Regulation of the advertising and promotion of OTCs in the US falls under the auspices of the Federal Trade Commission (FTC). This is different from the advertising and promotion of prescription products, which are directly regulated by the FDA. The FDA and FTC have distinct roles in consumer protection; nonetheless, both often engage in cooperative efforts when it is in the best interest of public health.26

The standards that FTC uses when assessing OTC advertising are:25

- Advertising must be truthful and non-deceptive; not likely to mislead consumers acting reasonably under the circumstances
- Advertisers must have evidence to back up their claims
- Advertisements cannot be unfair.

The FTC assesses advertising from the point of view of a "reasonable consumer" and evaluates the totality of the advertisement, ie, words, phrases and pictures. In this context, the FTC examines both "express" and "implied" claims to determine the message conveyed to consumers and whether it is appropriate and substantiated. Although "fair balance" is not strictly required as with prescription products, the FTC also looks at what the advertisement does not say, to ensure it is not misleading or deceptive by omission of information.

The level of substantiation required is directly linked to the nature of claims and must form a "reasonable basis" for the claims with objective evidence. For example, health or related claims would require credible scientific evidence gathered using methods that experts in the field accept as accurate.

Conclusion

OTCs deliver tremendous value to individual consumers and the US healthcare system as a whole. The general sales status of OTCs in the US marketplace provides the American consumer with convenient access to important self-care options. Non-prescription medicines are introduced to the US marketplace via two distinct regulatory pathways: the OTC monograph system for well-established ingredients and the NDA process for drugs that are "new" in terms of active ingredient, indications, doses or formulation. The OTC monograph process has the advantage of speed to market for qualifying products, since FDA pre-approval is not required. The NDA route is more time-consuming and data-intensive –potentially requiring studies to assess labelling, consumer behaviour and actual use in an OTC setting – however, exclusivity may be achieved if clinical investigation is required to achieve product approval. By understanding the regulatory framework and requirements for each class of products, regulatory professionals can better lead innovation in this exciting area of healthcare.

References

14 E P Brass. ‘Changing the status of drugs from prescription to over-the-counter availability, New England Journal of Medicine, 2001;345:810-6.