Crafting Changes for the Future: Increasing the Availability of Nonprescription Drugs

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The availability and use of nonprescription drugs is likely to increase in the near future due to rising health-care costs, patient interest in self-selection and self-treatment, and continued advances in technology. Recently, the Food and Drug Administration (FDA) has shown support for this proposition with its Nonprescription Safe Use Regulatory Expansion (NSURE) Initiative, which seeks to expand patient access to medications by making them available without a prescription.

Since 1951, the dispensing of drug products in the United States has been based on a two-class system: prescription and nonprescription.[1] Under section 503(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug must be dispensed by prescription if, "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug."[2] In contrast, a nonprescription or

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over-the-counter (OTC) drug is one that the FDA has determined is safe and effective for consumer OTC use and is generally recognized as having a benefit profile that outweighs its risks, a low potential for misuse and abuse, characteristics that support direct consumer use for self-diagnosed conditions, and an ability to be adequately labeled.

More than 300,000 OTC drug products are currently marketed in the United States.[3] U.S. consumers have ready access to these products from a variety of retail settings, including pharmacies, supermarkets and convenience stores, at all hours of the day and night. Notwithstanding the strong U.S. market demand and research addressing the value of OTC drugs in reducing healthcare costs and expanding self-care, the nonprescription drug industry is constrained by an antiquated system of complex regulation and challenges that hamper bringing OTC drugs to market and, in particular, impede prescription-to-OTC switch approvals.

During the past 10 years, very few prescription drugs have switched to OTC status. However, promising signals of an increase in FDA support for prescription drug switches emerged with the rare approvals of two first-in-class prescription-to-OTC switches: *Oxytrol for Women*[4] and *Nasacort 24HR*. These switch approvals may be a welcomed trend evidencing an agency willing to exercise its latitude to apply conditions of safe use to make a wider range of nonprescription drugs more available to consumers.

Further evidence of a changing regulatory environment for nonprescription drugs is FDA's NSURE Initiative. Under this new paradigm, the agency would approve the nonprescription use of medicines for certain diseases or conditions that otherwise would require a prescription if certain conditions of safe use are met. Since introducing the paradigm in 2012, FDA has clarified that NSURE is not an effort to establish a third class of drugs, often referred to as "behind the counter" at the pharmacy. Rather, NSURE is aimed at creating flexibilities in how FDA considers a drug's prescription status through conditions of safe use. Under NSURE, these conditions of safe use could include requiring pharmacist intervention to ensure appropriate nonprescription use, involve the use of innovative technologies such as diagnostics for use in the pharmacy or other settings, or moving to a dual-availability system where a medication is available by prescription and OTC.

Innovation in switches and the NSURE Initiative are examples of regulatory game changers that could lead to significant outcomes for the OTC industry and change the OTC landscape as a whole. It seems that the typical barriers to self-diagnosis of a condition, self-selection of treatment and self-management of therapy with nonprescription drugs are slowly coming down in favor of a modern-day revolution with innovative technology and enhanced self-care solutions around an expanded range of nonprescription treatment options for consumers. A look at future considerations for nonprescription drugs with conditions of safe use, as a novel solution for undertreated diseases or conditions, follows.

Prescription-to-OTC Switch

The central approval issue in any prescription-to-OTC switch applications is whether the drug is safe and effective for consumer OTC use. This issue requires consideration of whether the consumer can successfully self-recognize and self-treat the condition and, importantly, whether the drug label indications, directions and warnings can be understood by the average consumer without the assistance of a learned intermediary, i.e., physician, pharmacist or other health care provider.

A drug manufacturer can initiate a prescription-to-OTC switch by submitting a supplement to an approved new drug application (NDA). If the manufacturer plans to switch the entirety of the drug's indications from prescription to OTC without a change in the previously approved dosage form or route of administration, the manufacturer submits an efficacy supplement to the approved NDA. An NDA 505 (b)(1) should be submitted if the manufacturer is proposing to convert some but not all of the approved prescription indications to OTC marketing status. And, an original NDA (505)(b)(1) or 505(b)(2) is submitted if the sponsor plans to market a new product OTC whose active ingredients, indication or dosage form has not previously been marketed OTC.

Underlying an NDA for a prescription-to-OTC switch are the safety and efficacy data for the original prescription medication, information on adverse events reported in association with prescription use of the drug and, occasionally, information pertaining to OTC use in other countries. Special consumer-behavior research studies such as label-comprehension, self-selection and actual-use studies are often conducted to gain additional insights about consumer understanding and likely behavior in selecting and using the drug in an OTC setting. While these studies are not always required for a switch, consumer-behavior research may provide meaningful data for predicting if a drug can be used safely and effectively according to labeling in the OTC setting.

Drugs that are the first-in-class for a new indication, possess a novel mechanism of action or present unique concerns are designated for review by the Nonprescription Drugs Advisory Committee, which then makes recommendations to FDA. Such was the case in 2012, with the first-in-class FDA approval of *Oxytrol for Women*, a transdermal system indicated for women with overactive bladder. FDA approved another first-in-class prescription-to-OTC switch in July 2013 for the corticosteroid nasal spray *Nasacort*. The OTC-approved version, *Nasacort Allergy 24HR, is* planned for launch in spring 2014. And recently, there have been discussions about the possibility of a switch application for the prescription proton pump inhibitor (PPI) *Nexium*.[5] A change in prescription status for *Nexium* would follow other PPIs previously switched to OTC, including *Prilosec OTC, Zegerid and Prevacid*.

Looking forward, FDA's Nonprescription Drugs Advisory Committee is scheduled to meet on February 26, 2014, to discuss data submitted by Armstrong Pharmaceuticals, Inc. in support of an NDA for the OTC marketing of an epinephrine inhalation aerosol under the proposed trade name *Primatene HFA* for temporary relief of intermittent asthma.[6] This upward trend in switch applications is expected to continue through 2014 and beyond due to factors such as product lifecycle extension strategies, a market-driven health-care environment focused in part on consumer self-care, particularly for common chronic and recurrent diseases and conditions, and, as discussed below, a more welcoming regulatory landscape.

NSURE

Recognizing the impact on public health of under treatment of common diseases and conditions, the FDA is seeking to address one aspect of the issue, access to appropriate medications, through the NSURE Initiative. One of the most dynamic initiatives to come out of FDA in the drug area, NSURE seeks to allow prescription drug products to become available without a prescription through the use of innovative technologies and other conditions of safe use, such as consultation with pharmacists and other health-care professionals.[7] To initiate the conversation, the FDA held a public meeting in March 2012 titled "Using Innovative Technologies and Other Conditions of Safe Use to Expand Which Drug Products Can Be Considered Non-Prescription"[8] and since then has held three workshops in cooperation with the Engelberg Center for Health Care Reform at Brookings, to explore practical considerations in the development of the NSURE Initiative.[9] Although the conceptual framework for NSURE is still in development, the idea is that identifying the specific risks and safety issues for each drug can inform the development of targeted interventions and technologies that can serve as a condition of safe use in a nonprescription setting.

An interesting segment of the NSURE conversation is focused on the innovative application of technologies to facilitate the safe and effective use of a variety of products in a nonprescription setting. While the use of technology in health-care settings to enhance patient care is certainly not new, NSURE is considering several novel concepts, including (1) how applications developed for the Internet, smart phones, or other electronic devices can assist patients in making complex health-care decisions; (2) how portable and wireless diagnostic technologies that collect health information and transmit the data to providers and consumers to inform and optimize treatment can be used to address a range of critical barriers to self-care; (3) how technology can serve as a safety tool to allow for new prescription-to-OTC switch pathways; and (4) how technology driven conditions of safe use can be integrated into the practice and workflow of the pharmacist, physician and nurse.[10]

Conclusion

The use of nonprescription drugs is likely to proliferate based on advancing technologies, market influences and patient interest in self-treatment. Through the NSURE Initiative, FDA is providing an opportunity for drug manufacturers and other interested parties to propose novel methods and delivery systems to allow prescription medications to be available to patients without a prescription. As Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research (CDER), stated, "We are crafting changes for the future and want to incorporate innovations and new technologies into CDER's regulatory practices….The rules for nonprescription status were established in an age when widespread access to information technology did not exist. The world is evolving. It is clear there are now many interactive mechanisms that can help consumers through the process of self-diagnosis and medication selection in a much more comprehensive manner than a few words on a fact box."[11]

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1. *See* Durham-Humphrey Drug Prescriptions Act, 82 p.l. 215; 65 Stat. 648; 82 Cong. Ch. 578.
2. 21 U.S.C. § 353(b)(1)(A).
3. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/Over-the-CounterDrugs/default.htm

4. The NDA was submitted for the partial switch from prescription to OTC of the oxybutynin transdermal system.
5. http://www.drugstorenews.com/article/pfizer-will-shepherd-otc-nexium-through-switch-process
6. 79 Fed. Reg. 138, available at https://federalregister.gov/a/2014-00091
7. *See* http://www.fda.gov/downloads/ForHealthProfessionals/UCM330650.pdf
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