Legal Backgrounder

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FORCING DRUGS TO "OTC" STATUS TREADS ON LAW AND PATIENT SAFETY

by

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Of the many major decisions facing the next Food & Drug Administration (FDA) Commissioner, one of the most divisive and far-reaching will be whether to require that three allergy drugs currently available solely by prescription be shifted to an over-the-counter (OTC) status. The issue arose in the context of a July 22, 1998 Citizens Petition filed by Wellpoint Health Networks, a health insurer, requesting that three drugs, Allegra, Zyrtec, and Claritin, be reclassified from prescription to OTC status. On May 11, 2001, an FDA advisory panel that had been reviewing the petition recommended that FDA act positively on the insurer's petition.

As a matter of basic public health policy, consumers should have access to safe and effective medicines that can be appropriately used and labeled for self-care. At the same time, it is absolutely critical that any switch of a product from prescription to OTC status be supported by adequate data demonstrating that the products can be used safely and effectively by consumers without a physician's supervision. The manufacturer of a drug is in the best position to provide those data, and the manufacturer's active involvement in a switch is crucial. Recent proposals to impose a switch without the manufacturer's support reflect poor public health policy and raise serious legal issues. They depart from the fifty years of precedent governing OTC switches since enactment of the 1951 Durham-Humphrey Amendments to the Federal Food, Drug, and Cosmetic Act.

Historical Development of FDA's Approach to Rx-OTC Switches. Historically, FDA has used three mechanisms for switching drugs. First, following enactment of the Durhman-Humphrey Amendments in 1951, FDA switched a number of drugs to OTC status using a rulemaking approach referred to as the "switch regulation," which was authorized under section 503(b)(3) of the Federal Food, Drug, and Cosmetic Act. This rulemaking process made sense in the 1950s and 1960s as a way for the agency to gain control over a variety of drugs that were marketed by different companies under different conditions, some "Rx" (by prescription only) and some OTC, some with new drug applications (NDAs), and others without. The very same drug, with identical dosage and indications, might have been sold Rx by one company and OTC by another. Of course, that situation does not exist today, and FDA has not used this process to switch a drug for some 30 years (the last time being in 1971).

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Second, beginning in the early 1970s, FDA relied on the "OTC Drug Review" as the principal vehicle for switching drugs to OTC status. This, too, made a great deal of sense for its time, since it was part of the agency's comprehensive review of the safety, effectiveness, and labeling of OTC drugs following the landmark 1962 amendments to the Federal Food, Drug, and Cosmetic Act. FDA switched approximately 32 drugs through the OTC Drug Review in the 1970s and 1980s. However, the OTC Drug Review has largely run its course, and it is not the focus of switch activity today.

FDA entered the third, and current, switch era in the mid-1980s when it began switching drugs through the NDA process. With very few exceptions, every switch today is accomplished through approval of an NDA or NDA supplement. This is suited to today's environment. FDA comprehensively regulates new drugs, both Rx and OTC, through the NDA process. This process gives the agency the maximum degree of authority over all aspects of a drug, and provides the means by which manufacturers may invest in the development of proprietary data for submission to FDA in support of approval.

Collaboration Between Manufacturers and FDA is Key to a Switch. In evaluating a switch candidate, FDA requires evidence to show that the drug is intended to treat a condition that can be self-diagnosed and self-treated, that the drug will be safe and effective as used in an OTC setting, and that there is a safety margin based on prior prescription marketing experience. It is also critical to show that OTC labeling will be understood by consumers and provide adequate warnings and safety information. This is so consumers do not self-diagnose and self-medicate if they experience symptoms that should be evaluated by a physician. These standards are vital to the continued integrity of the non-prescription market.

For the past decade, the switch of a prescription product to OTC status has in nearly all cases been initiated by the holder of an approved NDA, or with its approval, through the submission of a new application or a supplement with extensive data to support safe and effective OTC use and appropriate OTC labeling for the specific drug. This makes public health sense. The company that developed the drug in the first place and obtained the approval for the prescription drug knows the most about the drug.

Evaluation of a switch is necessarily conducted product-by-product, based on the specific data and merits of each drug. Extensive prescription use is essential to the full characterization of a drug's clinical profile, and is thus a prerequisite for OTC consideration. New information is often learned through commercial use that cannot be identified based on the limited number of patients involved in the clinical trials conducted for initial product approval. Sponsors seeking OTC switches are routinely required to provide a large body of safety experience reflecting both clinical trial and actual use. They must also provide updated scientific information developed since the time of initial NDA approval, which would offer an enhanced understanding of the underlying disease, current medical practice, and the pharmacology of the drug.

A manufacturer's knowledge of all facets of a drug is indispensable to assessment of whether a drug meets the standards for a switch. The manufacturer has undertaken and maintains the full clinical development of the prescription drug, and is in the best position to understand the existing clinical and post-marketing surveillance data, evaluate a drug's current safety profile, and determine if an appropriate safety margin would support use without a physician's care.

The manufacturer is also in the best position to perform the new studies that are typically essential to ensuring that a drug will be safe as used in an OTC setting, and that labeling can effectively communicate information to consumers about warnings and precautions. Significant issues can arise under OTC use that do not exist, or are of considerably less concern, when a drug is used in accordance with a physician's prescription and supervision. For example, use of a drug may cause interactions with

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other drugs that a physician could identify and manage, if closely monitoring a patient. These risks need to be carefully scrutinized, and data must be collected to ensure that consumers will properly comprehend product labeling and will not self-diagnose and self-medicate if they experience symptoms that should trigger a physician consultation. Actual use and labeling comprehension studies can address these questions. A switch should generally not be permitted unless considerable data are developed in addition to the data already present in the NDA for prescription use. The drug manufacturer is best situated to design, fund, perform, analyze, and submit the needed studies.

Comparisons to Existing OTC Drugs Cannot Substitute for Genuine Study of the Drug's Safety and Effectiveness and Do Not Meet the Legal Standards for a Switch. Current law clearly provides that drugs must be evaluated on their individual merits, and does not permit comparative assessments of safety or effectiveness. This makes good sense, as attempts to rely on a comparative evaluation of different compounds are prone to error. Either data exist to support OTC use of a drug or they do not, and considerations of relative safety or effectiveness are not germane.

No more permissive standard may be applied to allow third parties without adequate data to initiate a switch based on purported product comparisons. To do so could put the public at risk. It would also constitute arbitrary and capricious action for FDA to apply one standard to a manufacturer-initiated switch and another to a third-party switch. *See*, *e.g.*, *Independent Petroleum Ass'n v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996); *Airmark Corp. v. FAA*, 758 F.2d 685, 691-92 (D.C. Cir. 1985); *United States v. Diapulse Corp.*, 748 F.2d 56 (2d Cir. 1984).

Switching a Drug Over the Manufacturer's Objections Would Violate Federal Laws and the Constitution. A forced OTC switch would fundamentally change the terms of the manufacturer's approved license for the prescription drug, and upset the settled expectations that the manufacturer had when it invested in development of the drug. Any compelled switch would also necessarily rely without the manufacturer's consent on proprietary data developed by the manufacturer. These actions would trigger core due process and property rights of the manufacturer, and would, at a minimum, require that the manufacturer be afforded a hearing and potentially just compensation.

Section 505(e) of the Federal Food, Drug, and Cosmetic Act specifically requires that FDA provide notice and a hearing in order to seek basic changes to an approved application. Section 505(e) provides important due process protections for the holders of approved NDAs, and is a central part of the current regulatory scheme.

These statutory protections are directly reinforced by the due process clause of the Constitution and longstanding principles of administrative law, which hold that an administrative agency must provide an individualized hearing before taking specific action to modify or withdraw an approved license. The due process rights of license-holders are recognized in a long line of judicial decisions tracing back to the seminal Supreme Court case of *Metallic Inv. Co. v. State Bd. of Education*, 239 U.S. 441 (1915), and its progeny. These due process protections are a fundamental safeguard against arbitrary and unreasonable agency action, and must be preserved.

In addition to raising due process concerns, almost any switch would also have to rely in part on data contained in the original NDA for the prescription drug to support OTC use. The company has proprietary rights in its NDA data, which could not be used without its consent, regardless of the regulatory procedures followed. Companies make substantial investments to generate the data that are contained in an NDA, and such non-public commercial information is protected from disclosure by federal statutes such as the Freedom of Information Act and the Trade Secrets Act. The unauthorized appropriation of proprietary data would also implicate the Takings Clause of the Constitution. This is

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particularly true because a company would be deprived of the benefits of a prior investment of millions of dollars in the research and development of a new drug with no prior notice that it might be compelled to convert the product from prescription to non-prescription use.

Mandated Switches Would Constitute Unprecedented Governmental Interference in the Drug Development and Marketing Decisions of Private Firms. Since the passage of the Durham-Humphrey Amendments in 1951, FDA has never switched a prescription product to over-the-counter status over the active objection of a manufacturer. In one prominent instance in which FDA effectuated a switch without the manufacture's support (involving the bronchodilator metaproterenol), the agency had to rescind its decision. This episode provides a cautionary tale for subsequent switches.

Further departures from the agency's settled precedent could seriously disrupt the drug development process. As indicated above, firms carefully establish research plans and development strategies for a product's life cycle. These plans would be jeopardized by unanticipated switches triggered by a third party. To allow such a practice would create uncertainty and unnecessarily complicate the already highly risky business of drug development. As it is, the Pharmaceutical Research and Manufacturers of America reports that only one in 5,000-10,000 compounds synthesized in the laboratory ever makes it to market, over 12-15 years at an average cost of $500 million. Adding greater uncertainty to the drug development process could chill new research and investment.

Once the Door is Open for Insurers and Other Third Parties to Initiate Switches, it Will be Difficult to Establish Appropriate Limits. Insurers have significant incentives to compel OTC switches, because a switch effectively shifts drug costs from the health plan to consumers. If current law and practice are changed to permit insurers and other third parties to seek switches, there could be an outpouring of requests. It would then be difficult, if not impossible, for FDA to control the process and decide who should and should not be permitted to seek a switch.

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