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**Review Paper**

# Regulatory Guidelines for Switching of Prescription Drugs to Over-The - Counter Status

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## ABSTRACT

The regulatory guidelines governing the transition of prescription drugs to over the counter (OTC) status across three major jurisdictions — the United States, the European Union, and Japan — with supplemental reference to the UK and Canada. By analyzing the statutory foundations, approval pathways, evidence requirements, and post market safety frameworks unique to each region, the study aims to identify both convergences and divergences in global Rx to OTC regulatory practice. A special focus is placed on recent innovations, including the FDA's "Additional Conditions for Nonprescription Use" (ACNU) final rule, the role of real world evidence, and emerging digital self selection tools. The analysis draws upon a review of 19 drug substances across 10 therapeutic areas to identify common reasons for switch rejections and opportunities for harmonization. The thesis concludes with evidence based policy recommendations designed to balance expanded consumer access with robust patient safety protections in an increasingly self care oriented healthcare environment

## INTRODUCTION

The prescription (Rx)-to-nonprescription (OTC) switch is a highly specialized, evidence-driven regulatory process through which a drug that has historically required a healthcare provider's authorization to dispense is reclassified for sale directly to the public without a prescription. This transition is not a mere administrative reclassification but a rigorous scientific and legal determination that the medication can be used safely and effectively by consumers for self-treatment of specific conditions, without the immediate oversight of a licensed practitioner. The process fundamentally shifts the risk-benefit analysis paradigm: the prescribing physician's role in diagnosis, dosage selection, and monitoring is replaced by the consumer's ability to self-diagnose, self-select, and self-administer the drug based solely on information provided on the

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product label. At its core, an Rx-to-OTC switch democratizes access to effective therapies, potentially reducing healthcare costs, improving medication adherence, and empowering patients to manage minor ailments autonomously[1]. However, this enhanced accessibility must never compromise public health, and the switch application must convincingly demonstrate that the benefits of wider availability outweigh any incremental risks associated with unsupervised use.

Approval of an Rx-to-OTC switch is contingent upon meeting stringent, multi-faceted regulatory criteria designed to ensure that the product's safety and efficacy profiles remain robust even outside the controlled clinical environment. In the United States, the legal foundation for this determination is rooted in the Federal Food, Drug, and Cosmetic Act (FD&C Act) as amended by the Durham-Humphrey Amendment of 1951, which established the modern distinction between prescription and OTC medications[2]. The FDA will approve an application only when it finds that prescription status 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 that "the drug is safe and effective for use in self-medication as directed in proposed labeling[3]. This statutory language encapsulates four interconnected approval pillars: intrinsic safety, low misuse potential, consumer self-selection capability, and labeling comprehension[4].

The first and most fundamental criterion is a favorable intrinsic safety profile, which encompasses both the drug's inherent toxicological properties and its track record of safe use in the prescription setting over an extended period[5]. A viable switch candidate must have a wide therapeutic index—meaning the margin between the effective dose and the toxic dose is sufficiently large to accommodate potential dosing errors by untrained individuals. The drug must be free from significant acute toxicity risks and must not require routine laboratory monitoring for safe use, such as blood counts, liver function tests, or drug level measurements, as these are impossible to enforce in the OTC setting[6]. Moreover, the product's adverse event profile must be well-characterized, manageable, and primarily consisting of mild, transient, and self-recognizable effects. Conditions that require careful dose titration, present high risks of serious organ toxicity, or interact perilously with common OTC drugs or dietary supplements are generally poor candidates. Chronic use or long-term safety considerations also come under scrutiny; a drug intended for frequent intermittent use (e.g., analgesics, antacids) must demonstrate no cumulative toxicity. As one analysis notes, "the drug must have a well-established safety profile, evidenced by its history of safe use in the prescription setting and clinical studies[7]. The safety dossier submitted to regulators must include data from randomized controlled trials, long-term safety extensions, and comprehensive post-marketing surveillance reports that substantiate this profile[8].

The second core criterion is the demonstration of low potential for misuse, abuse, and dependency. This is a distinct but related concept from intrinsic safety. A drug suitable for OTC availability cannot be a controlled substance or have significant reinforcing properties that would encourage non-medical use, dose escalation, or psychological or physical dependence. The regulatory agencies closely evaluate the drug's mechanism of action, receptor pharmacology, and real-world patterns of use to assess abuse liability[9]. For instance, while many analgesics containing opioids are effective for pain relief, their high abuse potential makes them inappropriate for OTC sale in nearly all circumstances—naloxone, as an emergency

reversal agent for opioid overdose, presents a unique case where the public health benefit of widespread layperson access is judged to outweigh the risks, but even then, it required specific regulatory accommodations[10]. The proposed OTC labeling must be designed to minimize opportunities for misuse, and the product's packaging may incorporate unit-dose blister packs or quantity limits to discourage excessive consumption. Additionally, the drug should have minimal interaction with alcohol or other common substances of abuse, as these interactions could be exploited or lead to unanticipated toxicity in unsupervised settings. As regulatory criteria evolve, concerns regarding misuse potential have become a leading cause of switch application rejections, with studies showing that "safety and misuse, significantly impact Rx-to-OTC switch rejections, highlighting the need for improved frameworks[11][12].

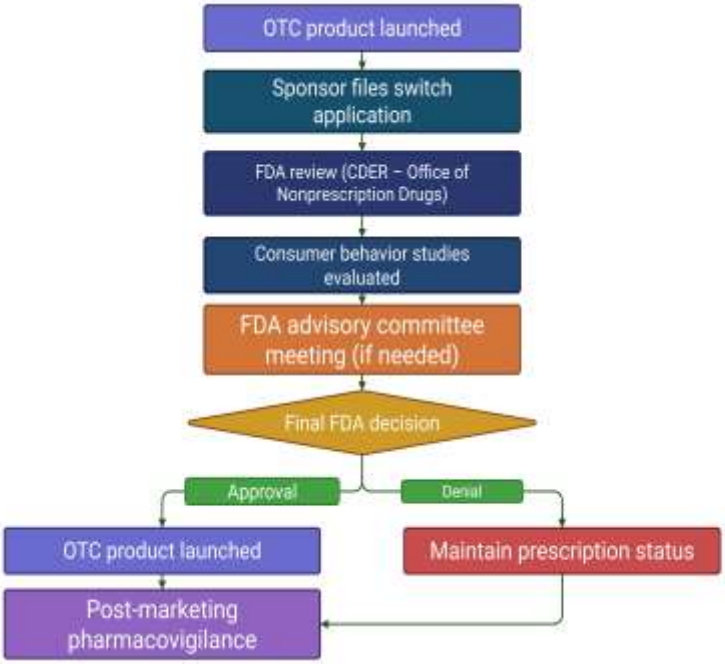


**Fig: 1: Flowchart of the Rx-to-OTC Switch Approval Process (FDA)**

The third criterion centers on the consumer's ability to self-diagnose the condition for which the OTC product is indicated[13][14]. The intended use must involve a condition whose symptoms are readily recognizable by a layperson and for which there is a low risk of serious underlying pathology being masked by symptomatic treatment. Common examples include heartburn, seasonal allergies, mild to moderate pain, constipation, or vaginal yeast infections. A switch will not be approved for conditions that require clinical judgment, diagnostic tests, or imaging to differentiate from more serious diseases[15]. For instance, a switch for a proton pump inhibitor (PPI) was approved only for the indication of "frequent heartburn" (≥2 days per week) rather than for the broader prescription indication of gastroesophageal reflux disease (GERD) or erosive esophagitis, as those require endoscopic diagnosis and monitoring. Similarly, an antihypertensive agent would never be switched to OTC because hypertension is typically asymptomatic and can only be diagnosed via blood pressure measurement; allowing unsupervised treatment would risk dangerous delays in diagnosing and managing underlying cardiovascular pathology. The labeling must include clear "Do Not Use" warnings and

exclusion criteria to guide consumers to seek medical advice when symptoms are atypical, severe, or persistent. Some regulatory frameworks have formalized lists of criteria for assessing switch eligibility, including "the use of the product is amenable to self-treatment" among other factors[16][17].

The fourth and arguably most evidence-intensive criterion is the demonstration of adequate self-selection and labeling comprehension. Regulatory agencies do not assume that consumers will automatically understand OTC labeling; rather, this must be proven through formal consumer behavior studies—a hallmark of modern switch applications[18][19]. Label comprehension studies are designed to evaluate whether the target audience (including individuals with lower literacy levels) can accurately interpret the Drug Facts label, including directions for use, contraindications, warnings, precautions, and signs that indicate medical attention is needed. Participants are presented with the proposed labeling and then tested on their understanding of key communication objectives, such as when to take the drug, how much to take, how often, when to stop, and which conditions preclude use. The study must demonstrate that a statistically significant majority of consumers achieve a prespecified level of correct comprehension, particularly for critical safety elements[20][21]. These studies are not merely academic exercises; they are predictive tools for assessing real-world safe use. One systematic analysis of advisory committee deliberations found that "18% of questions centered on comprehension of the proposed DFL; 42% of these label-comprehension questions were specific to the low-literacy population," underscoring the need to accommodate diverse health literacy levels. Self-selection studies take this a step further by simulating the actual point-of-purchase decision: consumers are presented with the label and package, then asked to determine whether the product is appropriate for a series of hypothetical scenarios. This assesses whether consumers can correctly identify situations where they should use the product versus those where they should consult a healthcare provider or avoid the product entirely[22][23]. Actual use studies involve providing the OTC product to consumers for real-world use over a specified period, with follow-up to document how they actually used it, any deviations from labeling, and the occurrence of adverse events. Together, these three types of consumer behavior studies provide regulators with high-confidence evidence that the proposed OTC product can be used safely and effectively by the intended population without professional oversight[24].

The classification of Rx-to-OTC switches is not monolithic; different pathways reflect the scope and nature of the transition. The foundational distinction, as codified by the FDA and recognized by other major regulatory bodies, is between a Full Switch and a Partial Switch.

**Types of Rx-to-OTC Switches**

A Full Switch represents a complete and permanent reclassification of the drug product from prescription-only to over-the-counter status for all its approved indications, dosage forms, strengths, and conditions of use. Under this scenario, the drug is no longer available by prescription anywhere, and the entire market for that active ingredient shifts to OTC availability for all intended uses[25]. To initiate a full switch, the sponsor typically submits an efficacy supplement to an existing New Drug Application (NDA) under 21 CFR 314.70(b) or may submit a 505(b)(2) application, depending on the specifics of the switch. After approval, the drug is only available as a nonprescription drug, and importantly, "all products marketed under the NDA and all ANDAs must be marketed as OTC". This means that

generic manufacturers referencing the original NDA are required to convert their products to OTC status as well, aligning labeling and patent considerations with the new regulatory status. In a full switch, the prescription and OTC product share the same approved uses, and no parallel prescription market for the same drug remains. Examples include diclofenac sodium topical gel for arthritis pain, ivermectin for head lice, and olopatadine ophthalmic solution for allergic conjunctivitis. The advantages of a full switch from a regulatory and commercial perspective include simplicity in labeling and consumer communication, as well as the elimination of potential confusion between coexisting prescription and OTC versions[26]. However, it also means that any condition of use that was previously treatable with the prescription product is now exclusively available OTC, which carries higher implicit risk and must be supported by robust consumer behavior data[27].

A Partial Switch is a more nuanced and increasingly common strategy wherein only a subset of the drug's approved indications, dosage forms, strengths, patient populations, or other conditions of use are switched to OTC status, while the same drug product remains available by prescription for other, typically more serious or complex, indications. This bifurcated marketing status creates a dual market: the drug may be purchased OTC for certain self-manageable conditions but still requires a prescription for others, often for the same underlying condition but at different severity levels or durations of treatment[29][30]. For example, proton pump inhibitors (PPIs) such as omeprazole and esomeprazole are available OTC for the treatment of frequent heartburn (≥2 days per week) but remain prescription-only for healing erosive esophagitis, maintenance of healing, and other more serious gastrointestinal conditions. Similarly, levocetirizine oral solution is available OTC for seasonal allergic rhinitis but remains prescription-only for chronic urticaria or other systemic allergic conditions. To initiate a partial switch, the sponsor submits a new NDA, typically a 505(b)(2) application, rather than a supplement to the existing prescription NDA. This allows the OTC product to be approved as a distinct legal entity with its own labeling, indications, and conditions of use, entirely separate from the prescription product. The regulatory pathway for a partial switch requires careful differentiation: the OTC labeling must clearly delimit the conditions for which the product is approved for nonprescription use, and adequate safeguards must prevent consumers from inadvertently accessing or misusing the product for the more serious prescription-only indications. The risk of misuse for the prescription-only indications remains higher in a partial switch scenario compared to a full switch, as the drug is available in two channels and consumers may attempt to self-treat conditions that require medical oversight[30].

**Switch Process and Application Requirements**

In addition to the traditional full and partial switch categories, recent regulatory innovations have introduced a third conceptual type: the Switch with Additional Conditions for Nonprescription Use (ACNU)[31] . This novel category, finalized by the FDA, acknowledges that some drugs may be safe and effective for OTC use only if additional conditions beyond conventional labeling are met—conditions that may involve technological aids, interactive digital tools, or other mechanisms that actively guide consumer behavior. For instance, an ACNU could require that the OTC product be packaged with a digital application that conducts a self-screening questionnaire before dispensing or that uses automated reminders to enforce dosing intervals or maximum daily limits. In contrast to a traditional switch, where the drug is completely moved to nonprescription status for

the specified conditions, an ACNU allows the same active ingredient to be sold simultaneously as a prescription drug and as a nonprescription drug, with the OTC version subject to the additional conditions. This pathway is intended to expand consumer options for drugs that have a favorable safety profile but may benefit from active risk mitigation strategies that cannot be fully achieved through static labeling alone. The FDA issued its final rule establishing application, labeling, and postmarketing reporting requirements for ACNU products effective January 27, 2025, representing a significant evolution in switch regulation[32].

Globally, the terminology and regulatory pathways exhibit some variation while maintaining core principles[33]. In Canada, Health Canada distinguishes between an "Rx to NPD switch" (nonprescription drug) and an "Rx to NHP switch" (natural health product), reflecting the country's separate regulatory frameworks for conventional drugs and natural health products. The guiding principles for Canadian switches similarly emphasize safety, consumer self-selection, and labeling comprehension[34]. In the European Union and the United Kingdom, switches are governed by Directive 2001/83/EC and national implementing legislation, with the European Medicines Agency (EMA) providing scientific guidance while individual member states retain responsibility for final classification decisions. The EMA and MHRA evaluate real-world use data, safety profiles in OTC conditions, and the suitability of indications for self-care. Emerging global initiatives, such as the ICH Q-series guidelines, are gradually harmonizing dossier expectations for switches, though regional nuances in self-selection study requirements and patient communication standards persist. The increasing focus on real-world data (RWD) and real-world evidence (RWE) is a notable trend across jurisdictions, with regulators incorporating data from pragmatic studies, pharmacy sales surveillance, and consumer usage tracking to support switch decisions. the Rx-to-OTC switch is a multidimensional regulatory process that balances the public health benefits of improved medication access against the risks of unsupervised use[35]. Approval requires meeting rigorous criteria related to intrinsic safety, misuse potential, self-diagnosis feasibility, and consumer behavior—backed by comprehensive clinical data and specialized labeling studies[36]. The classification into full switches, partial switches, and emerging ACNU pathways provides flexibility while maintaining regulatory fidelity to the core principle that OTC drugs must be safe and effective for self-medication as directed by labeling[37][38]. As healthcare systems worldwide continue to embrace self-care models, supported by digital tools and real-world evidence, the framework for Rx-to-OTC switches will likely continue to evolve, expanding treatment options for common conditions without compromising patient safety. The ultimate success of any switch depends on the integrity of the scientific evidence, the clarity of the consumer-facing communication, and the robustness of post-market surveillance systems that continuously monitor the drug's performance in the OTC environment[39].

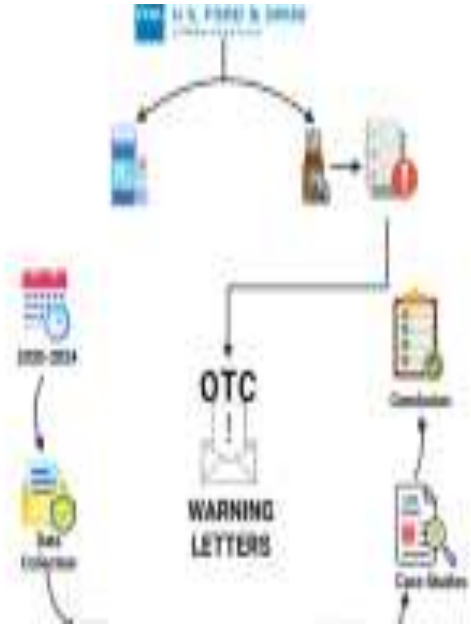


**Fig: 2 Three main Rx-to-OTC switch pathways: Full Switch, Partial Switch, and the newly established ACNU pathway**

The journey from a prescription (Rx) medication to a nonprescription (OTC) product is a rigorous, evidence-intensive process that demands a comprehensive submission dossier designed to convince regulators that a drug can be used safely and effectively by consumers without professional supervision. At the heart of this application are the **essential data** that must demonstrate not only the inherent safety and efficacy of the drug itself but also that these attributes are preserved when the medication is transitioned from the controlled clinical setting to the unpredictable and unsupervised consumer environment. The foundational requirement, as articulated by the U.S. Food and Drug Administration (FDA), is that an application or efficacy supplement for an Rx-to-OTC switch must contain both efficacy and safety data proving that the drug product is safe for use in the nonprescription setting. This core data package draws from multiple sources. First, it leverages data from the original New Drug Application (NDA) for the prescription drug, including the randomized, controlled clinical trials that initially established the drug's safety and efficacy[40]. However, a sponsor is not merely repackaging old data; the application often requires new randomized, controlled clinical trials conducted specifically to address the unique questions posed by the OTC context. These trials may evaluate the drug at a lower dose, for a shorter duration, or for a more limited indication than those approved for prescription use. For instance, while a drug might be prescribed for severe, chronic disease management, its OTC version might be approved only for mild, episodic symptoms that a consumer can readily self-diagnose. The types of data required also encompass new investigations that are not part of the traditional clinical trial paradigm. These include rigorous consumer behavior studies, such as label comprehension, self-selection, and actual use trials, which are vital for demonstrating that the target consumer population can understand the proposed Drug Facts Label (DFL) and use the medication safely. Furthermore, the application must incorporate post-marketing safety surveillance data, often drawn from the drug's long history on the prescription market, to build a robust case for its favorable safety profile in the intended OTC population. A sponsor must also

provide detailed chemistry, manufacturing, and controls (CMC) data, often through a prior approval supplement (PAS) to an approved application, which allows the FDA to review proposed postapproval changes, such as in the manufacturing process, as part of the switch. In some cases, the switch may involve new dosage forms or new routes of administration, which trigger additional requirements, including the submission of pediatric study plans under the Pediatric Research Equity Act (PREA). The core safety and efficacy data package is typically submitted through a formal NDA process, with the specific submission type differing based on the nature of the switch. For a full switch, where the entire drug product moves from prescription to nonprescription status for all its indications, a sponsor submits an efficacy supplement to the existing NDA. Conversely, for a partial switch, where only a subset of the conditions of use is transitioned, a sponsor must file a new, stand-alone NDA. The overarching standard for approval, codified in 21 CFR 310.200(b), is that the drug's prescription status is no longer necessary for public health protection, considering its toxicity or potential for harmful effects, and that the drug is safe and effective for use in self-medication as directed in the proposed labeling. The compilation of these diverse data streams into a cohesive dossier—encompassing an executive summary, clinical data, labeling mock-ups, and consumer study results—constitutes the submission that regulatory authorities will scrutinize. In this evolving landscape, the quality and completeness of this dossier, particularly the evidence supporting consumer comprehension and appropriate use, are paramount, with any inaccuracies or omissions risking significant delays or outright denial of the application.

**Labeling and Consumer Comprehension Role of Pharmacovigilance Post-Switch**

Once an Rx-to-OTC switch is approved and the product enters the consumer marketplace, the regulatory oversight does not end; instead, a new phase of safety monitoring, pharmacovigilance, becomes critically important. The post-marketing surveillance period is essential for confirming that the drug's safety profile, as predicted by pre-approval studies, holds true when the product is used by millions of consumers in an unsupervised, real-world setting. The shift from prescription to OTC amplifies potential safety concerns because the traditional "learned intermediary"—the prescribing physician—is removed from the equation, and adverse event reporting shifts from being primarily healthcare provider-driven to a system that must also capture spontaneous complaints directly from consumers. The legal and regulatory basis for this oversight is grounded in multiple guidelines, including FDA regulations under 21 CFR Part 314, which mandate that sponsors of all OTC products submit adverse event reports. A critical component of the post-switch safety strategy is the Risk Management Plan (RMP) . This comprehensive document outlines proactive strategies for risk minimization and is essential for demonstrating compliance with regulatory expectations. For a switched product, the RMP may include specific plans for further post-marketing surveillance, such as targeted epidemiological studies, and may require revisions to the labeling if new safety signals emerge. Additionally, sponsors are required to compile and submit Periodic Safety Update Reports (PSURs) to regulatory authorities like the FDA and the European Medicines Agency (EMA). These reports summarize all available safety data over a defined period, identify emerging safety trends, and provide a critical assessment of the product's benefit-risk balance. The primary goal of post-marketing surveillance is the detection of safety signals, which are indicators of a potential causal relationship between an adverse

event and the drug that was not previously known or fully characterized. Signal detection involves analyzing data from a wide array of sources, including spontaneous adverse event reports from consumers and healthcare providers, data from post-marketing studies, reports from regulatory databases, and published literature. For OTC products, which have extremely high sales volumes, detecting subtle or rare adverse events that might have been missed in smaller clinical trials is a particular challenge. To address this, methodologies have been developed to evaluate the long-term safety of approved drugs under real-world conditions. In some regulatory contexts, such as in Japan, a specific post-marketing surveillance (PMS) period—often a three-year mandatory surveillance immediately after an Rx-to-OTC switch—is required to confirm efficacy and safety in the OTC setting. During this period, health assessment sheets and other tools may be used to elicit spontaneous complaints from consumers and evaluate adverse reactions that might be induced by the drug. This targeted approach acknowledges that the behavior of consumers in the OTC environment is different from that of patients in a prescription setting. The role of the pharmacist is also vital in post-switch pharmacovigilance. Pharmacists, as the primary healthcare professionals interacting with consumers at the point of sale, are uniquely positioned to identify potential misuse, adverse events, and drug interactions. ASHP, in comments on FDA guidance, has recommended that post-marketing surveillance of switched medications include formal collaboration between the FDA, the product manufacturer, and pharmacists. As the industry moves towards more innovative switches, including those involving technology-assisted self-selection, regulators are increasingly exploring the potential of post-market monitoring to fill data gaps. The use of health assessment sheets and real-world data integration allows for faster signal detection, deeper contextual understanding, and stronger evidence for any necessary regulatory or clinical actions, ensuring that the product's continued availability as an OTC drug remains justified. Ultimately, robust pharmacovigilance is not just a regulatory checkbox; it is a continuous cycle of monitoring, analysis, and action that ensures the long-term safety of the public and maintains trust in the self-care model.

## CONCLUSION AND FUTURE OUTLOOK

For Rx-to-OTC switches is one of significant transformation, driven by the integration of digital health tools, the ascendance of real-world evidence (RWE), and evolving regulatory philosophies. The industry consensus is that the "low-hanging fruit" of simple analgesics and antihistamines have already been switched, and the next wave will involve more complex molecules for chronic conditions like high cholesterol, asthma, and even the use of digital technologies to facilitate the safe self-management of conditions that were previously solely within a physician's purview. A central theme in this future is the strategic use of real-world data (RWD) and real-world evidence (RWE) . The OTC industry has long argued for the potential of RWD—generated by digital consumer health technology such as apps and wearables, electronic health records, and pharmacy claims—to support switch applications. Regulators have traditionally favored data from randomized controlled trials (RCTs), which offer high internal validity but may not fully capture consumer behavior in the real world. However, this is changing. Recent research indicates that regulators, including the FDA, EMA, and MHRA, already use a variety of data sources, many of which could be considered RWD, even if not explicitly labeled as such. To gain broader acceptance, proponents suggest that incorporating elements of traditional trial design,

such as randomization, into RWE studies can enhance their credibility and persuade regulators to accept them as valid support for switch applications. The convergence of RWE and digital technology is most tangibly realized in the context of the ACNU framework. Digital tools are not just an adjunct to labeling; they are the condition for use. These tools can guide consumers through a pre-purchase questionnaire that screens for contraindications, provide personalized dosing reminders, and even link purchase data to medication records, creating a rich dataset for ongoing pharmacovigilance.

## REFERENCES


1. The legal basis for the distinction between prescription and OTC drugs in the U.S. is the Durham-Humphrey Amendment of 1951 to the FD&C Act.
2. The FD&C Act restricts drugs to prescription-only status if they cannot be used safely OTC, establishing the modern classification system.
3. The Durham-Humphrey Amendment divided drugs into two classes: prescription (Rx) and over-the-counter (OTC), with the FDA holding authority over categorization.
4. An Rx-to-OTC switch is defined as the process by which a prescription medication moves to nonprescription status for either the same or a related use, requiring an NDA containing both efficacy and safety data demonstrating safety in the OTC environment.
5. The FDA has not issued a dedicated guidance document on Rx-to-OTC switch principles, but the agency considers OTC drugs should have an acceptable safety window (benefit over risk), low potential for misuse and abuse, applicability to self-diagnosable conditions, and labeling that enables self-diagnosis, self-selection, and self-treatment without professional guidance.
6. The first core criterion is a favorable intrinsic safety profile, including a wide therapeutic index, no need for routine laboratory monitoring, and a well-characterized adverse event profile consisting primarily of mild, transient, and self-recognizable effects.
7. A systematic analysis of FDA advisory committee deliberations found that 18% of questions centered on comprehension of the proposed Drug Facts Label, and 42% of those label-comprehension questions were specific to the low-literacy population, underscoring the need to accommodate diverse health literacy levels.
8. The second criterion is low potential for misuse, abuse, and dependency. A drug suitable for OTC availability cannot be a controlled substance or have significant reinforcing properties, and labeling must be designed to minimize opportunities for misuse.
9. The third criterion centers on the consumer's ability to self-diagnose the condition for which the OTC product is indicated. A switch is not approved for conditions requiring clinical judgment, diagnostic tests, or imaging to differentiate from more serious diseases.
10. The fourth and most evidence-intensive criterion is adequate self-selection and labeling comprehension, which must be proven through formal consumer behavior studies – label comprehension, self-selection, and actual use studies.
11. The FDA categorizes Rx-to-OTC switches into two types: Full Switch and Partial Switch, with the Full Switch representing a complete reclassification of the drug product for all approved indications, dosage forms, and strengths.

12. For a Full Switch, the sponsor typically submits an efficacy supplement to an existing NDA under 21 CFR 314.70(b) or may submit a 505(b)(2) NDA, depending on the specifics of the switch.
13. In a Full Switch, the prescription and OTC product share the same approved uses, and "all products marketed under the NDA and all ANDAs must be marketed as OTC".
14. Examples of Full Switch products include diclofenac sodium topical gel for arthritis pain, ivermectin for head lice, and olopatadine ophthalmic solution for allergic conjunctivitis.
15. A Partial Switch involves switching only a subset of the drug's approved indications, dosage forms, strengths, or patient populations to OTC status, while the same drug remains available by prescription for other, typically more serious, indications.
16. Examples of Partial Switch products include proton pump inhibitors (omeprazole, esomeprazole) for frequent heartburn (prescription remains for healing erosive esophagitis) and levocetirizine oral solution for seasonal allergic rhinitis (prescription remains for chronic urticaria).
17. For a Partial Switch, the sponsor submits a new NDA, typically a 505(b)(2) application, rather than a supplement to the existing prescription NDA.
18. The FDA issued a final rule establishing requirements for a nonprescription drug product with an Additional Condition for Nonprescription Use (ACNU), effective January 27, 2025.
19. An ACNU is a drug product that could be marketed without a prescription if an applicant implements an additional condition – beyond static labeling – to ensure appropriate self-selection or appropriate actual use by consumers without practitioner supervision.
20. The final rule establishes application, labeling, and postmarketing reporting requirements for ACNU products, exempting them from the requirement to be labeled with adequate directions for use provided that certain labeling conditions are met and the ACNU is implemented as approved.
21. The ACNU pathway is intended to increase options for applicants to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products.
22. An ACNU may be an innovative computerized tool, a mobile app, a pharmacy kiosk, or other approaches that support the switch process.
23. An application for an Rx-to-OTC switch must contain both efficacy and safety data demonstrating that the drug product is safe for use in the nonprescription setting.
24. The core safety and efficacy data package draws from the original NDA's randomized controlled trials, but the application often requires new trials conducted specifically for the OTC context – evaluating the drug at a lower dose, for a shorter duration, or for a more limited indication.
25. For a Full Switch, the sponsor submits an efficacy supplement to an existing NDA under 21 CFR 314.70(b) or a 505(b)(2) NDA.
26. For a Partial Switch, the sponsor files a new, stand-alone NDA (typically a 505(b)(2) application) rather than a supplement to the existing prescription NDA.
27. The overarching standard for approval is codified in 21 CFR 310.200(b): prescription status is no longer necessary for public health protection considering the drug's toxicity or other potential for harmful effects, and the

drug is safe and effective for use in self-medication as directed in the proposed labeling.

28. The Drug Facts Label (DFL) is the primary – and in many cases the only – risk mitigation tool for OTC drugs, and the process of switching a prescription medication to OTC first involves designing a DFL that is well understood by potential consumers.
29. Three types of consumer behavior studies are used: Label Comprehension Studies (to assess understanding of key label messages), Self-Selection Studies (to assess making the right choice about the product), and Actual Use Trials (to assess using according to labeled directions).
30. Label Comprehension Studies evaluate whether the target audience, including individuals with lower literacy levels, can accurately interpret the DFL, including directions for use, contraindications, warnings, precautions, and signs that indicate medical attention is needed.
31. A successful Label Comprehension Study must demonstrate that a statistically significant proportion of the target population can correctly interpret the labeling, with outcomes viewed against a pre-specified target threshold reflecting clinical rationale.
32. Self-Selection Studies assess the ability of consumers to determine whether the product is appropriate for them based on their personal health history and the labeling. The individual endpoint is the consumer's determination if use of the drug is appropriate based on label considerations, evaluated as correct or incorrect.
33. Actual Use Trials (AUTs) provide consumers with the actual OTC product and DFL and instruct them to use it as needed for self-management of a specific condition over a defined period, observing how they use the drug in a real-world setting.
34. The FDA has issued guidance documents on Label Comprehension Studies (2010) and Self-Selection Studies (2013) outlining standardized approaches for these studies.
35. Pharmacovigilance requirements for NDA products are governed under 21 CFR Part 314, which includes post-marketing activities such as periodic reports, individual case safety reports (ICSRs), and electronic reporting formats.
36. Under 21 CFR 314.80(i), applicants must keep for 10 years records of all adverse drug experience reports known to the applicant and must notify FDA of any unexpected adverse reactions within 15 working days of receipt of the information.
37. The FDA Adverse Event Reporting System (FAERS) contains information reported by consumers or healthcare professionals and is used to make regulatory decisions regarding product use or labeling changes.
38. A Risk Management Plan (RMP) is a critical component of the post-switch safety strategy, outlining proactive strategies for risk minimization and demonstrating compliance with regulatory expectations.
39. Post-marketing surveillance (PMS) is essential for detecting safety signals – indicators of a potential causal relationship between an adverse event and the drug that was not previously known or fully characterized.
40. Signal detection involves analyzing data from spontaneous adverse event reports, post-marketing studies, regulatory databases, and published literature.
41. In the European Union, the primary regulations governing the Rx-to-OTC switch are provided under Directive 2001/83/EC as amended by Regulation (EC) No 726/2004.

42. The criteria for reclassification in the EU include a well-established safety profile through previous prescription use, clearly defined conditions for correct use, minimal potential for misuse, and the intended patient population's ability to use the product safely without healthcare professional supervision.
43. In Canada, the process distinguishes between switches to Nonprescription Drugs (NPDs) under the Food and Drug Regulations and switches to Natural Health Products (NHPs), requiring a New Drug Submission (NDS) or Supplement to a New Drug Submission (SNDS) with a Canadian Drug Facts

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