

Briefing Information on the Rx-to-OTC Switch Process

CHPA

The Consumer Healthcare Products Association (CHPA), founded in 1881, is a member-based association representing the leading manufacturers and distributors of nonprescription, over-the-counter (OTC) medicines and dietary supplements. Many CHPA member products provide millions of Americans with safe, effective, and convenient therapies for the treatment and prevention of many common ailments and diseases.

Preamble

The FDA Center for Drug Evaluation and Research occasionally convenes advisory committees to deliberate on issues concerning nonprescription, over-the-counter (OTC) drug products, particularly on decisions about the switch of a product from prescription (Rx) to OTC status. Usually the Nonprescription Drugs Advisory Committee (NDAC) meets jointly with at least one other therapeutic class-specific advisory committee to consider new drug applications (NDAs) for OTC availability and to make recommendations to FDA about approvals.

The 1951 Durham-Humphrey amendments to the Food, Drug, and Cosmetic Act require that, in the absence of a medical need to restrict distribution, nonprescription availability is the default status for FDA-regulated drug products.

Therefore, the central approval issue in any Rx-to-OTC switch is whether the drug product is safe and effective for OTC use. It requires consideration of consumers' ability to successfully self-recognize and self-treat a condition, particularly whether consumers understand product label uses, directions, and warnings.

Underlying an NDA for an Rx-to-OTC switch are the safety and efficacy data for the original prescription drug, 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 (e.g., label comprehension, self-selection, and actual use) are usually 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 will be used safely and effectively according to labeling in the OTC setting.

In addition to providing background on the unique studies and data sets for Rx-to-OTC switch candidates, this document discusses facts about how OTC products are regulated, including their labeling and post-marketing surveillance.

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I. Introduction

An Rx-to-OTC switch is the process by which a prescription medication moves from prescription to over-the-counter status for either the same or a related use. An application for an Rx-to-OTC switch follows the same New Drug Application (NDA) process required for the approval of a prescription drug. The NDA is a formal submission of data to FDA to enable the agency to make the determination whether prescription product restrictions are no longer warranted. The major difference between an Rx-to-OTC switch NDA and a prescription NDA is that, by the time a switch is considered, the molecule has been extensively characterized both from a safety and efficacy perspective.

Data to support the switch are derived from randomized, controlled clinical trials submitted in the original prescription NDA, as well as years of post-marketing safety surveillance and literature reports. In addition, new efficacy and safety data from controlled clinical trials are included in the switch application if the OTC indications or strength differ from those for the prescription drug product. A comprehensive review of safety is included in the switch application as well. Thus, the switch NDA builds on information from previous regulatory filings and the experience with use of the Rx product.

The switch NDA contains both efficacy and safety data demonstrating that the drug product is safe to use in the OTC environment. That is, that the benefits of OTC use outweigh potential risks. Data submitted by the sponsors typically address the following questions:

- (1) Does the product have an acceptable safety and efficacy profile for the OTC setting, in the potential absence of a learned intermediary?
- (2) Does the product have low potential for misuse and abuse?
- (3) Does the benefit of OTC availability of the proposed product outweigh the potential consequences of some consumers not complying with label directions and warnings or inappropriately self-selecting the product?
- (4) Can the condition be adequately self-recognized?
- (5) Can the consumer appropriately select and use the product in accordance with product labeling?

The types of studies that are conducted by sponsors to answer these questions may be unique to the OTC setting. Comprehension of the proposed labeling is formally assessed in label comprehension studies. Studies to build on the previous experience of prescription use may be conducted in a simulated live experience environment (actual use and self-selection studies) to evaluate consumer behavior in an OTC setting.

Typically, products that are the first-in-class for a new indication, possess a novel mechanism of action, or that present unique concerns, are brought before an advisory committee for review and recommendations to FDA.

This NDA process is distinct from the process by which many other OTC products are regulated. Ingredients such as aspirin are regulated by FDA under the OTC Drug Monograph system, a classification system for drug active ingredients that were on the OTC market before 1972, and have been found to be Generally Recognized As Safe and Effective (GRASE) and not misbranded for OTC use. Dietary supplements are regulated by FDA's Center for Food Safety and Applied Nutrition (CFSAN) as foods, not drugs.

II. Post-approval Oversight

A. On-going Safety Reporting

The post-approval review and safety monitoring requirements are exactly the same for prescription and nonprescription drugs approved via the NDA process. These requirements include the following types of post-marketing reports: 15-day, periodic, and annual reports for safety, as well as the other requirements for all NDAs.

III. OTC Labeling

OTC labeling is the primary communication tool with the consumer. The OTC Drug Facts labeling follows a standardized format, facilitating access to important health and safety information and allowing for quick and effective product comparisons, thereby helping consumers select the most appropriate product.¹ The “Drug Facts” rule includes very detailed requirements on the minimum type size, formatting, how to group warnings and how to bullet list them, etc. The “Drug Facts” format follows a standard outline, illustrated on the next page.

According to regulation, labeling should be presented in terms likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.² NDA sponsors and FDA pay particular attention to when and how to warn, because these labels are aimed directly at consumers.

Additional labeling may be included in a product’s packaging to provide supplemental information to the consumer. This information is also reviewed and approved by FDA.

¹ OTC “Drug Facts” rule, 64 *Fed. Reg.* 13254 (March 17, 1999), as codified at 21 CFR 201.66

² See 21 CFR 330.10(a)(4)(v).

WHAT'S ON THE **NEW LABEL**

All nonprescription, over-the-counter (OTC) medicine labels have detailed usage and warning information so consumers can properly choose and use the products.

Below is an example of what the new OTC medicine label looks like.

ACTIVE INGREDIENT

Therapeutic substance in product; amount of active ingredient per unit

USES

Symptoms or diseases the product will treat or prevent

WARNINGS

When not to use the product; conditions that may require advice from a doctor before taking the product; possible interactions or side effects; when to stop taking the product and when to contact a doctor; if you are pregnant or breastfeeding, seek guidance from a health care professional; keep product out of children's reach

INACTIVE INGREDIENTS

Substances such as colors or flavors

PURPOSE

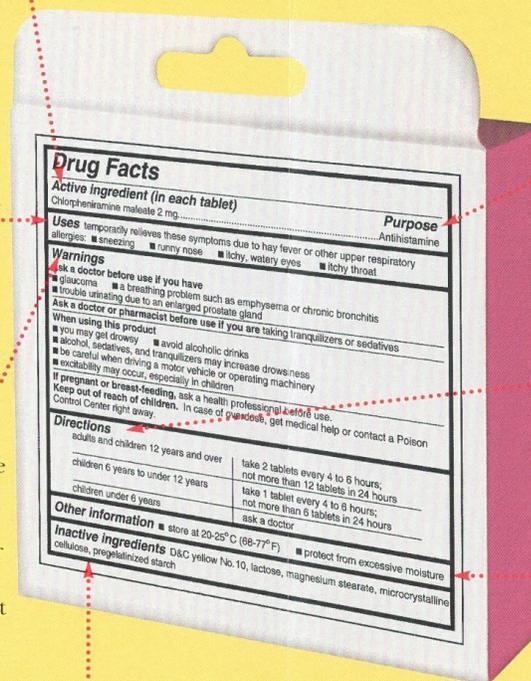
Product action or category (such as an antihistamine, antacid, or cough suppressant)

DIRECTIONS

Specific age categories, how much to take, how to take, and how often and how long to take

OTHER INFORMATION

How to store the product properly and required information about certain ingredients (such as the amount of calcium, potassium, or sodium the product contains)



The new Drug Facts labeling requirements do not apply to dietary supplements, which are regulated as food products, and are labeled with a Supplement Facts panel.

IV. Consumer Behavior Studies

One unique aspect of Rx-to-OTC switch is understanding how consumers will use the product in an OTC environment, especially when there is no learned intermediary involved in the process. Three tools are commonly used to evaluate consumer behavior with OTC drugs. These tools include label comprehension, self-selection and actual use studies. These studies provide an assessment of the consumer's ability to understand the OTC labeling, make an appropriate

determination of whether they should or should not use the product and whether they can use the product correctly in a “real world” OTC setting. These data provide support that switching a drug from prescription to OTC status will not result in significant adverse events from consumers not understanding the labeling and using the drug incorrectly.

A. Label Comprehension Studies

Label comprehension studies are a key component of the label development process, providing valuable insight into consumer understanding of important label messages. These studies usually involve an iterative testing process beginning with qualitative interview sessions and ending with rigorous pivotal quantitative studies with hundreds of subjects. This iterative learning and FDA input allows optimization of the label prior to any self-selection and/or actual use testing with consumers.

1. Role of Label Comprehension Testing in Rx-to-OTC Switch Programs

Label comprehension studies are used to show that consumers understand and comprehend what is written on the OTC Drug Facts label. The first step is usually an initial qualitative exploration intended to learn about clarity of key communication messages on the label, identify areas of confusion, and compare wording and design alternatives. This stage is limited to small sample sizes (n=20-40) in focus groups or one-on-one interviews. Quantitative “pilot” studies which are slightly larger in size, test label alternatives developed from the qualitative learning process. Finally, a quantitative “pivotal” study is conducted to confirm pilot study findings among a large, representative and generalizable sample of potential consumers. The size of these studies is based on statistical considerations.

These studies are effective in testing the potential consumer's ability to understand the label messages and to apply the information on the label to hypothetical individuals with varying demographic and medical characteristics (“scenarios”). This testing requires a higher degree of cognition than asking them to repeat what is written on the Drug Facts label. While data from label comprehension studies provide an indication that consumers understand and comprehend what is written on the label, they do not provide data on message recall (the package is available for review), self-selection (respondents may not represent target population and are not in an actual purchase situation), and usage patterns over extended time periods. In short, label comprehension studies do not predict how consumers will use the drug product. These questions are addressed by self-selection and actual use consumer testing which is discussed later.

2. Methodology for Quantitative Label Comprehension Testing

The FDA has issued (August 2010) a guidance document "*Label Comprehension Studies for Nonprescription Drug Products*" which provides general principles and describes the FDA's current best thinking on the design and conduct of this type of consumer behavior study.

Label comprehension studies are open-label, uncontrolled studies designed to evaluate the Drug Facts labeling but may also include other communication materials, such as a package insert or educational brochure. Study recruitment is accomplished through mall intercepts in geographically and demographically diverse markets. The study sample is representative of the general population of potential users and includes an adequate sub-sample of low literacy

respondents, who are usually identified by the FDA-accepted Rapid Estimate of Adult Literacy in Medicine (REALM) test for health literacy. Specific primary end points are pre-specified and the sample size should be large enough to provide a reliable answer to the primary communication objectives of the study and based on a statistical power analysis.

The process begins with the subject reading the package (e.g., Drug Facts), which is available for reference throughout the study. Questions are administered and answers recorded by trained interviewers according to a script that addresses message comprehension through direct questions, multiple-choice questions, and/or hypothetical situations (scenarios). Scenarios-based questions are often used to assess the ability to make a correct decision based on the information on the label. For example: Mary has heartburn and would like to take Drug X. Mary is also currently taking the heart medicine digoxin. According to the label, is it okay or not okay for Mary to take Drug X? All questions are designed to be non-biased and non-leading. After each question, subjects are usually asked the open-ended question “Why did you say that?” in order to understand the rationale for their answer.

Determination of whether or not a response for a question is classified as correct or incorrect is made on combinations of closed-end and open-end responses, based on pre-defined rules. An initial closed-end response which appears correct can become incorrect based on the open-end and vice versa.

3. Information Obtained

Results are generally analyzed and reported as a proportion of respondents classified as “correct” and “incorrect” for each label message. Open-ended “verbatim” responses to probe questions help the sponsor and FDA reviewers understand reasons for any incorrect answers. These open-ended responses often provide a logical rationale for an apparent incorrect answer and help in developing the final labeling. Communication goals or objectives and the method used can vary depending on the relative importance of the message and its medical significance. Generally, the most critical messages are considered to be safety cautions and warnings.

4. Challenges in Label Comprehension Studies

Label comprehension studies have a range of challenges and limitations. Respondents may not fully represent the population that would actually consider using and purchasing the product. They need to absorb and contemplate a substantial amount of information at one time, under potentially distracting and somewhat artificial testing conditions. Additionally, key communication messages must be written and organized within the mandated Drug Facts format which sometimes forces key messages into locations which are not optimal for gaining consumers' attention.

B. Self-Selection Studies

1. Objectives

Assessment of appropriate self-selection is an integral part of the evaluation of a switch of a product from prescription to OTC use. Unlike the prescription environment in which there is a healthcare intermediary who directs the consumer in product use, consumers can make this decision on their own when a product is available OTC. Self-selection studies are used to provide information on whether consumers can apply the label information to their personal medical situations and make a correct decision whether they should or should not use the drug product (self-selection). Self-selection studies are generally used for a new nonprescription indication and/or target population and when there are specific populations who should not use the proposed OTC drug product (e.g., diabetics, asthmatics, etc).

2. Methodology

Self-selection studies are generally open-label, uncontrolled studies in which not drug product is administered. The FDA draft guidance, *Self-selection Studies for Nonprescription Drug Products* (September 2011), provides general principles and describes the FDA's current best thinking on the design and conduct of this type of consumer behavior study. Self-selection studies may be separate studies or part of an actual use study as described below. Sometimes a self-selection study can involve laboratory testing and/or physician examination to verify correct consumer response.

The primary objective of a self-selection study is generally to assess if subjects, after reading the drug product label, can make a correct self-selection decision based on their medical history. The study population usually includes subjects who may have an interest in using the drug product regardless of age, sex, underlying medical condition(s) and use of concomitant medications. Other self-selection studies may target a specific population of interest such as subjects with a specific disease for whom use of the drug product may be contraindicated. Success criteria for these studies are based on pre-defined target levels of correct self-selection. Sample sizes should be large enough to provide a reliable answer to the primary communication objectives of the study and are based on a statistical power analysis. These studies also include an adequate sub-sample of low literacy respondents, who are usually identified by the FDA-accepted Rapid Estimate of Adult Literacy in Medicine (REALM) test for health literacy.

After reading the label, subjects are asked an open-ended self-selection question such as "Is it okay or not okay for you to use this medication?" This is followed by the non-leading question, "Why did you say that?" Medical history questions are asked after the self-selection question to prevent bias from alerting subjects to specific label elements.

3. Information Obtained

Results are generally analyzed and reported as a proportion of respondents classified as "correct" and "incorrect" for self-selection. As with the Label Comprehension study, open-ended "verbatim" responses to probe answers help the sponsor and FDA reviewers understand reasons for any incorrect answers. Importantly, in self-selection studies, there may be

reasonable mitigating factors that would allow what appears to be an incorrect self-selection decision to be considered correct (e.g., a subject who makes an incorrect self-selection decision based on age, but who is within 1-2 months of the labeled age and verbalizes an understanding of the correct age).

For some products, a consumer must consider multiple selection criteria from the product's labeled "Uses" and "Warnings." Consideration should be given to whether an overall cumulative or a hierarchical system will be used in reporting the self-selection response. The hierarchical approach ranks the importance of label messages with regard to how important they are in directing safe and effective self-selection, de-selection or product use. Sponsors should discuss with FDA the elements of self-selection that will be considered the most important in determining a successful outcome for self-selection for the "switchability" of the product.

4. Challenges for Self-Selection Studies

Self-selection studies have their own unique challenges and limitations. Subjects need to absorb and contemplate a substantial amount of information at one time, under potentially distracting and somewhat artificial testing conditions. Furthermore, subjects are asked to decide whether or not they would use the product at that moment and sometimes they might choose to consult with their doctor before use. This is not part of the testing procedure. Additionally, what consumers say and do may not be the same. What consumers will actually do is tested in the actual use study.

C. Consumer Behavior: Consumer (Actual) Use Studies

1. Objectives for Use Studies

Actual consumer use research can be an important component of the overall consumer behavior data package in evaluating the appropriateness of switching a product from prescription to OTC status. The purpose of a consumer (actual) use study is to simulate the use of a product in a "real world" setting using a market-ready package. Consumer use studies can assess: (1) compliance, or adherence, with the product labeling; (2) ability to deselect or stop use as directed by the label and (3) safety during actual consumer use.

Consumer use research can provide meaningful data for predicting whether a drug will be used safely and effectively in the OTC setting. Some issues that might warrant the need for a consumer use study include the following:

- New OTC indication
- New method of use for an OTC drug
- New OTC warning
- New OTC medical follow-up recommendations
- Specific concerns on self-selection and/or de-selection

2. Methodology

The study site placement and recruitment is designed so that a diverse population can have access to the product. This site placement as well as advertising reach can be enriched to target a specific subpopulation.

There is currently no FDA guidance on the conduct of Actual Use Studies. The Actual Use Study should be conducted with a near final or “ready-for-market” label and packaging. Additionally, advertising used to recruit should not bias the decision-making process.

Actual Use Studies are often multi-center, open-label studies and usually do not contain comparator product information. Other designs using different methods of consumer communication and education materials may also be considered, depending on the scope and complexity of the product labeling, as well as outcomes from prior interactions with FDA.

The goal of the study is to provide a venue that simulates, as closely as possible, the true OTC environment. Study design elements that help achieve a naturalistic environment include a “mocked” store shelf front, allowing study participants to purchase study drug, and no unsolicited healthcare provider involvement. Studies may be conducted in a mall or pharmacy setting. While an informed consent process may seemingly limit the naturalistic setting, most studies are conducted such that consumers see only a limited informed consent form prior to their purchase decision and then a more complete informed consent form is used after the purchase decision is complete. Data collection tools like diaries may also limit the naturalistic setting. The potential impact of these study elements should be addressed when considering the overall consumer OTC use of the product.

Consumer use study endpoints generally include appropriate compliance and de-selection with the proposed OTC labeling. Compliance endpoints are developed based on labeled “Uses,” “Warnings,” and “Directions.” A hierarchy of importance of compliance for the labeled “Uses,” “Warnings,” and “Directions” should be discussed with the FDA before study initiation to ensure the study design and endpoints will address the most critical questions. Sufficient data are collected, usually via assessments after purchase decision, and interviews conducted at the conclusion of the study to understand the reason behind a study participant’s decision for noncompliance with the drug product labeling or for discontinuation, and to ascertain whether there was contact with a healthcare professional. Diaries may be completed during product use. The pros of data verification must be weighed against the cons of potential introduction of bias.

Actual Use Studies are generally analyzed by evaluating consumers’ compliance with the drug product’s labeled “Uses,” “Warnings,” and “Directions.” The percentages for the pre-defined study endpoints, along with their 95% confidence intervals, are summarized to characterize the consumer behavior pattern. Other analyses are conducted as appropriate. Actual Use Studies are essentially the only opportunity to understand consumer behavior regarding any “stop use and ask a doctor” warning.

Similarly to self-selection studies, use studies may employ the mitigation process. This additional process is necessary in most consumer behavior studies in order to consider all subject data, usually due to the open-ended data collected in consumer behavior studies. The mitigation process usually involves a panel who review relevant data to determine if a subject is correct or incorrect for a specific endpoint.

D. Similarities and Differences in Procedures for Consumer Behavior Studies

The following table lists how study procedures for label comprehension, self-selection, and actual use studies are similar or different from those for more traditional phase III randomized controlled trials (RCTs) with objective measurements of efficacy.

Similarities and Differences in Study Procedures

Study Procedures	Phase III RCTs	Label Comp	Self-Selection	Actual Use
Protocol	Yes	Yes	Yes	Yes
IRB	Yes	N/A	N/A unless laboratory test(s) or physician exam is needed	Yes
Selected sites	Yes	Yes	Yes	Yes
Screened subjects	Yes	Minimal, except special pops	Minimal, except special pops	Minimal, except special pops
Informed consent	Yes	Confidentiality	Confidentiality unless laboratory test(s) or physician exam is needed	Yes
Medical history or procedures	Yes	Minimal	Minimal or moderate	Moderate
Enroll subjects	Yes	Yes	Yes	Based on self-selection and risk
Drug use	Yes	No	No	Yes
Diary or use data collected	Yes	1-day interview	1-day interview	Yes
Follow-up visits/procedures	Yes	N/A	Rarely	Minimal
Collect paperwork	Yes	Yes	Yes	Yes
Collect drug	Yes	N/A	N/A	Yes#
Post-approval studies	Phase IV	N/A	N/A	Phase IV rarely Used

Adapted from presentation by Julie Aker (Concentrics Research) at FDA Nonprescription Drugs Advisory Committee meeting, September 25, 2006

Not always

V. Data Sets

Drugs considered for an Rx-to-OTC switch have undergone extensive testing in randomized clinical trials and have a long history of clinical use. Hence, efficacy and safety profiles have been extensively evaluated.

A. Efficacy

For an Rx-to-OTC switch, efficacy data from the Rx NDA will be considered. Often the efficacy profile has already been established. Under certain circumstances, additional efficacy studies may be warranted, such as in situations where (1) the OTC population differs from the population studied to support the Rx indication (such as when a proposed OTC population is for consumers with moderately elevated cholesterol levels, while the NDA population had severely elevated levels), (2) when the Rx population may not have had the demographic profile that would be generalizable to a wider OTC population, or (3) when the OTC dose or indication differs from the Rx dose(s) or indication(s). Examples include the Zantac OTC dosage strength of 75 mg, which is lower than the Rx minimum dose of 150 mg, and OTC indications for heartburn prevention and relief, which are not Rx indications for the active ingredient. Standards for demonstration of efficacy are the same as in an Rx trial. Comparisons to other Rx or OTC products are not required.

Drug efficacy is rarely measured in actual use studies because the object of these studies is to understand the effectiveness of the label in guiding consumer behavior. In addition, collection of efficacy data may interfere with and bias the naturalistic environment that the actual use study simulates. Some form of efficacy assessment may be included, but because of the uncontrolled design of actual use studies, efficacy results may be informative, not definitive.

B. Safety

The safety profile of a drug considered for an Rx-to-OTC switch has been extensively characterized through prescription clinical trials and use, so that even rare side effects should have been identified. Information presented in the switch NDA includes the totality of safety data, which may include data for non-OTC indications. Data sets usually submitted or referenced in the Rx-to-OTC switch NDA include preclinical safety, pharmacokinetic, and pharmacodynamic studies; drug interaction studies; human safety data from randomized clinical trials, post-marketing surveillance, available safety databases, literature reviews, and safety data from Actual Use Studies. While safety data are also collected in Actual Use Studies, these data are often more useful in confirming the results of the label comprehension studies by demonstrating compliance with the proposed OTC label in an unsupervised setting. Data from an Actual Use Study can provide important information on the key safety questions:

- Is the Rx characterization of safety applicable to a wider OTC population?
- Are there certain side effects of the drug that could be worsened or become more frequent in the absence of supervision by a learned intermediary?
- Is OTC availability more likely to delay a diagnosis/treatment of a more serious underlying condition than Rx availability?

The safety issues relevant to these questions are frequently discussed in a dedicated section of the NDA.

VIII. Regulatory Issues

A. Advertising

Unlike prescription drug products where FDA has authority over all aspects of drug advertising, the authority over OTC medicine advertising rests with the Federal Trade Commission (FTC). However, FDA maintains control over the OTC labeling.

Beyond the FTC, there are other mechanisms used to assure OTC medicine advertising is truthful and not misleading. Pharmaceutical companies have an internal approval process for advertisements, which typically includes legal, medical/scientific, regulatory, and general management review. Major television networks also have their own clearance, or program standards which must be satisfied before the network will accept and air an advertisement.

The National Advertising Division (NAD) of the Council of Better Business Bureaus investigates complaints based on staff identification, challenges by competitors, or complaints from other parties (including consumers or local Better Business Bureaus) based on the truth and accuracy of the advertisement. The findings and conclusions of the NAD are published. Noncompliance with NAD decision results in escalation of the complaint to the FTC for enforcement action. The FTC places any cases referred to them by the NAD on high priority.

Lastly, competitive forces play an important role in how companies approach their advertising. The Lanham Act allows companies and private individuals to sue for damages when an advertiser misrepresents its products or a competitor's product in the marketplace and causes significant competitive injury.³

B. Reimbursement

FDA reviews and approves drug, including Rx-to-OTC switches, based solely on the drug's safety, effectiveness, and labeling. Considerations such as retail cost of the proposed OTC switch drug in the marketplace, reimbursement or coverage decisions are outside of FDA's jurisdiction and the drug approval process.

C. Multiple Languages

Suggestions are sometimes made to include portions of labels in a language other than English, such as Spanish. FDA regulations require all label information to be presented in English at the point of purchase, with the exception of products limited to distribution in Puerto Rico, where the predominant language is Spanish. FDA regulations also indicate that if the label contains any representation in a foreign language, all required label information shall also appear in that foreign language. Manufacturers may choose to include a toll-free number for Spanish-speaking consumers to call with inquiries.

³ See Lanham Act sec. 43(a), 15 USC sec. 1125(a).

D. On-going Safety Reporting

The post-approval review and safety monitoring requirements are exactly the same for Rx and OTC drugs approved via the NDA process. These requirements include the following types of post-marketing reports: 15-day, periodic, and annual reports for safety, as well as the other requirements for all NDAs.

E. Circumstances under which an Active Ingredient May Be Marketed In Both A Prescription and an OTC Drug Product

In several instances, an active ingredient is marketed simultaneously as both an OTC drug in one dosage form and strength for a specified indication(s) and also has uses or additional labeling under consultation with a health professional. In the latter case, these situations may be termed prescription use, professional labeling, professional information, or even off-label use.

(1) Dosage strength variations. Hydrocortisone is one example of different Rx and OTC strengths, where prescription-strength 2.5 percent hydrocortisone cream is indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. OTC 1.0 and 0.5 percent hydrocortisone creams are indicated for temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to a number of listed inflammatory and pruritic conditions, i.e., indications closely related to the higher-dose prescription indication.

(2) Indication variations. In addition to dosage strength variations, there are prescription and OTC variations based on the indication using the same dosage strength. Children's ibuprofen is available OTC to temporarily reduce fever or to relieve minor aches and pains. The same strength is available as a prescription for reduction of fever, for relief of mild to moderate pain, and for relief of signs and symptoms of juvenile arthritis.

(3) Age distinctions. An example here would be nicotine replacement therapy (NRT), where the directions advise potential users under 18 years of age to ask a doctor before use. NRT products are further labeled as not for sale to those under 18 years of age, and labeling states that proof of age is required. Levonorgestrel is another example, where the OTC indication is for emergency contraception to reduce the chance of pregnancy after unprotected sex for women 17 and over. The prescription indication is for emergency contraception in women under 17.

(4) Cosmetic and drug claims on the same product. Some products (i.e., antidandruff shampoo, fluoride toothpaste, moisturizers or makeup marketed with sun protection claims) meet the definition of both a cosmetic and a drug. These products must comply with the regulatory requirements for both cosmetics and drugs. Unlike drugs, cosmetic products and ingredients do not require FDA approval prior to marketing.

F. Approvals are on Individual Merits, Not on Comparisons to Other Products

Occasionally, there are questions around whether comparative assessments should be made in drug approvals. While companies may conduct comparative trials against competitor products during Phase III or IV testing, the merits of the approvability of the product must be based on the standards of the Food, Drug, and Cosmetic Act of the individual product's safety, effectiveness, and proper labeling. This is demonstrated through the clinical and consumer testing program of the switch candidate.

VII. Summary

In summary, approval and marketing of an Rx-to-OTC switch NDA follow many of the same steps and requirements as for the parent Rx medicine. While safety and efficacy of the product were shown in the clinical trials to obtain NDA approval, and extensive marketing experience has further confirmed the safety profile in large-scale use, the approval of an Rx-to-OTC switch may require additional studies that demonstrate consumers can safely use the product with limited or no assistance from a healthcare professional.