proposed rule or proposed monograph known as the "Advance Notice of Proposed Rulemaking," in the *Federal Register*. These evaluations took more than a decade for some product categories, and the last report was not issued until 1983.[12,13] Each advisory panel placed the nonprescription ingredients evaluated into one of three categories[1]:

- Category I: Sufficient evidence of safety and effectiveness
- Category II: Sufficient evidence that the ingredient is unsafe and/or ineffective
- Category III: Insufficient evidence to prove safety and/or effectiveness

The panel also considered such issues as proper labeling claims and the validity of combination products for that therapeutic class.

PHASE 2

Phase 2 for each therapeutic class began with the publication of the "Advance Notice of Proposed Rulemaking." Nonprescription manufacturers were most profoundly affected by the Advance Notice. If the ingredients in a given OTC product were all Category I, they could continue to market it without further work, assuming that their labeling was truthful and correct and conformed to suggested advisory-panel guidelines. However, if a product contained Category II or Category III ingredients, manufacturers had to address potential problems with the product. If a product contained Category II ingredients, but not Category III ingredients, manufacturers were put on notice that there was evidence of ineffectiveness and/or danger to patients. The manufacturers were forced to decide whether to continue to market these ingredients pending further FDA publications or to reformulate.

If a product contained Category III ingredients, manufacturers were allowed to continue to market the product in most instances while considering several options[6]:

- To continue marketing the product pending further review but not to conduct research themselves
- To reformulate to include Category I ingredients
- To undertake research to prove safety and efficacy on their own

If the products were produced in large quantities (e.g, Robitussin), companies often chose the third option. Research had to conform to the highest standards of scientific methodology, including double-blinding, placebo controls, crossovers when appropriate, washout periods, and proper application of the correct statistical test to prove significance in results. The expense of this approach precluded many companies from choosing this option for products that did not justify such a commitment of time and resources.

Any interested party could appear before the FDA during Phase 2 deliberations, including patients or physicians whose favorite products were in jeopardy. Without legitimate research, however, such testimonials received a polite hearing at best, but could not be allowed to alter the outcomes of scientific scrutiny.

Phase 2, which took nearly 15 years for some therapeutic classes, ended for a particular class when the FDA made a decision to terminate information gathering for that therapeutic class. All research submitted during Phase 2 was carefully assessed to decide the safety and efficacy of ingredients. Finally, the agency published in the *Federal Register* a Phase 2 document, known as a "Proposed Rule" or "Tentative Final Monograph." (This document may be referred to using either term; however, there are many other types of rules proposed by the FDA. The tentative final monograph is simply one type of rule proposed by the agency on a wide variety of topics.) The document detailed all comments about the Phase 1 document and presented the new data submitted.

In the Phase 2 documents, the FDA again assigned ingredients to Category I, II, or III. In most cases the FDA agreed with the report of its appointed advisory review panel, but ingredients were reassigned as appropriate.[11] Some ingredients moved from Category III to Category I because manufacturer-sponsored research proved safety and efficacy; other Category III ingredients remained unchanged because no new evidence was submitted or because the research that was done was flawed. (Flawed research such as bias in patient recruitment, insufficient blinding, or use of parametric statistics on nonparametric data was not considered acceptable.[14]) Ingredients also moved from Category I to Category II or Category III because of new information regarding safety. Ingredients originally placed in Category II had already accumulated sufficient evidence of lack of safety and/or efficacy. Thus most manufacturers considered it a waste of time to devote further resources to them, and they seldom, if ever, were reassigned to another category.

Also, the agency addressed the comments that were collected during the Phase 2 period in regard to labeling and combination products and issued preliminary conclusions on these issues.

Publication of the "Tentative Final Monograph" in the *Federal Register* ended Phase 2.

PHASE 3

Phase 3 gave the manufacturers of products containing Category III ingredients further time to either reformulate or design and carry out studies to prove safety and/or efficacy. During this phase the public and health professionals had one last chance to appear before the FDA.

Phase 3 lasted nearly 15 years also. As in Phase 2 the FDA eventually decided that information gathering must conclude for a therapeutic class, subsequently publishing a "Final Rule" that appears in the *Federal Register* in the form of a "Final Monograph."[11] On publication of the "Final Rule" or "Final Monograph" Categories I, II, and III were obsolete, and ingredients were placed in one of only two groups:

- Meets monograph conditions (safe and effective, the former Category I)
- Does not meet monograph conditions (former Categories II and III combined)

The manufacturers were given a period (usually 6 months from publication of the "Final Rule") during which products containing ingredients that did not meet monograph conditions had to be reformulated to contain only fully approved monograph ingredients. Products not reformulated by the end of the allotted time could be seized for adulteration and misbranding. Further, labeling had to conform in regard to indications, claims, hazards, directions for use, dosages, drug interactions, etc. Of course, only the approved combination products could be marketed.

Manufacturers may choose to petition the FDA to amend the final monograph. Such a petition may request that additional ingredients be included or that labeling be modified. Until the amendment is accepted, however, the ingredients cannot be marketed and the labeling cannot be modified.[2]

Criticism of the Review

The FDA OTC review, the first attempt to bring the power of scientific protocol to a poorly regulated group of products, was criticized on several grounds. First was the great amount of time it took. In most cases manufacturers were allowed to continue marketing ingredients in Category II or III pending publication of the Phase 3 document, even though the review process took more than 2 decades to complete. Consequently, consumers were exposed to ingredients that were already proven to be unsafe and/or ineffective or that were of unknown safety and/or efficacy.

To prevent this situation, the FDA could have chosen to force all products known to be lacking safety or efficacy or not yet proven to be safe and efficacious from the market after the publication of the Phase 1 document, and then to permit them to be remarketed only when their ingredients were proven both safe and effective (or they had been reformulated). Erring on the side of the pharmaceutical industry—another criticism—was seen as a compromise of the FDA's function. Specifically, the Congressional General Accounting Office charged that the FDA assigned such a low priority to OTCs that it did not carry out its mandate to protect the public.

One might argue that pharmacists were the last line of defense during the lengthy evaluation and deliberation period, prior to the issuance of the Phase 3 document. This argument assumes, however, that pharmacists were properly informed about category assignments of the various nonprescription ingredients. The *Federal Register* is not on the reading list of most pharmacists, and in practice most pharmacists were poorly informed about the FDA deliberations.[15] Failure to adequately publicize unapproved ingredients led to several decades during which the pharmacy profession was unable to act properly as patient advocates.

In 1995 *U.S. News & World Report* highlighted patient dangers from "FDA-banned pills and potions"—further exposing weaknesses in the drug-review process.[16] Specifically, the publication examined the FDA policy of placing ingredients in nonmonograph status, yet failing to recall them. "Once a ban takes effect, manufacturers are barred from shipping new supplies, but stores legally can sell banned drugs until their own and their wholesalers' inventories run out. It's consumers who remove banned items from drugstore shelves—by buying them." The publication highlighted cases in which consumers had been injured by banned products (e.g., quinine-induced renal failure). *Informed pharmacists should take the initiative to remove unsafe and ineffective products from the shelves,* returning them to the wholesaler for credit if permitted or discarding them if they cannot be returned.

Products Not Reviewed

Nonprescription ingredients marketed prior to 1938 (e.g., phenazopyridine) are sometimes spoken of as being protected from FDA scrutiny because they are "grandfathered."[9] However, personnel within the FDA stress that eventually these grandfathered ingredients will also be examined for safety and efficacy. Further, regardless of whether they were reviewed, the labeling claims of these products must be truthful.

Benefits of the Review

Eventually, when the FDA OTC review is finished (e.g., all amendments settled), pharmacists—and patients—will have assurance that nonprescription products (and combination products) that underwent the review contain ingredients that are both safe and effective for their labeled indications and thus can be recommended with confidence.[17] Further, labels will inform patients about the conditions for safe use, doses, contraindications, warnings, and ingredients. At this point OTC products sold at nonpharmacy outlets can be chosen with confidence also, assuming patients are correct in their self-diagnosis and that they read and understand all label information. FDA rulings should help eliminate deceptive advertising as well.[3] Of course, deceptive advertising and misleading products will always be offered to an unwary public (See Chapter 49, Precautions in Self-Care.)

After the review is complete, prospective manufacturers of nonprescription products may simply examine the pertinent copies of the *Federal Register* to see which ingredients can be included in their products and what information to place on the label. If a manufacturer wishes to market new ingredients, they must be submitted through the New Drug Application process if FDA approval is sought.

CURRENT FDA NONPRESCRIPTION PRODUCT OVERVIEW

The Nonprescription Drug Advisory Committee (NDAC)

The FDA created an Office of Over-the-Counter Drug Evaluation in 1991, to place renewed emphasis on the review of nonprescription drug products.[18] Shortly thereafter, the agency also formed a Nonprescription Drugs Advisory Com-

mittee (NDAC) to examine safety and effectiveness issues regarding OTCs. Serving as a replacement for the advisory panels utilized during Phase 1 of the FDA OTC review, which were disbanded as their work was completed, the experts appointed to the NDAC consider issues of importance as they arise.

The FDA OTC Review Process

The FDA OTC review process is ongoing. Final monographs are lacking for some therapeutic classes as of this writing. With the assistance of the NDAC to provide advice on various issues, the FDA is optimistic that the review will proceed in a timely fashion.

THE PRESCRIPTION-TO-NONPRESCRIPTION (RX-TO-OTC) SWITCH

The nonprescription marketplace has been kept in a state of flux for several reasons such as new product introductions and reformulations of established brands. The most exciting impetus to the market, however, has been a phenomenon popularly referred to as the "Rx-to-OTC switch." The Rx-to-OTC switch occurs when an ingredient or product formerly available only by prescription becomes available for nonprescription use.

Methods by Which Prescription Medications Gain OTC Status

Prescription medications may gain nonprescription status by a variety of methods. The discussions below describe the three primary Rx-to-OTC avenues:

- The FDA OTC review
- The "switch regulation"
- Processes related to the New Drug Application (NDA)

THE FDA OTC REVIEW

The FDA OTC review process has allowed some medications to attain nonprescription status, although it has not been utilized in recent years.[1,19] This may have occurred when the advisory panel or the FDA itself decided a prescription medication possessed sufficient safety to allow self-use. Examples of medications that joined the ranks of nonprescription agents through this route include hydrocortisone, diphenhydramine, oxymetazoline, and fluoride dental rinses. Proceedings are not confidential, which compromises manufacturer trade secrets.[20] Lack of confidentiality is one reason manufacturers prefer not to use this method.

THE "SWITCH REGULATION"

The switch regulation, which dates from the 1950s, allows any interested party to petition the FDA to switch any medication to OTC status.[1] Historically, manufacturers have usually been the sponsors. While one manufacturer might petition for a switch, another might not, resulting in Rx and OTC marketing of the same ingredient, a confusing situation. Lack of confidentiality of the proceedings is a major drawback, so that most manufacturers do not prefer this route to OTC status. The switch regulation was used for dextromethorphan and tolnaftate, but has not been used since 1971.[21]

PROCESSES RELATED TO THE NEW DRUG APPLICATION (NDA)

Processes related to the NDA are the most common paths from Rx to OTC. When a medication is originally approved as a prescription product, a full NDA must be submitted, which can take years and millions of pages of documentation. Following approval of the original NDA, if the manufacturer wishes to change a dosage or formulation, a full NDA may also be required. However, if a minor change is anticipated, the FDA may only request a supplemental NDA that addresses certain issues. If another manufacturer wishes to also market the same product (or one closely related), an abbreviated NDA may be all that is necessary, which is a shorter version of the original NDA submitted by the parent company. Manufacturers may proceed through Rx-to-OTC switching by three methods related to NDAs:

- Submit a full NDA for a medication currently available by prescription, but for a new dosage or formulation such as a lower strength than the Rx version
- Submit a supplemental NDA for a product for which the manufacturer already holds an approved NDA or holds an abbreviated NDA for a closely related product
- Submit an abbreviated NDA for products that are identical to an existing prescription product

If the company is not required to carry out clinical trials, an abbreviated NDA is approvable immediately. If the FDA requires a manufacturer to carry out new and possibly novel research by way of clinical trials (e.g., intravenous animal injections to prove safety for nonprescription status), the company is granted 3 years of marketing exclusivity against competing abbreviated NDAs.[6,22] (This provision of the Drug Price Competition and Patent Term Restoration Act of 1984 helps compensate the sponsor for the costs of the research.[2,21]) Thus other companies cannot market the same ingredient without also carrying out original research until 3 years have elapsed, at which time the ingredient will be eligible for an abbreviated NDA.[23,24]

Marketing exclusivity is a major draw for companies, who have used this method in ever-increasing numbers in the 1990s. Products switched under NDA-related processes include ibuprofen, loperamide, permethrin, vaginal antifungals, Actifed, Rogaine, Nicorette, NicoDerm CQ, Nicotrol, Tagamet HB, Pepcid AC, Zantac 75, Axid AR, and Nasalcrom.

All proceedings related to the NDA are confidential, which the pharmaceutical industry prefers.[20]

Types of Rx-to-OTC Switches

There are two types of Rx to OTC switches, as measured by the ingredient's status after the switch[25]:

- The complete switch
- The partial switch

THE COMPLETE SWITCH

In the complete switch the product becomes nonprescription—all dosage strengths if there were more than one—and no prescription version remains. Examples include Rogaine, vaginal antifungals, pyrantel pamoate for pinworm, Nix for head lice, and both strengths of Nicorette gum for smoking cessation (Fig. 2.1).

THE PARTIAL SWITCH

In the partial switch one or more doses that were formerly prescription become OTC, or lower strengths that were never available on an Rx basis become OTC, but higher doses remain only available through prescription order. Examples include clemastine (Tavist-1 [OTC] contains 1.34 mg of clemastine fumarate per tablet; Tavist Tablets [Rx] contain 2.68 mg each) and naproxen sodium (Aleve [OTC] contains 220 mg naproxen sodium per tablet; Anaprox [Rx] contains 275 mg each). Other examples include ketoprofen, all of the H2-blockers, and ibuprofen. Occasionally, the same strength is simultaneously available in both prescription and nonprescription versions (e.g., Imodium 2 mg capsules and Imodium A-D caplets, Tagamet 200 mg tablets and Tagamet HB 200 caplets) (Fig. 2.2).

Factors Considered in Rx-to-OTC Switch Decisions

The Durham-Humphrey Amendment of 1951 clearly delineated the differences between Rx and OTC medications.

Figure 2.1. Artistic representation of the labels of a product once marketed as a prescription product (*top*), but switched to nonprescription status (*bottom*).

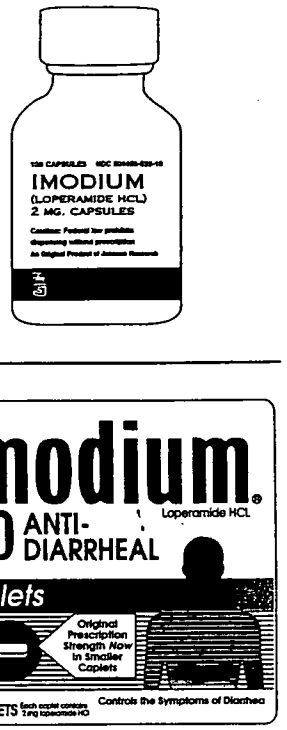

Figure 2.2. Artistic representation of a product marketed simultaneously in prescription (*top*) and nonprescription (*bottom*) versions.

Factors that mandate prescription status include the potential for harm such as unreasonable toxicity, the ability of the patient to understand the method of use or collateral measures necessary for use, and the possibility of patient misuse.[26] The FDA occasionally applies other factors as well. In 1985 the Director of the Office of Drug Standards listed four broad categories of considerations[27]:

- Safety
- Effectiveness
- Labeling
- Other issues

SAFETY

Safety, the first of the four factors, is a relative term, since no medication can be absolutely harmless in all potential patients at all times. Thus a decision of safety for potential nonprescription products focuses on several questions.

Toxicity or Other Potential for Harmful Effect

Overall Safety. The FDA examines the traditional measures of safety and toxicity such as the LD50, pharmacokinetic parameters, potential for drug interactions, carcinogenicity, possible adverse reactions, and safety in subpopulations (e.g., geriatric, pediatric, and pregnant patients).[27,28] Thus medications with high potential for toxicity that must be dosed under medical supervision (e.g., digitalis, phenytoin) are not suitable OTC candidates. The question of overall safety halted the po-

tential switch of terfenadine, for example, which may cause abnormal heart rhythms in patients taking other medications (e.g., ketoconazole, itraconazole, clarithromycin, erythromycin, and troleandomycin). Eventually, the product was withdrawn from the United States market completely.

Two additional illustrations of potential drug interactions help clarify this issue. If an interaction is common or of such serious potential that adequate labeling cannot be developed to allow safe use, the product will retain prescription status. Cholestyramine has been considered for a switch, but an FDA committee member raised the concern about serious interactions with medications such as anticoagulants, digitalis, thyroid supplements, and folic acid.[29] The agency member felt the company had downplayed the potential for such interactions, and the committee denied OTC status.

Cimetidine is another example. Although cimetidine can cause serious drug interactions with theophylline, phenytoin, and anticoagulants, the manufacturer was able to develop labeling that explained the problem clearly enough for the average patient, and the product was approved for OTC status.

Benefit:Risk Ratio. A medication proposed for OTC use should produce a low incidence of adverse reactions when used as directed and when patients are adequately warned against unsafe use.[30] This qualification may also apply in a larger sense to the larger group of potential patients.[28] For instance, topical erythromycin was under consideration for acne at one time. However, there was concern within the FDA that widespread, unsupervised use might cause resistance to develop in the population.[31] The same concern was partly responsible for lack of approval for nonprescription acyclovir for genital herpes.[32]

There also must be little risk that a medication would mask a serious underlying medical disorder. If the medication alleviated the symptoms of this disorder, it might progress without the patient receiving proper treatment. As an example, vomiting is a symptom of many serious problems that require physician screening. Thus nonprescription medication cannot be labeled for relief of vomiting, unless it is related to the minor etiology of motion sickness.

Potential for Abuse/Misuse. If the medication can cause addiction, it has high potential for abuse and is not allowed to be sold OTC. Potential misuse could include sales to those for whom the product is not intended. For instance, OTC nicotine products for smoking cessation were only approved with the understanding that measures to prevent abuse would be instituted. The products cannot be sold to individuals younger than 18, nor can they be placed in a vending machine or in any other retail sales situation where proof of age cannot be verified.

Need for Routine Medical Examinations or Lab Work. If a medication used in a certain condition requires periodic medical examinations to ensure that the medication is helping the condition or lab work to ensure that it is not causing toxicity, it must be disqualified from nonprescription sales for that condition, or its indications must be limited to other minor conditions that are less serious.[30] For instance, H2-blockers cannot be labeled for treatment of an ulcer, which requires periodic laboratory testing and physician evaluation.

This criterion disqualified metaproterenol from nonprescription status in 1982.[1] At that time the FDA indicated that the ingredient could be marketed OTC, and several manufacturers did so. However, health professionals quickly pointed out that patients with asthma might obtain short-term relief from metaproterenol, delaying physician visits for proper monitoring. After due consideration, the FDA reversed its opinion, forcing manufacturers to withdraw the product from OTC sales and returning it to Rx status.

Method of Use and Collateral Measures Necessary for Use

This criterion encompasses several important questions regarding the condition to be treated:

- Ability of patients to self-diagnose conditions
- Ability of patients to recognize symptoms
- Potential of the condition to be self-treated

Ability of Patients to Self-Diagnose Conditions. Nonprescription products are usually only appropriate for conditions that patients can self-diagnose.[27] This objective has caused manufacturers to go to great lengths to teach patients to self-diagnose certain conditions. For instance, when the FDA contemplated an Rx-to-OTC switch for Rogaine (topical minoxidil for hair loss), one vital point was the ability of the patient to differentiate self-treatable androgenetic baldness from other causes of hair loss. Extensive patient education material in the package insert was deemed sufficient to accomplish this, and the ingredient was approved for nonprescription sales. Conversely, the FDA does not feel that patients can self-diagnose genital herpes, which has caused difficulties in a proposed Rx-to-OTC switch of acyclovir.[32] This switch has not occurred at this time because of these issues.

Ability of Patients to Recognize Symptoms. The underlying cause of some symptoms might not be diagnosable by the patient. For instance, patients may not know the exact cause of headache, muscle ache, or upset stomach. However, as these symptoms do not usually reflect serious underlying pathology, they are considered to be self-treatable when patients can recognize them. For example, internal analgesic products treat headache effectively, even though patients might not be able to identify the specific type of headache.

Potential of the Condition to be Self-Treated. For a condition to be judged as self-treatable, the FDA considers three questions:

- What are the risks to the patient who uses the medication but does not have the condition for which the medication was intended?
- What are the risks to the patient who has the condition and does not seek medical attention but chooses to use the nonprescription medication instead?

- What is the potential length of time the patient might use the nonprescription product before seeking medical attention?

These criteria help ensure that nonprescription products are used primarily for minor conditions that would resolve even if they are not treated (e.g., motion sickness, the common cold). The criteria also help the FDA decide on time limits for self-use prior to seeking medical care. For instance, the male may treat androgenetic alopecia with Rogaine for 12 months before deciding that it does not work. On the other hand, one may only self-treat diarrhea for 2 days prior to seeking medical care. Obviously, the risks of uncontrolled diarrhea are far more serious (even deadly) than the risks of poorly treated androgenetic alopecia.

One notable exception to these criteria should be pointed out.[28] Insulin, a nonprescription product in the U-100 strength, is only available from pharmacies and retail outlets with a pharmacy. This restriction has been the case since insulin was first marketed in the 1920s. Few would argue that Type 1 and Type 2 diabetes mellitus are either self-diagnosable or self-treatable without physician monitoring. Nevertheless, Type 1 diabetics who cannot obtain insulin can become hyperglycemic, which can cause death. Nonprescription insulin sales evidently are allowed to make it easier for diabetics to obtain this crucial drug. Thus insulin is perhaps the most dangerous nonprescription product available, since only moderate overdoses can induce irreversible CNS damage and can cause death from hypoglycemia.

EFFECTIVENESS

Effectiveness is the second of the four factors in Rx-to-OTC switch decisions. For a given product a significant proportion of patients should experience the beneficial effect described on the product's label. (The proposed nonprescription use should be similar or identical to that of the approved prescription version of the product.[27]) If the proposed nonprescription dosage is lower than the Rx version, new studies may be required to prove that this lower dose is still effective.

LABELING

The product must be labeled with adequate directions for proper use.[28] Labeling must be stated clearly, so that "ordinary" patients can understand terminology, including patients with low reading comprehension. Adequate warnings must be developed also, warning patients against:

- Use in dangerous conditions
- Use by patients who are too young to use the product safely
- Unsafe dosages
- Unsafe durations of use
- Use longer than recommended prior to seeking medical attention
- Use in pregnancy and nursing, unless the medication is exempt (such as protectant ingredients applied topically for hemorrhoids)

OTHER ISSUES

The FDA occasionally considers other criteria in approving an Rx-to-OTC switch, even though they may not be part of formal policy. In 1993, for example, an FDA panel attempted to hold a meeting to discuss the possibility of switching oral contraceptives to OTC status.[33] There was an immediate outcry by public groups against any move in this direction. The agency canceled the meeting, citing concerns that they had consulted with too few interest groups such as family planning advocates. Apparently, the deciding factor in canceling the meeting was the social impact of allowing unrestricted sales of a potent and highly effective birth control product. This proposal has never been reopened.

Benefits to the Rx-to-OTC Switch Movement

BENEFITS TO INDUSTRY

Manufacturers can benefit in several ways by switching medications from Rx to OTC status. For example, OTC sales expand the potential market for products that are threatened by patent expiration.[34,35] To illustrate, all four H2-blockers (Axid, Pepcid, Tagamet, and Zantac) had either undergone patent expiration or were nearing those dates. As a result their market share was threatened by the potential introduction of less expensive generic competitors. By converting to OTC sales, the brand names gained new life through new OTC advertising campaigns and the 3-year extended-patent exclusivity for the nonprescription version of the product.[28,36,37] (See: Processes Related to the New Drug Application [NDA]") The sales of products switched from Rx to OTC often double or triple.[38]

Switching to OTC status also allows manufacturers to move into different competitive arenas. As an example, when Merck & Co. introduced Prilosec, a proton-pump inhibitor, it created competition for Pepcid, its H2-blocker. By switching Pepcid to OTC status (while retaining an Rx version) and retaining Rx status for Prilosec, Pepcid AC was allowed to enter the lucrative market for antacid products for gastroesophageal reflux.

BENEFITS TO PATIENTS

Rx-to-OTC switches provide several benefits to patients. Rx-to-OTC switches allow patients to self-treat conditions for which medical advice was once required—such as smoking cessation, androgenetic alopecia, vaginal candidal infections, and ophthalmic complications of allergic rhinitis—and thus gain more control over their health care.[39] Patients also save on the costs of physician visits (even with insurance deductibles which usually range from $10 to $15), reduce time taken from work (possibly with docked pay), and eliminate the need to purchase a prescription product. As a case in point, patients have saved an estimated $150 million yearly since hydrocortisone 1% switched to OTC status.[18]

BENEFITS TO PHARMACY AND PHARMACISTS

As more medications attain OTC status, the role of the pharmacist as a self-care advisor becomes more critical. Labeling

for products switched from Rx to OTC is often more complex than with older OTC products because the conditions require more sophisticated skills for recognition. Booklets enclosed with some newly switched products may have many pages, all of which should be read by patients before using the products.

To properly counsel the patients who request recently switched OTC products, pharmacists should ask patients the following questions to ensure that the medications are appropriate[40]:

1. Did a physician recommend that you purchase this medication?
2. How did you hear about this product?
3. Have you ever taken the prescription form of this product?
4. Have you ever had a reaction to this product in its prescription forms?
5. Do you currently have a prescription for this medication that you can get refilled?
6. Do you currently have a prescription for this medication for which refills have been denied by a physician? If so, why?
7. What condition do you intend to treat with this medication?
8. Has this condition ever been medically diagnosed?
9. Do you intend to take this along with any prescription product? (If so, the pharmacist should attempt to ascertain if the Rx product contains the same ingredient(s) as the OTC such as a Motrin prescription plus Nuprin.)
10. What prescription and OTC medications are you currently taking on a daily basis?

Pharmacists should anticipate questions such as the following from patients regarding switched OTC products[40]:

1. Is this safer than it was when it was prescription?
2. Why don't I need a prescription for this now?
3. Can I take/give it in the same amount as my doctor recommended when it was an Rx product (e.g., Children's Motrin)?
4. What is the difference between this product and that product since one tablet is fewer milligrams than the other (e.g., ketoprofen versus ibuprofen versus naproxen)?
5. Why can't I just take four of these tablets to get the same dose as I did when it was a prescription product?
6. Will this cost the same or more?
7. Does this mean that I never have to see my doctor again for this problem (e.g., vaginal fungal infections)?
8. My friend said she has the same problem as I do, but she didn't want to go to the doctor. Can I suggest the use of this product for her because you can get it without a prescription now?
9. I was taking this for [condition], but that's not printed on the label. I know how to use it for that condition, so can't I just treat myself since I can get it without a prescription?
10. Can you keep a record of this on your computer for me?

Problems with the Rx-to-OTC Switch Movement

REIMBURSEMENT PROBLEMS

Patients whose insurance plans provided full coverage for a prescription product usually discover that when the product changes to OTC status, it is no longer covered.[41,42] This is usually also true for patients who rely on Medicaid coverage, which often does not provide coverage for nonprescription products. With a product such as Rogaine, for example, no Rx version remains as an alternate for physicians to prescribe.

PATIENT CONFUSION

The Rx-to-OTC switch can result in confusion for patients because of the following:

- Dual Rx and OTC marketing
- Misperceptions regarding safety
- Misleading advertising
- Lost pharmacist counseling

Dual Rx and OTC Marketing

When simultaneous marketing of Rx and OTC versions of an ingredient is allowed, the OTC version is usually a lower strength. The FDA has considered allowing dual marketing of the same strengths, but the prescription and nonprescription packages would have to differ in size, shape, color, and name labeling and would have to be promoted differently.[43,44]

There are exceptions, however. For example, a certain strength of an ingredient may be suitable for self-treatment for one condition but not for another. Thus ingredients are sold at the same strength in both Rx and OTC forms.[24] For example, meclizine 25 mg is available as an OTC for motion sickness, but only as an Rx product for vertigo. Pharmacists must explain that motion sickness can be safely self-treated, but that vertigo may be caused by any of several serious medical problems that require sophisticated medical testing.

Simultaneous marketing of the same ingredient as an Rx and an OTC can lead to patient confusion, however, regardless of whether the strengths are identical. Patients are understandably confused when they discover that ibuprofen is in Advil and also in Motrin 800 mg, for example. They may feel that the product in nonprescription form allows them to simply take four tablets to duplicate the Rx doses.[45] (In this case, the pharmacist must explain that the only safe dosage is that listed on the label. Taking more than recommended could increase the risk of adverse reactions.)

Misperceptions Regarding Safety

Patients often see nonprescription products as safe in any dose and able to treat virtually any condition. OTC products are usually quite safe when used as directed for their labeled indications, although there is a risk of adverse reactions at even normal doses. Problems such as adverse reactions multiply when patients stray from the intended doses. For example, a patient may decide to use ibuprofen for rheumatoid arthritis, taking incorrect doses far in excess of the maximum duration recommended on the label, possibly resulting in gastric ulceration.

Misleading Advertising

Most consumers have limited medical knowledge, which hampers their ability to evaluate the veracity of advertising campaigns.[46] When products switch to OTC status, sponsors often resort to aggressive marketing, especially when there is strong competition (as with the H2-blockers). The result may be misleading advertising. In 1995 a New York federal court examined advertising for Pepcid AC and Tagamet HB.[47–49] The court ruled that both companies had misled consumers regarding such issues as effectiveness and onset of action. The companies agreed to withdraw or modify the offending ads, but, of course, the ads had been seen by an unknown number of impressionable consumers by that time.

Lost Pharmacist Counseling

FDA-mandated OTC labeling does not specifically recommend that the patient speak with a pharmacist prior to purchase. In fact, the FDA assumes that switched OTC products will be used without any pharmacist involvement.[50] Although pharmacist counseling was considered to be mandatory when these ingredients were prescription items, apparently the FDA feels it has no place in nonprescription sales of the same ingredient. Unfortunately, this deprives patients of the rich storehouse of knowledge pharmacists have amassed when counseling patients on the ingredient as a prescription item.

PHYSICIAN RESISTANCE

Some physicians view the Rx-to-OTC switch as "putting a scalpel in the hands of a child."[51] Often when a nonprescription product switches to OTC status, the specialty journals for physicians in that field predict adverse consequences.[52] For example, when hydrocortisone was proposed for an OTC switch, dermatology literature carried cautions about a patient who misdiagnosed herpes simplex as poison oak dermatitis and applied hydrocortisone. Another patient treated a bacterial infection of the face with hydrocortisone, thinking it was contact dermatitis.[53] In both cases, the infection worsened.

INSUFFICIENT PHARMACIST PREPARATION

Because of the proprietary nature of NDA-related Rx-to-OTC switches, manufacturers are not forced to disclose before product introduction what the approved labeling of a newly switched product will contain. Consequently, the product hits the shelves with the advertising campaign in full swing. Patients might ask questions about warnings, contraindications, drug interactions, durations of use, etc., while pharmacists struggle to become informed about the product. Of course, much of the usage information on new OTC products is in booklets sealed in the package, preventing the pharmacists from reviewing it. The solution is to sacrifice a package, which can be opened, studied, and used in patient counseling.

The problem is worsened for pharmacists when manufacturers cannot ship sufficient product, hampering pharmacists' attempts to obtain labeling. Some companies have tried to inform pharmacists by sending "launch kits" to pharmacies. Timed to coincide with the arrival of the OTC versions of the product, these kits might contain booklets, videotapes, etc.

A THIRD CLASS OF DRUGS

What are the implications when medications switch from Rx-to-OTC status? By abruptly moving a product from Rx to OTC status, the FDA communicates the following message to consumers and the profession: Today this medication is so dangerous that it must be prescribed by a physician; tomorrow you may purchase it from a vending machine in a hotel lobby or gas station whenever you desire.[54] There is no middle ground.

Many health-care professionals and consumers believe it would be more logical to place newly switched products into a different class of medications—essentially a "third class of drugs"—so that newly switched drugs can be monitored more carefully for a few years. Debate continues over this hotly contested proposal, although the FDA has not been supportive. Interestingly, the United States and South Africa are the only countries without such a class of drugs. A third class would only be available in the 65,000 pharmacies nationwide, rather than the 750,000 retail outlets that now sell nonprescription products.[55] (Under the current rules, the OTCs can be bought in one million retail outlets.)

The Pharmacist's Responsibilities with a Third Class of Drugs

Although there has been no clear consensus, the pharmacist's responsibilities with a third class of drugs might include the following:

- Stocking the third-class items behind the counter, with signage announcing their availability, and referring the patient to the pharmacist
- Training supportive personnel not to sell these items without the pharmacist's knowledge and approval
- Conducting counseling appropriate to ensure that the product is indicated
- Demonstrating use of the product to the patient

The Various Proposals for a Third Class of Drugs

Proponents of a third class of drugs have offered two methods by which it might be accomplished.

- A fixed class: A class for permanent placement of switched OTCs, medications that would never be placed into another class.
- A transition class: A "way-station" class where Rx-to-OTC drugs would remain for 2 to 5 years.[56] During this period the FDA should be notified of any adverse reactions. At the end of the transition period the agency would consider any adverse reactions reported and decide whether to move to full OTC sale status. Proponents of this approach argue that it could actually increase the number of OTC products available to patients. Further, they assert that it would reduce drug misuse since patients would receive

pharmacist counseling (since counseling would be mandatory prior to sale to determine whether the product is indicated). Also, proponents point out that a transition class could lower health-care costs by freeing physicians to spend more time with seriously ill patients because more minor ailments could be treated by pharmacists.

Supporters of a Third Class of Drugs

THE NATIONAL ASSOCIATION OF BOARDS OF PHARMACY (NABP)

The NABP passed a resolution in 1995 calling for legislation to create the third class.[57] This was a unanimous vote despite a recommendation from the executive committee against the measure, citing concerns that it would restrain consumer choice.

THE PHARMACISTS PLANNING SERVICE, INC. (PPSI)

The PPSI, a pharmacy advocacy group, petitioned the FDA to place ipecac, promethazine, hydrocortisone 1%, metaproterenol, phenylpropanolamine, and naproxen into a third class in 1991.[55] In 1995 the group presented a series of citizens' petitions in support of a third class of drugs to the FDA.[58,59]

The PPSI has charged that opponents of a third class of drugs are ignoring health problems associated with OTC-Rx interactions, as well as OTC products such as phenylpropanolamine, ephedrine, and ibuprofen. The PPSI has pointed out that OTC packaging is ineffective in conveying warnings.[58] The PPSI initially asked for a pharmacist-only class, but it now is seeking approval for a transitional class.

CONSUMER GROUPS

The National Consumers League (NCL), an organization that backed the establishment of the FDA in the early 1900s, strongly supports the third class.[58,60] The NCL is joined by the Consumer Federation of America, the Consumers Union, the National Insurance Consumer Federation, and the Public Health Citizen's Health Research Group.[61]

PHARMACISTS

Pharmacists as a whole back the concept of a third class. Understandably, pharmacy is seen by opponents as a special interest desirous of a monopoly to boost their profits at the expense of other retailers, who now enjoy a significant portion of the OTC market.[28,61–63]

THE NATIONAL COMMUNITY PHARMACISTS ASSOCIATION (NCPA)

The NCPA (formerly the National Association of Retail Druggists or NARD) passed a resolution calling for an interim drug category in 1982 (to be known as a "pharmacist legend" class) and has supported the concept since that time.[64,65] A NARD spokesperson suggested that a transition class would create a "buffer" period during which pharmacists can learn about newly switched medications before they are sold in locations with no health professional.

OTHER PROFESSIONAL ASSOCIATIONS

The American Pharmaceutical Association (APhA) and the American College of Apothecaries support a concept of the third class of drugs.[66,67]

Opponents of a Third Class of Drugs

THE FDA

The FDA, which has opposed a third class for many years, denied petitions from consumers and the NCPA (then known as NARD) for a third class in 1984.[55] The FDA contends that proponents have yet to show justification for a third class of drugs.[68] The FDA maintains that all OTC drugs are supposed to be properly labeled for safe and effective use and stresses that the agency acts appropriately when products do not provide proper information for safe and effective use.[68]

The FDA insists it lacks the authority to establish the third class, but given the power of the FDA, that position is debatable.[58]

THE NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

This manufacturers organization (formerly known as the Proprietary Association) is understandably against anything that might restrain consumers in buying their products.[55,69] In a 1990 position paper the NDMA stated their objections as follows[70]:

- Druggists (the term used by this organization) would have a monopoly, denying consumers the right to buy safe products at convenient locations of their own choice and at competitive prices and also denying general merchants (grocery stores, discount stores, department stores, and convenience stores, etc.) the right to sell these safe products.
- The restrictions imposed on a third class would result in increased costs and inconvenience to consumers by removing these products from grocery, discount, and convenience stores and other general retail outlets without any public health benefits.
- The concept had been rejected by the FDA.
- The concept had been rejected by the American Medical Association (AMA). (See "The American Medical Association [AMA]".)

An NDMA spokesman stated in 1992 that drugs are either safe for self-treatment or not, adding that the current two-tiered system is suitable.[58]

A former FDA commissioner has charged that drug manufacturers are concerned that the third class would cut into profits. The NDMA rebutted this charge, stating that the issue is consumer access.[55] The NDMA also cited the 1995 finding by the General Accounting Office (GAO) that a third class of drugs is not needed.[65] (See "The General Accounting Office [GAO]".)

THE GENERAL ACCOUNTING OFFICE (GAO)

The GAO, the chief investigating arm of the U.S. Congress, looked at the third class issue in 10 countries and decided that the success of the third class is tied to the role of pharmacists in the drug distribution system.[71] The GAO also determined, however, that, in countries with a third class of drugs, pharmacists often gather incomplete information on patient symptoms and histories and that pharmacist counseling was infrequent and incomplete.[72] Further, safeguards to

prevent drug misuse were circumvented. The GAO also stated that a third class of drugs would saddle pharmacists with time-consuming, costly tasks such as recording patient symptoms and medical conditions, names of practitioners who recommended products, amount of product purchased, patients' experiences with given products (including efficacy, side effects, and interactions with foods and drugs), and medical conditions.[65]

As a result of its investigation, the GAO concluded in 1995 that the need for a third class was not demonstrated.[55,73] The agency did note that the then-emerging concept of pharmaceutical care might change these views, but that it had not yet been implemented sufficiently to know its impact on OTCs.

THE AMERICAN MEDICAL ASSOCIATION (AMA)

The AMA passed a resolution against the third class in 1984. The organization has maintained that position ever since. The view of physicians is typified by a dermatologist who pointed out the lack of clinical diagnostic skills in pharmacists, the inability of the pharmacist to physically examine patients, and the difficulty the pharmacist would have in keeping complete medical records.[74]

OTHER OPPONENTS

The third class is opposed by companies and associations in the retail food, retail merchants, and direct selling industries, chambers of commerce, senior citizens' organizations, labor unions, farm organizations, the U.S. Department of Justice (on antitrust grounds), Congress, state legislatures, federal and state courts, and the Association of State Attorneys General.[67] Advertising agencies and television networks, which subsist on convincing consumers to buy OTC products through direct-to-consumer OTC ads, understandably are also opposed to the revenue loss that would result from the third class.

THE FUTURE OF A THIRD CLASS OF DRUGS

The outlook is not bright for a third class of drugs. Ironically, however, some pharmacists are voluntarily creating a third class by placing certain medications behind the counter such as asthma medications and laxatives abused by anorexics. Unfortunately, this gesture is meaningless when patients can simply go next door to buy the products in question. The action may even be counterproductive if it results in patients shopping at nonpharmacist outlets where counseling is not an option.

An alternative is for concerned pharmacists to place newly switched products under a sign that states: "This product has recently been released for use without a prescription. Your pharmacist would like to discuss the safe and effective use of the product if you have not yet used it without a prescription."[75]

SUMMARY

The FDA began an exhaustive process of review for most nonprescription product ingredients in 1972. During this three-phase process, which has taken close to three decades, drug manufacturers submitted evidence of ingredient safety and effectiveness. After data on drug ingredients were reviewed by expert advisory panels and FDA staff, the FDA specified the drug ingredients that pharmacists can recommend with confidence. The FDA also specified labeling requirements for nonprescription products. The FDA OTC review is ongoing, with new information emerging each year.

A large number of ingredients have become available to the consumer for self-care through a process known as the Rx-to-OTC switch. In some cases entirely new categories of nonprescription products have been created (e.g., vaginal antifungals, smoking cessation products, and androgenetic alopecia treatment). For these conditions patients often require more sophisticated counseling than was the case with older products.

Because of the dangers inherent in switching medications directly from tight prescription control to unrestricted sales, many groups have called for a third class of drugs, medicine that might be restricted to sales by a pharmacist. The concept is strongly supported by pharmacists and various pharmacy groups, but is vigorously opposed by physicians, the FDA, and those who manufacture nonprescription drug products.

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資料 3

4

CHAPTER

Legal and Regulatory Issues in Self-Care Pharmacy Practice

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This chapter analyzes the federal laws and regulations that govern the manufacturing, distribution, labeling, and marketing of the products commonly used by consumers for self-care. There are differences in the way that nonprescription drugs are regulated when compared with prescription drugs and other consumer health care products, such as dietary supplements and homeopathic medicines. It is important that health care providers have a basic understanding of these regulations so they can respond to their patients' questions and concerns about the self-care products they use.

Regulation of Nonprescription Drugs

The first major federal legislation enacted in the United States to regulate drugs was the Pure Food and Drug Act of 1906. "Unsafe" and "noneffícacious" drug products were not actually prohibited by the statute; drugs were required to meet only the standards of strength, quality, and purity claimed by the manufacturers. Laws did not mandate drug safety until passage of the 1938 Federal Food, Drug, and Cosmetic Act (FD&C Act). In 1951, an amendment to the FD&C Act in essence established two classes of drugs: prescription and nonprescription (also referred to as over-the-counter, or OTC). Prior to that time, manufacturers were free to determine to which category their drug product belonged. Drugs that could be used safely without medical supervision and had labeling that includes adequate directions for use could be marketed without a prescription. In 1962, a major amendment to the FD&C Act was enacted, requiring that all new drugs be shown to be effective, as well as safe, for their intended uses. As a result of this amendment, the Food and Drug Administration (FDA) undertook a review of the effectiveness of 4500 new drug products, including 512 nonprescription drugs that had been approved for safety since 1938.

In 1966, FDA contracted with the National Academy of Sciences/National Research Council to review these drugs. FDA took the information from the council and, by a procedure called the Drug Efficacy Study Implementation (DESI), determined the effectiveness of a majority of marketed prescription drugs. Drug products that were marketed prior to 1938 were "grandfathered" and were exempt from this DESI review. As DESI was nearing completion, focus turned to an extensive examination of the nonprescription drugs on the market. In 1972, FDA initiated a massive scientific review of the 700 active ingredients in 300,000 nonprescription drug formulations to ensure that they were safe and effective, and that they bore fully informative labeling. This review process, which is still underway, is often referred to as the "OTC Drug Review."

FDA is also responsible for the labeling of OTC drugs and for reclassifying (switching) drugs from prescription to nonprescription status. Consequently, nonprescription drugs that are on the market today fall into one of the three following categories (from a legal and regulatory perspective):

1. Approved via the drug approval process and either (1) reclassified (i.e., switched) from prescription to nonprescription or (2) approved directly as a nonprescription drug
2. Approved via the monograph process
3. On the market pending a determination under the OTC Drug Review monograph process as to the drug's disposition

Drug Approval Process

The FD&C Act requires that all new drugs introduced for marketing after 1938 be cleared in advance through a new drug application (NDA), which requires that the drugs be proven safe and effective for human use before being marketed. Products marketed before 1938 were exempted from the NDA requirement under a grandfather clause. Some currently marketed nonprescription drugs, such as aspirin, still fall under this clause. However, FDA's Division of OTC Drug Products has evaluated, or is in the process of evaluating, all nonprescription drugs

Editor's Note: Views presented in this chapter do not necessarily reflect those of the Food and Drug Administration.

for safety, effectiveness, and labeling, regardless of the date of marketing entry.[1]

A new chemical entity never before marketed in the United States would be classified as a new drug and, in most cases, initially be approved for prescription use only. An NDA for a nonprescription drug product can also be approved directly (without reclassification), which is what occurred with ibuprofen 200 mg (a dose that was never available by prescription). When a new drug is used for many years by many patients (referred to in the FD&C Act as "used for a material time and material extent"), it may be considered generally recognized as "safe and effective" and qualifies for marketing as a nonprescription drug. Additionally, under new regulations, certain data regarding the safety, efficacy, and use of the product in a foreign country can be used to determine if a drug can be marketed as a nonprescription product in the United States.[2]

Some drugs are available by prescription and nonprescription in the same strength, but marketed for different uses. For example, meclizine is available OTC for motion sickness, which is easy to diagnose, and by prescription for vertigo, which is a complex condition that is not easy to diagnose and treat.

New Drug Application

An NDA is necessary for a drug that is defined by the FD&C Act as not being recognized as safe and effective until it has been reviewed and approved by FDA.[3] The approved NDA is manufacturer specific and allows only the sponsor (applicant) to market the product. Any other manufacturer interested in marketing a similar product would first need to seek FDA approval through its own NDA. In some cases, a full NDA is not necessary for the second manufacturer; an abbreviated NDA may be submitted instead, eliminating the need for duplicative testing. All NDAs must contain complete labeling information, with final printed labeling being the usual last step before approval (see Drug Facts Labeling for Nonprescription Drugs).

OTC Monograph Process

An OTC monograph is developed for therapeutic classes of ingredients that are generally recognized as safe and effective. A manufacturer desiring to market a product containing an ingredient covered under an OTC monograph need not seek FDA's prior approval. In this case, marketing is not exclusive; any manufacturer may market a similar product without specific approval. Under the monograph approach, all data and information supporting safety and efficacy of the product and its nonprescription status are publicly available. The FDA Division of OTC Drug Products has established the monographs through a complex, administrative process called rulemaking, which allows for comments from the general public, manufacturers, and other interested parties. Each individual rulemaking has resulted in an administrative record that is extensive. Figure 4–1 illustrates the process by which the OTC drug monographs are reviewed.

Under a final OTC monograph, the manufacturer has considerable flexibility in labeling. All the required monograph labeling must be included; for example, antacids must include terms such as heartburn, acid indigestion, and sour stomach. In addition, certain language not included in the monograph may be used in specific places on the label without prior approval. For example, *hospital-tested* or *pleasant-tasting antacid* are terms considered outside the scope of the monograph, but permissible in antacid labeling. However, even though these permissible terms are not pre-cleared, they are subject to the general labeling provision of the FD&C Act and may not be false or misleading.

Monographs primarily address active ingredient(s) in the product and, in most cases, final formulations are not subject to monograph specifications. Manufacturers are free to include any inactive ingredients that serve a pharmaceutical purpose, provided those ingredients are safe and do not interfere with either product effectiveness or any required final product testing. In a few instances, even though the product contains generally recognized safe and effective ingredients, it may need to meet a monograph-testing procedure; for example, antacids must pass an acid-neutralizing test.

Because the drugs in the OTC monograph system are generally recognized as safe and effective, there is no legal or regulatory requirement to report adverse events associated with these products. Historically, any changes in ingredient status and labeling have occurred as a result of adverse drug findings reported in the literature or through similar public mechanisms. FDA's MedWatch program is a safety information and adverse event reporting system for medical products, including OTC drugs. Health care professionals and consumers are encouraged by FDA to report serious adverse events that they suspect may be associated with the drugs they dispense, prescribe, or use. Reporting can be done online, by phone, fax, or mail. The Web site is www.fda.gov/medwatch.[4] FDA uses this information to examine adverse trends and take appropriate action, if necessary (see Adverse Event Reporting).

Labeling and Packaging Issues

"Drug Facts" Labeling for Nonprescription Drugs

It is essential that the labeling of OTC drug products clearly communicate to the consumer the important information on how to use the product safely and effectively. In recent years, FDA and consumers have been

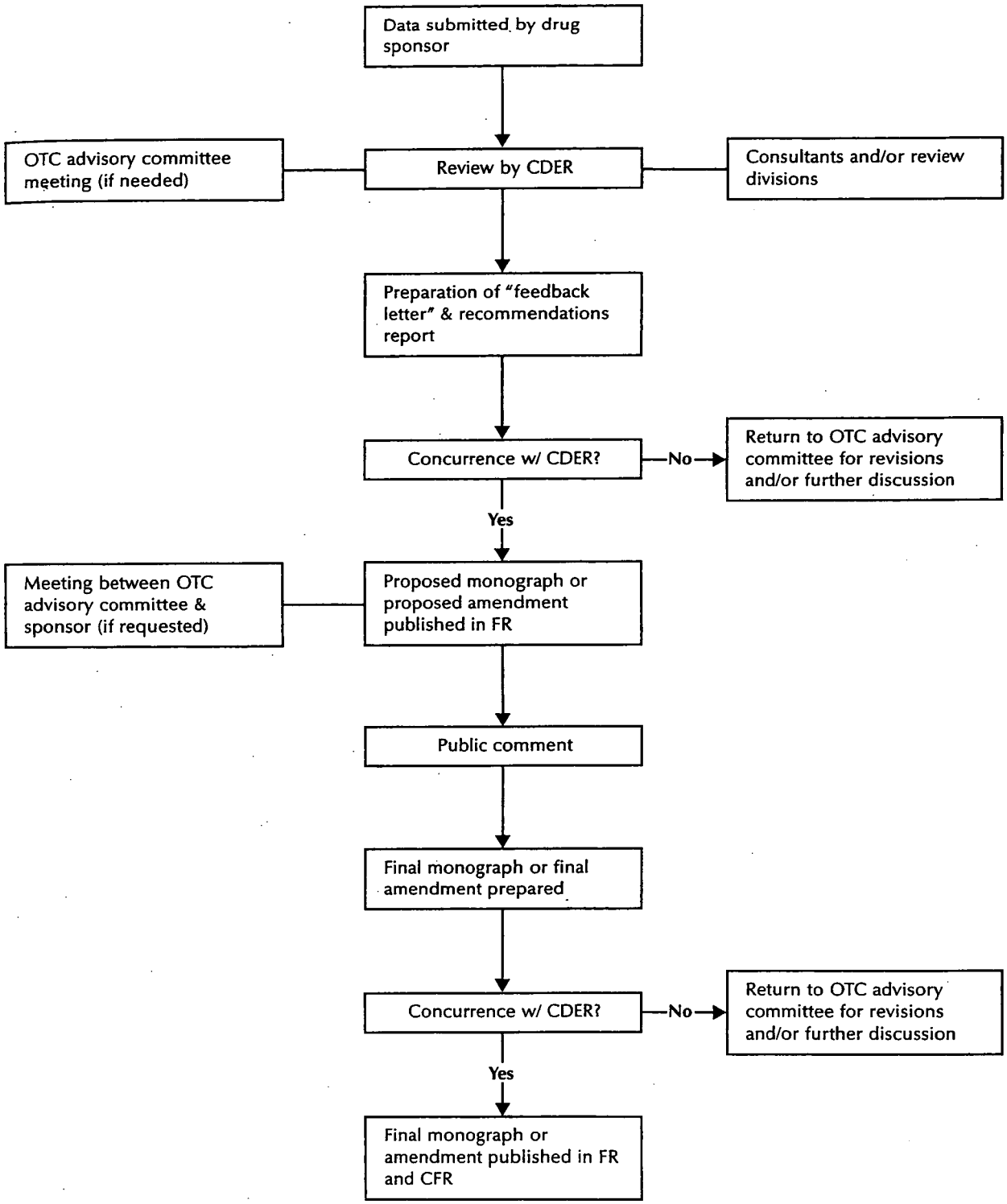


FIGURE 4–1 Over-the-counter drug monograph review process. (Adapted from U.S. Department of Health and Human Services, Food and Drug Administration. The CDER Handbook. Available at: http://www.fda.gov/cder/handbook. Accessed October 3, 2003.) Key: CDER, Center for Drug Evaluation and Research; FR, *Federal Register;* CFR, *Code of Federal Regulations.*

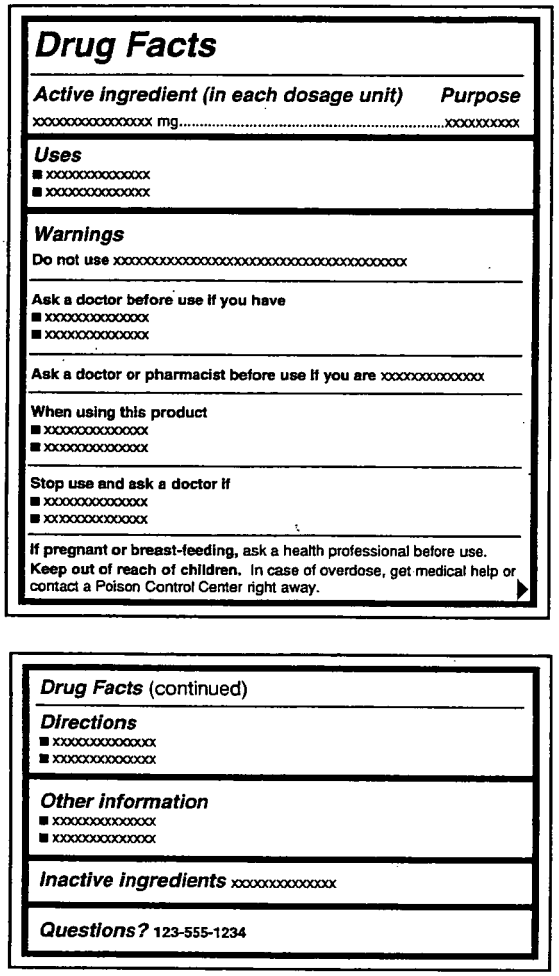


FIGURE 4–2 Drug facts labeling outline. (Source: 21 CFR 201.66.)

concerned about the adequacy of labeling for nonprescription drugs. This concern is heightened because an increasing number of prescription drugs are being switched from prescription to OTC status. Many of these "switch" drugs require the consumer to perform more sophisticated self-diagnostic and self-monitoring evaluations. Therefore, to provide adequate directions and safety information to consumers, a greater number of sophisticated messages must be communicated through the OTC label.

Recognizing these concerns, OTC drug labeling is changing. FDA regulations now require a standardized content and format for the labels on the estimated 100,000 OTC drugs on the market.[5] OTC drug labels will have an area on the package designated as the "Drug Facts" box, which contains the information that is required by FDA to be on the label.[6] FDA established an implementation plan dependent on the monograph and approval status of the product; most OTC labels must use the Drug Facts format by 2006. An OTC product that lacks the labeling after its required implementation date may be considered misbranded and subject to the same enforcement approach that FDA can take with other misbranded drugs, including issuance of a warning letter, product seizures, and injunctions.

The new regulations are intended to make it easier for consumers to read and understand information about the product's benefits and risks and how it should be taken. It will also help to ensure that consumers select the right product to meet their needs. The format will enable consumers to more readily and easily determine whether a product contains ingredients that they need, do not need, or should not take. It will also be easier for consumers to compare similar products to determine which product has the appropriate ingredients for their symptoms or personal health situation.

The Drug Facts labeling format, with standardized headings and subheadings, will use terms that are more familiar to consumers. For example, the new label will refer to *uses* instead of *indications*, and it will no longer use the terms *precautions* or *contraindications*. Lay terms will be used, instead of medical jargon(e.g., *lung* instead of *pulmonary*).

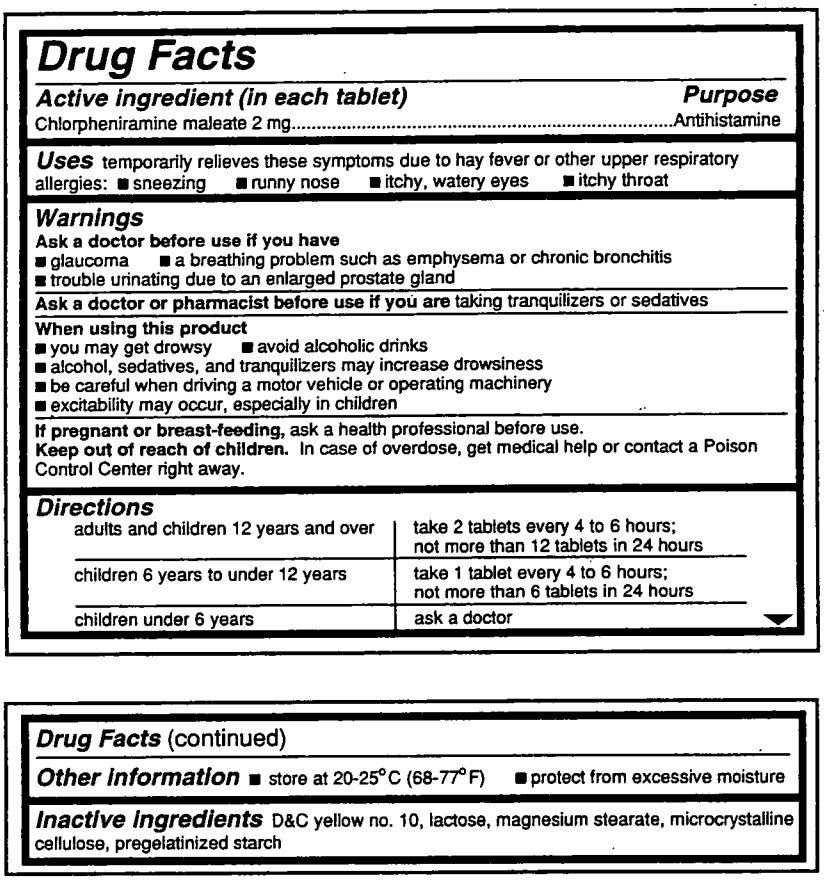
The population of persons 65 years of age or older is increasing. Older people are significant users of OTC products, and they may have greater difficulty reading product labels because of decreasing visual functioning. The labeling requirements set a minimal type size that labels must use, and labels cannot use any type smaller than the minimal standard. An easy to read font style is also required, as are other graphical features that enhance the ability to read the information on the label clearly.

Pharmacists should become familiar with the Drug Facts format. It is an essential counseling tool for OTC drugs. The Drug Facts format allows pharmacists to readily find information on the label and to point it out to the patient. Figure 4–2 illustrates the basic Drug Facts format and the standardized headings and order of information. Figures 4–3 and 4–4 show examples of the Drug Facts format.

Dietary supplements are not regulated as "drugs" under the FD&C Act. Consequently, they do not follow the Drug Facts format. Dietary supplements must be labeled in accordance with the regulations discussed in Dietary Supplements.

Expiration Date Labeling

Most OTC drug products are required to include an expiration date on the labeling.[7] This date is the date beyond which the product should not be used because the stability, potency, strength, or quality may have been affected over time. FDA regulations govern how this date is determined and tested. Most OTC drug product



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Chlorpheniramine maleate 2 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings

Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ you may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)

Other information ■ store at 20-25°C (68-77°F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

FIGURE 4–3 Drug facts labeling example for an antihistamine product. (Source: 21 CFR 201.66.)

labels must also include any special storage conditions or requirements for the product. OTC drug products that do not have a dosage limit and are stable for at least 3 years are exempt from the requirement to include the expiration date on the label. Such products include certain topical drugs, skin protectants, lotions, and astringents.

Health care providers should remind patients to check their OTC product labels periodically to ensure that the expiration date has not passed. Patients often ask whether an OTC drug product that they have at home is still good if the expiration date has passed. Although rarely does a safety issue arise from using a drug that is modestly passed its expiration date, the patient should be advised that the product probably has lost some of its ability to work as effectively as possible for the particular symptom or medical problem and it should be discarded.

Tamper-evident Packaging

In the wake of several high-profile tampering incidents involving OTC drug products, FDA instituted several packaging, labeling, and certain manufacturing requirements in an effort to protect consumers. Historically, the term *tamper-resistant* was used to describe methods used to prevent tampering. The focus is now shifted to "tamper-evident," to heighten consumer awareness to any evidence of tampering, rather than implying that a particular product is difficult to breach or is tamper-proof.

OTC drug products must have one or more barriers to entry that, if breached or missing from the package, provide consumers with evidence that tampering may have occurred.[8] Packages must contain unique designs or other characteristics that typically cannot be duplicated. Additionally, to alert the consumer to the specific tamper-evident features, the retail package must contain a statement that identifies the feature, is prominently placed on the package, and is placed in a way that it will be unaffected if the tamper-evident feature is missing or breached. For example, the statement on a bottle with a shrink band might say, "For your protection, this bottle has an imprinted seal around the neck."

Consumers should be educated to look and check for the tamper-evident features on every OTC product

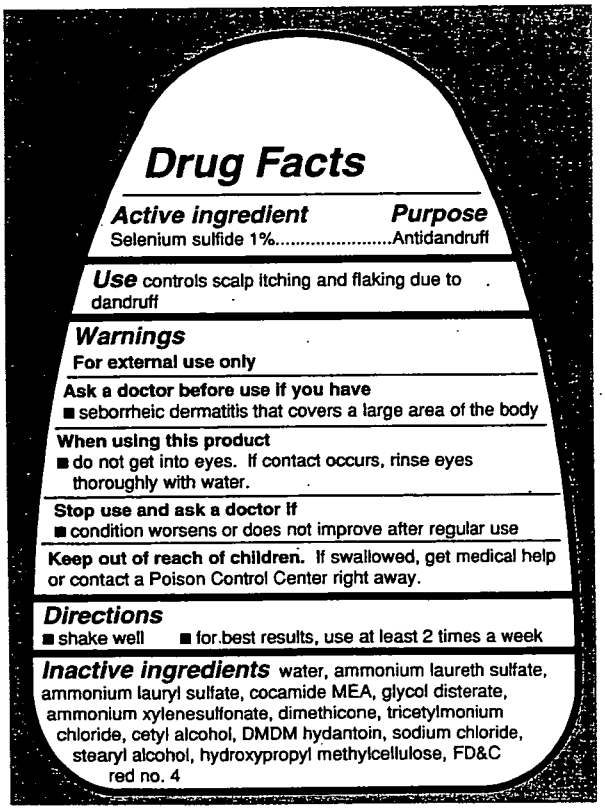


FIGURE 4-4 Drugs facts labeling example for an antidandruff product. (Source: *Federal Register.* 1999;64:13301).

that they purchase and, if the features are missing or look suspicious, to return the product to the pharmacy or store where it was purchased.

Drug Reclassification: Prescription-to-OTC Switch

Traditionally, a prescription-to-OTC switch occurs in one of three ways:

1. The drug is switched through the OTC drug review process.
2. The manufacturer requests the switch by submitting a supplemental application to its approved NDA.
3. The manufacturer or other party petitions FDA.

Through the OTC drug review process, panels of nongovernment experts are reviewing the prescription drug products that were on the market before 1962 to determine if some are appropriate for OTC marketing. This ongoing process has produced more than 40 reclassifications from prescription-only to nonprescription status since the 1970s. Overall, there are more than 700 OTC drug products on the market today that use ingredients or dosages that were at one time available only by prescription. The categories of drug products that have seen the most activity in this area are analgesics, histamine antagonists, antifungal medications, smoking deterrents, and topical medications used to treat minor skin conditions. Drug products in these categories are good candidates for prescription to OTC switching because they are used to treat self-limiting conditions that are easily identified by lay persons, with or without the assistance of a health care provider.

Another common way that a prescription drug is switched to OTC status is by submission of data by the manufacturer to FDA, in the form of a supplemental NDA, demonstrating that the drug is appropriate for self-administration. Typically, these applications include studies showing that the product's labeling can be read, understood, and followed by a consumer without the guidance of a health care provider.[9] FDA reviews this information, along with any information known about the drug from its prescription use history. All of this information is usually presented to FDA's Nonprescription Drug Advisory Committee, which is composed of nongovernment experts. This committee serves as a forum for the exchange of ideas and provides a recommendation to FDA as to whether the drug in question should be switched to OTC status. FDA is not bound by the committee's recommendation, but it usually follows their advice.

A company, usually the manufacturer, can also petition FDA to switch a drug or class of drugs to OTC status. In recent years, however, FDA has received petitions originating not from the drug's manufacturer, but from third-party payers.[10] Citing FDA's statutory authority under Section 503(b) of the FD&C Act to remove the prescription requirement for a drug when doing so will not create a threat to public health, third-party payers have petitioned FDA, seeking to have certain drugs switched from prescription to OTC status. Three recent examples include the nonsedating antihistamines loratadine, fexofenadine, and cetirizine. In 2002, loratadine was switched to OTC status after the manufacturer dropped its original opposition to the switch. As of this writing, fexofenadine and cetirizine have retained their prescription status.

It is easy to understand why third-party payers, employers, and state and federal health care programs have taken a strong interest in increasing the number of prescription to OTC switches. The availability of OTC products for consumer self-treatment may save millions of dollars in health care costs by reducing the number of physician visits, preventing unnecessary sick days from work, and decreasing costs associated with the advancement of disease states that could have been limited by treatment with an OTC product. In one study, it was estimated that Americans saved approximately $1 billion in health care costs in the first 3 years after topical hydrocortisone acetate was switched from prescription to OTC status.[11]

Exact standards or switch criteria are very difficult to set because many factors must be carefully considered.

TABLE 4–1 Selected List of Reclassified Drugs

Ingredient	Indications	Ingredient	Indications
Acidulated phosphate fluoride	Dental rinse	Loperamide	Antidiarrheal
Brompheniramine maleate	Antihistamine	Miconazole	Antifungal
Butoconazole	Antifungal	Minoxidil	Baldness
Chlorpheniramine maleate	Antihistamine	Naproxen	Analgesic
Cimetidine	Heartburn	Nicotine	Smoking cessation
Clemastine fumarate	Antihistamine	Nicotine polacrilex	Smoking cessation
Clotrimazole	Antifungal	Nizatidine	Heartburn
Cromolyn sodium	Allergy prevention/treatment	Omeprazole	Heartburn (proton pump inhibitor)
Dexbrompheniramine	Antihistamine	Oxymetazoline	Decongestant
Diphenhydramine	Antihistamine	Phenylephrine	Decongestant
Docosanol	Cold sore/fever blister	Pseudoephedrine	Decongestant
Doxylamine	Sleep aid	Pyrantel pamoate	Pinworm treatment
Dyclonine	Oral anesthetic	Ranitidine	Heartburn
Ephedrine sulfate	Bronchodilator, vasoconstrictor	Sodium fluoride	Dental rinse
Famotidine	Heartburn	Stannous fluoride	Dental rinse or gel
Haloprogin[a]	Antifungal	Terbinafine	Antifungal
Hydrocortisone	Antipruritic, anti-inflammatory	Tioconazole	Antifungal
Ibuprofen	Analgesic	Tolnaftate	Antifungal
Ketoconazole	Antifungal (shampoo only)	Triclosan	Antigingivitis
Ketoprofen	Analgesic	Triprolidine	Antihistamine
Loratadine	Nonsedating antihistamine	Xylometazoline	Decongestant

[a] Although FDA approved haloprogin for nonprescription use, no currently available nonprescription antifungals contain this agent.

The information that must be gathered from the expert opinions of advisors and consultants regarding a drug's classification as nonprescription includes, but is not limited to, the following:

- Is the condition self-diagnosable?
- Is the condition self-treatable?
- Does the product possess misuse and/or abuse potential?
- Is the product habit forming?
- Do methods of use preclude nonprescription availability?
- Do the benefits of availability outweigh the risks?
- Can adequate directions for use be written?

Further scientific scrutiny typically addresses the following questions as well:

- Does the reclassification candidate have an adequate margin of safety?
- Has the reclassification candidate been used for a sufficiently long time (e.g., 3–5 years) on the prescription market to yield a full characterization of its safety profile?
- Has a vigorous risk analysis been performed? If so, what are the results?
- Has the efficacy literature been reviewed in a way that supports the expected use and labeling of the reclassification candidate?
- Have potential drug interactions for the reclassification candidate been characterized?

Table 4–1 lists some of the prescription drugs reclassified as nonprescription since 1975. The most recent addition to this list is omeprazole, a proton pump inhibitor. FDA had initially rejected omeprazole for OTC status based on concerns about the ability of the average consumer to comprehend the proposed labeling, and concerns about the efficacy of the OTC dosage proposed by the petitioner, which was 10 mg, or half of the

prescription dose.[12] FDA's concerns were addressed by the petitioner, and the drug is now available without prescription in the same 20 mg dosage as was previously available only by prescription.[13]

Other drugs that have been considered for a switch to OTC status include two of the statins, lovastatin and pravastatin. The issue of whether a cholesterol-lowering drug should be granted OTC status has raised concerns, including the ability of the public to understand cholesterol in general, and the need for routine blood testing in particular. Also, if approved for OTC status, the statins would be the first OTC drugs indicated for long-term use to manage and control a potentially life-threatening condition, as opposed to short-term use to control symptoms, such as a runny nose or heartburn. The manufacturers for these recently rejected drugs have renewed their petitions seeking OTC status for their products.

Activity in the area of prescription-to-OTC switches is certain to increase in the coming years. Health care providers can reasonably expect that more prescription drugs will be subjected to review in the coming years, as payers, the pharmaceutical industry, and FDA continue to grapple with the difficult task of balancing economic pressures with safety concerns. As more drugs are switched to OTC status, health care providers will be called on to play a greater role in assessing the need for treatment and in monitoring the use of these drugs.

Marketing Issues

Product Line Extensions

Product line extensions are increasingly becoming more commonplace in the OTC market. Product line extensions include new doses, formulations, combinations of ingredients, or even a totally different therapeutic entity (e.g., a device) of a brand name product that was originally marketed as a single-ingredient product at a specific dose to treat a specific symptom. In developing product line extensions, manufacturers hope to capitalize on the loyalty created by consumer recognition and trust of a brand name.

Product line extensions can create consumer confusion and inappropriate patient drug selection and use. Pharmacists must be familiar with the range of products within a brand name to recommend safely and correctly and to counsel patients on these products. Particular care must be taken with respect to the active ingredients because these often differ within a product line. Some product line extensions that carry the original brand name as the prefix retain the active ingredient of the original product, but strengths may vary. Some manufacturers with many product line extensions continue to use the original brand name as the prefix, but use none of the active ingredients of the original products and attach a suffix for differentiation (e.g., PM, EX, DM, AF, Cold and Flu, Non-Drowsy, Extra, Allergy-Sinus-Headache, Advanced Formula, PH, Day/Night, and Plus).

Nonprescription Drug Advertising

The Federal Trade Commission (FTC) is responsible for matters involving claims made in advertisements for OTC drug products. FDA handles most matters involving the labeling, as opposed to the advertisement, of OTC drugs. In the 1970s, the FTC Act was amended to prohibit advertisers from using language to describe the therapeutic benefits of an OTC drug product that differs from language approved by FDA for use in the labeling of the product.

The FTC Act requires that advertising be truthful and nondeceptive. Depending on the claim, advertisers may be required to back up their representations with competent and reliable scientific evidence, including tests, studies, or other objective data.

In 1973, the National Association of Broadcasters and the Consumer Healthcare Products Association developed a code of guidelines for manufacturers to follow in creating television advertisements for nonprescription drugs. The guidelines, which are updated periodically, set standards for truthfulness and honesty, and suggest that an advertisement should, among other things, do the following:

- Comply with all relevant applicable laws and regulation.
- Urge the consumer to read and follow label directions.
- Contain no claims of product effectiveness that are unsupported by clinical or other scientific evidence, responsible medical opinion, or experience through use.
- Present no information in a manner that suggests the product prevents or cures a serious condition that must be treated by a licensed practitioner.
- Emphasize the uses, results, and advantages of the particular product.
- Reference no doctors, hospitals, or nurses, unless such representations can be supported by independent evidence.
- Present no negative or unfair reflections about competing nonprescription drug products, unless those reflections can be supported scientifically and presented in a manner so consumers can perceive differences in the uses.

Consumers should be analytical when listening to or reading marketing messages, particularly because some can be subjective, superficial, vague, or potentially misleading. Health care professionals, particularly the pharmacist and the primary care provider, are well positioned to assist patients in separating fact from ambiguity with regard to OTC drug use and serve the public

interest as an objective, informed source of OTC drug information.

Dietary Supplements

During the past decade, one of the fastest growing areas of consumer self-care has been the use of dietary supplements. It is important for consumers, as well as health care providers, to understand that dietary supplements are *not* drugs. Unlike drugs, dietary supplements are not intended to diagnose, cure, or treat a medical disease or condition. Nor are dietary supplements regulated by FDA, or any other state or federal governmental agency, as stringently as are prescription and nonprescription drugs.

Dietary supplements are regulated under the federal Dietary Supplement Health and Education Act of 1994 (DSHEA). DSHEA established a formal definition of *dietary supplement* using several criteria. According to DSHEA, a dietary supplement is a product (other than tobacco) that is:[14]

- Intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- Intended for ingestion in pill, capsule, tablet, or liquid form.
- Not represented for use as a conventional food or as the sole item of a meal or diet.
- Labeled as a "dietary supplement."

Dietary supplements include products such as an approved new drug, a certified antibiotic, or a licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

Since the passage of the DSHEA, dietary supplement sales have grown by nearly 80%, from $8.8 billion to an estimated $15.7 billion in 2000. Scientific research on the associations between supplements and health is accumulating rapidly. The number of products and the variety of uses for which they are promoted have increased significantly in the last few years. Consider these statistics.

- Fifty-seven percent of Americans of advanced age used dietary supplements.
- Fifty-three percent of Americans of advanced age are satisfied with dietary supplements.
- Sixty percent of women and 46% of men have used a dietary supplement.
- Thirty percent of women and 23% of men have used dietary supplements to treat common ailments.
- Thirty-five percent of postmenopausal women used dietary supplements for a condition associated with menopause.
- In 2000, the two leading categories of supplements were "general health" and "sports/energy/weight loss," with sales of $4.4 billion and $4.7 billion, respectively.
- The top selling herbal supplements in the United States in 2000 were the three Gs: garlic, ginkgo biloba, and glucosamine.[15]

Many consumers swear by the health benefits of the dietary supplements they use. A growing body of scientific evidence supports the health benefits of many supplements. As an example, one study estimates that 130,000 hip fractures and $2.6 billion of direct medical costs could have been avoided in 1995 if patients aged 50 and older habitually consumed about 1200 mg/day of supplemental calcium.[16]

Along with the rapid increase of the use of dietary supplements, there has been an increase in the reported adverse effects associated with these products. Since 1993, FDA has received about 7000 dietary supplement–related voluntary adverse event reports. Since 1999, the annual number of voluntary adverse event reports submitted to FDA has more than doubled:[17]

- 1999: 528 adverse event reports
- 2000: 500 adverse event reports
- 2001: 553 adverse event reports
- 2002: 1214 adverse event reports

Ephedra, kava, and comfrey are three examples of dietary supplements that have come under scrutiny by FDA as a result of the number and severity of adverse events associated with their use.[18] Whether these reported adverse events are related to dangers inherent with the use of the product, consumer misuse, or any other reason, because of the widespread use of dietary supplements for self-care, it is incumbent upon all health care providers to understand the uses, benefits, and potential hazards associated with these products.

Regulatory Oversight of Dietary Supplements

FDA regulates dietary supplements differently from the way it regulates prescription and nonprescription drugs. Before DSHEA, dietary supplements were generally subjected to the same regulatory requirements that applied to food products. DSHEA amended the FD&C Act, and prohibits Congress or FDA from regulating supplements as food additives or drugs.[19]

The regulations applicable to dietary supplements under DSHEA are far less stringent than those that apply to drugs. First, unlike prescription and nonprescription drugs, which must be proven to be safe and effective by