

THE FOOD & DRUG LETTER®

Issue No. 666
Dec. 20, 2002

CLARITIN APPROVAL MARKS SIGNIFICANT SHIFT IN RX-TO-OTC SWITCHES

The switch of Schering-Plough's Claritin to over-the-counter (OTC) status set new precedents whose implications will reach far beyond drugstore shelves and affect the pharmaceutical industry for years.

FDA's Nov. 27 approval of OTC Claritin, the non-sedating antihistamine (loratadine) culminated an extraordinary odyssey through the regulatory system. The small tablet is at the confluence of powerful interests – drug companies, regulators, payers and consumers.

Previously one of the nation's top-selling prescription drugs, Claritin is the latest in a number of prescription drugs that have switched to OTC status (*see "Rx Drugs Switched to OTC," Page 3*). Some industry observers have forecast a rising tide of Rx-to-OTC switches, and indeed a slew of drugs are reportedly waiting in the wings to seek OTC status (*see "Rx-to-OTC Switch Candidates," Page 3*).

Switching a product from prescription to OTC involves critical decisions for drug makers. A properly executed Rx-to-OTC switch can maximize a company's revenue from a drug, and may provide an additional bonus of exclusivity. But the transition to OTC is also fraught with risks and may not always be in the best interests of pharmaceutical companies or patients, experts say.

Opening Of OTC Floodgates Uncertain

Whether the OTC approval of Claritin heralds an opening of the floodgates remains to be seen. What's clear is that the rules of the game are changing. In this issue, *The Food & Drug Letter* explores some of the lessons gleaned from the Claritin switch and examines key issues facing drug makers eyeing switches.

Claritin has been a success since its approval as a prescription-only drug in April 1993. One of the first of a new generation of antihistamines, Claritin is less likely to cause drowsiness than traditional antihistamines based on diphenhydramine. Its safety profile offers important benefits for the 10 percent to 30 percent of adult Americans who suffer from seasonal allergy symptoms. Claritin generated \$3.1 billion in sales annually for Schering-Plough. That figure represented almost one-third of the company's revenue.

Other second-generation antihistamines include Aventis' Allegra (fexofenadine) and Pfizer's Zyrtec (cetirizine).

EDITOR'S NOTE: *The Food & Drug Letter* will not be published Jan. 2. The next issue will be Jan. 8.

On July 22, 1998, Wellpoint Health Networks petitioned the FDA to switch Claritin, Zyrtec and Allegra from prescription to OTC status. Formed in 1992 by Blue Cross of California's managed care business, Wellpoint is

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one of the nation's largest health insurers, providing benefits for more than 40 million members.

In its petition, Wellpoint argued that the second-generation antihistamines were safer and more effective than antihistamines currently sold OTC, and therefore do not meet the criteria for prescription status. The insurer said that consumers want easy access to affordable healthcare and would prefer to use less expensive medications that don't require an office visit for a prescription.

"The OTC status of loratadine, whether Claritin or a generic, is in the best interest of allergy sufferers nationwide," said Robert Seidman, Wellpoint's chief pharmacy officer. "It lowers the cost and eases access. Any member who feels they need to consult with a physician can consult today just like they did yesterday."

Wellpoint's interests also include financial considerations. The OTC switch of the third-generation antihistamines is expected to save the company about \$90 million – \$45 million from prescription costs and \$45 million for copays.

"Our responsibility, whether to an employer group or an individual subscriber, is to provide broad access to pharmaceuticals in an affordable manner," said Seidman. "We're going to take every opportunity to encourage our members who have chronic diseases to stay on their meds, to think about gold standard generic drugs, and we're going to foster conversion of safe and effective drugs from prescription to OTC status. It's a complicated but complete strategy to protect the affordability of the prescription drug benefit."

Wellpoint's move took many in the pharmaceutical industry by surprise. Never before had a payer group asked that a class of drugs be designated OTC. When such a request is filed with FDA, it is typically from a drug company that also provides scientific data to back up the claim that the product is safe for OTC use as labeled – none of which Wellpoint submitted with its petition.

Can a payer force a medication to go OTC without the consent of the drug company sponsor? The definitive answer, according to some of the nation's top experts surveyed by *The Food & Drug Letter*: Maybe.

Switch Criteria

Under the Food, Drug and Cosmetic Act (FDCA), a drug is presumed available OTC unless it has toxic effects, requires a doctor's supervision, or there is some other compelling reason to protect the public health. For a drug to be sold OTC, a patient must be able to safely diagnose his or her condition, understand the drug regimen and use the drug appropriately without professional guidance. Also, the drug itself must not have any significant side effects.

There are three ways that a prescription drug can be switched to OTC status:

1. The FDA can remove prescription restrictions if it determines they are not necessary to protect public health and if it deems the drug safe and effective for self-medication.
2. Any "interested person" – usually a drug sponsor – can file a supplemental new drug application (NDA) for an approved prescription drug.
3. Any interested person who wants an Rx-to-OTC switch can file a citizen petition asking the FDA to consider changing a drug's status.

Wellpoint's petition seeking the OTC switch for Claritin, made under the third of the above options, drew fire from Schering-Plough and other drug makers.

During a May 2001 hearing before the Nonprescription Drugs and Pulmonary and Allergy Drugs Advisory Committees, which met to consider the OTC switch of second-generation antihistamines, Schering-Plough contended that switching Claritin to OTC would not be in the best interest of patients. Changing the prescription status of Claritin would force patients to

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Rx DRUGS SWITCHED TO OTC

Drug	Company	Type	Year
Gyne-Lotrimin (clotrimazole)	Schering-Plough	Topical antifungal	1990
Aleve (naproxen)	Bayer	Analgesic	1993
Femstat (butoconazole)	Bayer	Topical antifungal	1995*
Imodium (loperamide)	McNeil	Antidiarrheal	1995
Lamisil (terbinafine HCl)	Novartis	Topical antifungal	1995
Orudis (ketoprofen)	Lederle	Analgesic	1995
Pepcid (famotidine)	Johnson & Johnson	Antacid	1995
Tagamet (cimetidine)	GlaxoSmithKline	Antacid	1995
Tavist (clemastine fumarate)	Novartis	Antihistamine	1995
Zantac (ranitidine HCl)	GlaxoSmithKline	Antacid	1995
Axid (nizatidine)	Lilly	Antacid	1996
Monistat (miconazole nitrate)	McNeil	Topical antifungal	1996
Nicorette (nicotine polacrilex)	GlaxoSmithKline	Nicotine replacement	1996
Rogaine (minoxidil)	Pharmacia	Hair loss	1996
NasalCrom (cromolyn sodium)	Pharmacia	Bronchodilator	1997
Nizoral (ketoconazole)	McNeil	Dandruff shampoo	1997
Vagistat (tioconazole)	Bristol-Myers Squibb	Topical antifungal	1997
Claritin (loratadine)	Schering-Plough	Antihistamine	2002

*Discontinued in January 2001

Rx-TO-OTC SWITCH CANDIDATES

Drug	Company	Type
Allegra (fexofenadine HCl)	Aventis	Antihistamine
Beconase (beclomethasone)	GlaxoSmithKline	Bronchodilator
Celebrex (celecoxib)	Pharmacia/Pfizer	Analgesic
Denavir (penciclovir)	Novartis	Antiviral
Diflucan (fluconazole)	Pfizer	Vaginal yeast infection
Famvir (famciclovir)	Novartis	Antiviral
Flonase (fluticasone propionate)	GlaxoSmithKline	Antihistamine
Imitrex (sumatriptan)	GlaxoSmithKline	Analgesic
Lescol (fluvastatin)	Novartis	Anti-cholesterol
Mevacor (lovastatin)	Merck	Anti-cholesterol
Nasonex (mometasone furoate monohydrate)	Schering-Plough	Antihistamine
Pravachol (pravastatin sodium)	Bristol-Myers Squibb	Anti-cholesterol
Prevacid (lansoprazole)	TAP	Antacid
Prilosec (omeprazole)*	AstraZeneca	Antacid
Protonix (pantoprazole sodium)	Wyeth	Antacid
Proventil (albuterol)	Schering-Plough	Bronchodilator
Spectazole (econazole nitrate)	Johnson & Johnson	Antifungal
Sporanox (itraconazole)	Johnson & Johnson	Antifungal
Vancenase (beclomethasone)	Schering-Plough	Antihistamine
Vanceril (beclomethasone)	Schering-Plough	Bronchodilator
Ventolin (albuterol)	GlaxoSmithKline	Bronchodilator
Vioxx (rofecoxib)	Merck	Analgesic
Zocor (simvastatin)	Merck	Anti-cholesterol
Zovirax (acyclovir)	GlaxoSmithKline	Antiviral
Zyrtec (cetirizine HCl)	Pfizer	Antihistamine

*OTC switch pending

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diagnose themselves, self-treat and pay the entire cost of their allergy medications.

“We believe that prescription status of these medications is necessary to protect and optimize public health,” Robert Spiegel, the company’s chief medical officer, told the committees.

Other drug company officials also tried to poke holes in Wellpoint’s arguments. Francois Nader, senior vice president for North American medical and regulatory affairs at Aventis, said that while Wellpoint described sedating antihistamines as “dangerous,” the insurer’s own formulary reserved the second-generation antihistamines for patients “who have failed or are unable to tolerate over-the-counter therapy.”

Schering-Plough and Aventis also argued that improper use of OTC second-generation antihistamines could lead to health problems by masking serious illness, since sniffing and sneezing could be symptoms of asthma or other conditions. Among others that opposed the switch was the National Consumers League, which contended that the OTC switch would eliminate an entire class of nonsedating antihistamines. Making the drugs OTC would reduce consumers’ choice to self-medication with less expensive sedating drugs, putting them in danger of accidents. Others against the switch were:

- ◆ The American Academy of Asthma, Allergy and Immunology
- ◆ The American Academy of Otolaryngic Allergy
- ◆ The patient advocacy group Asthma Network/Mothers of Asthmatics

By a vote of 19 to 4, the committee overwhelmingly recommended the OTC switch of Allegra, Claritin and Zyrtec. More than a year later, the FDA, which usually follows the recommendations of its advisory committees, still has not issued a decision on the Wellpoint petition.

In theory, the agency could grant Wellpoint’s petition based on safety and efficacy data already

received. However, the FDA is unlikely to take such dramatic unilateral action, agency officials said.

“There is something in the law that if a drug can be sold without a prescription, it should be,” said David Hilfiker, project manager in the Drug Center’s Division of Over-the-Counter Products. “We traditionally haven’t put ourselves in the position to force a company to take a drug [OTC].”

Pharmaceutical Research and Manufacturers of America (PhRMA) strongly opposes the Wellpoint petition and the strategy of switching by fiat.

“We believe that’s inappropriate,” said spokesman Jeff Trehwitt. “FDA should take a drug over the counter only in active collaboration with the sponsoring company. It’s the company that took this through the 12-15-year drug approval process, generating an NDA with as many as 100,000 pages of scientific data. They truly know the medicine best.”

If Wellpoint succeeds, observers have forecast a flood of citizen petitions requesting OTC switching for a range of drugs, including those for asthma, diabetes, osteoporosis, oral herpes infection and contraception.

Wellpoint has no plans to target any other drugs. “There aren’t any other easy home-run hits,” said Seidman.

However, the insurer has asked that Schering-Plough’s therapeutic follow-up to Claritin, Clarinex (desloratadine), also be switched to OTC status.

Battles Against Generics

Schering-Plough faced a deadline with Claritin, whose patent expired Dec. 19. A growing list of competitors announced plans to launch generic versions of loratadine, and the new Clarinex was meant to lay claim to the market segment that Claritin had held.

But the Clarinex launch was delayed by an FDA investigation into Schering-Plough’s manufacturing

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practices, leaving the door open for generic competitors to win over Claritin users before the brand maker could convert them to Clarinex, which was finally approved in February 2002.

Potential generic competitors got a jump on Claritin several years before its patent expiration. Geneva filed an abbreviated new drug application (ANDA) in February 1998, contending that Schering's patents were unenforceable. Four other generic manufacturers submitted ANDAs for loratadine in 1999, three in 2000 and five the following year, including McNeil Consumer Health Care. In 2001, Whitehall-Robbins, now Wyeth, filed an ANDA for its version of loratadine, also contending Schering's patents were invalid and unenforceable.

By mid-2002, Schering-Plough had launched 15 lawsuits against generic companies to defend its loratadine patents, and lost key rounds in court.

Clarinex gave Schering-Plough a foothold in both the OTC and prescription markets for second-generation antihistamines. "The approval of Clarinex provided us with the opportunity to move Claritin to the OTC category while still maintaining a presence in the prescription field," said company spokesman William O'Donnell.

Faced with a losing battle, Schering-Plough capitulated and filed its own supplemental NDA to switch Claritin to OTC March 8, 2002. After contending that OTC Claritin posed a risk to the public health before the FDA's advisory committees the previous year, the company switched gears and made the case that the drug was safe to use OTC when directed by the label.

The FDA approved all five formulations of Claritin for OTC sale for allergic rhinitis. Based on additional data provided by the company, FDA subsequently approved Claritin for the OTC treatment of chronic idiopathic urticaria. However, Schering is far from alone in the market for OTC antihistamines.

Industry observers expect the introduction of OTC loratadine to shake up the consumer antihista-

mine market. The absence of drowsiness and cholinergic effects are powerful selling points that experts have said will give diphenhydramine-based antihistamines a run for their money.

OTC Claritin enjoyed a full 10 days of market exclusivity after its introduction Dec. 10 before generic competitors hit the market. Wyeth received tentative approval for the ANDA on its version of loratadine, which will be sold as Alavert and could hit the shelves by the end of December.

Wyeth also plans to launch its version of Claritin-D (loratadine/pseudoephedrine sulfate) in 12-hour and 24-hour formulations in early 2003. Novartis also has a loratadine version waiting in the wings and generic maker Andrx is considering selling the drug in the private label market.

Competitive Market Expected

Industry observers forecast that the OTC market will be flooded with loratadine products starting in early 2003. Competition from generic versions of loratadine is expected to drive the price from the prescription rate of more than \$2 per pill down to about \$1 per pill, comparable to currently available OTC antihistamines.

Health insurers are expected to drop coverage for second-generation OTC antihistamines. Wellpoint already has. Aetna, the nation's second-largest health insurer, said it will no longer cover Allegra, Claritin or Zyrtec unless a doctor makes a special request. Several other insurers have announced similar plans.

According to industry sources, health plans intend to encourage a trial of OTC loratadine by making sure patients' out-of-pocket copayment for Rx versions plus the physician office copay is not appreciably less than the amount they pay for OTC products – about \$30 per month.

Other drug companies also are closely watching the Wellpoint petition as they maneuver the Rx-

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to-OTC switch for their products. One drug in a situation similar to Claritin is AstraZeneca's Prilosec (omeprazole), one of a new generation of proton pump inhibitors that treat gastroesophageal reflux and ulcers. Prilosec's move to OTC will follow a similar shift for the earlier generation of H2 blockers that switched to OTC status in the mid-1990s, including Tagamet (cimetidine) and Zantac (ranitidine).

The top-selling prescription drug in the world for several years, Prilosec is key to AstraZeneca's financial health. It generated \$3.7 billion in worldwide sales for the company, or nearly 35 percent of AstraZeneca's revenues from continuing operations. AstraZeneca found its patents challenged by generic-drug companies in the U.S. and Europe. Despite winning U.S. court challenges, five companies pounced with generic versions in the United Kingdom after a court overturned its omeprazole patent.

In anticipation of an eventual switch, AstraZeneca sold OTC rights to Prilosec to Johnson & Johnson in 1997. Both companies have declined to disclose the details of their arrangement.

The FDA approved the first generic form of omeprazole Nov. 4, giving the nod to an ANDA from KUDCO, the U.S. unit of Schwarz Pharma. KUDCO, the only firm to emerge from litigation with AstraZeneca with a valid patent for the drug, is marketing its version of omeprazole in agreement with generic makers Genpharm and Andrx.

With the patent noose tightening, AstraZeneca filed a supplemental NDA for an OTC version of Prilosec. A joint session of the FDA's Nonprescription Drugs Advisory Committee and the Gastroenterological Drugs Advisory Committee recommended the approval of OTC Prilosec June 21. Johnson & Johnson received an "approvable" letter from the FDA Aug. 8, with a request for additional information.

If fully approved, an OTC version of Prilosec is expected to be on the market by mid-2003. It

would be the only OTC drug available at prescription strength for the prevention of heartburn.

Several companies are champing at the bit to get OTC approval for cholesterol-lowering statin drugs, a huge potential market. In July 2000, an FDA advisory committee rejected OTC switch applications for Merck's Mevacor (lovastatin) and Bristol-Myers Squibb's Pravachol (pravastatin). The committee asked for the firms to provide more studies to demonstrate the public's ability to self-diagnose the need for statin therapy, and to show that consumers can use the product with minimal instruction.

Merck is reportedly ready to try for approval again, and has formed a joint venture with Johnson & Johnson for the OTC switch of Mevacor.

One of the stumbling blocks to the OTC approval of statin drugs is the need to monitor serum cholesterol and lipid levels, which involves office visits for blood tests. Among the solutions being bandied about is for pharmacists to become more involved in monitoring drug treatment, taking a greater role in the management of cholesterol-lowering and anticoagulant therapy. Statins are among the candidates for a proposed third class of regulated drug, between prescription and OTC (*see related story, Page 9*).

Dual Regulatory Status

When a product goes OTC, the manufacturer typically discontinues its prescription counterpart. There are cases in which it makes more sense for a prescription version to remain available in certain strengths or for certain indications. "Dual regulatory status" refers to drugs with the same molecule and the same brand name sold simultaneously in the prescription and OTC markets.

Prescription drugs may differ from their OTC versions in strength, dosing, indication, packaging or other factors. Typically, OTC drugs are sold at a lower dose than their prescription counterparts. Dual regulatory status was the strategy used for products such as Imodium (loperamide) and Pepcid (famotidine).

(*See OTC SWITCH, Page 7*)

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Although a costly and complex endeavor, seeking dual regulatory status offers advantages and disadvantages to drug companies. Dual regulatory status can extend patent protection and market exclusivity while taking full advantage of brand recognition created by direct-to-consumer advertising.

With dual status, however, companies risk spreading their resources too thin over different markets. "Do you want to be competing against both prescription and OTC products?" asked Richard Tinsley of the pharmaceutical consulting firm Putnam and Associates.

Thus, for financial as well as regulatory reasons, industry experts advise that drug makers should consider carefully whether it is worth it to switch a product to OTC status.

To Go OTC Or Not

Drugs considered for OTC switching have usually been on the prescription market for at least five years and have been taken by large numbers of patients.

"There's a certain amount of time we like to see prescription products on the market, to get a level of comfort with the safety reporting experience as a prescription product," said the Drug Center's Hilfiker.

The FDA considers a number of factors in an Rx-to-OTC switch to determine whether consumers can use a drug safely. The safety of a drug when used in an OTC setting is a complex issue involving far more than the toxicity of the compound itself.

"We look at whether the condition that the product is intended to be used for can be perceived by consumers, whether they recognize that they indeed have that condition and no other," Hilfiker said. "We want to make sure there won't be any harm come to the consumer as a result of misdiagnosis of their condition or use of the product."

The secret to a successful OTC switch is to make the indications and labeling sufficiently clear so that

patients can self-diagnose, according to said regulatory strategist Thomas Blake, who has been involved in the Rx-to-OTC switches of such products as Acutrim (phenylpropanolamine), Gyne-Lotrimin and Lotrimin AF (clotrimazole) and Nicorette (nicotine polacrilex). "Theoretically, most prescription drugs can be switched," he said.

In the case of antacids, companies are better served by avoiding an indication such as duodenal ulcer or gastroesophageal reflux, which a patient is not able to recognize, and sticking to easy-to-understand signs and symptoms such as heartburn. "You don't really switch a drug, you switch the labeling," Blake said.

Among the arguments against removing the prescription restrictions on topical antifungals for the treatment of vaginal yeast infection was that women may not be able to accurately diagnose their condition and may not recognize the signs of other serious pelvic disease. Treatment with an OTC product may delay appropriate health care or mask the symptoms of more serious disease.

"When we switched the vaginal yeast infection drugs, we had concerns that using the drug would mask the symptoms of something else," said Blake. "We did a ton of research to show that the itch of candidiasis is not dupli-

(See **OTC SWITCH**, *Page 8*)

Timetable for OTC Switches

Development Step	Time
Team market analysis	1-2 months
Market research	4-6 months
Product formulation	6-9 months
Accelerated stability testing	4-5 months
Packaging tooling	3-9 months
Clinical/usage testing	6-18 months
Regulatory submission	2-3 months
Regulatory review and approval	21-27 months
Labeling approval/manufacturing	2-3 months
Total	49-82 months

Source: *Francesco International*

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cated by the other vaginal infections, so the label was geared toward that indication. And just to be sure, we put on the label for the new OTC drug that if you don't see relief in three days, see your doctor."

The process of switching a drug to OTC can take years, and should begin early in the product's life cycle (see "Timetable for OTC Switches," Page 7). Preparations for the switch include label comprehension studies in which subjects are tested on their ability to read a product label and explain their intent to follow specific label instructions. "You present the label to the consumer and ask them questions about it," explained Hilfiker. "You refine the label until it's something you're confident that consumers will understand."

An in-use study may be required to determine consumer usage patterns, including compliance with dosage directions, concurrent use of OTC and prescription drugs, effectiveness and the occurrence of rare side effects. In an in-use study, patients are presented with a drug and asked to determine whether it's appropriate for them, then given the drug, sent home and told to use it according to the label. "We look for use patterns, whether consumers use it appropriately or run into any problems when trying to follow the label instructions," said Hilfiker.

As more pharmaceutical companies switch products to OTC, it's important for them to appreciate the ethical, marketing and clinical challenges posed by the nonprescription market.

"Bottom line, when you make a drug over the counter, you have to find ways to take the place of the physician," said Blake. "With prescription drugs, you have the physician buffer, so the drugs can be more toxic and have monitoring built in. The challenge to the industry is taking the place of the physician. That is a very high ethical standard."

Taking a drug over the counter often makes good sense, particularly for an innovative prod-

uct backed by the momentum of brand identity in the OTC setting. There are cases, however, in which a company chooses not to take the OTC route, for whatever reason. As the Wellpoint case illustrates, other companies may find themselves in a situation similar to Pfizer, Aventis and Schering-Plough.

Avoiding the Switch

According to industry experts, drug companies can employ a number of strategies to delay or derail efforts to take product OTC against the sponsor's wishes:

- ◆ Health care attorney Susan Burke suggests that drug makers develop their marketing efforts with an eye towards OTC implications. Pharmaceutical companies should review their marketing and advertising materials to make sure the health insurer's position in favor of self-diagnosis and self-medication is not supported. Marketing materials should give a prominent role to the doctor and reinforce the importance of his diagnosis and care.
- ◆ Drug makers should foster contacts with physician, medical and consumer groups that oppose OTC switches without the manufacturers' consent. The more grassroots consumer support for keeping a prescription status, the less likely the FDA is to buy the insurer's claim that it is widening consumers' access to effective and affordable drugs, according to Burke.
- ◆ Firms can find a scientific issue that will give the FDA pause, Blake suggests. "Dredge safety data that may show a different light on the product," Blake said. This is the tack Aventis took in the May 2001 meeting to consider the OTC status of non-sedating antihistamines. Aventis argued that switching Allegra to OTC could have unintended health and safety consequences, and that as a relatively new drug it was still undergoing post-approval safety and effectiveness trials and post-marketing

(See **OTC SWITCH**, Page 10)

REGULATORS CONTINUE TO EYE POSSIBLE THIRD CLASS OF DRUGS

When the topic of switching drugs from prescription to over-the-counter (OTC) comes up, the idea of creating a third class of FDA-regulated drugs between prescription and OTC often accompanies it.

While the U.S. has traditionally used a two-tiered system, a third class exists in many other western nations, including Canada and Europe.

A third class for drugs “is certainly something that has been talked about a lot at recent meetings,” said David Hilfiker, advisory project manager in the Drug Center’s Division of OTC Drug Products. “The interest is to possibly creating new opportunities for converting additional drug categories to something other than prescription, such as cholesterol-lowering agents.”

The proposal for a third class of drug under FDA purview was first raised in 1974. The third class would cover drugs available without a prescription, but only through a pharmacist, similar to the Canadian and European systems. Drugs in the third class would not be sold in other retail stores, convenience stores or supermarkets that lack a pharmacy.

Competition Concerns

Although several medical groups supported the proposal, the U.S. Department of Justice objected that a third class would restrict competition, limit consumer availability and choice, and ultimately lead to higher prices.

FDA analysis of the issue revealed that “no controlled studies or other adequate research data have been supplied to support the position that any class of OTC drugs must be dispensed only by pharmacists to ensure their safe use.” The agency concluded, “There is at this time no public health concern that would justify the creation of a third class of drugs to be dispensed only by a pharmacist or in a pharmacy.”

The issue regained currency as the number of formerly prescription products going over-the-

counter grew in the 1990s. The matter was addressed again by a 1995 report by the General Accounting Office (GAO).

“Other countries’ experiences do not support a fundamental change in the drug distribution of the U. S., such as creating an intermediate class of drugs,” the GAO report said. “The evidence that does exist tends to undermine the contention that major benefits are being obtained in countries with a pharmacist or pharmacy-only class.”

The prospect for a third class of drugs next arose in 2000 during FDA public hearings on OTC switches. Proponents of a three-tier system argue that the third class could facilitate the OTC transition of drugs, such as cholesterol-lowering statins, several of which are in line for nonprescription status. A major obstacle to approval of OTC statins is patients’ inability to self-diagnose their cardiovascular health and monitor the course of therapy. Regular visits to a doctor are necessary for monitoring and blood tests.

Statins As Third Class Candidates

The third class has strong support within the pharmacy community, which has long advocated a more central role for the pharmacist in the health management of patients, particularly in chronic disease areas such as diabetes, high blood pressure, asthma and high cholesterol.

Lining up against a third class of drugs are Pharmaceutical Research and Manufacturers of America (PhRMA), the Consumer Healthcare Products Association (CHPA), the American Medical Association (AMA) and a long list of drug companies.

While the issue isn’t dead, it is unlikely that the FDA will move to a three-class system any time soon.

“It’s being discussed and considered still, but there are issues that are making us pause,” said Hilfiker. “There are logistical considerations, and the entire health care industry would have to invest a considerable amount of money to make it a reality.”

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safety monitoring. The company also reminded FDA that the agency had requested the assessment of unanticipated adverse reactions in pediatric patients, and had also asked that electrocardiographs be performed on all pediatric patients in clinical trials.

- ◆ When all else fails, firms can stall, Blake recommends. "If a company doesn't want to switch a drug, the way you handle it is by dragging your feet," he said. "The onus is on the company to create labeling. It may take a week or it may take 10 years. The ball is always in the company's court."

And even when a decision to make the switch has been reached, the transition from Rx to OTC status will not necessarily be smooth.

The first time the FDA initiated an OTC switch was in October 1982, when it proposed OTC availability for the bronchodilator Alupent (metaproterenol) in a metered-dose inhalation aerosol for asthmatics. The agency's proposal – formulated without input from an advisory committee, drug companies or the public – met with almost immediate criticism.

Medical societies and consumer groups claimed that improper use of metaproterenol inhalers could harm young children. The FDA's position was that while there were some risks

associated with self-diagnosis and self-treatment of asthma, and some potential for misuse of the product, the benefits of easy availability to consumers were greater than the risks.

In addition, the agency suggested that labels for the inhalers warn that the product should be used only after a physician diagnoses asthma.

The FDA's Pulmonary-Allergy Drugs Advisory Committee discussed the switch at a public meeting in May 1983. After lengthy debate among committee members, invited experts and the public, the panel recommended that FDA rescind its proposal to make metaproterenol a nonprescription drug, which the agency did a month later.

Another problem occurred a few years ago when the agency was considering Hoechst's non-sedating antihistamine Seldane (terfenadine) for OTC status. Approved on a prescription basis in 1985, Seldane appeared safe when used alone but was associated with potentially fatal cardiac arrhythmia when taken with certain other drugs.

Hoechst, now Aventis, developed a related compound, Allegra (fexofenadine), which provides the same benefits of terfenadine without the risk of arrhythmia. Allegra was approved as a prescription drug in 1997, and the following year all products containing terfenadine were voluntarily withdrawn from the market. Now Allegra is among the products on deck for an OTC switch.



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