The H2 Blockers' Rx-to OTC Switch: For Whom Will It Spell Relief?

Student # 104-2106-30

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Tylenol. Advil. Monistat 7. Imodium AD. These are some of the most commonly used, widely available, and successful drugs in the United States. All of them began as drugs only available by a prescription. All of them made a successful prescription-only to over-the-counter (Rx-to-OTC) switch through the switch mechanisms of the Food and Drug Administration (FDA). Due to the amount of money that pharmaceutical companies can make with an Rx-toOTC switch, the FDA has received dozens of switch requests **in** the last few years, and it expects to receive many more in the near future.

Four of the drugs that either currently have switch applications pending before the FDA or expect to have switch applications pending before the agency before the end of the year fall into the category known as histamine2-receptor antagonists, or H2 blockers. The H2 drugs, which help cure ulcers and other gastrointestinal disorders, have been available in the United States since 1977, and are some of the most widely prescribed drugs in the country.

This paper has several aims. First, it will briefly explain the FDA mechanisms through which a pharmaceutical company can switch its drug to OTC status. Second, it will describe the reasons that so many companies are eager to have their drugs make the Rx-to-OTC switch, and highlight some of the other important interest groups involved in the switch process. Then, it will explain the particular situation of the H2 blockers: the particular reasons that their companies want to make the switch, whether and when the switch will happen, and whether the switch reaily should happen. Because the H2 blockers are so widely used and widely agreed to be safe, their progression through the FDA switch process will be instructive for all other companies

considering making the switch. Finally, the paper will attempt to describe some possible alternatives and changes to our curent Rx-to-OTC process.

The HZ Blockers

As a preliminary matter, it will be helpful to briefly differentiate among the HZ blocker drugs currently being discussed as switch candidates, and to outline the FDA-approved uses of the drugs. Cimetidine, the active ingredient in SmithKline Beecham's Tagamet, was released as a prescription drug in the United States in 1977. It is the least potent of the HZ blockers.' Ranitidine, the ingredient in Glaxo's Zantac, gained FDA approval in 1983, and nizatidine, the ingredient in Lilly's Axid, entered the U.S. perscnption market in 1988. The most potent of the HZ blockers is famotidine, which Merck introduced into the United States as Pepcid in $_{1987}$•Z

The FDA has approved the prescription of HZ blockers for the treatment of duodenal and gastric ulcers (including for the prevention of recurrent ulcers), for gastroesophageal reflux disease (GERD), and for acid hypersecretion. Despite this limited list of approved uses, doctors also commonly prescribe HZ blockers off-label for other uses, such as the treatment of non-ulcer dyspepsia and the prevention of ulcer formation in patients taking regular amounts of nonsteroidal anti-inflammatory drugs (NSAIDs), which may irritate the gastrointestinal system.[3]

1 M. Feldman, Pros and Cons of Over-the-Counter Availability of Histamine2-Receotor Antagonists. 153 Archives of Internal Medicine 2415, 2416 (1993). 2 Ed. at 2416.

˜ Id. at 2415; see also LR. Levine ˜Lai±, Nizatidine Prevents Peotic Ulceration in High Risk P 153 Archives of Internal Medicine 2449 (1993).

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History of the Prescription to Over-the-Counter Switch[4]

The idea of making potent medications available to the public without a physician's approval is not new, nor did it arise with modern consumer advocates and health care cost trimmers. Neither the Biologics Act of 190Z[5] nor the original Food and Drugs Act of 19066 designated that certain drugs or characteristics in drugs requlred a doctor's prescription. Under federal law, the manufacturer chose whether to distribute its product through doctors and pharmacists or directly to consumers. Only narcotic drugs, first regulated in 1914, required a physician's prescription.[7]

In 1938, Congress supplanted the 1906 Food and Drug Act with the Food, Drug, and Cosmetic Act (FDCA),[8] which emphasized affirmative labeling and adequate directions for use ,9 but which did not address a prescription-mandatory class of drugs. Later in 1938, the Food and Drug Administration, without Congressional approval, created with regulations a mandatory prescription status for drugs.[10] Congress finally adopted the FDA's prescription-mandatory classification in the 1951 Durham-Humphrey Amendments to the FDCA.[11] By doing so, Congress agreed with the FDA that for some drugs, it is impossible to provide a lay person with adequate directions for use. In § 501(b)(1) of the post-1951 FDCA, Congress defined a prescription drug as one which either (i) fails into an explicit, statutory list of habit-forming drugs; (ii) is limited to prescription-only sale in its New Drug

˜ The information in this section largely comes from Peter Barton Hun, A Le˜aI Framework for Future Decisions on Transferring Drugs from PrescriDtion to NonDrescription Status 37 Food Drug & Cosmetic U. 427, 428-29 (1982).

˜32 Stat. 728 (1902).

6 34 Stat. 768 (1906).

˜ 38 Stat. 785 (1914).

8 52 Stat. 1040 (1938), 21 U.S.C. §§ 301 et sea. (1976).

˜ 52 Stat. at 1051, 21 U.S.C. §352(0. 10 3 Fed. Reg. 3161 (Dec. 38, 1938).

˜1 65 Stat. 648 (1951).

Application (NDA) procedures; or (iii) is not safe for use without a physician's supervision. The last category, which generally adopted the FDA's regulation that prescription-only drugs are those that can be adequately labeled for proper use by a lay person, is the one that presents the heart of the over-the-counter debate, for it is the only one open to FDA discretion and interpretation. The statute provides guidelines for applying this definition: toxicity, other potentiality for harmful effect, and methods of use and collateral measures necessary to use. As we shall see, these guidelines can be expanded to include almost any concern the FDA has about a drug.

Mechanisms of the Rx-to-OTC switch

Currently, there are three ways in which a drug can make the Rx-to-OTC switch. The first is through a petition. The petition process, developed by FDA regulation in 1956,12 can be instituted by any interested person, not only the manufacturer of the drug. This petition process is rarely used. The second method for a switch is through the OTC Drug Review.[13] The Drug Review, initiated by the FDA in 197Z, was established as the OTC component of the climcal efficacy demonstration required of all drugs under the 1962 amendments to the FDCA.[14] The Drug Review uses a monograph system for categorizing OTC drugs. The third Rx-to-OTC method is the filing of a supplemental new drug application (NDA) with the FDA. Under the supplemental NDA process, the FDA determines whether the drug has been shown to be safe and effective for OTC use.

1.2 The regulations, and the list of drugs approved through the petition process, are in 21
C.F.R §§ 3 10.200-310.201.

13 21 C.F.R. Pt. 330.

14 76 Stat. 780 (1962).

The two HZ blocking drugs currently under FDA switch review, cimetidine and famoditine, are being reviewed under the third method, as supplemental NDAs. As shall be soon be explained, the supplemental NDA procedure for switching is attractive to manufacturers because, if successful, the drug manufacturer receives a period of market exclusivity for the OTC drug.

Pressures on the FDA to approve Rx-to-OTC switches

The debate surrounding the Food and Drug Administration's decision over which drugs will be sold over-the-counter and which will require a physician's prescription involves incredibly high stakes. The OTC market in this country is worth around $11 billion each year, and it will continue to grow.[15] A large percentage of the increase will likely come from the switch drugs. In 199Z, the Nonprescription Drug Manufacturers Association estimates that the FDA will receive more than 50 switch requests from manufacturers before 1997.16 The pressures on FDA from pharmaceutical manufacturers, generic drug companies, pharmacists, organized medicine, and consumer groups are intense now and will only become more intense as the country continues its efforts to lower health care costs.

Pharmaceutical Manufacturers. Several factors have led the pharmaceutical industry to its current push for more Rx-to-OTC switches. One of the most important is the national push to lower health care costs. Managed care in an already highly competitive industry has reduced the big drug companies' power to set prices. From 1988 to 199Z the earnings per share of

A. N. Burnstein, Anatomy of a Successful Rx-to-OTC Switch Medical Marketing &

Media, June 1994, at 10.

16 Big Sales in the U.S. OTC Market. Pharmaceutical Business News. May 1, 1992.

the ten largest U.S. drug companies grew by 18 percent each year,[17] but times have changed. Analysts estimate that earnings for the biggest U.S. drug companies will rise only 4.5 percent in 1995, even though sales will rise 13 percent.[18] The switch of a popular drug to OTC status is seen throughout the industry as, if the pun can be forgiven, the peffect prescription for increased sales and profit margins. Estimates for the power of the switch vary, but all are encouraging for drug companies: average sales may increase by three- or even five-fold.[19]

Another major reason that pharmaceutical companies are eager to have their drugs approved for OTC use is that the newly FDA-approved use can extend their patents on the drugs and provide periods of market exclusivity. In the next five years, drugs representing an estimated $13.5 billion each year in sales will lose their patent protection.[20] The end of patent protection means huge competition from generic drug manufacturers and the driving down of the drug's price. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act (DPC-PTR)[2] 1, which strikes a compromise between the name brand manufacturers and their generic competition. A drug company can get a three-year period of market exclusivity, in which no generic applications may be approved, if the company pioneers a new drug through an NDA or supplemental NDA. The pioneer drug does not have to be a new chemical entity; it can be a new application of an old chemical entity. This means that by getting the new OTC use of the old drug formulation

17 5. Tully, Why Drug Prices Will Go Lower Fortune, May 3, 1993, at 56.

18 j. Weber and J. Hamilton, Take Two Aspirin and Call in the Morning Business Week,

Jan. 9, 1995, at 79.

19 See. e.g. Big Sales. suora note 16; P. Abrahams, OTC Sales Prove Addictive. Financial

Times, August 21, 1992. at 15.

~ Galore Drug & Cosmetic Industry. September 1, 1994. 2198 Stat. 1585 (1984).

approved through a supplemental NDA, and conducting new clinical investigations on the drug, a pharmaceutical company can hold off the approval of any new applications to create a generic version of their drug for three years.[22]

The DPC-PTR Act also provides pharmaceutical companies with a patent extension option, under which the company can receive up to, provided that certain conditions are met, as many as five extra years on the term of one of a drug's patents.[23] This part of the law compensates the company for the time lost on its patent while the drug went through the testing and regulatory phase. Because of the requirements for a patent extension, it will be more difficult for companies to take advantage of these provisions for their OTC switch drugs, but it is certainly possible that a company could receive an extended patent life with a switch. Both the market exclusivity provisions and the patent term extension provisions in the DPC-PTR Act clearly gives pharmaceutical firms a reason to look to get an OTC use of their previously developed drugs approved.

Getting a period of market exclusivity or a patent extended seems even more attractive to drug companies when they consider their other option for new income: research, development, and FDA approval of an entirely new drug compound. Such a process can take over a decade, cost a company hundreds of millions of dollars, and still not lead to an approved new drug. These daunting figures have led the industry to the point where it is cutting its research & development budgets, despite a current dearth of big, new ideas coming through the research pipeline.[24]

22 Ellen J. Flannery and Peter Barton Hutt, Balancing Comoetition and Patent Protection in the Drug Patent Term Restoration Act ot I2˜4J 40 Food Drug & Cosmetic LI. 269, 286-287 (1985).

23 Id. at 302-307.

24 j˜ Weber and J. Hamilton, suora note 18, at 79.

Consumer Advocates. According to a Heller Research Group Study, 64 percent of Americans would like to have direct OTC access to more prescription drugs that can be safely self-administered.[25] Seeking lower costs, convenience, and greater selection, consumer groups are pushing for more drugs to be available on an OTC basis. On the other hand, these same groups, particularly those representing the elderly, are also concerned with safety and fully informative labeling. Organizations and publications are demanding less paternalism from the government on the distribution of drugs, while they also encourage their members and readers to be vigilant.[26]

Organized Pharmacy and Organized Medicine. Physicians and pharmacists may see their importance and their incomes decline somewhat as more drugs make the OTC switch. Yet neither group has maintained an adversarial position to the switch process, as long as each is a part of the decision-making. The FDA has recognized the importance of having doctors and pharmacists involved in the switch process: In 1982, the FDA approved the OTC use of metaproterenol, but when the medical community and an advisory committee objected, the agency rescinded the switch.[27] Organized medicine has much less to lose in the OTC switches, and can be expected to support the switch of many drugs, provided that the doctor-patient relationship is not interfered with. Pharmacists have more to lose from the OTC switches, since OTC drugs can be sold from almost anywhere, although some studies do show that drug stores are far more successful in the Rx-to-OTC switch drugs than are non-drug stores such as grocery stores and convenience shops.[28] Organized

25 **Study** cited in A. Cole, Patient. Treat Thyself. Modern Maturity, October 1993, at ii.

26 Id. at 11; OTC Drugs: Prescriotion for Danger? Consumer Reports, Sept. 1994, 101.

27 48 Fed. Reg. 24925 (June 3, 1983), cited in Peter Barton Hun and Richard A. Merrill,
Food and Drug Law 2d ed., at 418 (1991).

28 Drug Chains' Advantage in Rx-to-OTC Products Chain Drug Review, June 20, 1994, 40.

pharmacy continues to push for a third class, or pharmacy only class of drugs. This issue will be addressed later in the paper.

The Federal Government and the FDA. The government, as we have observed in the last several years, is intensely concerned with lowering health care costs in this country. Allowing more drugs to switch to OTC status can help cut costs in two ways: it may remove the cost of an appointment with a doctor, and it removes the cost of reimbursement for the drug.[29] Of course, because it must be concerned both with the economy and with the protection of the public, the federal government's interests in any particular OTC switch are complicated.

Recent FDA activity does show that the government generally sees Rxto-OTC switches as an important and beneficial trend. For example, in 1991 the FDA created and appointed an expert Nonprescription Drugs Advisory Committee (NDAC). The NDAC spent a large percentage of 1994 in joint meetings, discussing possible switches with prescription drug committees, and the Chair of the NDAC has made speeches encouraging innovation in the OTC arena.[30] Further, the FDA is considering future rules on simplifying OTC drug labeling and making clearer the drug interaction and side effects warnings.[31] Such concern by the various divisions in the FDA demonstrates the agency's awareness that more drugs, and more potent and complicated drugs, will soon be entering the OTC market.

29 While Medicare does not reimburse patients for the cost of prescription drugs,
Medicaid and many private health insurance plans do.

30 FDA, The Pink Sheet December 20, 1993, at 16-17.

3˜ FDA, The Tan Sheet June 13, 1994, at 1.

Specific issues of the HZ blockers' Rx-to-OTC applications All of the pressures and interests discussed above apply to the current

battle to get the HZ blocker drugs approved for OTC use. In addition, there are a few twists in the HZ blockers situation that make their companies even more concerned with getting the switch.

Exoirin˜ Patents. The HZ blockers' manufacturers are exceptionally concerned with patent protection and market exclusivity, as each of them is reaching the end of its patent life. In fact, SmithKline Beecham's patent on Tagamet's cimetidine already expired in May of 1994. This helps explain why in December of 1991 cimetidine became the first of the HZ blockers to begin the Rx-to-OTC application process. Despite the fact that the patents on cimetidine have expired and generic companies can now develop the drug, if the OTC switch is approved, SmithKline Beecham will be the only company allowed to market cimetidine on the OTC market for a three year period.

Glaxo, the producers of Zantac, has had its own patent troubles. Zantac/ranitidme is the most commercially successful of all the HZ blockers.[3]Z Glaxo holds a form 1 patent on ranitidine which will expire in 1995, and a form Z patent which will expire in 2002. Comfortable with the extra patent life, Glaxo allowed itself to fall behind in the OTC development process. The form 2 patent on ranitidine narrowly escaped a challenge by a generic drug company in 1993.˜˜ In response to these patent pressures and the realization that cimetidine was already before the FDA and that famotidine would be before the end of the year, Glaxo has refocused its efforts towards getting an OTC switch application before the FDA.[34] Clearly, all the HZ manufacturers are aiming for a period of OTC market exclusivity for their drugs.

32 FDA, The Pink Sheet March 9, 1992, at T&G-1.

˜ Glaxo. Inc. v. Novooharm. Ltd.. 830 F.Supp. 871(1993).

3˜ FDA, The Pink Sheet February 1, 1. 993, at T&G-l,2.

Less Use of H2 Blockers for Ao˜roved Rx Uses. It is common practice among U.S. physicians today to prescribe drugs for uses that are off-label, in other words, that have not been approved by the FDA. Because of the slowness and the expense of getting a new use approved by the FDA, reputable and extensive research on new uses of drugs often appears long before FDA approval does. This practice is particularly common with the HZ blockers, where symptom relief leads patients to request the medicine, and the safety of the HZ blockers relieves physician's worries about the off-label use. In 1990, it was estimated that more than 60 percent of the revenue manufacturers derive from the sale of HZ blockers may emanate from the use of these drugs in nonapproved indications.[35]

Even since the 1990 estimates, important research on peptic ulcers has almost certainly led to an increase in the proportion of HZ blockers that are prescribed for off-label uses. While the HZ blockers are very effective at healing peptic ulcers, they do not effectively prevent new ulcers from forming. More than 50 percent of patients whose ulcers are healed using HZ blockers will suffer a relapse within the year; 25 percent will suffer a relapse even if they continue to take the medicine at the daily, prevention-aimed dosage.[36] However, beginning in 1982, researchers began to discover a link between *heliobacter pylon,* a bacterium, and peptic ulcers, and in February of 1994, the National Institutes of Health officially announced the connection, proclaiming that by treating the heliobacter infection with antibiotics, the relapse rate of ulcers can be reduced by 90 percent.[37] This new information has led to a standard of care of ulcers involving antibiotics, and not

35 5. HoIt, Alcohol and H2-Receotor Antagonists; Over the Counter. Under the Table? 85
American Journal of Gastroenterology 516 (1990).

36 Ulcer Freedom Fighters The Economist, March 5, 1994, at 93.

˜ Id. at 94.

necessarily HZ blockers. Currently, since the necessary combination of antibiotics is tough for many patients to take, the proper standard of care is to test all peptic ulcer patients for the presence of the *heliobacrer,* and if the bacteria is found (as it will be between 80 and 90 percent of the time), treat with a combination of an antibiotic, Pepto-Bismol or an HZ blocker, and a proton-pump inhibitor such as omeprazole.[38]

This new standard of care for peptic ulcer patients has clear implications for the manufacturers of HZ blockers. Assuming that *heliobacter* is discovered, the doctor may choose not to prescribe an HZ blocker in the treatment. Even if an HZ blocker remains in the treatment process, it is clear that the overall need for HZ blockers in fighting ulcers will decrease dramatically. Antibiotic treatment can prevent most relapses of the peptic ulcers, so there will be little repeat demand for peptic ulcer treatment. This trend away from use of HZ blockers in ulcer treatments forces the HZ blocker manufacturers to rely solely on prescriptions for GERD and off-label uses, and thereby increases the financial pressure to go OTC with their products.

Will the switch happen?

The overwhelming consensus among physicians, drug companies. and even the FDA is that the HZ blockers will eventually be switched to OTC status.[39] The only questions seem to be when, and who will get there first. Currently, the FDA is considering the NDAs for Tagamet/cimetidine and Pepcid/famoditine, and Zantac/ranitidine and Axid/nizatidine are likely to file NDAs within the year. In terms of who will get the OTC approval first, cimetidine seems to have the edge. Famotidine is more potent than cimetidine

38 Informal conversation with author's father, who is a gastroenterologist.

39 See Statement by FDA Monograph Review Staff Director William Gilbertson, reported in

the FDA Pink Sheet October 4, 1993.

and can therefore be effective at lower doses, but the supplemental NDA for cimetidine appeared almost two years before famotidine, so Tagamet HB will probably be the first HZ blocker on the OTC market.

The race to be first out of the OTC gate can carry a big prize for the winner. The HZ blockers will be competing in an already crowded field of OTC antacids, so it is likely that the first manufacturer who is able to advertise directly to consumers about HZ blockers will dominate the market.[40] The period of market exclusivity discussed above will also increase the spoils of the successful HZ blocker manufacturer. Currently, each of the HZ blocker manufacturers is spending a great deal of money advertising to doctors **in** order to create a brand loyalty with patients, so that when the drugs go OTC, there will already be substantial name recognition. Such Rx-to-OTC strategies have proven successful for American Home Products' Advil and Proctor & Gamble's Alleve.[41] To aid them in their race for OTC approval, each of the HZ blocker manufacturers has engaged in multi-million dollar joint ventures to develop and market the OTC versions of their products.[42]

Important moves toward approval have already been made by the HZ blockers' companies. In March of 1993, the FDA's Gastrointestinal Drugs Advisory Committee concluded that while three of the HZ blockers (cimetidine, ranitidine, and nizatidine) caused increased levels of blood alcohol absorption, the increased levels were of no significant clinical effect.[43] The Committee chose not to recommend a change in the drugs' prescription labels regarding the alcohol interaction. This decision by the committee bodes well for the

˜ P. Weisz, Rx for Profitable Switch to OTC: Brand Before Others loin the Fray Brandweek, September 12, 1994, at 30.

41 Id at 31.

42 ˜ FDA, TheTan Sheet July 4, 1994, at 13-15; FDA, The Pink Sheet August 2,
1993, at 9; FDA, The Pink Sheer August 24, 1992, at 5.

˜3 FDA, The Pink Sheet. March 22, 1993, at 4.

prospects of an OTC switch: although the FDA could certainly require affirmative labeling about interactions with alcohol in the future, the fact that the committee ruled the interactions insignificant means that one more hurdle to switch approval has been cleared.

The HZ blockers' manufacturers have suffered two sets of major setbacks in their NDA approval process. The first involves the efficacy of their products at the OTC doses. In September of 1993, the FDA's Nonprescription Drugs and Gastrointestinal Drugs Advisory Committees unanimously agreed that SmithKline Beecham's clinical trials were unable to demonstrate that cimetidine relieves heartburn symptoms at its OTC strength.[44] The committees expressed that the OTC-strength cimetidine showed no significant advantages over OTC antacids. However, at the same joint meeting, the drug manufacturers received some good news as well. The committees unanimously agreed that cimetidine is safe enough to be marketed as an OTC heartburn remedy, and voted 10-4 that all concerns about drug-drug interactions could be overcome by effective labeling.[45]

The same advisory committees changed their tune about the danger of drug-drug interaction at their joint meeting in July of 1994, and dealt the HZ blockers' manufacturers another setback. At this meeting, the committees were satisfied with Sm.ithKline Beecham's new OTC dosing regimen for cimetidine and with the new efficacy data on heartburn treatment, but voted 12-1 against recommending approval for the OTC switch because of concerns about drug-drug interactions.[46] Merck, the maker of famotidine, also suffered

˜ FDA, The Tan Sheer September 13, 1993, at 1.

˜ Ed. at 1-2.

46 FDA, The Tan Sheet August 1, 1994, at 4-6.

a setback at the July 1994 meetings, as the committees were critical of that company's efficacy test results.[47]

In response to these setbacks, many have questioned whether the mood at FDA regarding OTC switches has changed.[48] It seems possible that the FDA may be looking for a higher standard of safety and efficacy in switches than it requires in prescription drugs,[49] and such a policy does not seem unreasonable considering that patients do not necessarily have the advice and supervision of their doctors when they choose an OTC drug. However, these setbacks for the HZ blockers will probably approve to be temporary. Other recent switches, including Syntex's Naprosyn, suffered a similar level of scrutiny and setbacks, and have still enjoyed successful switches. In fact, the committees voted that the OTC switch of cimetidine could be approved without further committee review, provided that the drug interaction studies return satisfactory results.[50]

Does the switch make sense?

As the above discussion demonstrates, the interests at stake in a Rx-toOTC switch of the HZ blockers will most likely lead to the drugs' appearance on the over-the-counter market within the next few years. Nevertheless, there is an unanswered question buried deeply and almost lost in the economics of the whole debate: does the switch, from a medical and patient care-oriented perspective, make sense?

'˜7 Setbacks Galore suora note 20.

See. e.g. suora note 20.

˜9 FDA, The Tan Sheet October 24, 1994, at 2.

˜0 FDA, The Tan Sheet August 1, 1994, at 4.

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In analyzing this question, I will use the guidelines provided by Congress in the Durham-Humphrey Amendments to the FDCA.[51] As discussed above, the relevant clause of the law here is § 503(b)(1)(B). which says that if a drug is not safe for use without a physician's supervision, it should be available by prescription only. The statute provides guidelines for applying this definition: toxicity, other potentiality for harmful effect, and methods of use or collateral measures necessary to use,

I˜i˜ixy± In this category, the H2 blockers are excellent switch candidates. The H2 blockers are less toxic than many drugs currently on the OTC market. Cimeditine, the drug in Tagamet, has in particular undergone a tremendous amount of safety testing, but all the H2 blockers have been tested in clinical trials and in post-marketing trials, and none show a significant amount of adverse from treatment with the drugs.SZ The toxicity of the drugs is low, and the serious non-reversible reaction is extremely rare. In addition, the experience in Denmark, whose government switched cimetidine and ranitidine to OTC status in 1989, has shown no increase in adverse reactions to the drugs.[53]

Other ˜otentialitv for harmful effect. This broader category allows the consideration of ways in which a relatively non-toxic drug may harm its users, and has been used by the FDA to consider the potential for dangerous

51 The reader may be interested to know that, of all the medical literature analyzing the

pros and cons of an OTC switch for the H2 blockers the author read while researching this

paper, not one mentioned Durham-Humphrey. I found this phenomenon interesting, but

for the subject of another paper.

52 See. e.g. M. Andersen and J. Schou, Adverse Reactions to H2-Receotor Antagonists Before and After Transfer of Cimeditine and Rainitidine to OTC Status 69 Journal of Pharmacology and Toxicology 253(1991); J.B. Porter ˜ Long-term Follow-up Study of ˜Jm˜ditine 4 Pharmacotherpy 381 (1984).

53 Andersen and Schou, ˜ Andersen and Schou, Safety Implications of the OTC Availability of HZ-Anta 8 Drug Safety 179 (1993). It should be noted, however, that the Danish results also show that most people using H2 blockers are still choosing to get a prescription for the drug, probably in order to receive reimbursement for it.

drug-drug interactions and for abuse by the users of the drug.[54] As mentioned above, there is enough concern about the drug-drug interactions with HZ blockers that the advisory panels considering the HZ blockers' switch ordered further studies. However, it seems that these concerns will be assuaged by the on-going tests, and by informative labeling. Given that drug interaction concerns are present regarding many of our OTC drugs today, including most OTC antacids, and given an increasingly informed marketplace of consumers, the possible drug interactions with the HZ blockers should not keep the product from OTC status.

However, the HZ blockers, while relatively non-toxic, do present a potentiality of harmful effect for their users. The drugs present enormous possibilities for misuse that could cause harm. The HZ blockers will be switching to the OTC market at a much lower dose than is available with a prescription, and it will be switching to the OTC market only for relief of heartburn and upset stomach. This situation presents the problem that many purchasers of the drug may, simply by doubling or tripling the approved OTC dosage of the drugs, take themselves out of the safe range of the drug. Of course, this argument might be made about almost any drug sold OTC, but it seems particularly likely that people will over-medicate themselves with the HZ blockers because they will be looking for immediate relief of dyspepsia. When the drug doesn't provide quick relief, and it should be noted that dyspepsia relief actually comes slower (and lasts longer) with the OTC dose of HZ blockers than it does with OTC antacids,[55] chances are that the consumer will simply take several pills until he or she feels better. There is a serious potential for harmful effect in this situation, and the situation seems common

˜ Hutt, suora note 4, at 435.

˜ S. Holt, OTC Histamine H2-Receotor Antagonists 47 Drugs 1, 8 (1994).

enough that perhaps the FDA should take better note of it. In addition, there seems to be potential for harmful effect and abuse of the OTC HZ blockers in the fact that many people may use the new availability of the HZ blockers to treat their ulcers or suspected ulcers. This situation seems very dangerous and very possible, yet it is unclear whether discussions by the expert advisory committees have addressed it. No one has argued that lay persons can safely treat their own ulcers, and the new information about antibiotic treatments for ulcers makes such a suggestion even less likely, yet it seems that such misuse of the OTC HZ blockers will certainiy occur.

Method of use or collateral measures necessary for use. This consideration, clearly the broadest of the FDCA's provisions, allows the FDA to weigh general questions such as the ability of patients to successfully treat themselves using the HZ blockers and social policy.[56] One of the factors that the FDA may consider is whether the condition for which the drug is to be used can be self-diagnosed by a lay person; however, self-diagnosis of the problem is not a prerequlsite for an OTC switch of the treatment. Even if self-diagnosis were required, the HZ blockers might pass this test. Dyspepsia is a term with no precise definition, yet most lay persons are probably capable of knowing when they feel it, particularly if a physician has already diagnosed it once for them.[57] It is true that dyspepsia and similar pain may be a symptom of a larger problem that lay persons cannot diagnose, this concern is certainly equally present with other drugs currently on the OTC market, including aspirin and antacids.

Another, more important consideration under the general method of use and collateral measures category is the ability to self-treat with the drug.

56 Hutt, suora note 4, at 436-439. Professor Hutt's analysis provided the foundation for

the issues I considered in this section of my analysIs.

˜ M. Feldman, supra note 1, at 2416.

It is here that questions about efficacy of the drug at its OTC doses present themselves. The FDA's flip-flop on the efficacy of cimetidine described above demonstrates the fact that effectiveness of the HZ blockers for their labeled non-prescription use of relieving non-ulcer-related dyspepsia is far from settled. One major study, developed with decision analysis techniques and computer models, estimated that approximately 5.7 million people experience dvspepsia during any given quarter-year. and that 3.5 million, or 61.8 percent, of these people are currently self-medicating with antacids. The study predicted that with OTC availability of HZ blockers, the number of people who will self-medicate during a quarter will increase to 3.8 million, or to 64.1 percent. The model further predicts that the increased self-medication and the effectiveness of the H2 blockers will increase the proportion of people who obtain complete relief from dyspepsia from the current 37.9 percent to 43.? percent.[58] Unfortunately, ˜ '˜'r'iies are *less* enthusiastic about the Mf˜˜ctP˜eness of th˜ **loiAr-Iiose** H? blockers.5[9] While the effectiveness of H? blockers in alleviating acid-related symptoms is recognized, there is no scientific consensus that they are effective, particularly at lower doses, at relieving non-ulcer dy˜pepsia.[6]O

Besides efficacy. other issues that arise under the self-treatment question include the possibility that the OTC availability of the drug will.. rather than helping people heal themselves faster, actually lead their health to deteriorate. Given that the HZ blockers are relatively safe, this situation may arise **in** two distinct situations. First, most doctors agree that lifestyle factors, such as alcohol consumption, smoking, and perhaps stress, play a

G. Oster, et al. The Risks and Benefits ot an Rx-to OTC Switch: The Case of OTC H2

˜ 28 Medical Care 834, 844-845 (September 1990).

˜ See e.g. 0. Nyren ˜ Absence of Theraoeutic Benefit from Antacids or Cimeditidine in Non-Ulcer Dvspepsi˜i 314 New England Journal of Medicine 339 (1986).

60 Feldman, sunra note I, at 241 &

significant role in the development of dyspepsia[61]. If patients are able to get relief of their symptoms from OTC HZ blockers, they may lose the opportunity for medical advice and intervention. Second, there is a possibility that people with problems much more serious than dyspepsia, such as malignant ulcers and gastric cancer, may get relief from OTC HZ blockers that prevents them from seeking medical care. While it is true that both the lifestyle and the masking issues also apply to the OTC antacids, the concerns about masking are greater for the HZ blockers, which are better at masking the symptoms of malignancy in the upper gastrointestinal tract.[62]

Many of the factors considered above, such as the drug-drug interactions and the possibility of HZ blocker therapy masking problems as serious as cancer, lead to the essential requirement that the drug be labeled with adequate directions for use by a lay person. The labeling requirements, discussed earlier, are becoming more important as more complicated drugs enter the OTC market. It seems that proper labeling of OTC HZ blockers is possible. The label will need to include the complete list of drugs to avoid interaction with, warnings about the limits of safe dosage of the drug, explanations of the symptoms of gastric cancer and ulcers along with indications that the symptoms mean the consumer should seek medical care, and of course, the list of possible side effects of the drug. This is a hefty labeling requirement, but it does not seem unreasonable, particularly if the drugs' manufacturers agree to provide an advertising campaign that also addresses these concerns.

The final step in the FDCA analysis is social policy. In the final decision over whether the HZ blockers will make the OTC switch, concerns about social

61 Holt (1990), supra note 35.

62 M.J.S. Langman, Antisecretorv Treatment and PredisDosition to Cancer in Advances in Drug Thera˜v of Gastrointestinal Ulceration Garner & Whittle, eds, at 67 (1989).

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policy will most likely have the deciding vote. Of course, social policy is partially determined by all the above aspects of the safe without the supervision of a licensed practitioner analysis, but it will also be determined, as it will be in any regulatory agency, by politics. There is a powerful array of interest groups that want the HZ blockers to make the OTC switch, and therefore the switch will most likely take place. In addition, the government and the FDA see two valuable social gains arising from this and other Rx-to-OTC switches: self-reliant health care consumers who take responsibility for their own health, and cost savings. While the author agrees that both of these goals are worthy and should be sought after, the assumption that Rx-to-OTC products will help the country meet these goals is not proven, and needs to be challenged. For example, it may be true that less people will miss work due to dyspepsia because HZ blockers are available OTC and that these people will no longer have to pay for the doctor's visit **in** order to get the medicine; however, if a certain percentage of those people later develop gastric cancer, which responds well to treatment only if it is diagnosed and treated early,[63] the cost savings, in terms of days missed at work, drug therapy, and doctor visits, may be lost. In addition, it is important to remember that the Rx-to-OTC switch does not immediately lead to competition and lower-priced drugs. In fact, the law will grant the switching HZ blockers periods of market exclusivity that, combined with the tremendous burst of advertising that accompanies an Rxto-OTC switch, may actually create a period when the drug increases in price.[64]

As the discussion in this section indicates, following through with the complete FDCA § 503(b)(1)(B) analysis for the HZ blockers leads to mixed

E˜ Holt (1994), suPra noteSS, at 9-10.

64 ˜. Meier, Widening Drug Availabilitv˜ T˜v Views. The New York Times, February 23,

1991, at 48.

results. While the drugs are relatively safe and may lead to cost savings and more complete relief of dyspepsia than most people have previously achieved, there are serious concerns about the masking of more serious disease, drug interactions, and misuse of the OTC versions of the drugs for their prescription uses. The mixed results of this analysis are probably not unique to the HZ blockers. Whenever a Rx-to-OTC application comes before the FDA, it will be faced with these competing interests and goals. Besides making it clear that the job of the FDA and its advisory committees is not easy, this dilemma raises the following question...

Is there a better way to do all this?

It seems that some improvements on our drug approval system might make this process more sensible, less pressured, and maybe less political. I will explore a few possibilities here.

The third class nossibility. The United States is one of the few developed countries with only two classes of drugs. Most countries, including all of the European Community, have a third class of drugs, known as the legend or pharmacy only class. In these countries, most non-prescription drugs can only be purchased from licensed pharmacists[65]. The idea, of course, is that the pharmacist will serve as the necessary intermediary to supply information and answer questions about drug interactions, efficacy, possible side effects, and the like. Because these countries rely on their pharmacists to provide these important health care provider functions, there is less regulation and testing and concern about selling drugs without a prescription.

65 In thinking about the third class possibility, I relied largely on two sources˜ our class discussion of the topic, and Gregory M. Fisher's Third Class of Drugs - A Current View 46 Food Drug & Cosmetic LI 583 (1991).

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The reliance in the pharmacist as the necessary intermediary means that the governments are free to focus more on cost concerns and social policy when considering a switch away from prescription-only status. An example of this phenomenon took place **in** Denmark, where, in 1989, the government simply transferred several of the prescription-only drugs, including HZ blockers, to the OTC list. The government, which runs the health care delivery system in Denmark, was interested in cutting spending on prescription drug reimbursement and on doctors' consultation fees; it was also seeking to **pr'cniir˜a˜** ***more*** cons1mPri˜t **liriu1˜˜** ˜ bout self-reliance in health care.[66] The government, by relying on the status of its pharmacists. was able to narrow its focus in making its decisions.

In the United States, despite the consistent efforts of different national pharmacy organizations working on the state and federal level, the idea of this third class of dt-uo'˜ h˜ **n˜v9r h˜n ˜iircp˜d'ii1_67** Many fnrep'i˜ h2vP ˜pp˜ aligned behind the FDA's consistent refusal to make any changes that would Doint to a federal avvroval of the Dharmacv-onlv class: organized medicine. consumer groups, retail and grocery stores' organizations, organized labor. the Nonorescriotion Drug Manufacturers Association, and the Devartment of lustice highlight the list of those concerned about monopolies. high prices. reduced consumer choice, and the increased middle-man vower that a pharmacy-only class might bring. As it has during every major drug policy trend, organized pharmacy is now making substantial arguments in favor of a i-hire-i class of dri.tgs during the current Rx-to-C)TC switch atmosphere.[68] As the OTC switch of the H2 blockers draws closer, the National Association of Retail

66 K. Kristensen, Denmaric H2 Antagonists OTC. 339 Lancet 418 (1992). b7 For a thorough review of the third class proponents' arguments over the years, see
Fisher, suora note 65, at 593-604.

68 w. **G˜nv˜,'n, NAPE) Will K˜ti** Pr˜ina fnr ˜n OTC t˜˜nd Ch˜s 137 Dtg Tonic˜ **1˜9**
(1993).

Druggists (NARD) will argue that many of the concerns in favor of keeping the HZ blockers prescription-only can be solved by allowing the OTC sale of the drugs only in pharmacies. And once again, there is almost no public support for NARD's position.

No studies have been done on how much advice is really given at pharmacies in Europe, but regardless of how well that system really works, it could not work in the United States. There are many reasons for this, but one of the primary ones is that the U.S. market is just plain different than the European one. Our system is based much more on competition than is Europe's, and there are not the same kind of giant supermarkets and chain drug stores in Europe as there are in the U.S. Even if pharmacists in Europe are truly giving meaningful advice to their customers, in the modern U.S. pharmacy, where pharmacists are incredibly busy already, and the clerks who actually complete the transaction with the customers are relatively uneducated about the drugs, there is no way that the pharmacists could find the time to be responsible for advising all the customers. In addition, the creation of a pharmacy only class of drugs will probably lead to the imposition of greater tort liability for all pharmacists. In conclusion, although the idea of a third class of drugs sounds wonderful in theory, it simply would not work in practice in the United States.

Change the drug manufacturers' incentives. One reason that the battle for the OTC switch is so urgent for the pharmaceutical companies is that these companies are not doing the kind of R&D that they have done in the past. Given the delays, the incredible costs, and the riskiness of new chemical development, the companies are afraid to invest in new research, so they need an OTC market to provide their new income source. This trend away from R&D is not a healthy one for the country. The 1984 DPC-PTR Act helped to give the

pharmaceutical industry the incentive to continue R&D, but it was not enough. The time spent waiting for FDA approvals of new drugs and new therapies simply must be reduced somehow. Drug companies cannot be expected to help bear the burden of reducing health care costs if they lose tremendous amounts of money every time they try to develop a new product. If the new drug application process had less delays, the drug companies would not be so focused and insistent upon OTC switches, so the switch process could move in a less heated atmosphere.

Establishment of a nernianent. ongoing review mechanism The considerations involved in the Rx-to-OTC switch process are extremely important, life-or-death concerns. Yet these concerns are not currently addressed by the FDA until the eleventh hour, when an enormous amount of testing, development, and advertising to create loyalty among patients has already been invested by the drug companies. By the time the supplemental NDAs reach the FDA, the issue of the OTC switch has already become a political battle, with enormously powerful interests pushing the FDA toward an OTC approval. Perhaps the establishment of a permanent mechanism, involved in a constant review process with the pharmaceutical companies, would create less of a pressured situation.[69]

The creation of the Nonprescription Drugs Advisory Committee is a valuable step in this direction, and NDAC has the potential to develop into a useful, ongoing forum for experimentation. The NDAC, along with the other committees and divisions of the FDA, has already shown interest in getting involved in the switch process at an earlier date and in the development of smaller, phased clinical trials for the switch review.[70] A permanent

[69]See **Hun, ˜ note 4, at** 440.

70 FDA, The Tan Sheet December 19, 1994, **at** 5.

mechanism for the review of data from other countries and analysis of the issues will be able to keep a steady, efficient pace notwithstanding the economic and political pressures pushing the debate.

Conclusions

As one researcher has explained, The perceived need for OTC antisecretory drugs may be more a function of political, economic or commercial interests rather than any readily apparent clinical requirement for the introduction of the widespread availability of the HZ-receptor-antagonists •71 This paper has attempted to explain some of the interests behind the Rx-to-OTC debate in the context of a specific group of commonly prescribed drugs, and it has tried to communicate some of the problems in our current switch environment and some suggestions for improvement. In a society that will push for more OTC switches, it seems essential that Congress and the FDA be prepared to improve the Rx-to-OTC switch system.

The wisdom of the likely increase in the pace of drugs that will be switched from prescription-only to over-the-counter is not an easy thing to analyze. There is no way to run clinically controlled experiments on the health and economy of our nation. The social goals of cost-cutting and more consumer responsibility that will likely induce the FDA to allow the HZ blockers and other drugs to make the switch are important ones, but it seems important for the FDA to remember its primary responsibility is for the safety of the American public, not for the furthering of goals that the whole society must take on together.

71 Holt (1994), suora note 55, at 1.