

THE LONG SHADOW OF PATENT EXPIRATION:
DO RX TO OTC SWITCHES PROVIDE AN AFTERLIFE?

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I. INTRODUCTION

Within the next few years, a number of the US's best-selling prescription pharmaceuticals -- Prilosec, Prozac, Pepcid, and Claritin, for example -- are likely to face patent expiration. What should we reasonably expect to happen as these products approach the end of their patent product life cycle? Will prescription drug only to non-prescription over-the-counter (Rx to OTC) switches occur, and if so, what will be their effects on prices and utilization? Does the Rx to OTC switch significantly mitigate the effects of Rx patent expiration?

In this paper we address a number of issues surrounding the economic behavior of pioneer branded pharmaceutical firms facing patent expiration and the consequences of generic entry. We focus on three main sets of policy instruments: (i) pricing and marketing strategies by branded pioneer drug manufacturers on their Rx drugs pre- and post-patent expiration, including both traditional physician-oriented marketing and direct-to-consumer (DTC) marketing; (ii) the impact of generic entry on the price, utilization and revenues of the molecule post-patent expiration; (iii) the effects of Rx to OTC switches on cannibalization of same-brand Rx sales, and on total brand sales.

As best we can determine, the research we report here is the first systematic empirical examination of the interactions among Rx and OTC versions of a "sunset" branded pharmaceutical as it faces Rx patent expiration.¹ In this study we focus on the US markets for antiulcer and heartburn drugs, for they are large and in the last decade they have experienced both patent expiration and extensive OTC introductions. We examine how the various product life cycle forces have operated in this market over the last decade.

Our research integrates data from various sources, such as prescription drug sales and marketing data from IMS Health, scanner OTC data from Information Resources Inc. (IRI), as well as DTC marketing data from Leading National Advertisers. Although we readily

acknowledge their prevalence and importance, legal maneuvers and tactical issues involving the use of patent challenges and the judicial system to enforce and/or delay patent expiration are outside the scope of this research.

II. BACKGROUND

In 1977 SmithKline introduced a pharmaceutical product branded Tagamet (an H₂-antagonist, chemical name cimetidine) into the US market. Tagamet promoted the healing of ulcers by blocking receptors on parietal cells that stimulate acid production, thereby reducing the secretion of stomach acid. The introduction of Tagamet marked the beginning of a new medical era in which ulcers were to be treated pharmacologically on an outpatient basis, rather than on the traditional inpatient basis that had involved more costly hospitalizations and surgeries.

In the years that followed, a number of additional new H₂-antagonist (hereafter, H₂) launches occurred, first involving Zantac (ranitidine, introduced by Glaxo in 1983), then Pepcid (famotidine, by Merck in 1986) and finally Axid (nizatidine, by Eli Lilly in 1988). Since their introductions, the four H₂s have expanded medical uses far beyond just the treatment of existing ulcers. For example, over the last two decades the FDA has approved use of the H₂s for the treatment of: hypersecretory conditions; gastroesophageal reflux disease (GERD, a common but severe form of heartburn); the prevention of stress ulcers; long-term maintenance therapy for the prevention of duodenal and gastric ulcer recurrence; and for the treatment and prevention of episodic heartburn, acid indigestion and sour stomach. The H₂s have also often been prescribed to offset stomach-related side effects from other medications, as well as from anaesthesia, radiological and chemotherapy treatments.²

Along with the benefits of patent protection, the widespread utilization of the H₂s resulted in spectacular revenue sales growth for their manufacturers. In the early to mid 1990s, for example, not only was Zantac the number one dollar sales volume prescription drug in the US, but Tagamet was typically in the top ten, and Pepcid and Axid were also usually among the 50 or so best-selling prescription drugs.

The H₂s revolutionized medical treatments for gastrointestinal disorders. But they soon

faced forces of creative destruction in the form of a new and sometimes superior generation of drugs for the treatment of ulcers and GERD, namely the proton pump inhibitors (PPIs).³ The more potent PPIs suppressed acid secretion by directly inhibiting the acid producing pump system of the parietal cell, had very few side effects, and had convenient once-a-day dosing.

The first PPI on the US market was Prilosec (omeprazole, renamed Prilosec in 1990 after initially being branded Losec by Merck in 1989), then came Prevacid (lansoprazole, TAP-Abbott in May 1995), Aciphex (rabeprazole, Janssen in August 1999) and most recently Protonix (pantoprazole, Wyeth Ayerst, in May 2000). Concerned about safety and risks from long-term use of the potent Prilosec, initially the FDA only approved its use for short-term treatment. But after being presented with long-term use evidence, in March 1995 the FDA permitted Prilosec to remove the "black box" warning regarding possible risks from long-term use in its product labeling, and in June 1995 the FDA explicitly granted long-term maintenance use approval for Prilosec.

Although the H₂s provided effective treatments for many individuals, in some cases the PPIs were even better. For example, already at the time of its obtaining initial marketing approval in May 1995, the manufacturer of Prevacid was permitted by the FDA to claim superiority over ranitidine (then the most prescribed H₂) for the treatment of heartburn.⁴

With long-term safety issues laid to rest, and superiority over the H₂s established, beginning in the mid-1990s the PPIs were marketed intensively. Remarkably, sales of the PPIs have exceeded even those of the record-setting H₂s. By 1997, for example, Prilosec had overtaken Zantac as the US's (and the world's) largest revenue prescription drug, and by 1999, Prevacid ranked not far behind.⁵ These and other developments in the antiulcer and heartburn markets are summarized in timeline form in the Appendix.

In addition to facing intense rivalry from the next generation PPIs in the 1990s, the H₂s also faced imminent loss of patent protection. Tagamet's patent was the first to expire on May 17, 1994, and after considerable litigation, Zantac's market exclusivity was terminated in late July 1997.

In this paper we focus on the "sunset" H₂ branded products as they approach the end of their product life cycle. In addition to examining the impacts of generic entry on prices and utilization following patent expiration, we also devote considerable attention to the use and consequences of strategies that switched the H₂s from prescription-only to OTC status in anticipation of Rx patent expiration.

In this context, one specific provision of the Waxman-Hatch Act of 1984 has been particularly important to the H₂ prescription drug manufacturers in the 1990s. This provision permitted pioneer manufacturers to gain an additional three years of market exclusivity, provided that the manufacturer obtained FDA approval for a new presentation and indication for the chemical entity.⁶ Expecting eventual loss of patent protection in the mid-1990s, for example, a decade earlier SmithKline had already discussed with the FDA the possibility of it seeking and gaining approval for an OTC version of Tagamet for the treatment of heartburn.⁷ If the timing of the OTC launch could coincide approximately with the pioneer Rx patent expiration date, then although its Tagamet Rx sales could still plummet, nonetheless SmithKline could possibly benefit from an additional three years of market exclusivity on the OTC version of Tagamet. Consumers, not just branded manufacturers, could enjoy welfare gains from the switch. Provided the OTC drug was safe, consumers could benefit by having access to an effective medication without needing to bear the time and dollar costs of obtaining a physician's prescription (Rx).⁸

This provision of the Waxman-Hatch Act created clear incentives for SmithKline, the manufacturer of the pioneer H₂ Tagamet, to be the first to switch from Rx to OTC. Observing this, however, the later H₂ Rx entrants (Zantac, Pepcid and Axid) noticed that they too faced incentives to develop and launch OTC versions of their Rx products, else as later OTC entrants they might forego potentially large OTC sales. For the later Rx entrants, however, OTC entry could possibly occur even *prior* to their own Rx patent expiration. All H₂ manufacturers realized that the order of exit from patent protection in the Rx market need not be the same as the order of entry into the OTC market, nor would first mover advantages in the Rx market necessarily

transfer over to the OTC environment.⁹

Moreover, in conceiving of possible effects on total brand revenues of implementing Rx to OTC switches, manufacturers had to consider two possible offsetting forces. On the one hand, the branded Rx manufacturers needed to take into account the possible cannibalization of sales of their branded Rx product that could result by introducing a same-brand OTC variant. On the other hand, positive spillovers could result from increased brand awareness when both OTC and Rx same-brand products were marketed simultaneously. Would positive spillover or negative cannibalization effects dominate?¹⁰

Because two of the four H₂ brands (Tagamet and Zantac) have already faced patent expiration, two still have patent protection (although both Rx Axid and Pepcid are expected to lose patent protection by spring 2001), and all four have implemented Rx to OTC switches, the historic variation among the H₂s, and over time, should help us quantify the importance of the various factors affecting sales of these molecules. Moreover, since Prilosec, currently the leading-selling drug in the world, is expected to lose U.S. market exclusivity and face generic competition in fall 2001, an examination of the recent historical record involving the H₂s might help us gain insight into what one might expect concerning developments in the market for the PPIs as patent protection ends, and possibly, as Rx to OTC switches occur for the PPIs as well.

The outline of the remainder of this paper is as follows. In Section III we review conceptual bases that provide hypotheses involving pricing, marketing and switching between Rx and OTC products, and as Rx brands face Rx generic competition. In Section IV we discuss data sources and the construction and interpretation of various price, quantity and marketing measures, first for prescription drugs, and then for OTCs. With this as background, in Section V we present a number of stylistic facts that appear to characterize these markets in anticipation of and following Rx patent protection, and provide some preliminary evidence on our hypotheses. In Section VI we formulate a number of relatively straightforward econometric models that quantify relationships more precisely, and report initial results from our econometric analyses of these models. Finally, in Section VII we summarize and conclude.

III. CONCEPTUAL FOUNDATIONS AND HYPOTHESES TO BE EXAMINED

The existing literature in economics and marketing provides a conceptual basis and rationale for a number of hypotheses. First, with respect to pricing, Frank and Salkever [1992,1997] have shown that if, following patent expiration, one can segment the market into the more and less price sensitive components, then it may be optimal for the profit-maximizing branded pioneer not to lower price to meet competition from the generics (for many consumers will in any case migrate to the lower cost generic producers), but rather to maintain or even increase price to that market segment that is brand-loyal and less price sensitive.¹¹ Other things equal, the larger the price insensitive segment is relative to the more price responsive segment, the greater the branded pioneer's post-patent expiration price. Hence, in essence the magnitude and speed of the price response by the branded pioneer following patent expiration is an empirical one. We hypothesize, however, that branded firms will not lower prices following patent expiration.¹²

With respect to marketing efforts, economic theory provides some very useful general guidance and intuition. In particular, as enunciated by Dorfman and Steiner [1954], for profit-maximizing firms facing downward-sloping demand curves and having market power such as that provided by patent protection, the optimal ratio of marketing expenditures to revenues turns out to be equal to the ratio of two elasticities, i.e.,

$$\text{\$/Marketing}/\text{\$/Sales} = \varepsilon_M/\varepsilon_P, \quad (1)$$

where ε_M is the elasticity of demand with respect to marketing efforts, and ε_P is the absolute value of the price elasticity of demand.¹³

There is considerable evidence that early in the product life cycle pharmaceutical marketing efforts involving detailing and journal advertising provide long-lived benefits in the form of additional current and future sales, i.e. evidence suggests that up to the mature phase of the product life cycle ε_M is positive and significant. Moreover, ε_M is larger in the long run than over the short term. The substantial amount of marketing commonly observed at the time of initial product launch is of course consistent with a large and long-lived ε_M during that time

period.¹⁴

However, as patent expiration approaches, one would expect that brand manufacturers would anticipate that ε_M would decline, for the pioneer branded manufacturer would not be able fully to recoup sales from additional marketing, a large portion of which would instead be captured post-patent expiration by lower-priced generic entrants. Notice that if marketing efforts were not long-lived, one might instead expect them to occur unabated until the day of patent expiration. On the other hand, if marketing efforts were long-lived, it is reasonable to expect that ε_M would decline as patent expiration approached. Once patent expiration actually occurred, not only would ε_M likely fall further, but it is also reasonable to expect that price competition would intensify, increasing the denominator of the right side of Eqn. (1) and thereby further reducing the ratio. We hypothesize, therefore, that the pioneer's marketing to sales ratio will fall as patent expiration approaches, and that once patent expiration occurs, the marketing to sales ratio might even fall further, close to zero.

For generic entrants, because any single generic entrant will find it difficult to appropriate to itself any sales benefits from marketing of the molecule, ε_M will be very small, and since price competition among generic manufacturers will be substantial, ε_p (the denominator in Eqn. (1)) will be large. Hence, post patent expiration, we hypothesize that generic manufacturers will have marketing to sales ratios of close to zero, where marketing efforts consist of detailing and journal advertising.¹⁵

Finally, in terms of understanding demand factors affecting the success of Rx to OTC switches, we build from the traditional economic theory of demand, mindful however that in the Rx market, principal-agent issues involving physicians and patients, and moral hazard resulting from the presence of insurance coverage, complicate matters considerably. Nonetheless, we expect that in addition to being affected by relative OTC to Rx prices and relative marketing efforts, the ratio of OTC to Rx Hs will be affected positively by real average wage rates (raising the opportunity cost of the patient taking time to see a physician), and positively by the physicians real office visit fee (raising the direct cost of a physician visit).

One other possible factor affecting the split between OTC and Rx H₂s involves competition from the next generation PPIs. The Rx PPIs are considerably more expensive than the branded Rx H₂s, which in turn are more expensive than the branded OTC H₂s. The Rx PPIs have been marketed extensively, both to physicians and directly to consumers. How this PPI marketing affects the OTC-Rx H₂ split is unclear. It is possible that patients discussing possible use of PPIs with their physician might first be directed to use the lowest-cost OTCs. On the other hand, since their dosage is lower, the OTCs may not be as effective, and in order to avoid additional physician visits, the patient might instead be prescribed either an Rx H₂ or an Rx PPI as first-line therapy. Thus, how marketing of the PPIs affects the split between Rx and OTC versions of the H₂s remains an empirical issue.

IV. DATA SOURCES, DESCRIPTIONS AND INTERPRETATIONS

Empirical research on interactions among prescription drug and OTC markets at the time of patent expiration requires integrating data from a number of diverse sources. We now briefly summarize our data sources. We begin with prescription drugs, and then move on to the OTCs.

A. PRESCRIPTION DRUG MARKETS

Price, quantity, revenue and marketing data for antiulcer and heartburn prescription drugs are taken from IMS Health, monthly from January 1988 through June 1999. IMS' Retail PerspectiveTM tracks monthly shipments from manufacturers and wholesalers to retail warehouses and outlets. The revenue data are those to manufacturers and wholesalers, and not to the retail outlets (who add retail margins). Although revenues are net of chargebacks (discounts given purchasers and channeled through wholesalers), rebates (payments made to providers who often do not take title to the pharmaceuticals, e.g., managed care organizations) are not included in the IMS revenue data, nor are prompt payment discounts. The exclusion of rebates from the revenue data implies an overstatement of Rx revenues and prices, but the extent of this overstatement is unknown, for data on rebates tend to be highly proprietary. In spite of this drawback in the IMS data, however, a very high proportion of branded and generic pharmaceutical companies are known to purchase and utilize the IMS data for their internal

research.

The level of aggregation of the IMS retail purchase data is at the presentational form, e.g., bottles of 30 tablets each having a 150 mg strength. We convert these various presentational sales measures into quantity or unit data by using the recommended daily dosage for active duodenal ulcer treatment as the transformation factor. The resulting quantity data can then be interpreted as the hypothetical patient days of therapy per month were all patients taking the recommended active duodenal ulcer daily dosage.¹⁶ Data on recommended daily dosages are taken from Physicians' Desk Reference [2000]. Price per day of therapy is then computed as revenues divided by the quantity of therapy days in that month. Further details on price, quantity and revenue measurement are found in the Data Appendix of Berndt, Bui, Lucking-Reiley and Urban [1997].

The price, quantity and revenue data we employ only cover sales into drug stores. While drug store sales constitute on average about 70-80% of sales in all outlets, the drug store data exclude sales to hospitals, long-term care facilities, and to mail order distributors.¹⁷ Since hospital usage and marketing differs considerably from the outpatient environment, we confine our attention here to the traditional retail sector.

To measure marketing efforts involving pharmaceutical sales representatives' ("detailers") physician office visits, we employ IMS Health data from their Office Contact ReportTM. Based on a panel of about 3800 physicians who report the number of visits and minutes spent with detailers discussing particular products, IMS extrapolates monthly detailing efforts by drug to the national level. Using an estimated cost per detailing visit, IMS also estimates total detailing expenditures.

Medical journal advertising pages and expenditures are estimated by IMS in their National Journal AuditTM. The universe measured by this audit includes journal pharmaceutical advertising directed to practitioners in all types of medical practice, including pharmacists, nurses, podiatrists, dentists as well as medical and osteopathic practitioners. Based on circulation, the number of square inches and pages of advertisements, as well as copy

characteristics such as premium positioning and the number of colors in each advertisement, IMS uses standard rate sheets from over 300 major medical journals to estimate total dollars of journal advertising, monthly, by drug. Further details on these marketing measures can be found in the Data Appendix of Berndt, Bui, Lucking-Reiley and Urban [1997], and in IMS Health [1998].

The Rx H₂s have been marketed not only to physicians, but also more directly to consumers (DTC). As noted in Berndt, Bui, Lucking-Reiley and Urban [1997], for example, in March 1988 Tagamet Rx launched "Tommy Tummy" and "stomach TLC" DTC marketing campaigns, and soon thereafter Glaxo initiated an extensive TV and print DTC effort for Zantac. Given the interpretation of FDA regulations regarding DTC advertising at that time, the advertising was quite restrictive in that if a brand name was mentioned in the advertisement, extensive product labeling information was required to accompany the advertisement.

These restrictions regarding DTC marketing were relaxed and clarified in 1997 when the FDA issued new draft guidelines. For example, a manufacturer could now advertise an Rx drug's name and the condition for which it was indicated, but without needing to issue as fully detailed a summary regarding the product's side effects and other risks. A prominently positioned 800 phone number (or website address) must now be found on the advertisement, which the consumer can call for further information.

While relatively little is known to date regarding the ultimate impacts of DTC marketing of Rx products on consumers' utilization and health status,¹⁸ there is little doubt that relaxation of the DTC restrictions by the FDA has resulted in a very substantial increase in DTC marketing of Rx products. In the context of Rx to OTC switches, DTC marketing of Rx products permits manufacturers to build up consumer brand awareness in anticipation of the future launch of OTC variants.

Data on DTC marketing of Rx brands from Leading National Advertisers (LNA)/Media Watch Multi-Media Service is published on a quarterly basis by Competitive Media Reporting. This service reports Rx brand advertising expenditure estimates in ten major

media: consumer magazines, Sunday magazines, newspapers, outdoor, network television, spot television, syndicated television, cable television, network radio, and national spot radio. The LNA/Media Watch Multi-Media Service includes only brands of companies spending a total of \$25,000 or more year-to-date in the ten media measured. The data we employ are taken from Class D21X, which reports advertising expenditures by company, and then lists brands for each company. Currently our DTC data are available only through 1998Q4. We have gathered quarterly Rx brand advertising data for the companies selling the branded H₂s, the PPIs, and the pro-motility agent Propulsid. To transform the quarterly data into monthly periodicity, we employ the STATA command "ipolate".¹⁹ The monthly expenditure data are then deflated by the Bureau of Labor Statistics' Advertising Agency Producer Price Index to convert them into constant-dollar figures.²⁰

B. OVER-THE-COUNTER DRUG MARKETS

Quantity, price and revenue data used to analyze the OTC H₂ market are taken from InfoScan™, based on store-level optical scanner data purchased and collected from multiple retail outlets by Information Resources, Inc. (IRI).²¹ These scanner data are collected weekly from more than 29,000 chain drug stores, mass merchandisers, food stores and chain convenience stores located in major metropolitan areas and rural areas. They are then projected to national levels for these chains. The IRI data provide detailed information on sales, pricing, and promotion on a stock-keeping unit basis. The volume of sales is recorded for each package size of each brand on an average weekly basis. The weekly data is aggregated to the monthly level.

Since our research goal is to examine interactions between the Rx and OTC markets, we need to establish comparable units of consumption. For each OTC brand, we aggregate the data across presentations and regional outlets so that the quantity measure reflects the total milligrams sold each month nationally. For instance, if 5,000 packages of Tagamet HB each having 25 tablets of 200 mg cimetidine) are sold, we compute the total number of mg of Tagamet HB sold that month as $5000 \cdot 25 \cdot 200 = 25$ million mg. Since unlike the IMS Health data on Rx sales to

drug stores, the IRI data record sales from drug stores, mass merchandisers and foodstores to consumers, the IRI data includes both wholesale and retail margins. Moreover, while the IMS data reflect inventory stocking behavior by, for example, chain drug store warehouses, the IRI data only include actual sales to final consumers.

To make the quantity units of the various OTC H₂ brands comparable with each other, we normalize the total number of mg per brand sold each month by the daily dosage recommended to be used to treat active duodenal ulcers.²² Although we describe our quantity measure as patient days of therapy, in fact this is not literally true, for both the Rx and OTC versions are used for the treatment of a number of related disorders, often at varying dosages, and by individuals having different body masses.²³ Rather, the quantity measures should be interpreted as the number of patient days of therapy which would be consumed hypothetically were all the OTC H₂s used for the treatment of active duodenal ulcers at recommended Rx dosages. It is worth emphasizing here that we do not wish to imply or suggest here that any or all patients actually (mis)use the OTC H₂s to treat active duodenal ulcers.²⁴ We make this transformation solely for the purpose of standardizing units of active ingredient.

Once quantity units are calculated, we divide total revenues by quantity, thereby obtaining a price per patient day of therapy. It is useful to note that both the revenue and price OTC data reflect the impacts of periodic "sales" and discounts, as well as the effects of coupons redeemed by consumers at the time of the retail transaction.

OTC drugs are marketed in ways that differ somewhat from their Rx counterparts. In the OTC market, pharmacists have tended to play a more active role in guiding consumer choice than they have with Rx products. Although physicians with capitated drug budgets now face incentives to guide consumer choice of OTC products (drug insurance most commonly covers only Rx, not OTC purchases), traditionally pharmacists have played a prominent role along with physicians in consulting consumers regarding choice of OTC medications.

OTC medications are marketed intensively to consumers. For example, for the seven largest-selling antacid OTC products in 1994, the median real advertising to retail sales ratio was

approximately 34% between 1990-1996.²⁵

To obtain measures of monthly advertising of the OTC H₂s, we again employ data from Leading National Advertisers/Media Watch Multi-Media Service. LNA distinguishes consumer-oriented OTC brand advertising from that for Rx brands. Quarterly data on media advertising over the ten media mentioned earlier for the H₂ OTC brands are taken from Class D213, Over-the-counter Digestive Aids and Antacids. Currently these data are only available to us through 1998Q4. The "ipolate" command in STATA is again employed to convert expenditure data from quarterly to monthly. Monthly advertising expenditures in current dollars are then deflated by the BLS' Producer Price Index for Advertising Agencies, as discussed above.

V. OBSERVED PATTERNS NEAR THE END OF THE PATENT PRODUCT LIFE CYCLE

"Nostalgia isn't what it used to be." - Unknown

We now turn to a description and preliminary analysis of market developments as the Rx H₂ manufacturers anticipated, realized and dealt with loss of patent protection. We also examine the impacts of the pre-emptive launch of OTC H₂ variants, and the effects of competition from generic Rx H₂ producers.

A. MARKETING AND PRICING OF RX DRUGS IN ANTICIPATION OF AND FOLLOWING PATENT EXPIRATION

We begin by examining how branded pioneer firms change their marketing behavior in anticipation of, and following loss of patent expiration. To assess the hypotheses suggested earlier, we examine marketing efforts for the two H₂s losing patent expiration, Tagamet (May 1994) and Zantac (August 1997).²⁶ We compare average marketing efforts when the date of patent expiration is quite some time away (between 25 and 48 months ahead), as it becomes much closer (between 1 and 24 months ahead), and after (0 to 23 months after). For each time frame, we compute average monthly minutes of detailing, and average journal pages, as well as the Dorfman-Steiner dollar ratio of average marketing expenditures to average sales revenues. Differences between the 1 - 24 vs. 25 - 48 time periods prior to patent expiration are called "near

vs. far away", while those between 0 - 23 months after vs. 25 - 48 months before are called "after vs. far away". The results of these calculations are given in the Tagamet and Zantac columns of Table 1, the top panel in terms of marketing quantity levels, and the bottom in dollar marketing to sales ratios.

For Tagamet marketing levels, average monthly minutes of detailing fell by 30% as its patent expiration approached (May 1992 - April 1994 vs. May 1990 - April 1992), and by 87% following patent expiration in May 1994 (May 1994 - April 1996 vs. May 1990 - April 1992). Journal page advertising fell even more sharply, at 55% and 97%, respectively. In terms of marketing to sales dollar ratios (bottom two rows of the bottom panel of Table 1), the total dollar marketing (detailing plus medical journal advertising) expenditure to total sales revenue ratio fell by 43% as Tagamet patent expiration approached, and then fell by a smaller amount subsequently, -30%, after patent expiration. For Zantac, the decline in marketing efforts was even more dramatic. Average monthly minutes of detailing fell by 59% as Zantac patent expiration approached (August 1995 - July 1997 vs. August 1993 - July 1995), and by 94% following patent expiration in August 1997 (August 1997 - July 1999 vs. August 1995 - July 1997). As with Tagamet, journal page advertising fell even more dramatically than detailing minutes, at 99% and 100%, respectively.²⁷ In terms of marketing/sales dollar ratios, as seen in the bottom two rows of Table 1, as patent expiration approached the total marketing/sales fell by almost 60%, and by an additional 13% after patent expiration.

It is also of interest to examine how the competitors of Zantac, then the leading selling H₂, reacted when they observed Zantac cutting back on marketing in anticipation of and following its patent expiration. Since the entire H₂ prescription drug market was in decline during this time (due to competition from the more potent PPIs and the introduction of OTC versions that potentially cannibalized H₂ Rx sales), would Pepcid and Axid Rx also cut back on marketing efforts, or would they perceive this as a strategic opportunity to fill a void given the dramatic cutbacks by Tagamet and Zantac, and instead increase their marketing efforts?²⁸ The marketing responses of Pepcid and Axid surrounding the time of Zantac's patent expiration are

TABLE 1

CHANGES IN MARKETING EFFORTS IN ANTICIPATION OF AND FOLLOWING
PATENT EXPIRATION, H₂-ANTAGONIST PRESCRIPTION DRUGS

<u>MARKETING LEVELS</u>	<u>TAGAMET</u>	<u>ZANTAC</u>	<u>PEPCID</u>	<u>AXID</u>
Minutes of Detailing				
Near vs. Far Away	-30.2%	-59.3%	-19.6%	-36.0%
After vs. Far Away	-86.6%	-94.4%	-28.3%	-48.5%
Pages of Journal Advertising				
Near vs. Far Away	-55.1%	-99.3%	257.7%	-16.1%
After vs. Far Away	-96.7%	-100.0%	-16.2%	-94.7%
<u>DOLLAR MARKETING TO</u> <u>DOLLAR SALES RATIOS</u>				
Detailing Dollars to Sales Ratio				
Near vs. Far Away	-37.8%	-57.4%	-39.1%	-36.3%
After vs. Far Away	-32.3%	-71.2%	-36.7%	-35.1%
Total Detailing Plus Journal Advertising Dollars to Sales Ratio				
Near vs. Far Away	-43.1%	-59.8%	-33.3%	-36.0%
After vs. Far Away	-30.1%	-72.8%	-35.3%	-35.5%

Notes: For Tagamet, "Far Away" is May 1990 - April 1992, "Near" is May 1992 - April 1994, and "After" is May 1994 - April 1996. For Zantac, Pepcid and Axid, "Far Away" is August 1993 - July 1995, "Near" is August 1995 - July 1997, and "After" is August 1997 - July 1999.

summarized in the last two columns of Table 1.

As is seen in Table 1, Pepcid and Axid had rather different responses. For Axid, average

minutes of detailing fell by about 36% as Zantac's patent expiration approached, and following it, they fell by another 13%. The journal page advertising cutback was more varied, being 16% as Zantac's patent expiration approached, and 95% following it. For Pepcid, however, the decline in minutes of detailing was much more modest -- only 20% in the time leading up to Zantac patent expiration, and an additional 8% following it. By contrast, journal page advertising for Pepcid actually increased by 258% as Zantac patent expiration approached, and then following patent expiration fell to 16% less than that far before Zantac patent expiration occurred. Thus the Pepcid response as Zantac cut back on its levels of marketing efforts was somewhat different from that of Axid. In terms of total marketing/sales dollar ratios, however, Axid and Pepcid were quite similar, each reducing these ratios by about 33-36% as patent expiration approached, and then maintaining them at approximately those values after Zantac patent expiration.

Finally, in terms of the marketing of generic drugs, IMS data indicate zero recorded detailing efforts by generic manufacturers as reported to the IMS by its physician panel. However, for about 12-18 months following patent expiration, for both cimetidine and ranitidine there was a very modest amount of journal advertising by generic manufacturers.²⁹ Interestingly, while the generic firms' medical journal advertisements announced the new availability of cimetidine or ranitidine, frequently they were relatively more "institutional" than specific product-focused, prominently noting the larger portfolio of other generic drugs also offered by the generic manufacturer.

We now turn our attention to pricing behavior prior to and following patent expiration. Price per day of therapy for Rx Tagamet and generic Rx cimetidine, monthly from January 1988 through December 1998, are plotted in Figure 1, while those for Rx Zantac, generic Rx ranitidine and OTC Zantac 75, January 1988 - June 1999, are plotted in Figure 2; also plotted are the average price per day of therapy over all Rx and OTC forms for each molecule ("Total Molecule"), and the average price over branded Rx and generic Rx ("Total Rx"). All prices are in current (not deflated) dollars.

As is seen in Figure 1, following patent expiration in May 1994, Tagamet's price continued to increase, and by June 1999 it was about 10% greater than five years earlier when it lost patent protection. The price of generic cimetidine fell considerably since 1994, with an apparent flattening out occurring in about mid-1997. By mid 1999, the Tagamet Rx brand price was about eight times that of generic cimetidine Rx. For Tagamet Rx, therefore, there does not appear to be any major change in pricing following patent expiration. Instead of meeting price competition from the generics, Tagamet maintained and even slightly increased its price.

For cimetidine consumers, on balance patent expiration provided considerable benefits. In particular, since the May 1994 patent expiration the total Rx price of cimetidine (a sales-weighted average over Tagamet Rx and generic cimetidine Rx) fell to about 20% of its 1994 level. The total Rx price at mid-1999 was about a sixth that of the Tagamet Rx brand price.

Figure 2 presents the comparable price paths for Zantac Rx and generic ranitidine Rx. Following loss of market exclusivity in July 1997, the Zantac brand price increased steadily, and by mid-1999 it was about 21% higher than at patent expiration. The rate of price decline for generic ranitidine immediately following patent expiration appears to be greater for ranitidine than cimetidine (compare Figures 1 and 2). This could reflect greater entry incentives for ranitidine since at the time of patent expiration, the branded Zantac Rx was a larger dollar and unit sales market than was branded Tagamet Rx. Relative to the price of Zantac at the time of patent expiration less than two years earlier, by June 1999 the price of generic ranitidine was about a quarter that of Zantac. In mid-1999, the Zantac brand price is almost five times that of generic ranitidine. Compared with the years preceding Zantac Rx loss of market exclusivity, therefore, Zantac pricing in the post-patent expiration era does not appear to differ in any dramatic way, although its prices have increased more sharply than has Tagamet Rx post-patent expiration.

For consumers, on balance Zantac's loss of patent protection resulted in lower average prices. Specifically, as seen in Figure 2, by mid-1999 the average ranitidine Rx price (a sales-weighted average over Zantac Rx and generic ranitidine Rx) was about 63% lower than it was at

the time of Zantac patent expiration in July 1997.

In summary, both Tagamet Rx and Zantac Rx appear to have adopted a policy of not competing with generics on price following patent expiration, and instead increased prices, in the process losing very substantial market share but retaining sales to a small but relatively price-insensitive segment of brand-loyal customers.

B. MOLECULE RX VOLUME BEFORE AND AFTER PATENT EXPIRATION

Next we examine quantity (patient days of Rx therapy) data for cimetidine and ranitidine, before and after patent expiration. As seen in Figure 3, during the four years prior to patent expiration in May 1994, sales of branded Tagamet were relatively flat. Following patent expiration in May 1994, however, sales of branded Rx Tagamet plummeted rapidly even as generic Rx cimetidine sales flourished. By mid-1999, generic cimetidine Rx units were more than ten times that of Tagamet, i.e., of the cimetidine Rx market, generic cimetidine had more than 96% market share. When sales of generic Rx cimetidine are added to those of brand Rx Tagamet (labeled "Total Rx" in Figure 3), we see that the quantity of brand plus generic Rx cimetidine sales fell considerably (about 32%) since Tagamet lost patent protection in May 1994. This decline in quantity demanded occurred even though the average price per day of therapy for the Rx cimetidine molecule (over its brand and generic Rx versions) fell considerably (see Figure 1). The cimetidine Rx sales decline could reflect new competition from generic ranitidine following Zantac Rx patent expiration, increased rivalry from the PPIs, cannibalization from the introduction of the OTC variant Tagamet HB, and/or sharply curtailed marketing efforts.

For ranitidine Rx, the picture is slightly different, as is seen in Figure 4. In particular, branded Zantac Rx sales appear to have fallen steadily since early 1995 (around the time Pepcid AC, the first OTC H_2 came on the market), and prior to Zantac Rx patent expiration. Reflecting perhaps the effects of OTC cannibalization, branded Zantac Rx sales continued a steady decline until August 1997, when Rx patent expiration took place. Thereafter, as with branded Tagamet Rx, branded Zantac Rx quantity units fell dramatically, and by June 1999 Zantac Rx unit sales were only about 8% of their 1994-95 peak levels. When generic cimetidine Rx sales are added

to Zantac Rx sales ("Total Rx" in Figure 4), we observe a continued decline following August 1997 patent expiration. The post-patent expiration decline in total Rx sales for ranitidine is smaller than that for cimetidine (compare Figures 3 and 4), but the fall in average Rx price for ranitidine from the time of patent expiration is also smaller for ranitidine Rx than cimetidine Rx (compare Figures 1 and 2).

C. ORDER OF ENTRY AND MARKETING EFFECTS IN THE OTC H₂ MARKET

The four branded H₂s all entered within 13 months of one another – first Pepcid AC in June 1995, then Tagamet HB in August 1995, Zantac in April 1996 and finally Axid AR in July 1996. Thus order of entry into the OTC market was not the same as that in the Rx segment, in which Tagamet had been first, then Zantac, Pepcid and finally Axid. Would Zantac's heritage of being the best-seller in the Rx market help it to overcome Pepcid AC, or would Pepcid AC be able fully to exploit the potential first mover advantages it had achieved? Would Tagamet HB being second in the OTC market help it overcome the Zantac Rx heritage and enable Tagamet HB to outsell Zantac 75, the third OTC entrant? Was there any hope for fourth entrant Axid AR? A detailed empirical analysis of the effects of order of entry, as well as other factors, on the eventual market success of the four OTC branded H₂s is beyond the scope of this paper, but here we briefly comment on results of a preliminary analysis.

Order of entry effects can manifest themselves in a number of ways. In the Rx H₂ market, for example, a clear finding was that one year, two years and three years after initial launch, marketing/sales ratios (cumulative detailing minutes divided by cumulative units sold) were smallest for the pioneer, and successively increased for each subsequent Rx H₂ entrant.³⁰

To construct a comparable marketing/sales ratio for the OTC H₂ market, we compute cumulative advertising dollar expenditures (summed over the ten advertising media) for each OTC H₂ and divide this by cumulative OTC H₂ revenues, separately for one year after launch, then two years, and finally, three years. Results of this calculation are quite striking, and are given in Figure 5. Advertising/sales dollar ratios for pioneer Pepcid AC are about 0.42 in the year of product launch, are higher at 0.53 for second entrant Tagamet HB, and are much higher

at 0.88 for third entrant Zantac 75 and 0.87 for fourth entrant Axid AR. Since advertising efforts are particularly intense immediately following product launch, it is not surprising that all four advertising/sales ratios are smaller two years relative to one year after launch. After two years, a perfect ranking occurs between the magnitude of the ratio and the order of entry -- lowest for Pepcid AC (0.38), larger for second entrant Tagamet HB (0.41), higher still for third entrant Zantac 75 (0.52), and highest for the last entrant Axid AR (0.54). Since our OTC marketing data end in 1998Q4, we are able to obtain corresponding three-year cumulative ratios only for Zantac 75 and Axid AR. These strictly follow the order of entry ranking, 0.34 for pioneer Pepcid AC and 0.38 for second entrant Tagamet HB.

An important aspect of rivalry in the Rx H₂ market involved the indications for which the FDA granted approval. Zantac Rx, for example, was the first H₂ to obtain approval for GERD (a severe form of heartburn), and having this approval allowed Zantac Rx detailers to expand their marketing efforts significantly by visiting offices of general practitioners and internists, not just the smaller number of gastroenterologists who treated ulcers.

In the OTC H₂ market, a different but related rivalry developed that also involved FDA indication approvals. In April 1995 pioneer Pepcid AC received FDA approval not only for the *treatment* of episodic heartburn, but also for its *prevention*. Thus Pepcid AC could be marketed as a pre-emptive treatment, used prior to eating spicy foods, for example. By contrast, when Tagamet HB received its initial FDA approval in June 1995, it was for the *relief* of symptoms of occasional heartburn, acid indigestion and sour stomach, but not for their *prevention*. This placed Tagamet HB at a competitive disadvantage in its ability to market, for the prevention market was likely to be very large, and until Tagamet HB had explicit FDA approval for prevention, it could not market this claim. Tagamet HB realized this, but was not able to obtain FDA approval for prevention of meal-induced heartburn, acid indigestion and sour stomach until November 15, 1995. Interestingly, the last two OTC entrants each received approval for only the prevention of, or only the relief of heartburn, but not both. Zantac 75 received FDA relief approval on December 19, 1995, while Axid AR received approval on May 9, 1996 for

prevention of meal-induced heartburn, acid indigestion and sour stomach.³¹ In addition to its prevention indication disadvantage, at launch time Tagamet HB had a dosage requiring two 100 mg tablets per dose, whereas the Pepcid dose required only one 10 mg tablet. Eventually in October 1996 Tagamet HB was able to change this to one 200 mg tablet per dose.

Pepcid AC thus enjoyed two first-mover advantages: Pepcid AC was the first H₂ to obtain OTC approval from the FDA, and it was also the first to obtain approval for the prevention of heartburn, and not just symptomatic relief. We hypothesize that this dual first mover advantage provided considerable benefits to Pepcid AC.

To describe sales developments for the OTC H₂s since their launch in 1995-96, in Figure 6 we plot monthly days of therapy for each of the OTC H₂s, while in Figure 7 we plot corresponding revenue shares. In interpreting these figures, recall first that the OTC prices are actual average consumer prices paid at mass merchandisers, food stores and drug stores that use scanner checkout equipment and sell their chain store data to IRI. Thus, sales from convenience and other stores that do not employ scanner data are not included in the IRI data; also excluded are sales from stores having scanning equipment but that are not part of chains selling their data to IRI. This implies that the OTC quantity and revenue data understate total US sales. Second, to make Rx and OTC data comparable, we have converted OTC quantities to Rx daily dosage equivalents, multiplying the maximum recommended daily OTC dosage by two. Hence, for example, a day of OTC therapy for Pepcid AC consists of four 10-mg tablets, while a day of Rx therapy for Pepcid consists of two 20-mg tablets.

Third, in August 1996, at \$1.60 and \$1.53, Zantac 75 and Axid AR average daily prices were considerably higher than those for Pepcid AC (\$1.31) and Tagamet HB (\$1.26). As the average number of tablets per package increased over time, however, for all four OTCs, average daily prices fell. By July 1999, there was little price dispersion: Axid AR, \$1.09; Zantac 75, \$1.12; Tagamet HB, \$1.14; and Pepcid AC, \$1.16.

With this in mind, we now examine monthly sales units and revenue shares. As is seen in Figure 6, order of entry effects were apparently important in the OTC market, but they were not

entirely invincible. Specifically, first entrant Pepcid AC has been the market leader ever since its launch in June 1995, and last entrant Axid has sustained apparently permanent last mover disadvantages. However, Tagamet HB, the second mover in the OTC market, has not been able to maintain second place in sales, but instead lost that to third entrant Zantac 75 within two months of the Zantac 75 launch in April 1996. Apparently, the very successful Rx heritage of Zantac loomed large enough to enable Zantac 75 to overcome Tagamet HB's order of entry and prevention indication approval advantages, but the benefits of the Rx heritage to Zantac 75 (along with the disadvantage of not having the heartburn prevention indication FDA approval) did not enable Zantac 75 to overcome the 10-month earlier OTC entry advantage of first entrant Pepcid AC.

A second strong result depicted in Figure 6 is that the OTC market for H_2 s has become a large one. In mid-1999 the sum of patient days of therapy over the four OTC products is about 48 million days of therapy per month. Recall that this only includes the IRI countable scanner sales. For the same time period, by comparison, the total patient days of Rx H_2 therapy sold to drug stores was about 70 million. But OTC vs. Rx sales portions differ by brand. For Pepcid, OTC patient days of Pepcid AC therapy were approximately twice those for Pepcid Rx. However, in mid-1999, total days of therapy for Zantac 75, Tagamet HB and Axid AR were only about 35% that of their Rx (branded plus generic) sales. OTC sales of the branded H_2 s have therefore become a quite substantial component of brand equity. For Zantac, this implies brand equity that can persist even after the Rx product loses patent protection.

In Figure 7 we plot revenue shares for the four branded OTC H_2 s. Given the information conveyed in Figure 6, it is not surprising that the revenue share of Pepcid AC is largest, hovering around 60% ever since mid-1996. The revenue share for Zantac 75 has ranged from 20% to slightly under 30%, and generally has a slow but unsteady increase over time. The launch of Zantac 75 appears to have hurt Tagamet HB, but Tagamet HB appears also to have lost some of its share to Axid AR, the fourth entrant. At the end of the sample time period in mid-1999, the Tagamet HB revenue share was just under 10%, while that for Axid AR was 2-3%.

D. L(A)UNCHING WITH CANNIBALS: EFFECTS OF OTC'S ON RX SALES

Next we turn to an exploratory empirical assessment of the impact of a brand's OTC introduction on its own Rx sales. In theory, most any outcome is possible. If cannibalization is extensive, then patients taking Rx versions will switch to the OTC product, and the trend of overall OTC plus Rx sales for that brand will be largely unaffected. On the other hand, if because of extensive marketing and increased consumer awareness of the OTC product, previous non-users of the Rx product now ask their physicians about the OTC product, and if the physician instead recommends the stronger brand version (either because the OTC version is not sufficiently strong, and/or because the Rx version is covered by third party insurance whereas the OTC version is not), then positive spillovers could occur. If these spillovers are sufficiently large, overall OTC plus Rx sales for that brand could increase. Whether cannibalization or positive spillovers dominate is therefore an empirical issue.

We expect that since it was the largest selling Rx product, Zantac was the most likely to experience extensive cannibalization from OTC introductions, particularly its own. In contrast, with patent expiration already behind it, Tagamet had the most to gain from its OTC launch. We now assess the net effects on brand sales of OTC introductions by brand.

First, in terms of price, it is instructive to compare OTC and Rx prices. Recall that for comparability, the OTC price per day of therapy assumes twice the recommended daily OTC dosage, so that the Rx and OTC versions have the same amount of mg strength each day. In Figure 1 we see that by June 1999 the OTC Tagamet HB price per day of therapy is about 45% the Rx Tagamet price, but OTC Tagamet is slightly more than three times the Rx generic cimetidine price. Note, however, that the Rx generic cimetidine price does not include the retail margin, which is often larger than that for the branded Rx product, while the OTC Tagamet HB price is gross of the retail margin. Hence, for most cash customers, the comparison between OTC and Rx prices of the brand overstates the relative OTC magnitude. In spite of this OTC price overstatement bias, for consumers paying cash, purchasing a day of therapy is much less expensive with the OTC Tagamet HB than with its branded Rx variant. The OTC purchase also

avoids the time and other costs of obtaining a physicians' prescription.

From Figure 2 we observe that by mid 1999, on a per patient day of therapy basis, the price of OTC Zantac 75 is about one and a half times that of Rx generic ranitidine, but only about a third that of Zantac Rx. Hence for both Tagamet and Zantac, price per day of therapy for the OTC version is considerably less than that of the branded Rx variant.

Although to save on space we do not present comparable figures here for Pepcid and Axid, it is also the case that by mid 1999, prices per day of therapy for Pepcid Rx and Axid Rx are about 2.4 and 2.7 times their comparable OTC price, respectively.

Second, in terms of quantity sold, as seen in Figure 3, for Tagamet the OTC sales in mid-1999 are about 7-8 times larger than Rx sales, and in 1995 they comprised a substantial portion of the resuscitation of sales following the 1994 loss of patent protection. Because its brand Rx sales had fallen so sharply following patent expiration, there were few sales left to cannibalize, and thus for Tagamet the OTC introduction was a clear spillover winner. But by mid 1998 total Rx plus OTC Tagamet unit sales were again falling, and by mid 1999 they reached levels only about the same as (actually, 1% less than) just prior to patent expiration in May 1994. Through its OTC launch, Tagamet averted the gradual brand franchise death, but only temporarily.

For Zantac, as seen in Figure 4, the introduction of Zantac 75 in May 1996 appears to have resuscitated the Zantac brand franchise, temporarily raising total Zantac Rx plus Zantac 75 OTC patient day sales. By fall 1997, immediately following Zantac Rx patent expiration, total Zantac unit sales were about the same as those in early 1996, just prior to the launch of Zantac 75. Zantac OTC unit sales have continued a slow but steady increase in recent years even as Zantac Rx sales have declined sharply, and by mid-1999 patient days of Zantac OTC are 3-4 times those of Zantac Rx. Although (unlike Tagamet) in some ways the Zantac franchise benefited from an OTC introduction prior to its Rx patent expiration, it also appears the Zantac franchise suffered in the form of cannibalization of Zantac Rx by Zantac 75. As the best-selling Rx therapy, Zantac stood to lose the most from the various OTC introductions, including its own.

In terms of revenues (not shown), by mid-1999 Tagamet OTC revenues were about three

and a half times greater than those for Tagamet Rx, while OTC Zantac 75 revenues were approximately the same as those from Zantac Rx. Summed over both OTC and Rx versions, however, Zantac revenues were about 45 times larger than those for Tagamet. Hence, while on a relative basis the OTC introductions appear to have benefited Tagamet more than Zantac, on an absolute revenue basis over both OTC and Rx forms, Zantac has been a larger beneficiary.

The most interesting OTC-Rx interaction, however, appears to be that for Pepcid, as is seen in Figure 8, which plots Pepcid Rx, Pepcid AC and total Pepcid revenues over time. As discussed earlier, the Pepcid AC product launch was a very successful one, and fully exploited the potential advantages accruing the first entrant in the OTC market. Monthly Pepcid AC revenues have ranged from \$35-40 million since early 1996. Moreover, as seen in Figure 8, for Pepcid positive spillovers from the Rx-OTC interaction have clearly predominated. Pepcid Rx revenues have actually *increased* slightly since the OTC launch of Pepcid AC in June 1995, unlike those for both Tagamet Rx and Zantac Rx which fell sharply following loss of patent expiration. To this point, for Pepcid there appears to be little cannibalization, and positive spillovers clearly dominate. For the Pepcid brand franchise, OTC monthly revenues are approximately the same as from the Rx side. Note, however, that Pepcid Rx patent expiration is expected to occur in spring 2001. Whether the introduction of generic famotidine Rx following Pepcid Rx patent expiration will have an adverse interactive effect with Pepcid AC remains to be seen. Moreover, as the leading selling OTC product, Pepcid AC can be expected to attract significant generic OTC entry as well.

Finally, in Figure 9 we plot revenues for Axid, the only other H₂ not yet experiencing patent expiration, for its Rx and OTC (Axid AR) versions, and in total. For Axid the picture is quite different from that for Pepcid. As discussed above, being a late entrant into the H₂ OTC market placed Axid at a disadvantage. Moreover, its initially small OTC share has steadily fallen over time. As is seen in Figure 9, by mid-1999, Axid AR monthly revenues were only about \$1.5 million, down from over \$5 million following its launch in mid-1996. Additionally, on the Rx side, unlike Pepcid, Axid has not been able to arrest the decline in Rx revenues.

Although Axid Rx sales revenues increased in the months immediately following the OTC introduction of Axid AR, in early 1997 Axid Rx sales began falling, and this trend has continued steadily since then.

VI. A TIERED ECONOMETRIC MODEL OF THE DEMAND FOR H₂S

To model the demand for Rx and OTC H₂s, we conceive a four-tiered framework.³² At the top, we model total (Rx plus OTC) H₂ sales. In the second tier we consider factors affecting the split between Rx H₂s and OTC H₂s. The third tier has separate branches, one in which we model the split among the four Rx H₂ molecules, while in the other we model the split among the four OTC H₂ brands. At the bottom tier, for the cimetidine and ranitidine Rx molecules, we consider factors affecting the shares of the pioneer brand and generic entrants following patent expiration.³³

In each of the top three tiers, we specify quantity demanded as a function of price, marketing efforts and other factors. As noted earlier, it is reasonable to expect that marketing efforts are long-lived, having sales impacts far beyond the month in which marketing expenditures originally occurred. Thus the appropriate measure of marketing effort is cumulative in nature. In previous research, it has been common to assume that the rate of depreciation of the impact of marketing efforts on sales is constant over time. We follow that tradition here, although research that generalizes the depreciation rate to allow it to fall as patent expiration approached deserves high priority. Thus, here we specify that the marketing stock is a weighted sum of previous monthly marketing expenditure flows. According to the perpetual inventory method,

$$Z_t = (1 - \delta) \cdot Z_{t-1} + M_t, \quad (2)$$

where δ is the monthly depreciation rate. Thus, the marketing stock at the end of month t is that depreciation-adjusted amount carried over from the previous period, plus this month's new (inflation-adjusted) marketing efforts. If $\delta = 0$, then Z_t is simply the cumulative sum of all previous real marketing efforts, and if $\delta = 1$, then the effects of this period's marketing efforts completely disappear at the end of the month and $Z_t = M_t$. In the econometric implementation,

we estimate $\hat{\alpha}$, rather than assume a priori values for it.

In formulating and reporting econometric results from the tiered framework, it is useful to begin at the bottom and work up to the top level. The results reported below are preliminary not only in the sense that we have not yet taken into account possible simultaneity among marketing, pricing and quantity demanded, but we also expect to explore other specifications (such as those associated more closely with demand systems based on explicit consumer optimization), as well as use of more recent data, beyond December 1998.

A. THE BOTTOM TIER: GENERIC/BRAND RX SHARES

Consistent with modeling by Frank and Salkever [1997], we specify the generic/brand share for Rx cimetidine and ranitidine to be a function of the relative generic-brand price, and time since patent expiration. We do not expect that marketing efforts affect the post-patent expiration of brands and generics.

Specifically, the generic/brand share equation relates the log of relative quantities (with GEN denoting generic, and BRN brand) to log relative prices, the number of months the Rx drug has been off-patent, the log of the molecule's market size in patient days of therapy six months prior to patent expiration, and the interaction between these last two variables, $INTER = \ln(MKTSIZE)*RXOFFPAT$. OLS estimates are based on the pooled set of observations for off-patent cimetidine and off-patent ranitidine ($n = 109$). The estimated equation is as follows, where estimated standard errors are in parentheses:

$$\begin{aligned} \ln(QGENDAY/QBRNDAY)_{jt} = & 5.035 - 0.533*\ln(PGENDAY/PBRNDAY)_{jt} \\ & (2.197) \quad (0.115) \\ & - 0.143*RXOFFPAT_{jt} - 0.467*\ln(MKTSIZE)_j + 0.017*INTER_{jt}. \quad R^2 = .881 \\ & (0.096) \quad (0.215) \quad (0.010) \end{aligned}$$

The price elasticity estimate of -0.533 is significant ($p < 0.001$) and negative as expected. Since the coefficients on $RXOFFPAT$ and $\ln(MKTSIZE)$ are both negative while that on their interaction is positive, these results suggest that eventually, the larger the market size pre-patent

expiration, the greater the relative generic penetration.³⁴ The statistical significance on RXOFFPAT ($p = 0.140$) and on INTER ($p = 0.080$) is, however, quite low. Since we are dealing with but two off-patent molecules, MKTSIZE takes on only two values over the entire set of observations. When the MKTSIZE and its interaction are deleted, the price elasticity estimate changes only slightly to -0.560 , while the RXOFFPAT coefficient estimate becomes positive and significant (0.029 , t -statistic of 10.99).

B. THE THIRD TIER: SHARES WITHIN OTCS

The third tier has two branches -- one for the split among OTC H₂s, and the other for that among the Rx H₂s. We begin with factors affecting choice among the OTCs. For the OTC branch, owing to different dates of product launch, the panel of OTC brands is an unbalanced one. Although theoretical developments in the economic theory of demand now permit empirical specifications in which the number of alternative goods in the choice set changes over time, due to their computational complexity, to date empirical implementations (based on the multinomial logit or generalized extreme value distributions) have been few.³⁵ Thus in specifying this within-OTC branch, as in Berndt, Bui, Lucking-Reiley and Urban [1992,1997], we instead follow the marketing and order of entry literature in which it has been traditional to specify the dependent and explanatory variables all relative to the pioneer in an unbalanced panel framework.

Let $QDAYOTC_{jt}$ be the number of days of therapy for OTC brand j in month t , $PDAYOTC_{jt}$ be the corresponding price, $ZOTCDTC_{jt}$ be the marketing stock of OTC advertising of brand j via direct-to-consumer media, $ZRXMD_{jt}$ be the marketing stock of the Rx variant of OTC drug j directed to physicians (detailing and medical journal advertising), and let $ZRXDTC_{jt}$ be the marketing stock of the Rx version of OTC drug j advertising based on DTC media. Then define a variable $OTCORDER_j$ as the order of entry of OTC brand j in the OTC market, and $RXOFFPAT_{jt}$ as the number of months the Rx version of OTC brand j has been off-patent.

We specify a regression equation having the form

$$\ln(QOTCDAY_{jt}/QOTCDAY_{PAC,t}) = a_0 + a_1 * \ln(POTCDAY_{jt}/POTCDAY_{PAC,T}) +$$

$$\begin{aligned}
& a_2 * \ln(\text{ZOTCDTC}_{jt} / \text{ZOTCDTC}_{\text{PAC},t}) + a_3 * \ln(\text{ZRXMD}_{jt} / \text{ZRXMD}_{\text{PAC},t}) + \\
& a_4 * \ln(\text{ZRXDTC}_{jt} / \text{ZRXDTC}_{\text{PAC},t}) + a_5 * \text{OTCORDER}_j + a_6 * \text{PREVENT}_{jt} + \\
& a_7 * \text{RXOFFPAT}_{jt} + \varepsilon_{jt}, \tag{3}
\end{aligned}$$

where the PAC subscript is the OTC pioneer Pepcid AC, j = Tagamet HB, Zantac 75 and Axid AR, and ε_{jt} is an i.i.d. random error term. The PREVENT variable takes on the value of 0 if drug j has FDA approval for prevention of heartburn (representing parity with pioneer Pepcid AC), and -1 if drug j does not have FDA approval for the prevention of heartburn (representing a disadvantage relative to Pepcid AC). We "stack" the Tagamet HB, Zantac 75 and Axid AR observations ($n = 104$), and estimate the unbalanced panel by OLS, assuming ε is normally distributed. Since by Eqn. (2) the marketing stock variables depend on an unknown monthly deterioration rate δ , we perform a grid search over δ from 0% to 25% monthly, in steps of 0.5%, and then choose as our preferred model that combination of δ and the remaining parameters that minimizes the sum of squared residuals.³⁶

The within-OTC share model employs IRI scanner data for the OTC H₂S, IMS Health data on Rx physician-oriented marketing, and LNA data on direct-to-consumer marketing of OTC and Rx products. In the initial regressions, both OTCORDER and PREVENT had unexpected signs, and were insignificant. Since all four OTC products entered within 13 months of each other, the impacts of order of entry, and of any PREVENT advantages, may instead be captured by the OTC marketing stock measures. With OTCORDER and PREVENT omitted, we obtain the following estimated equation:

$$\begin{aligned}
\ln(\text{QOTCDAY}_{jt} / \text{QOTCDAY}_{\text{PAC},t}) &= -1.469 - 0.793 * \ln(\text{POTCDAY}_{jt} / \text{POTCDAY}_{\text{PAC},t}) \\
&\quad (0.150) \quad (0.376) \\
&+ 0.825 * \ln(\text{ZOTCDTC}_{jt} / \text{ZOTCDTC}_{\text{PAC},t}) + 0.017 * \ln(\text{ZRXMD}_{jt} / \text{ZRXMD}_{\text{PAC},t}) \\
&\quad (0.101) \quad (0.022) \\
&+ 0.093 * \ln(\text{ZRXDTC}_{jt} / \text{ZRXDTC}_{\text{PAC},t}) - 0.0002 * \text{RXOFFPAT}_{jt}, \quad R^2 = 0.820. \\
&\quad (0.015) \quad (0.0001)
\end{aligned}$$

The price-elasticity estimate of -0.793 is negative and significant ($p = 0.038$). The estimated monthly depreciation rate (based on the grid search procedure) is 10.5%, with a 95% confidence interval of 6.3% to 15.0%. Relative OTC quantities demanded are strongly positively related to relative direct-to-consumer marketing stocks (an elasticity of 0.825), and, somewhat surprisingly, are also positively related to direct-to-consumer marketing stocks of their Rx brands, although this latter elasticity is much smaller at 0.093. However, relative OTC quantities demanded are not significantly related to relative physician-oriented stocks of their same-brand Rx products (elasticity of 0.017, $p = 0.438$). The number of months the same-brand Rx product has been off-patent has a small negative effect, suggesting less overall brand awareness as the Rx variant loses patent protection, but this coefficient estimate is not significant ($p = 0.239$).

We find, therefore, that there are significant and positive Rx to OTC interactions involving direct-to-consumer marketing, but that these interactions are much stronger for OTC than for Rx marketing efforts.

C: THE THIRD TIER: SHARES WITHIN THE RX H₂S

For the Rx brand of the H₂s, we employ a similar approach to that used for the OTCs, but in the Rx market, Tagamet is the pioneer, and thus variables for Rx drug j are measured relative to Tagamet/cimetidine. Let $QRXDAY_{jt}$ and $PRXDAY_{jt}$ be the quantity and price of a day of Rx therapy for drug j , and let $ZOTCDTC_{jt}$, $ZRXMD_{jt}$, $ZRXDTC_{jt}$ and $RXOFFPAT_{jt}$ be as above. Define $RXORDER_j$ as the order of entry of Rx drug j in the Rx H₂ market, and $ADVERSE_{jt}$ as the number of other molecules with which drug j is known to have a significant adverse interaction potential, as indicated in the product label reprinted in annual editions of Physicians' Desk Reference.

The launching and successful marketing of the more potent PPIs could have a non-neutral effect on the quantity shares of the Rx H₂ molecules. Since the number of adverse drug interactions for Rx Tagamet was much larger than that for the other three Rx brands, and since the PPIs had very few known adverse drug interactions, the growth of the PPI markets could have come at the expense of the "lowest quality" H₂, namely, Tagamet (cimetidine). On the

other hand, extensive direct-to-consumer marketing of the PPIs could have resulted in physicians' first starting a patient on any of the three "higher quality" but less expensive H₂s, namely, Zantac (generic ranitidine), Pepcid or Axid. To allow for these possible non-neutral spillover effects from the PPIs, we specify as regressors the stock of PPI marketing efforts directed toward physicians, ZRXPPIMD_t, and the corresponding stock of PPI marketing efforts directed to consumers, ZRXPPIDTC_t; in both cases, marketing efforts are summed over the two PPIs, Prilosec and Prevacid.

With these variables defined, we specify the within-Rx H₂ regression as having the form

$$\begin{aligned} \ln(\text{QRXDAY}_{jt}/\text{QRXDAY}_{\text{CIM},t}) = & b_0 + b_1 \ln(\text{PRXDAY}_{jt}/\text{PRXDAY}_{\text{CIM},t}) + \\ & b_2 \ln(\text{ZOTCDTC}_{jt}/\text{ZOTCDTC}_{\text{CIM},t}) + b_3 \ln(\text{ZRXMD}_{jt}/\text{ZRXMD}_{\text{CIM},t}) + \\ & b_4 \ln(\text{ZRXDTC}_{jt}/\text{ZRXDTC}_{\text{CIM},t}) + b_5 \text{RXORDER}_j + b_6 (\text{ADVERSE}_{jt}/ \\ & \text{ADVERSE}_{\text{CIM},t}) + b_7 (\text{RXOFFPAT}_{jt} - \text{RXOFFPAT}_{\text{CIM},t}) + b_8 \text{GERD}_{jt} + \\ & b_9 \text{ZRXPPIMD}_t + b_{10} \text{ZRXPPIDTC}_t + u_{jt}, \end{aligned} \quad (4)$$

where u_{jt} is a normal i.i.d. random disturbance term. The GERD_{jt} variable takes on the value zero if Rx drug j has a parity FDA approval for GERD compared with Tagamet/cimetidine, a value of +1 if Rx drug j has FDA approval for GERD but Tagamet/cimetidine does not, and a value of -1 if Rx drug j does not have FDA approval for GERD whereas Tagamet/cimetidine does.

We now turn to econometric results on factors affecting shares among the four Rx H₂s. Again we employ data from IRI, IMS Health and LNA. Based on a ten-year balanced monthly panel from January 1989 through December 1998 ($n = 360$), we have estimated parameters in Eqn. (4) by OLS. Results from initial regressions yielded unsatisfactory estimated coefficients on the relative direct-to-consumer Rx marketing stocks, and on relative adverse interactions. The direct-to-consumer Rx marketing stocks are small in comparison to the physician-directed Rx marketing stocks. The time series component of our sample begins in January 1989, and by that time it was already widely known that Tagamet had considerably more adverse interactions with other molecules than did Zantac, Pepcid and Axid; thus the effects of this relatively low

quality ADVERSE attribute are likely instead to be picked up by trends in competitive marketing stocks.

When the $ZRXDTC_{jt}$ and $ADVERSE_{jt}$ variables are omitted, we obtain the following estimated equation:

$$\begin{aligned} \ln(QRXDAY_{jt}/QRXDAY_{CIM,t}) = & 0.709 - 0.196*\ln(PRXDAY_{jt}/PRXDAY_{CIM,t}) \\ & 0.113) \quad (0.065) \\ & - 0.024*\ln(ZOTCDTC_{jt}/ZOTCDTC_{CIM,t}) + 0.796*\ln(ZRXMD_{jt}/ZRXMD_{CIM,t}) \\ & (0.038) \quad (0.087) \\ & - 0.803*RXORDER_j - 0.0008*(RXOFFPAT_{jt} - RXOFFPAT_{CIM,t}) + 0.315*GERD_{jt} \\ & (0.023) \quad (0.0002) \quad (0.053) \\ & + 0.109*ZRXPPIMD_t - 0.020*ZRXPPIDTC_t, \quad R^2 = 0.896. \\ & (0.006) \quad (0.006) \end{aligned}$$

The estimated value of the marketing monthly depreciation rate δ based on the grid search procedure is 2.5%, with a 95% confidence interval of 0.9% to 4.2%. Thus marketing efforts depreciate more rapidly in the OTC H_2 market than in the Rx H_2 segment. In terms of the other estimated parameters, the price-elasticity estimate of -0.196 is surprisingly small in absolute value; recall that the IMS Health Rx price measures do not include rebates, and thus measurement error could be biasing this parameter estimate toward zero.

In the Rx H_2 market, there appear to be fewer OTC-Rx marketing spillovers than in the OTC market. Specifically, the relative quantities of Rx H_2 s are not significantly related to relative direct-to-consumer marketing stocks of the same-brand OTC H_2 products (elasticity estimate of -0.024, $p = 0.528$), but relative Rx quantities are strongly and positively related to the relative physician-oriented Rx marketing stocks (0.796, t -statistic of 9.176). As in Berndt, Bui, Lucking-Reiley and Urban, order of entry effects are negative and very strong (-0.802, $p < 0.001$). Differences in months following Rx patent expiration significantly affect relative quantities, with longer times off-patent reducing that molecule's sales. While significant ($p < 0.001$), this patent expiration effect is small in magnitude. Those brands having a GERD

indication approval advantage relative to Tagamet/cimetidine have considerably larger sales, ceteris paribus; when exponentiated, the GERD coefficient implies about a 37% increase as one moves from a parity to an advantageous GERD position.

The final results concern non-neutral spillovers among the Rx H₂s resulting from aggressive marketing by manufacturers of the PPIs. The positive and significant estimate on ZRXPPIMD (0.109, p , 0.001) implies that physician-directed marketing of the Rx PPIs positively affected relative sales of the three "premium" H₂s -- Zantac, Pepcid and Axid, all relative to Tagamet/cimetidine. Hence, if a physician prescribed an H₂ instead of the PPI, the H₂ chosen was more likely to be a "premium" H₂. The negative estimate on ZRXPPIDTC indicates that DTC marketing of the Rx PPIs reduced sales of the premium H₂s. This latter result is consistent with physicians' responding to DTC marketing of the PPIs by substituting away from the premium Rx H₂s and instead prescribing the PPIs.

D. THE SECOND TIER: TOTAL OTC VS. TOTAL RX H₂S

In the second tier of the demand framework we specify factors affecting the quantity shares of H₂s between the total Rx and total OTC components. We define QRXDAY_t (now without the subscript j) and PRXDAY_t as the quantity and price of days of Rx H₂ therapy, and QOTCDAY_t and POTCDAY_t as the corresponding OTC variables. The total Rx and OTC marketing stock variables summed over the four H₂s are ZOTCDTC_t (direct-to-consumer marketing of OTCs), ZOTCMD_t (physician-oriented marketing of OTCs), ZRXMD_t (physician-oriented marketing of Rxs) and ZRXDTC_t (direct-to-consumer marketing of Rxs). Marketing stocks for the PPIs are ZRXPPIMD_t (physician-oriented) and ZRXPPIDTC (consumer-oriented). Finally, to capture possible opportunity time and direct costs of a physician visit to obtain an Rx prescription, we include as regressors logarithms of AVGWAG (average real wages) and MDVISIT (the CPI for physicians' services divided by the overall CPI).

With these variables defined, we estimate by OLS a specification in which the relative OTC to Rx quantities depend on relative prices, relative physician-oriented marketing stocks, relative consumer-oriented marketing stocks, stocks of PPI marketing to physicians and to

consumers, and the time and fee costs of a physician visit:

$$\begin{aligned} \ln(\text{QOTCDAY}_t/\text{QRXDAY}_t) = & c_0 + c_1 * \ln(\text{POTCDAY}_t/\text{PRXDAY}_t) + c_2 * \ln(\text{ZOTCMD}_t/ \\ & \text{ZRXMD}_t) + c_3 * \ln(\text{ZOTCDTC}_t/\text{ZRXDTC}_t) + c_4 * \ln(\text{ZPPIMD}_t) + \\ & c_5 * \ln(\text{ZPPIDTC}_t) + c_6 * \ln(\text{AVGWAG}_t) + c_7 * \ln(\text{MDVISIT}_t) + v_t, \end{aligned} \quad (5)$$

where v_t is an i.i.d. normal random disturbance term. The time period of observations is June 1995 - December 1998 ($n = 43$). As above, we do a grid search over various values of $\ddot{a}$.

Results from an initial analysis indicated a negative and strongly significant impact of the MDVISIT real price index (the ratio of the CPI for physician's services to that of the overall CPI) on relative OTC/Rx quantities, a result we regard as implausible. Since the CPI price index for physicians' services is thought by some to overweight cash-paying relative to insurance-covered office visits, use of the MDVISIT variable may simply be inappropriate here.³⁷ We therefore delete it. With MDVISIT deleted, we obtain the following OLS estimated equation:

$$\begin{aligned} \ln(\text{QOTCDAY}_t/\text{QRXDAY}_t) = & -11.043 - 0.336 * \ln(\text{POTCDAY}_t/\text{PRXDAY}_t) \\ & (5.067) \quad (0.183) \\ & - 0.155 * \ln(\text{ZOTCMD}_t/\text{ZRXMD}_t) + 0.625 * \ln(\text{ZOTCDTC}_t/\text{ZRXDTC}_t) \\ & (0.166) \quad (0.170) \\ & - 0.349 * \ln(\text{ZPPIMD}_t) - 0.016 * \ln(\text{ZPPIDTC}_t) + 6.165 * \ln(\text{AVGWAG}_t), \\ & (0.260) \quad (0.009) \quad (3.021) \end{aligned}$$

with an R^2 of 0.939. Use of the grid search method resulted in the best estimate of $\ddot{a}$, the monthly marketing depreciation rate, being 0.0%. However, the log-likelihood is quite flat over a reasonable range of $\ddot{a}$ estimates. For example, as $\ddot{a}$ goes from 0 to 2.5% to 5% per month, the root mean squared error increases only by 4.69% and 11.3%, respectively.

In terms of the other parameter estimates, the price elasticity estimate of -0.336 is negative but only trending toward statistical significance ($p = 0.074$). The estimated effect on OTC/Rx relative quantities of the relative physician-oriented marketing stocks is negative as well, but is not different from zero ($p = 0.359$). By contrast, relative OTC/Rx direct-to-consumer marketing stocks are positive and significantly associated with relative OTC/Rx quantities, with

the marketing stock elasticity being 0.625 ($p = 0.001$). Marketing efforts by the Rx PPI manufacturers also negatively impact relative OTC/Rx H_2 quantities, though neither the physician-oriented marketing stock (-0.349 , $p = 0.188$) nor the consumer-oriented marketing stock (-0.016 , $p = 0.078$) is significant at usual confidence levels. Finally, although we expect the coefficient on $\ln(\text{AVGWAG})$ to be positive, reflecting impacts of patients' opportunity cost of time, the very large estimate of 6.165 (standard error of 3.021, $p = 0.049$) is implausible. We attribute this large wage elasticity as reflecting the fact that over the January 1995 - June 1998 43-month time period, measured hourly real wages increased by only 7.2%, even as sales of the OTCs grew dramatically

E. THE TOP TIER: TOTAL RX PLUS OTC DEMAND FOR H_2 S

At the very top of the tiered demand system is the total H_2 days of therapy (the sum of Rx and OTC components). We expect that the total quantity of H_2 s ($QH2DAY$) is negatively related to its real price $PH2DAY$. With respect to marketing efforts, to the extent marketing efforts increase the size of the overall H_2 market, the marketing stock coefficients should be positive. But if marketing efforts primarily affect Rx/OTC H_2 splits, shares within the OTC H_2 s, and/or shares within the Rx H_2 s, then their impacts on total (Rx plus OTC) patient days of therapy may be close to zero. Similarly, we do not have an a priori expectation on the signs of coefficients on average real wage ($AVGWAG$) and the real price index of a physician office visit ($MDVISIT$).

Define the real marketing stock of physician-oriented H_2 marketing as $ZH2MD_t$, the real marketing stock of consumer-oriented H_2 marketing as $ZH2DTC_t$, the real marketing stock of consumer-oriented PPI marketing as $ZPPIDTC_t$, and the real marketing stock of physician-oriented PPI marketing as $ZPPIMD_t$. The top tier total Rx plus OTC H_2 demand equation we specify has the following form:

$$\ln(QH2DAY)_t = d_0 + d_1 * \ln(PH2DAY)_t + d_2 * \ln(ZH2MD)_t + d_3 * \ln(ZH2DTC)_t + d_4 * \ln(ZPPIMD)_t + d_5 * \ln(ZPPIDTC)_t + d_6 * \ln(AVGWAG)_t + d_7 * \ln(MDVISIT)_t + w_t, \quad (6)$$

where w_t is an i.i.d. normal random disturbance term.

We have estimated parameters of Eqn. (6) by OLS, using ten years of monthly data,

January 1989 through December 1998 ($n = 120$), as well as the implicit monthly depreciation rate using a grid search procedure. For the monthly marketing stock depreciation rate $\bar{\alpha}$, the best-fitting estimate occurs when $\bar{\alpha}$ equals 14.5%. This is somewhat large, and could reflect the rather modest effect of marketing efforts on total H_2 sales (not their composition), in the mature phase of their product life cycle. The 95% confidence interval for $\bar{\alpha}$ ranges from 6.8% to 30.0%. Results for the remaining parameters are as follows:

$$\begin{aligned} \ln(QH2DAY)_t = & 19.901 - 0.170*\ln(PH2DAY)_t - 0.141*\ln(ZH2MD)_t + \\ & (1.929) \quad (0.091) \quad (0.040) \\ & + 0.009*\ln(ZH2DTC)_t + 0.007*\ln(ZPPIMD)_t - 0.006*\ln(ZPPIDTC)_t \\ & (0.003) \quad (0.004) \quad (0.003) \\ & - 3.859*\ln(AVGWAG)_t + 2.960*\ln(MDVISIT)_t \quad R^2 = 0.942. \\ & (0.877) \quad (0.320) \end{aligned}$$

The effect of real H_2 price on H_2 total quantity is negative as expected, but the elasticity is modest and of marginal significance (-0.170 , $p = 0.064$).³⁸ In terms of H_2 marketing stocks, physician-oriented marketing is significantly negatively related to total H_2 quantities (elasticity of -0.141 , $p = 0.001$), while consumer-oriented marketing is significantly positively related (0.009 , $p = 0.005$). Both H_2 marketing stock elasticities are quite small in magnitude, however. The PPI marketing stock elasticities are also small in magnitude, and only trend toward significance; the physician-oriented marketing stock elasticity is 0.007 ($p = 0.099$), while that for the consumer-oriented marketing stock is -0.006 ($p = 0.077$).

Finally, in terms of elasticities with respect to the costs of seeing a physician, the real average wage elasticity (opportunity cost of time) is -3.859 ($p < 0.001$), while that for the fee for a physician visit (direct office visit cost) is 2.960 ($p < 0.001$). We regard these last two elasticities as implausibly large. Additional research is needed to obtain more reliable estimates at this top tier level.

VII. SUMMARY AND CONCLUSIONS

In this paper we have reported results of our research examining the "sunset" H₂s up to and following their Rx patent expiration, and as they faced forces of creative destruction from the next generation of more potent antiulcer and heartburn drugs, the proton pump inhibitors (PPIs).

As expected, we find that the branded H₂ manufacturers have not competed on price with generic entrants following Rx patent expiration, but instead have maintained or even slightly increased brand prices, losing market share and retaining sales to a small but relatively price-insensitive segment of brand-loyal customers. Eventual generic penetration appears to be larger for molecules the greater is the size of the pre-patent expiration Rx market.

In terms of marketing, consistent with the Dorfman-Steiner framework, we find that branded firms cut back considerably on marketing efforts already several years prior to patent expiration. This is plausible since marketing efforts having long-lived impacts. Following patent expiration, there is relatively little marketing, by brands or generics.

The lower prices brought about by post-patent expiration generic entry have resulted in average molecule prices (weighted over brand and generic) being about 20-35% of their pre-patent expiration levels. In spite of this substantial average price decline that benefited consumers, following patent expiration the combined (brand plus generic) sales of the two off-patent H₂ molecules have fallen. This utilization decline could reflect the impacts of decreased marketing efforts, competition from the more potent PPIs, and/or cannibalization of Rx sales by the introduction and marketing of a same-brand over-the-counter (OTC) product. On a per patient day basis, in mid-1999 brand OTC prices were 30-50% of their brand Rx prices, but brand OTC prices were still several times larger than same molecule generic Rx prices.

Order of entry effects in the OTC market were substantial, but not insurmountable as third OTC entrant Zantac 75 garnered larger market share than second OTC entrant Tagamet HB. However, in mid-1999 the first and last OTC entrants ranked first and last, respectively, in terms of market share. As was found in the H₂ Rx market in earlier research, in the H₂ OTC

market the ranking of advertising/sales ratios closely followed order of entry: two years after entry, this dollar ratio was lowest for first entrant Pepcid AC, was slightly higher for second entrant Tagamet HB, was even higher for third entrant Zantac 75, and was highest for the last entrant, Axid AR.

In terms of Rx to OTC switches, we find substantial interactions between the Rx and OTC market segments, with direct-to-consumer marketing (DTC) efforts playing a major role. Among the OTC H₂s, relative shares were strongly positively affected by relative OTC stocks of DTC marketing, but not by relative Rx stocks of physician-oriented marketing. DTC marketing of Rx brands also had a positive, but much smaller, impact on OTC share. Price effects were substantial as well.

Turning to the Rx side of the H₂ market, we find relative Rx shares were modestly negatively related to relative Rx prices, were strongly negatively affected by Rx order of entry, and were positively affected by that drug having an FDA approval advantage for treatment of gastroesophageal reflux disease (severe heartburn). While relative Rx stocks of physician-oriented marketing positively affected relative Rx sales, the relative OTC stocks of DTC marketing were not significantly related to relative Rx sales. Physician-oriented Rx marketing of the more potent PPIs was positively related to shares of the "premium" Rx H₂s (Zantac, Pepcid and Axid), but an interesting result we obtain is that DTC Rx marketing of the PPIs was negatively related to shares of the premium Rx H₂s. This latter result is consistent with DTC marketing of the PPIs resulting in physicians substituting away from the premium H₂s and toward the more potent (and more costly) PPIs.

We find considerable diversity among the four H₂ brands in terms of the net sales impacts of cannibalization vs. positive spillovers following Rx to OTC switches. The Pepcid brand franchise has been a clear winner from the Rx-OTC switch, with even its Rx unit sales increasing following the switch, suggesting very little cannibalization but positive spillovers. For Pepcid in 1999, OTC revenues are about the same as those from Rx sales. Since Zantac executed the OTC switch prior to its 1997 patent expiration, it suffered considerably from OTC cannibalization of

Rx sales, but ultimately the substantial amount of OTC Zantac 75 sales has resuscitated the brand franchise. Because Tagamet lost patent protection prior to its OTC switch, it had the least to lose by going OTC, and in fact on a relative basis, its OTC/Rx sales ratio has grown, though levels of both Tagamet OTC and Rx are small. As last entrant in both the Rx and OTC H₂ market segments, Axid has struggled without much success.

This research represents our first step in a more expanded OTC-Rx research program. Considerable economic theory and empirical evidence exists suggesting that marketing efforts should be viewed as endogenous variables, not only for example in anticipation of Rx patent expiration, but also in conveying information on new FDA indication and dosing approvals, and on highlighting results from clinical trials published in peer-reviewed journals.³⁹ In future research, in addition to employing updated data, we plan to model Rx and OTC marketing efforts explicitly, as well as address possible simultaneity issues with prices. There is also evidence that rates of depreciation of marketing efforts vary by type of marketing instrument.⁴⁰ In the next step of our research, we will allow for differing depreciation rates among the DTC and physician-directed marketing media. The extent to which consumption externalities involving the PPIs have affected the diffusion of the various PPIs, and the decline in sales of the H₂S, merits attention as well.⁴¹ The impact of Rx to OTC switches on prices paid by consumers, after accounting for insurance coverage and patient copays, is a most interesting research topic, as is the more general issue of the effects of such switches on consumer welfare. Finally, we believe it would be useful to utilize more fully and explicitly recent developments in the economic theory of consumer demand that allow for preference estimation even when the number of available products changes over time.⁴² The existence of principal-agent and moral hazard issues, particularly in the Rx market, makes such research very difficult, however.

Our research involving the antiulcer and heartburn markets over the 1989-1998 decade is particularly timely, for within the next eight months, it is widely expected that Pepcid and Axid will be facing patent expiration in both the Rx and OTC segments. Moreover, Prilosec (omeprazole, the pioneer PPI, and currently the US' best selling Rx drug) is expected to lose

patent protection later in 2001. It is fascinating to us to speculate on what our research implies as Prilosec considers executing an Rx to OTC switch, and as its competitors not only observe this, but also wonder what will be the effects on their brand Rx sales from generic Rx omeprazole entry. Will omeprazole molecule sales increase following patent expiration, or will they decrease as occurred with both H₂ molecules?

Whether the long shadows of imminent patent expiration for well-known Rx drugs in other therapeutic areas -- Prozac, Claritin, and Mevacor, for example -- turn out to be similar to those in the H₂ market, also remains to be seen.

APPENDIX

TIMELINE OF SIGNIFICANT DEVELOPMENTS IN THE ANTIULCER AND HEARTBURN MARKETS

<u>Late 1980s - Early 1990's</u>	<u>1995</u>	<u>1997</u>
H. pylori identified as bacteria causing some forms of ulcers	January 1 - Prilosec co-promotion initiated by Astra-Merck and Marion Merrill Dow	August - Zantac loses market exclusivity; much generic entry
Merck announces joint venture with J&J to manage Rx-OTC switches	March 13 - FDA approves removal of long-term use warning ("black box") for Prilosec	<u>1998</u>
SmithKline Beckman merger with Beecham, strong OTC company	April 28 – FDA approves OTC use for Pepcid AC – for treatment and prevention of episodic heartburn – first H ₂ with OTC approval	April - generic Rx ranitidine gains 72% market share
Lilly signs agreements with American Home Products to manage Rx-OTC switches	May 11 – Prevacid (TAP-Abbott) receives FDA approval as second proton pump inhibitor	August - Tagamet HB loses OTC patent protection
Prilosec (omeprazole) re-enters Rx market with brand name changed from Losec - first proton pump inhibitor	June 19 – FDA approves OTC use for Tagamet HB – second H ₂ in OTC market – FDA wants warning label on drug interactions	October – Pepcid launches RPD (rapid dissolve version)
<u>1993</u>	June 26 – FDA approves long-term maintenance use of Prilosec for healing of erosive esophagitis	<u>1999</u>
July - Glaxo & Wellcome announce agreement with Warner-Lambert to market OTC version of Zantac	December 19 – FDA approves OTC use of Zantac 75 - launched April 24, 1996	April - Zantac 75 loses OTC patent protection
August - Propulsid launched by Janssen as promotility agent	<u>1996</u>	Adverse interaction troubles- Propulsid
<u>1994</u>	May 9 – FDA approves OTC use of Axid AR – launched July 10	April - Aciphex entry as third PPI - Abbott
May 17 - Tagamet patent expires - significant generic cimetidine entry	Prilosec (Losec in rest of the world) overtakes Zantac as US's and world's best selling drug	<u>2000</u>
December - generic cimetidine achieves 60% dollar and 80% volume share	Fourth quarter launches of Tritac and Helidac as combination products with antibiotic for treatment of H. pylori	May - Protonix enters as fourth PPI (Wyeth-Ayerst), discounted price
		Propulsid pulled from market by FDA
		November – Axid Rx patent expiration

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FOOTNOTES

¹For related empirical research on Rx to OTC switches, see Temin [1992].

²For more detailed discussions of the H₂ market up until 1994, see Berndt, Bui, Lucking-Reiley and Urban [1995,1997].

³A London Business School case study dealing with how the H₂ manufacturers could respond to competition from the new PPIs is that by Dell'Osso. Also see Perloff and Suslow [1994].

⁴Electronic Orange Book [2000].

⁵That Prilosec even made it to the market was remarkable, since its Swedish developers nearly terminated research on it several times, viewing its research program as a likely failure. For a history of its development, see Eliasson and Eliasson [1997].

⁶See Section 505 of the Federal Food, Drug and Cosmetics Act, 21 USC Section 355 (c)(3)(B)(iii). Empirical analyses of the effect of the Waxman-Hatch Act include those by Grabowski and Vernon [1992], Caves, Whinston and Hurwitz [1991], and Frank and Salkever [1997]. For an historical overview of FDA regulation of the drug industry prior to 1980, see Temin [1980].

⁷For a Harvard Business School case study discussion of the race to develop and launch the first OTC H₂ in the US, see King, Silk, Klein and Berndt [2000].

⁸For discussions of possible benefits and costs to consumers, manufacturers and insurance providers from the Rx to OTC switch, see Hesselgrave [1997], Jaroff [1995], McCarthy [1999], Smith [1998,1999], Tanou and Burton [1993], and Temin [1983,1992]. More general discussions of consumers' response to drug prices, and the factors affecting substitution between Rx and OTC drugs, are found in, inter alia, Leibowitz [1989], Leibowitz, Manning and Newhouse [1985], O'Brian [1989], Phelps and Newhouse [1974], and Stuart and Grana [1995].

⁹On first mover advantages and their rationale in the market for pharmaceuticals, see Bond and Lean [1977], Berndt, Bui, Lucking-Reiley and Urban [1995,1997], King [2000] and King, Silk, Klein and Berndt [2000]. The theoretical foundations and empirical evidence on first mover advantages in other markets are discussed in, among others, Robinson, Kalyanaram and Urban [1994], Samuelson and Zeckhauser [1988], Schmalensee [1982] and Urban, Carter, Gaskin and Mucha [1986].

¹⁰It is interesting to note that when joining up with or creating joint ventures with the more retail-oriented consumer product companies, the Rx drug manufacturers also created cannibalization possibilities for the traditional antacids used to treat heartburn. For example, for SmithKline Beecham, OTC Tagamet competed with its antacid products, Tums and Gaviscon. For Glaxo Wellcome, pairing with Warner-Lambert meant that OTC Zantac would compete with Rolaid.

Finally, for the J&J•Merck joint venture, the OTC Pepcid would compete with Mylanta and Imodium. Ling [1999] provides an empirical analysis of the interaction between the incumbent antacid and the newer H₂OTC products.

¹¹On this, also see Scherer [1993,2000], Griliches and Cockburn [1994], and Ellison, Cockburn, Griliches and Hausman [1997].

¹²Empirical evidence presented in Frank and Salkever [1997] and Berndt, Cockburn and Griliches [1996] is consistent with the Frank-Salkever segmented market hypothesis. Related econometric evidence from Berndt, Griliches and Rosett [1993] suggests that over the 1986-1991 time period, prices of older drugs increased more rapidly than those on newer products.

¹³The original Dorfman-Steiner formulation was in the context of static optimization. Extensions to dynamic optimization are presented in Schmalensee [1972]. Most of the intuition generalizes to the dynamic environment. For additional discussions, see Hurwitz and Caves [1988] and Leffler [1981].

¹⁴See, for example, Berndt, Bui, Lucking-Reiley and Urban [1995,1997], Perloff and Suslow [1994], and King [2000].

¹⁵Generic firms may, however, engage in other marketing efforts for which the benefits are more easily internalized. We understand that generic firms market very differently from brand firms. Instead of engaging in detailing and journal advertising, generic firms tend to have home office major account representatives for particular customers, such as drug store chains, staff model managed care organizations, and mass merchandisers such as WalMart.

¹⁶The transformation factors are: Tagamet (cimetidine), 800 mg/day; Zantac (ranitidine), 300 mg/day; Pepcid, 40 mg/day; Axid, 300 mg/day; Prilosec, 20 mg/day; Prevacid, 30 mg/day; and Propulsid, 40 mg/day. Since Propulsid never had FDA approval for active duodenal ulcer treatment, we use the recommended daily dosage for treatment of nocturnal GERD.

¹⁷IMS Health [1998].

¹⁸For an initial and preliminary analysis, see Prevention Magazine [1999]. Also see Wilkes, Bell and Kravitz [2000].

¹⁹See STATA Reference Manual [1999].

²⁰For July 1995 onward (when the deflators first became available), we construct this deflator as the arithmetic average of the Producer Price Index for "Advertising agencies, ad creation, billed separately", and "Advertising agencies, media placement, including ad creation not billed". For months prior to July 1995, we employ the Producer Price Index for All Finished Goods.

²¹See Information Resources Inc. [1997], Guadagni-Little [1983], and Bucklin-Gupta [1999]. The IRI website is www.infores.com.

²²This follows procedures utilized by Ling [1999] and Berndt, Bui, Lucking-Reiley and Urban [1995,1997].

²³Recommended dosages vary by indication. For example, while the recommended dosage of Zantac for treating active duodenal ulcers, active gastric ulcers, and GERD is 300 mg per day (either 300 mg once daily or 150 mg twice daily), the recommended dosage for duodenal ulcer maintenance therapy is only 150 mg per day.

²⁴For each of the four OTC H₂s, the transformation of OTC to Rx involves using twice the maximum daily recommended OTC dosages.

²⁵Ling [1999]. The seven brands are Tums, Mylanta, Gaviscon, Maalox, Alka Seltzer, Roloids and Pepto Bismol.

²⁶For Zantac, patent expiration actually occurred on Friday, July 25, 1997. Since this was near the end of July and began on a weekend, we approximate the beginning of patent expiration as August 1997.

²⁷Why the journal page advertising decline was so much larger than detailing is not clear. It is possible that since the IMS measure of detailing involves minutes of conversation regarding the product, portions of some conversations might have been initiated by the physician rather than the detail person. Thus the detailer might instead have preferred a different topic for discussion. Moreover, detailers often discuss several products with a physician during a single detail, and thus product portfolio considerations might have led to a smaller decline in detailing than in journal advertising. Unlike details which frequently can involve discussion of several products, medical journal page advertising typically focuses on only one product, and thus it can be more tightly concentrated and controlled than details.

²⁸Note that the patents of Axid and Pepcid do not expire until late 2000/early 2001.

²⁹For cimetidine, medical journal pages with generic cimetidine advertisements in the 18 months following Tagamet patent expiration were only about 14% of the corresponding Tagamet pages in the 18 months prior to its patent expiration. For ranitidine, in the 18 months prior to Zantac patent expiration, Zantac had no medical journal advertising, and thus no direct comparison with generic post-patent advertising is available. The number of pages of generic ranitidine advertising in the 18 months following Zantac patent expiration was only about 17% of Tagamet's pages in the 18 months prior to Tagamet's patent expiration. For both generic cimetidine and ranitidine, journal page advertising beyond 18 months following the brand's patent expiration date is essentially zero.

³⁰See Figure 7.7, p. 293 in Berndt, Bui, Lucking-Reiley and Urban [1997].

³¹See the Electronic Orange Book [2000] for FDA indication approvals and dates.

³²Hierarchical or tiered models have a long heritage in econometric demand frameworks. For examples in the context of pharmaceuticals, see Berndt, Bui, Lucking-Reiley and Urban [1992,1997] and Ellison, Cockburn, Griliches and Hausman [1997]. The first model using scanner data appears to be that of Guadagni and Little [1983].

³³In principle, we could also model the split between generic and Tagamet HB OTC cimetidine, following Tagamet HB's loss of patent expiration in June 1998. But currently our OTC marketing data end in December 1998, and thus only seven monthly observations are available. We plan to add this to our analysis once more recent OTC data become available.

³⁴Modeling the number of generic entrants is somewhat problematic, for entrants include both generic manufacturers and generic repackagers, and how one empirically distinguishes them is problematic.

³⁵ See, for example, Berry, Levinsohn and Pakes [1995] and Bresnahan, Stern and Trajtenberg [1997].

³⁶This yields numerically equivalent estimates to a nonlinear least squares estimator that repeatedly substitutes in for lagged values of $Z_t \hat{\phi}$, and thereby makes Z_t a weighted power series over all previous marketing flow expenditures. However, the standard errors based on this grid search method are likely slightly underestimated. In a subsequent version of this paper, we will incorporate that adjustment.

³⁷For a discussion, see Berndt, Cutler, Frank, Griliches, Newhouse and Triplett [2000].

³⁸Note that if the dependent variable were real total H₂ revenues rather than quantity (days of therapy), the coefficient on price would be 0.830 (-0.170 plus 1), and coefficients on all other regressors would be unchanged.

³⁹See, for example, Azoulay [1999], Berndt, Bhattacharyja, Mishol, Arcelus and Lasky [2000], and Ehrlich and Fisher [1982].

⁴⁰Ling [1999].

⁴¹Consumption externality effects at the individual brand and aggregate H₂ level are analyzed by Berndt, Pindyck and Azoulay [2000].

⁴²See, for example, Berry, Levinsohn and Pakes [1995], and Bresnahan, Stern and Trajtenberg [1997].

Figure 1: Cimetidine Price

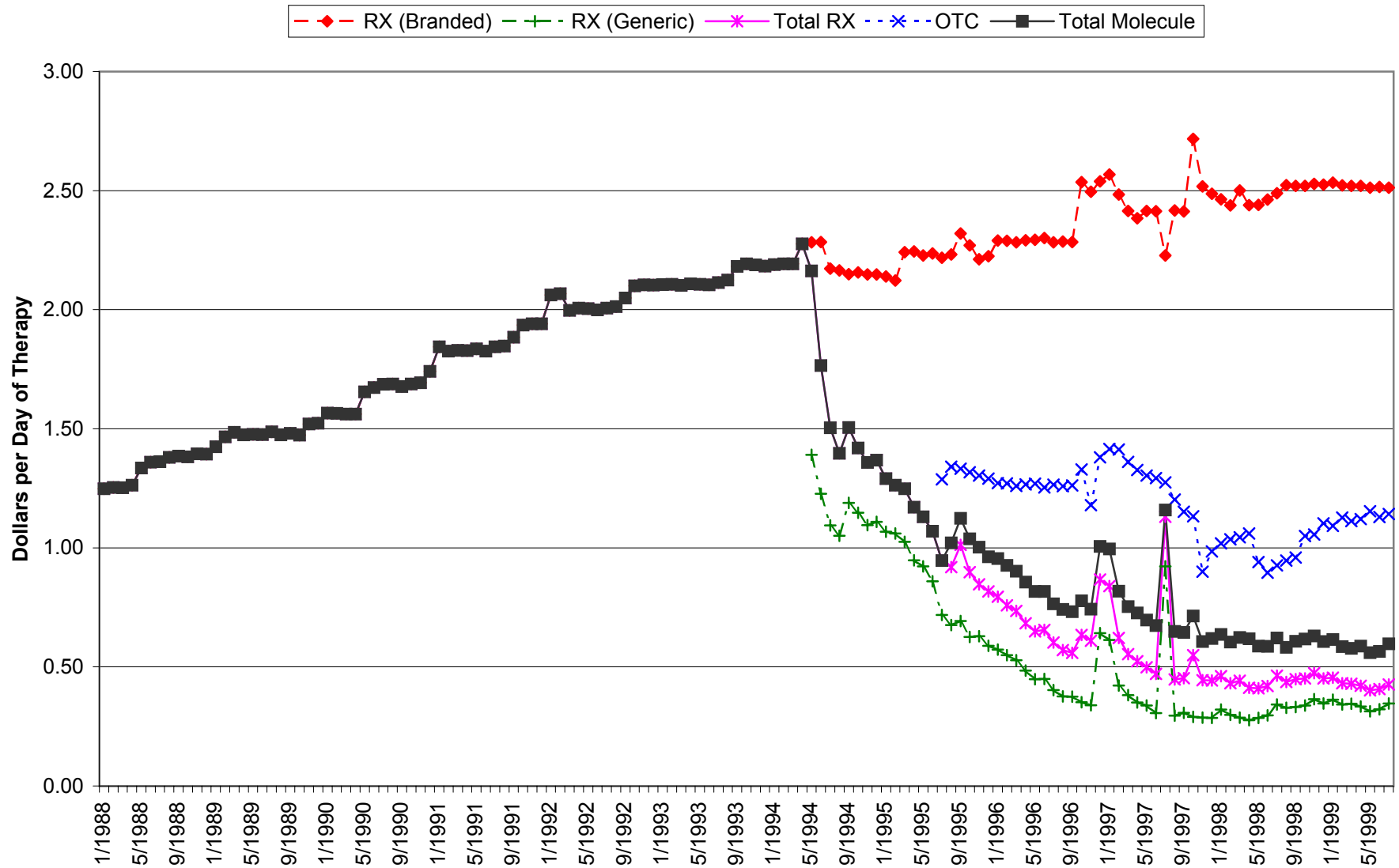


Figure 2: Ranitidine Price

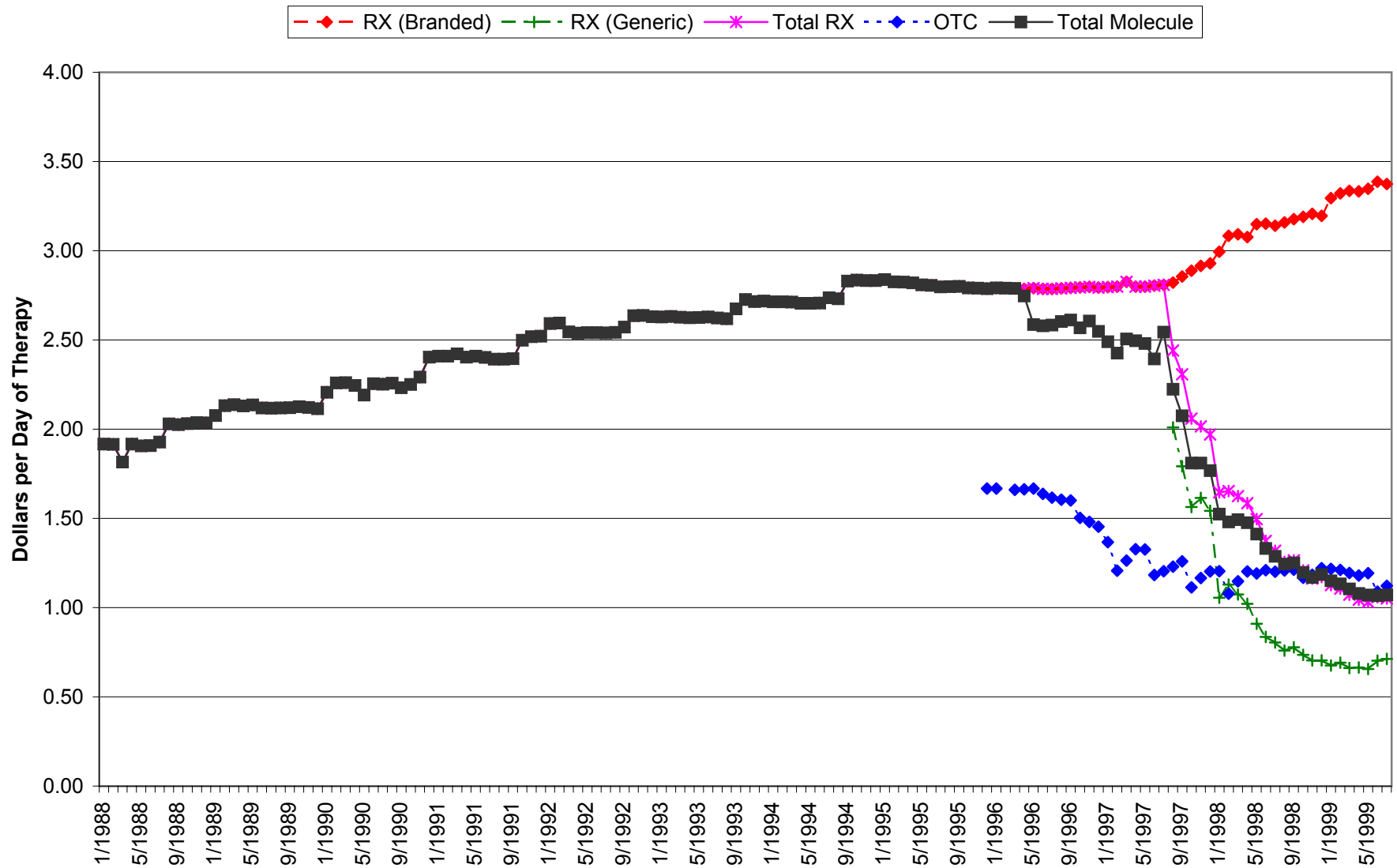


Figure 3: Cimetidine Units, Monthly

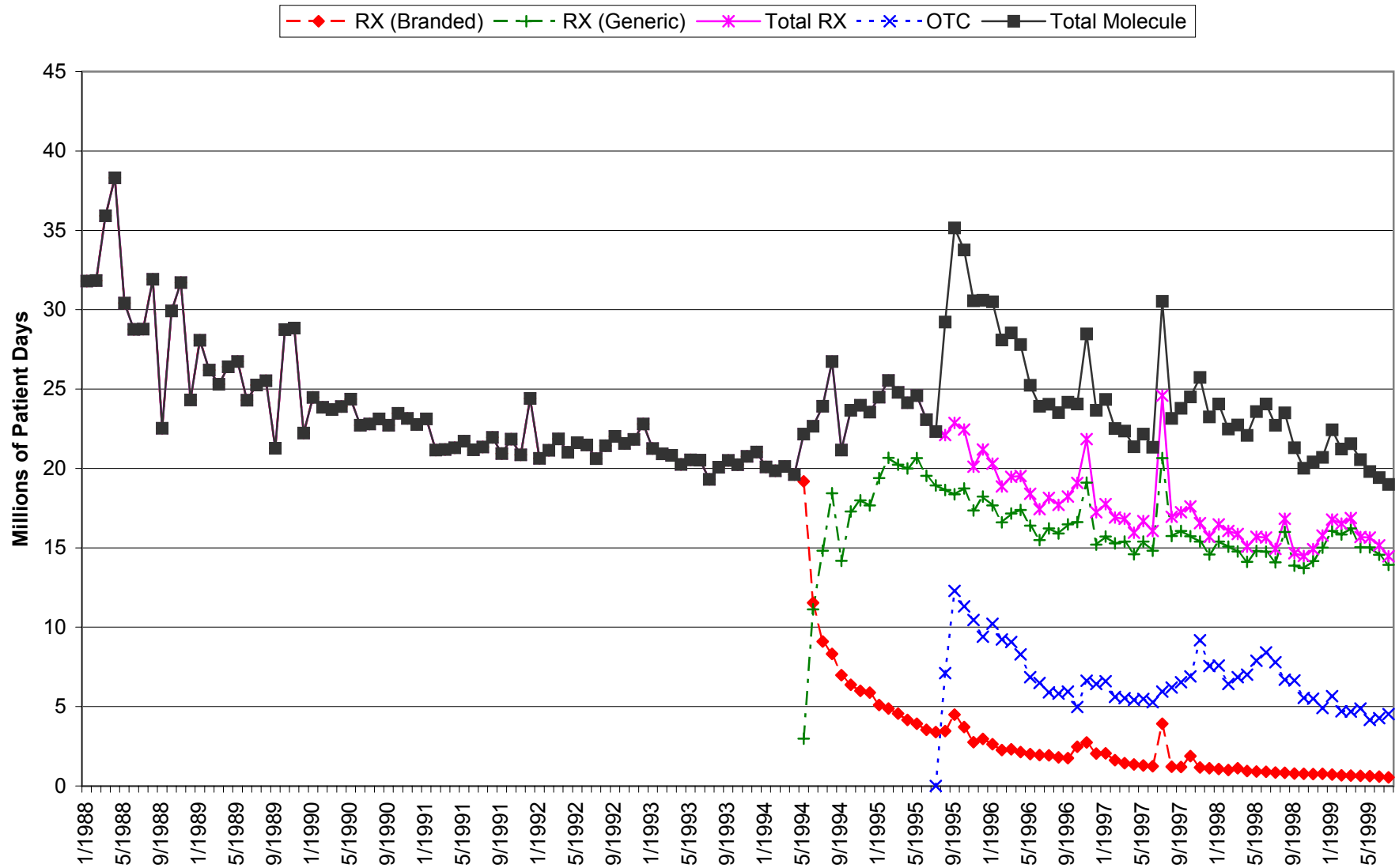


Figure 4: Ranitidine Units, Monthly

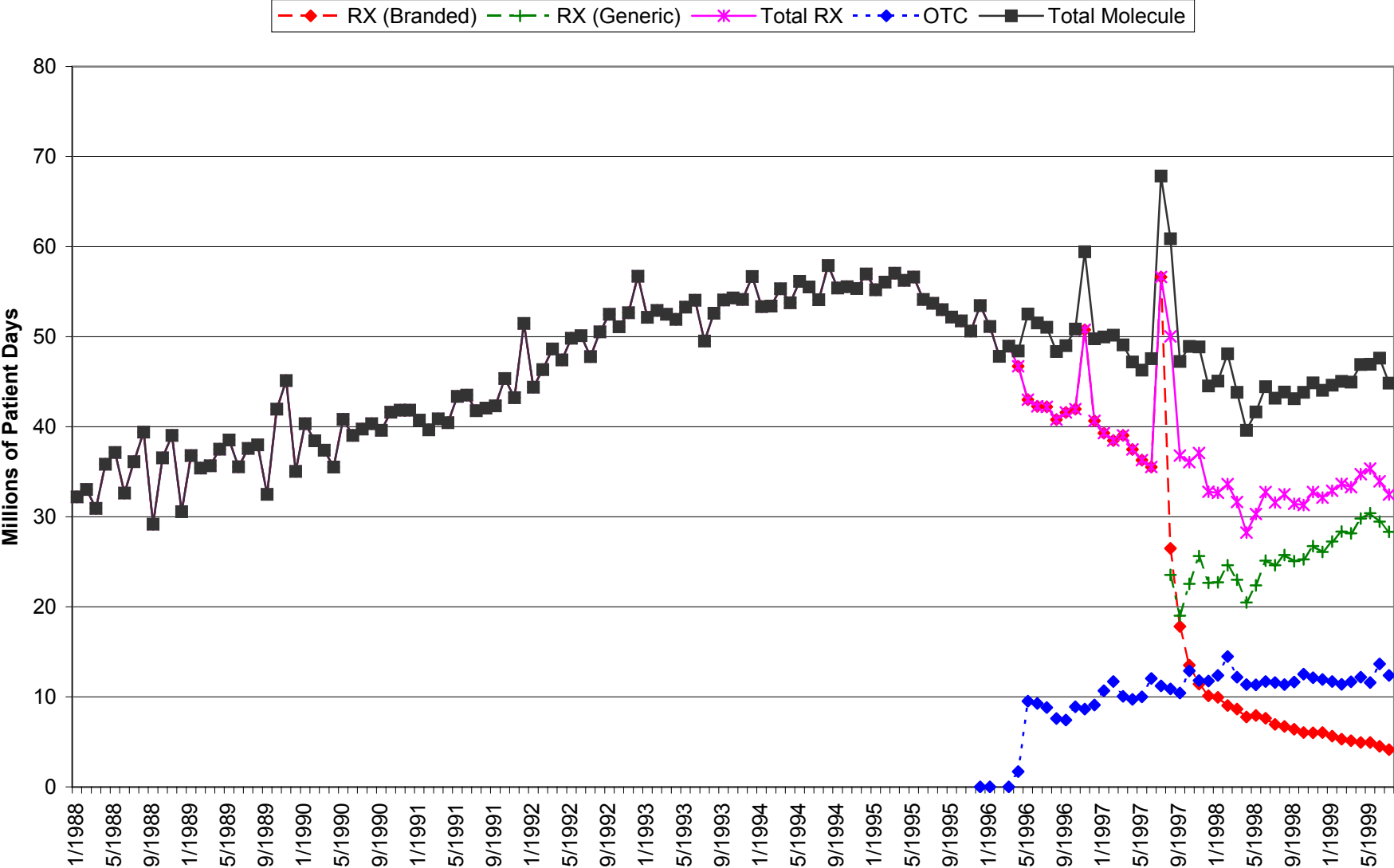


Figure 5: Cumulative Advertising-Sales Ratios for OTC H₂-Antagonists

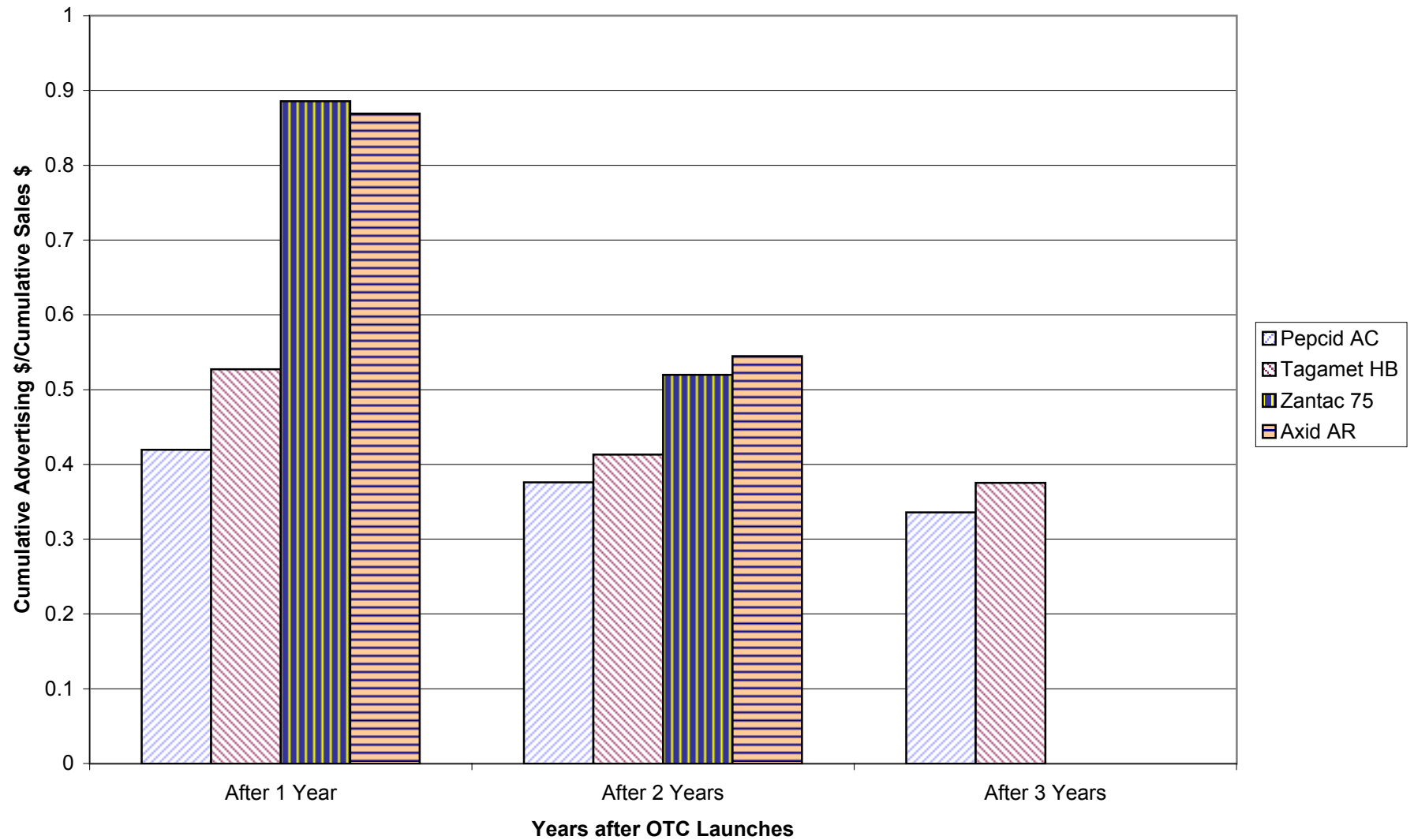


Figure 6: Units of OTC H₂-Antagonists, Monthly

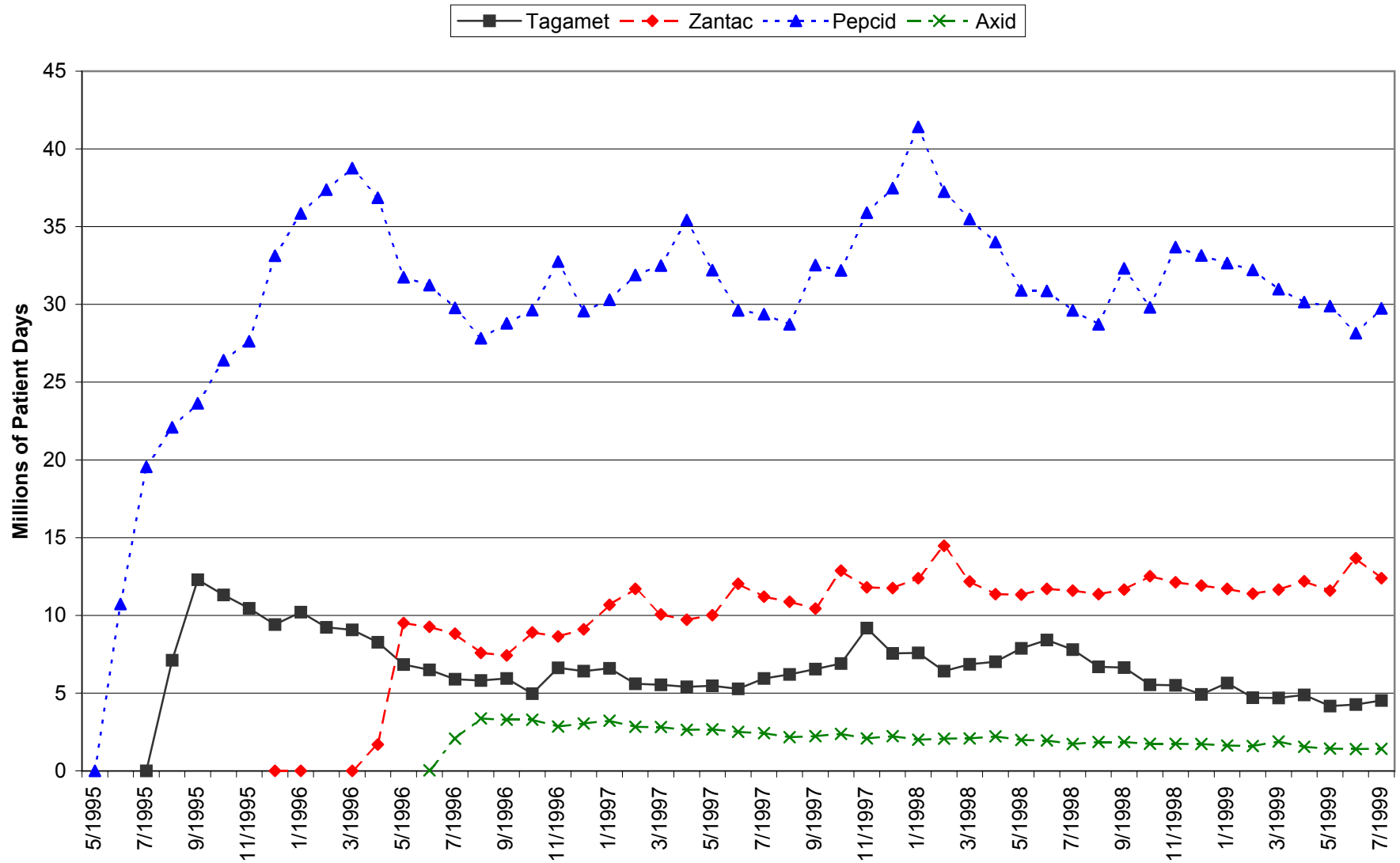


Figure 7: Revenue Shares of OTC H₂-Antagonists

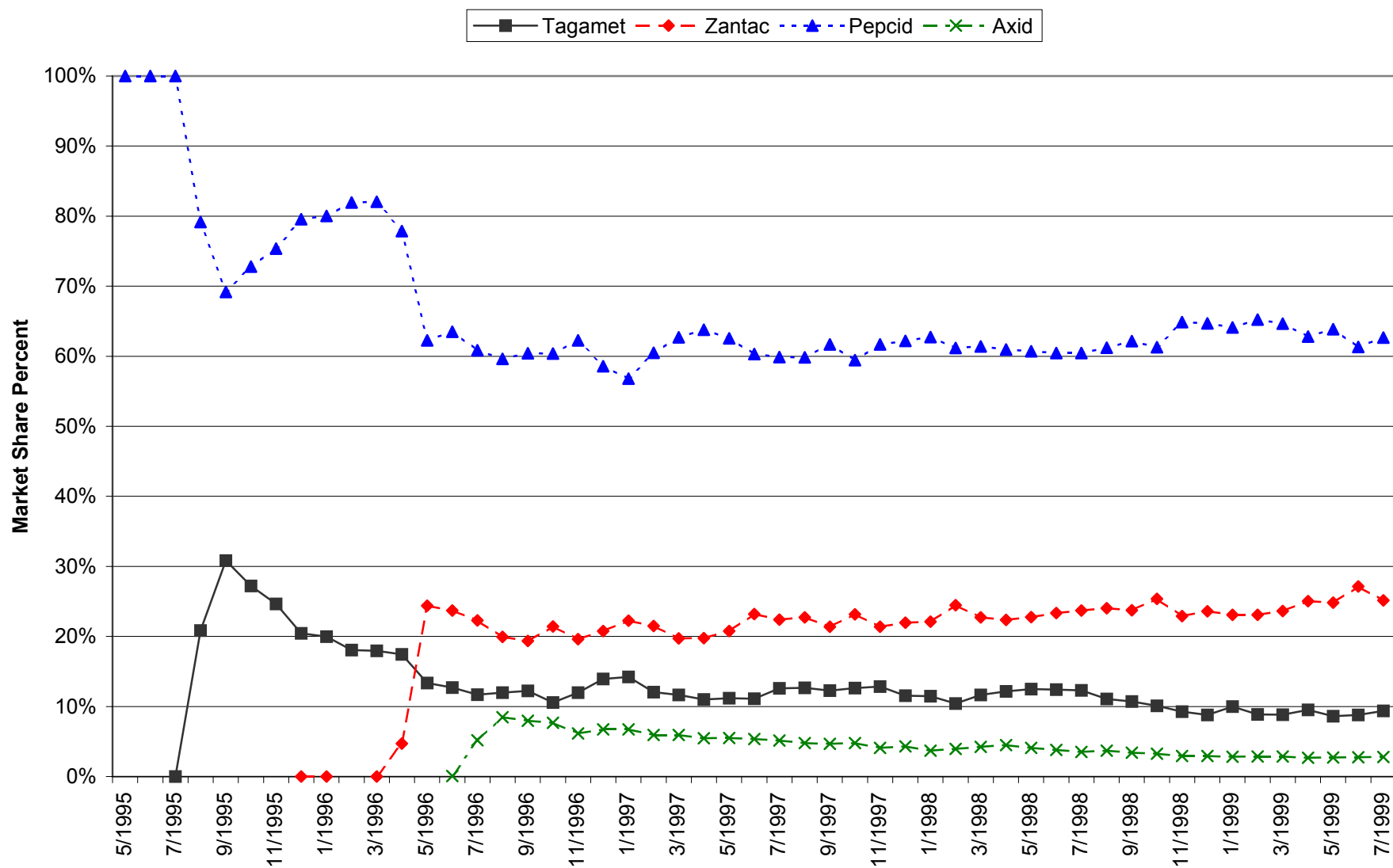


Figure 8: Pepcid Monthly Revenues

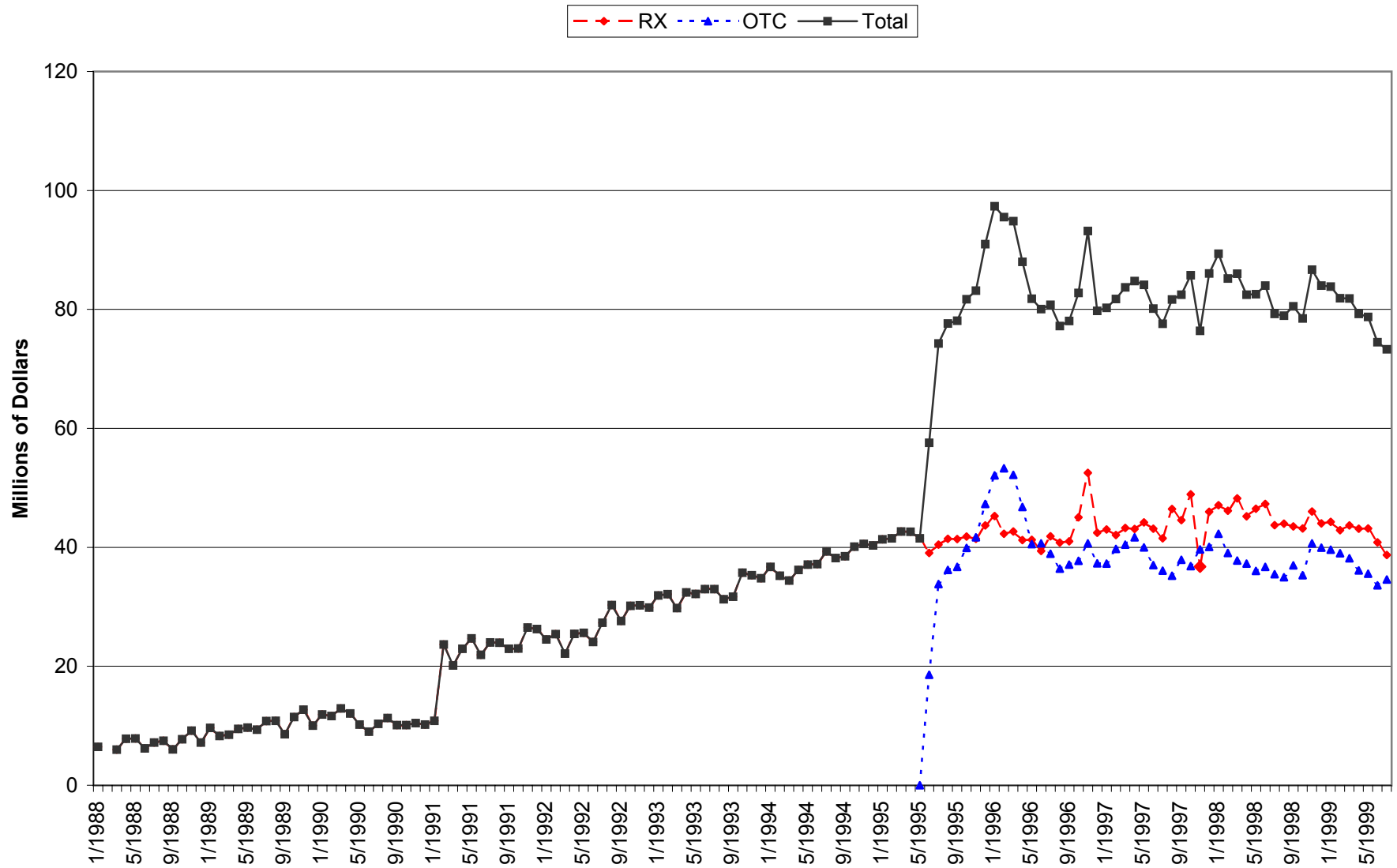


Figure 9: Axid Monthly Revenues

