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THE ROLES OF MARKETING, PRODUCT QUALITY AND PRICE COMPETITION IN THE GROWTH AND COMPOSITION OF THE U.S. ANTI-ULCER DRUG INDUSTRY

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ABSTRACT

The introduction of Tagamet in the United States in 1977 represented both a revolution in ulcer therapy and the beginning of an important new industry. Today there are four prescription H_2-antagonist drugs: Tagamet, Zantac, Pepcid and Axid, and they comprise a multi-billion dollar market for the treatment of ulcers and other gastric acid conditions. In this paper, we examine the determinants of sales in this market, using a carefully constructed data set made possible by IMS America. We concentrate particularly on the marketing of these drugs to physicians through detailing and medical journal advertising, and we make an innovative attempt to distinguish between "industry-expanding" and "rivalrous" marketing efforts. We find that the impact of total marketing on the expansion of overall industry sales declines as the number of products on the market increases. In addition, we find that the stock of industry-expanding marketing depreciates at a near-zero rate, while the stock of marketing oriented towards rivalrous market share competition depreciates at a 40% annual rate. We also find that the products' sales are affected significantly by price, quality attributes (such as number of FDA-approved indications and number of adverse drug interactions), and order of entry into the market.

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THE ROLES OF MARKETING, PRODUCT QUALITY AND PRICE COMPETITION IN THE GROWTH AND COMPOSITION OF THE U.S. ANTI-ULCER DRUG INDUSTRY

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I. INTRODUCTION

The introduction of Tagamet into the U.S. market in 1977 marked the beginning of a revolutionary treatment for ulcers, and the emergence of a new industry. What distinguished the products of this new industry was their ability to heal ulcers and treat pre-ulcer conditions pharmacologically on an outpatient basis, thereby substituting for traditional, and costly, hospital admissions and surgeries. Tagamet, known medically as an H_2-receptor antagonist, promoted the healing of ulcers by reducing the secretion of acid by the stomach.

A striking feature of the anti-ulcer market is that it has sustained growth in sales (quantity, not just revenue) for over fifteen years, and still shows no sign of slowing. New prescribing habits have clearly diffused to an ever-increasing number of physicians. Today there are a total of four H_2-receptor antagonists: Tagamet, Zantac, Pepcid and Axid. Zantac is now the United States' (and the world's) largest selling prescription drug, having estimated worldwide sales in 1992 of about $3.5 billion. Moreover, both Zantac and Tagamet are among the ten top selling prescription drugs in the U.S.[1]

In this paper we attempt to explain the growth and changing composition of the anti-ulcer drug market. Although we examine the impacts of pricing and product quality, we devote particular attention to the role of firms' marketing efforts. We distinguish between two types of marketing: (i) that which concentrates on bringing new consumers into the market ("industry-expanding" advertising), and (ii) that which concentrates on competing for market shares from these consumers ("rivalrous" advertising). Note that of these two types, the market-expanding advertising has particular economic importance in a new market, because no matter how potentially beneficial is the new product, it can generate no consumer surplus until consumers have been informed about the new product and have been induced to experiment

with it.

As others have done, we estimate the effects of industry-expanding advertising on sales. However, we also examine how the effectiveness of this socially-beneficial type of advertising varies with market structure. We exploit two facts. First, in the earliest years of the market when Tagamet was a monopoly product, by definition, all of the Tagamet advertising was market-enhancing. Second, the timing of entry is largely exogenous in this industry, for patent protection ensures that firms cannot enter until their research laboratories develop a new molecule that has the desired impact and approval for use is given by the Food and Drug Administration (FDA).

We also analyze factors affecting the market shares earned by the limited number of firms in this market. A principal theme is that the patent and pioneer advantages to Tagamet were overcome by Zantac, the second entrant, through costly but effective marketing efforts, especially efforts that interacted with the apparent existence of favorable adverse drug interaction profiles relative to Tagamet. Moreover, Zantac's relative price, although higher than Tagamet's, declined substantially over time. Thus, evidence from this industry suggests that while the barriers to entry from patent and first-mover advantages are considerable, they are not insurmountable.

Our empirical analysis is based on an unusually rich and detailed data set. Beginning with the introduction of Tagamet in July 1977, we have obtained monthly data, for each of the products in this market, on quantity and average price of sales (separately for the retail drug and hospital markets), marketing efforts (minutes of detailing by sales representatives to physicians, and professional medical journal advertising), as well as product quality information including side effect profiles, adverse drug interactions, efficacy, dosage forms, and indications for which the product had received approval from the U.S. Food and Drug Administration.

We begin in Section II by providing background information on ulcers and ulcer treatments.

Then in Section III we present an overview of data trends. We describe the growth of the anti-ulcer market, as well as the pricing and marketing behavior of the various market participants. We move on in Section IV to develop an econometric framework for modeling the growth of the anti-ulcer industry. In particular, we examine the effects of "informative" or market-expanding marketing efforts on industry sales. In Section V we report findings from an analogous attempt to model factors affecting market shares earned by the various products in this industry. Here we examine in particular the roles of rivalrous marketing, product quality, order of entry and price competition. Finally, in Section VI we offer some concluding observations and suggestions for future research. The paper also includes a data appendix.

II. BACKGROUND ON ULCER TREATMENTS[2]

Peptic ulcer disease occurs in 10-15% of the U.S. population. Ulcers located in the stomach proper are termed gastric ulcers (GU), while those in the duodenum (the bulb connecting the stomach to the small intestine) are called duodenal ulcers (DU). A related non-ulcerous condition is gastroesophageal reflux disease (GERD), which occurs in the esophagus. What the three conditions have in common is that they involve inflammation of tissue in the digestive tract that is exacerbated by the presence of the body's naturally occurring gastric acid. GERD and duodenal ulcers have roughly the same rates of occurrence in the U.S. population, whereas gastric ulcers are about one-fourth as likely. The incidence of ulcers in adult males is about twice that in adult females, and appears to be most common in individuals twenty to fifty years old.

Ulcers have a long history of clinical treatment. There is evidence that already in the first century A.D., coral powder (calcium carbonate, an antacid) was used to relieve symptoms of dyspepsia.[3] Early in the 20th century, conventional medical wisdom conformed to the notion "no acid, no ulcer." As a result, until the 1970's recommended treatments sought to neutralize gastric acid, and often

consisted of hourly feedings of milk and/or antacids, as well as a dietary reduction of acidic food and drink. If ulcers persisted, surgery was undertaken. It is worth noting that while antacids such as Maalox and Mylanta neutralize gastric acid, they do not decrease the rate of gastric secretions (they may in fact increase them). Moreover, the required dosages of antacids are typically quite large, side effects can be considerable, and adverse interactions with other drugs are not uncommon. As a result, with antacids patient compliance can be problematic.

An alternative ulcer treatment involves acid suppression with anticholinergics, such as Pro-Banthine and Atropine. Anticholinergic agents decrease acid secretion by inhibiting receptors for the hormone acetylcholine in the acid-producing cells of the stomach lining. However, these agents have considerable unpleasant and adverse reactions, since acetylcholine is involved in a number of biochemical processes other than the secretion of gastric acid, and anticholinergics tend to be non-selective. The side effects of dry mouth, blurred vision, urinary retention, abnormally rapid heartbeat, and drying of bronchial secretions are particularly frequent.

In 1977 a revolutionary form of anti-ulcer drugs was introduced in the U.S., known as an H_2-receptor antagonist.[4] The H_2-receptor antagonists act by blocking the histamine-2 (H_2) receptor on parietal cells in the lining of the stomach -- cells that produce gastric acid. Histamine-2 is one of three "messenger molecules" (along with gastrine and acetylcholine) that can stimulate the production of acid by the parietal cells. By blocking the receptor for H_2 (and, unlike the anticholinergic drugs, avoiding any interference with other biochemical processes), an H_2-antagonist (henceforth referred to as an H_2) can decrease overall acid concentration in the stomach. H_2-antagonist healing rates are very high. A four- to six-week treatment period, for example, is associated with a healing rate of 70-80% for patients suffering from a duodenal ulcer.

SmithKline was the first pharmaceutical company to introduce an H_2-antagonist into the U.S.

market (August 1977), and they dubbed it Tagamet (its chemical name is cimetidine). Thereafter three companies followed -- Glaxo with Zantac (ranitidine) in June 1983, Merck with Pepcid (famotidine) in October 1986, and Lilly with Axid (nizatidine) in April 1988. Each of these four H_2-antagonists is a slightly different chemical entity; Tagamet's patent protection could not prevent entry by such therapeutic substitutes.

Zantac was marketed very aggressively by Glaxo, in partnership with Hoffman-LaRoche, and was also priced at a premium over Tagamet. Detailers (sales representatives who call on physicians) emphasized that unlike Tagamet whose original dosage required it to be taken four times daily, Zantac needed to be taken only twice per day. Moreover, Zantac detailers highlighted side effect profiles that had accumulated with Tagamet -- nausea, diarrhea, drowsiness, decreased sperm count, gynecomastia (swelling of the breasts in males) and adverse drug interactions.[5] Within eighteen months Tagamet responded to Zantac by introducing a twice per day version of its drug, but it continued to find itself on the defensive in terms of alleged side effect and adverse interaction profiles. A prolonged rivalry then ensued, first between Tagamet and Zantac in the form of new versions whose dosages were but once per day (thereby facilitating patient compliance even further), and later including additional competition from the newly entered Pepcid and Axid, each available with a once-daily dosage regimen.

In addition to side effect profiles and frequency of dosage, another form of rivalry among the four H_2-antagonists involved FDA-approved treatments (indications). Since several distinct types of ulcerous conditions exist, similar drug products can compete on the basis of efficacy for different indications. In the U.S., before a drug can be introduced into the market, the Food and Drug Administration must grant approval for at least one indication. When Tagamet was originally introduced into the U.S. market in August 1977, its approval was for duodenal ulcers; Tagamet was also the first to be approved for duodenal ulcer maintenance treatment (to prevent recurrence of a newly-healed duodenal ulcer, in April 1980)

and gastric ulcers (December 1982). However, Zantac was the first to obtain approval for the GERD indication (May 1986),[6] and it was not until March 1991 that Tagamet obtained FDA approval for GERD. It is worth noting that, once FDA approval for an indication is granted, the manufacturer is permitted to provide promotional and marketing material **only** for approved indications. Thus, even though Tagamet had very similar clinical effects to Zantac, suggesting that it would probably be effective in the treatment of GERD, Tagamet promotions were not permitted to mention GERD until 1991. Although physicians often prescribe drugs for indications not approved by the FDA (called off-label prescribing), not having FDA approval for an indication which is held by a competitive product may constitute a significant disadvantage in the marketplace. Hence, even though Tagamet pioneered in the three anti-ulcer indications, that it lagged Zantac in the relatively populous GERD market was of considerable importance.

Today the four H_2-antagonist drugs are frequently viewed as being "...equally efficacious in their ability to suppress acid secretion,"[7] but different in their pharmacological profiles. McKenzie et al. [1990, p. 58] note that Tagamet is "the H_2-antagonist implicated with the most side effects and drug interactions," and that such adverse impacts occur "to a lesser extent" with Zantac. The third and fourth entrants -- Pepcid and Axid -- appear to have even less drug interactions and side effects.[8] What is not yet clear, however, is the extent to which apparent differences in side effect profiles simply reflect differential lengths of time over which the various drugs have been able to accumulate medical experience.

Modern ulcer medicines are not necessarily restricted to H_2-antagonists. One alternative therapy is Carafate (sucralfate), introduced into the U.S. by Marion Labs in August 1981. Instead of inhibiting acid secretion, Carafate acts by forming a protective coating over the ulcer that in turn promotes healing. While it is relatively free from side effects, Carafate has problems of convenience and compliance, since

it must be taken four times per day, always on an empty stomach (before meals). It also acts more slowly than the acid inhibitors in relieving pain. For these reasons, Carafate serves a market niche, being used predominantly for older patients, and patients in intensive care.

Another entrant in the anti-ulcer market is Cytotec (misoprostol), introduced in December 1988. Cytotec has been targeted at ulcers associated with the use of non-steroidal anti-inflammatory drug (NSAID) therapy (pain relievers, such as Motrin). Its rather small market niche consists of patients who take NSAIDs chronically and are at greater risk for the development of peptic ulcer disease, or complications from peptic ulcers -- particularly the elderly, those with previous ulcers, concomitant debilitating diseases, and/or patients who smoke. A common side effect of Cytotec, however, is diarrhea, although it can often be mitigated by adjusting dosage.

The most recent treatment innovation to enter the anti-ulcer market is Prilosec (omeprazole), introduced into the U.S. by Merck, Sharp and Dohme in September 1989.[9] Prilosec is a powerful new drug known as a proton pump inhibitor. It acts by directly blocking the action of the proton pump, which is the biochemical mechanism that actually produces the acid in the stomach. Initially approved for only the GERD indication, in June 1991 Prilosec was approved by the FDA for duodenal ulcer treatment. Although it is considerably more potent than the H_2-antagonists, there is some evidence from long-term studies on rats that Prilosec is associated with carcinoid tumors; hence it is approved only for short-term use. Dosing for Prilosec is unique in that it is supplied in a timed-release capsule, thus reducing dosage to once per day but yielding continuous levels of the drug within the body throughout the day.

With this brief overview on ulcer drugs and ulcer treatments as background, we now move on to a discussion of the pricing and marketing behavior of the manufacturers, the sales and market shares they attained, and the data sources underlying these statistics.

III. OVERVIEW OF THE DATA

Most of the data used in this study originated with IMS America, a Philadelphia-based firm that independently collects data on the sales and marketing of pharmaceutical products. IMS sells its data to pharmaceutical manufacturers, among others, for their use in formulating marketing strategy.[10] IMS sales data track prescription pharmaceutical purchases made by hospitals and by retailers; market segments not monitored by IMS include foodstores, dispensing physicians, HMO's, mail order, nursing homes, and clinics. IMS estimates that its drugstore audit covers 67% of the U.S. pharmaceutical market, and that its hospital audit encompasses an additional 16%.[11]

The level of aggregation of the IMS purchase data is at the presentational form, e.g., bottles of 30 tablets of a 150mg pill. For each presentational form, we compute average price as dollar purchases divided by number of units. We also convert these price and quantity measures into patient days and price per patient day, using the recommended daily dosage for duodenal ulcer treatment as the transformation factor. These monthly data series begin in August 1977 and continue through May 1993.

In addition to price and quantity data on drug purchases, we employ IMS data on marketing efforts from their Personal Selling Audit, earlier called the IMS National Detailing Audit. Based on a panel of about 3500 physicians who report the number of visits and minutes spent with detailers discussing particular drug products, IMS computes monthly detailing efforts by drug.[12] Using an estimated cost per detailing visit, IMS also estimates total detailing expenditures. Medical journal advertising expenditures are estimated by IMS in their National Journal Audit. Based on the number of square inches and pages of advertisements in about 300 major medical journals, as well as features such as the number of colors of each advertisement, IMS uses standard rate sheets to estimate total dollars of journal advertising, monthly, by product. We convert these current dollar expenditures into constant dollar magnitudes using the BLS Producer Price Index for Advertising in Professional Journals.

Discussions with industry personnel suggest that while these detailing and journal advertising expenditures likely understate total promotion costs (booths and promotions at conferences are not included, for example), there is no reason to suspect that the proportions differ across products, and thus we are led to believe that the relative expenditure data series are likely to be reasonably accurate. It is worth noting, incidentally, that according to one observer, in the early 1990's in the U.S. pharmaceutical industry, approximately $3.1 billion was spent on detailing, about $700 million was spent annually on journal advertising and direct-mail promotions, medical education expenses accounted for about $400 million, and other forms of media and communication amounted to approximately $300 million annually.[13]

Finally, data on recommended daily dosages and product-specific attribute information are taken from Physician's Desk Reference, annual issues from 1978 to 1993, and U.S. Pharmacopeia Convention, Dispensing Information. Further details regarding data sources and transformations are presented in the Data Appendix.

With this as background regarding data sources, we now present an overview of data trends. In Figure 1 we plot the quantity of U.S. sales (number of patient days of therapy) over time, separately for the retail drugstore and hospital markets, disaggregated into the H_2-antagonist (Tagamet, Zantac, Pepcid and Axid) and other anti-ulcer drugs (Carafate, Cytotec and Prilosec). Starting from zero in August 1977, by May of 1993 total monthly sales were almost 130 million patient days; of this, approximately 93% is sold via retail drug hospitals. Broken down by drug type, the H_2-antagonist class accounts for approximately 84% of total sales, while the other anti-ulcer drugs make up the remaining 16%. Because of this market dominance, hereafter we confine our analysis to the H_2-antagonist drugstore market.

The growth of H_2-antagonist sales over time has been remarkably steady. For example, if one runs a simple regression of log sales on a constant and a time counter, one obtains:

$$\ln(Q_{H2}) = 16.4 + 0.012t, \qquad R^2 = 0.82,$$

implying an average annual growth rate (AAGR) of about 15%.

In Figure 2 we plot market shares of H_2-antagonist drugstore sales for the four H_2-antagonist drugs. Although Tagamet is the pioneer, Zantac enters in July 1983, and within one year it already captures about 25% of the total Tagamet-Zantac market. Tagamet's share continues to decline when Pepcid enters in October 1986, but Pepcid is less successful than Zantac; one year after entry, Pepcid has only approximately 8% market share. The sales of Zantac grow remarkably quickly and steadily, and by January 1988 Zantac sales overtake those of Tagamet. At about the same time (April 1988), Axid enters the market; as fourth entrant, however, Axid faces considerable competition, and after one year, its sales account for about only a 4% market share. By the end of our sample in May 1993, Zantac has captured about 55% of the quantity market share, Tagamet 21%, Pepcid 15%, and Axid 9%.

Although the entry of Zantac into the H_2-antagonist market increased total market sales, the sales of Tagamet fell. As seen in Figure 3, drugstore sales of Tagamet grew at a very rapid rate after entry in 1977, they began to level off a bit from 1981 to 1983, and although they peaked at about 46 million patient days in April 1984, after Zantac's entry in 1983 Tagamet's sales tended to decline. This general decline in sales continues to the end of our sample, when Tagamet monthly sales are less than half their peak -- about 21 million patient days. By contrast, sales of Zantac have generally increased over time, and by May 1993 Zantac accounted for about 54 million patient days per month. Although Zantac sales increase with time, as is seen in Figure 3, there is a modest decline in the growth slope beginning early 1988, coinciding with a slight rebound in Tagamet sales and the effects of entry by the fourth entrant,

Axid. Although both Pepcid and Axid record considerable growth in sales, they clearly are dominated by the two earliest entrants, Tagamet and Zantac.

An interesting phenomenon occurs in the pricing behavior of the four products over this tumultuous time period. Price per day of duodenal therapy (based on recommended dosages, and adjusted for inflation using the overall Consumer Price Index with 1982-84 = 1.00) is displayed for the four products in Figure 4. After original entry until it faced competition from Zantac, Tagamet gradually decreased its real price from about $1.00 to about $.80 per day. When Zantac entered in late 1983, it charged a substantial premium ($1.25 per day, a 56% premium). Thereafter, prices of both Zantac and Tagamet rose with time, although Tagamet's prices increased more rapidly. By the end of the sample, the Zantac price premium had narrowed from about 56% to 25%.

The third and fourth entrants, Pepcid and Axid, followed price policies that fell generally somewhere between that of Tagamet and Zantac. At the end of the sample period covered by our data (May 1993), the price per day of therapy ranged from a low of about $1.41 per day for Pepcid, $1.44 for Tagamet and $1.62 for Axid, to a high of $1.80 per day for Zantac. An interesting recent development is that in November 1993 (after the end of our sample), Tagamet announced a major change in its pricing policy, offering rebates directly to consumers.[14]

Finally, as is seen in Figure 4, there does not appear to be any substantial competitive pricing policy response by incumbents to the entry of new competitors in the H_2-antagonist market. Indeed, the only price trend break that coincides with entry is that for Tagamet upon entry by Zantac, which resulted in the incumbent Tagamet increasing rather than decreasing its price.[15] Note also that price trends do not show breaks around the time of entry by Pepcid and Axid.

Pricing policy, however, is not the only instrument for competitive rivals. In the U.S. pharma-

ceutical industry, marketing plays a very significant role. In Figure 5 we plot monthly detailing minutes for the two principal rivals, Tagamet and Zantac; cumulative detailing minutes since original product launch are plotted for each H_2-antagonist drug in Figure 6.

As seen in Figure 5, the launch of Tagamet coincided with a very substantial detailing effort -- about 180,000 minutes in September 1977, after which detailing efforts gradually diminished. High levels of Tagamet detailing occurred in mid-1980 and early 1983, apparently in response to Tagamet receiving FDA approval for the new indications of duodenal ulcer maintenance (April 1980) and gastric ulcer therapy (December 1982). When Zantac entered with a very aggressive detailing effort in July 1983 (over 350,000 minutes), Tagamet responded with about a 50% increase in its own detailing efforts. More detailing peaks for both Tagamet and Zantac occurred in 1986, a year in which Pepcid entered and Zantac obtained FDA approval for the treatment of GERD. Both Tagamet and Zantac appear to have anticipated the entry of Axid in April 1988 by increasing their detailing in February 1988 (substantially for Tagamet, more modestly by Zantac), but both detailing levels declined again after Axid's entry.

Although month-to-month variations are apparent in Figure 5, there are definite trends in the intense Zantac-Tagamet detailing rivalry. As is seen in Figure 6 where cumulative detailing minutes are plotted for all four products, over its entire life Tagamet has out-detailed Zantac. However, in terms of detailing minutes per year, Zantac has considerably outpaced Tagamet. In part, Zantac has been able to do this because it has had two sales forces resulting from Glaxo's co-marketing agreement in the U.S. with Hoffmann-LaRoche. In terms of cumulative minutes of detailing through the end of our sample, the relative magnitudes are for every one minute of Axid detailing, there have been 3.21 minutes of detailing for Tagamet, 2.60 minutes for Zantac, and 0.88 for Pepcid.

According to Bond and Lean [1977], one way in which pioneering advantages occur in the pharmaceutical industry is in the effectiveness of advertising. Bond and Lean argue that to convince physicians to switch from an existing drug to a new one and thereby to overcome advantages accruing to early entrants, the later entrant may be expected to offer either a lower price and/or a heavier promotion.[16] The Bond-Lean conjecture relates of course to the considerable theoretical and empirical literature in marketing and economics dealing with first mover advantages.[17] It is therefore of interest to examine whether this conjecture is consistent with the data from the H_2-antagonist drug market. Although we present econometric evidence on order of entry effects later in Section V, in Figure 7 we display cumulative detailing/cumulative sales ratios as a function of order of entry after one year in the marketplace (the leftmost set of bars), after two years (the middle set), and after three years (the rightmost set). The results are striking. Given any duration of time, cumulative detailing/sales ratios are always lowest for the pioneer (Tagamet), are always larger for the second entrant (Zantac), always increase further for the third entrant (Pepcid), and are always highest for the final entrant (Axid). Moreover, since a disproportionate amount of detailing occurs immediately following product launch, for all four H_2-antagonist products the cumulative detailing/sales ratios decrease as the time interval since launch increases.

Detailing is not the only form of marketing rivalry, however. Another instrument for bringing product information to the attention of prescribing physicians is via medical journal advertising. It is worth mentioning that relative to detailing, estimated expenditures on journal advertising are rather modest; as observed earlier, expenditures on detailing are approximately four to five times as great as expenditures on journal advertising in the overall U.S. pharmaceutical industry, although substantial variations occur across products.

It might be noted that to convert nominal to real dollars, one must employ a deflator. We use the BLS price index for scientific and professional journals. Based on a preliminary analysis of advertising rates charged by two major medical journals, the New England Journal of Medicine and the Journal of the American Medical Association, however, we found that the BLS deflator appeared to rise less rapidly in the 1980's than did advertising rates in these journals. An alternative measure of real medical journal advertising involves a simple page count. This measure does not account well, of course, for variations in copy quality, or in journal circulation. Later in this paper we discuss these two measures further. For our current purposes, it is sufficient to note that the two measures are reasonably highly correlated. In Figure 8 we plot cumulative medical journal dollars spent for each of the four H_2- antagonist products, using the BLS deflator. Clearly the launch of Tagamet coincided with a considerable journal advertising campaign. Thereafter until receiving FDA approval for duodenal ulcer maintenance in April 1980, Tagamet journal advertising was relatively modest, with temporary increases around the time of FDA approval for gastric ulcer treatment (December 1982) and for GERD (March 1991). It is noteworthy that Tagamet journal advertising increased only moderately after the entry of Zantac in August 1983, and it did not respond aggressively when Pepcid entered in late 1986. In terms of its response with journal advertising to entry by Pepcid and Axid, Zantac was roughly similar to Tagamet. Spurts in Zantac journal advertising appear to follow closely the obtaining of FDA approval for gastric ulcer treatment (June 1985), and the simultaneous approval for duodenal ulcer maintenance and GERD (May 1986). Finally, a comparison of Figures 6 and 8 reveals that Pepcid and Axid differed considerably in their choice of marketing medium in the sense that Axid has relied much more heavily than Pepcid on detailing, and much less on medical journal advertising.[18]

With this overview of price, product quality and marketing competition data trends in the H_2-

antagonist market, we now turn our attention to modelling the growth in overall industry sales, and to modelling changes in the shares earned by the various products. We begin in Section IV with an analysis of overall industry growth, and then consider market shares in Section V.

IV. ECONOMETRIC ANALYSIS OF GROWTH IN INDUSTRY SALES

In this paper we consider the four H_2-antagonist products as constituting a distinct market or industry. However, since Tagamet and Zantac so clearly dominate the H_2-antagonist market, we shall also consider a separate, simpler market -- that consisting only of Tagamet and Zantac. We first digress to consider theory and measurement issues, and then present econometric results.

IV.1. Theoretical and Econometric Considerations

The traditional approach to modelling demand for a product involves calling upon the economic theory of consumer demand, in which consumers are assumed to maximize utility given prices of products and an overall budget constraint; additional assumptions are then employed to aggregate up from the individual consumer to an overall industry demand. In the context of pharmaceutical products, this approach is unlikely to be useful, for the typical decisionmaker (the physician) is not the consumer (the patient) who actually pays for the prescription drug product. Moreover the marginal price paid by the patient often differs considerably from the price received by the dispensing pharmacy, due to the existence of third-party insurance and various co-payment schemes. While a discussion of such principal-agent problems is beyond the scope of this paper, we believe the existence of these institutional arrangements clearly suggests that rigid adherence to the traditional neoclassical approach of demand analysis is unlikely to be useful here.

Although we eschew here the direct use of conventional utility-maximizing economic behavior, we still wish to incorporate the most important insights of demand analysis. Thus we specify that quantity demanded depends on the price of the product, product characteristics, and marketing efforts.

We now discuss these three factors affecting demand in further detail.

In terms of price, economic theory suggests that quantity demanded depends on real rather than nominal price; since we employ time-series data, we deflate average product price by the Consumer Price Index (CPI). Also, although product-specific price data are available, for examining overall industry demand one must construct an industry price index. The important point here is that since we wish later on in this paper to investigate the extent of price-substitutability among drugs, when constructing an aggregate price index for the industry it is important we not implicitly assume a value for such substitutability. In particular, if one simply summed up patient-days of therapy across drugs, then summed up total revenue across drugs, and finally, calculated price as total industry revenue divided by total industry patient-days, one would implicitly be assuming that the various drugs are perfectly substitutable. To circumvent this problem, we employ the economic theory of price indexes, and calculate the industry price using the Fisher-Ideal price index.[19]

In terms of quality, to the extent that product quality characteristics affect the size of the potential market, they should be included in an overall industry demand equation. We would expect that the size of the potential patient market would depend on the specific indications for which the FDA has granted approval. We shall concentrate on one particular indication, GERD, which represented an especially large potential new market, and for which the H_2-antagonists first received FDA approval relatively late in the sample. Specifically, when the FDA granted approval to Glaxo's Zantac for GERD, Zantac detailers were permitted to provide specific information to physicians concerning the treatment of GERD. This was significant, for instead of being confined to detailing to gastroenterologists who saw ulcer patients, now Zantac detailers also made calls on general practitioners who commonly saw patients having GERD symptoms. This undoubtedly expanded the potential market.

Such reasoning suggests that a dummy variable, say, GERD (taking on the value of one following

FDA approval) be employed in the overall industry demand equation. However, it is worth noting that information concerning efficacy of drugs for different indications typically diffuses prior to formal FDA approval. The medical community is often aware of results of clinical trials prior to the FDA reviewing the clinical trial data and coming to a final decision concerning approval for a new indication. As a result, a great deal of prescribing is done off-label, prior to the FDA granting approval. Thus, it is not clear how reliable the GERD dummy variable will be in capturing major changes in the size of the potential patient base.

The third set of factors affecting industry demand involves marketing efforts. Earlier we noted that in this industry, the two principal forms of marketing efforts are minutes of detailing and either pages or deflated dollars of medical journal advertising. There are several important issues concerning the measurement of marketing efforts. First, since drug marketing is largely a matter of providing information about the existence and usefulness of the product, we expect its impact to be long-lived; once a physician has been informed, it is hard to see how such information might be destroyed. Indeed, precisely because of this durability, firms typically expend a particularly large amount of marketing effort in the early stages of a new product's life. Hence the impact of marketing on sales is likely better measured by a cumulative stock of marketing efforts since product launch, rather than simply by the flow of current monthly expenditures. We will also want to allow for the possibility that this stock of information depreciates or deteriorates over time, although we expect the depreciation rate to be quite low.

We therefore employ the well-known perpetual inventory method. Let M_t be the *stock* of marketing effort at the end of month t, (as measured by the stocks of journal advertising or detailing minutes), let δ be the monthly rate of depreciation of this stock, and let m_t be the flow of marketing effort during time period t. Define M_t as the depreciation adjusted stock of marketing effort carried over from the last month, $(1 - \delta)M_{t-1}$, plus new marketing efforts during month t (m_t), i.e.,

$$(1) \qquad M_t = (1 - \delta)\, M_{t-1} + m_t = \sum_{\tau=0}^{t} (1 - \delta)^{t-\tau}\, m_{t-\tau}.$$

We construct separate stock measures for detailing and for journal advertising. Unlike the typical case for capital stock accounting, we have no problem with establishing benchmark or "starting values" since we know that prior to August 1977, the Tagamet journal (and detailing) stocks were zero. To implement Eq. (1), one must however assume rates of depreciation for each of these stocks. As discussed below, we will use the historical data on marketing and sales to estimate δ econometrically, rather than assume its value a priori.

The other major issue in measuring the effects of marketing efforts entails an innovation of this paper. Other authors have pointed out that advertising be modeled as having two simultaneous effects in the market: overall advertising by all firms affecting overall market demand, and relative levels of advertising among firms affecting the individual firms' market shares.[20] We take this modeling one step further here by hypothesizing that firms may choose to direct their marketing efforts to emphasize one of the two effects more than the other. Although the degree to which firms' marketing efforts are directed, say, at overall market expansion cannot be directly observed from data on quantities of market ing done by firms, we now propose a method for estimating this effect econometrically.

To clarify this concept, we now discuss it in the context of the anti-ulcer drug market. When SmithKline (SK) marketed Tagamet from its introduction in 1977 until the entry of Zantac in 1983, SK did not worry about competing for market share in the H_2-antagonist market, for patent status conferred on them a temporary monopoly position. In this monopoly position, the goal of marketing for SK was to convince more and more physicians of the utility of H_2-antagonists in treating ulcer patients. SK, and no other firm, reaped the rewards of having expended efforts on diffusing information on H_2-antagonist

drugs to physicians, since SK held 100% market share. However, once Zantac entered the market, another SK marketing goal appeared: to preserve market share against Zantac among those doctors who had already adopted the H_2-antagonist technology. Similarly, although Zantac detailers could benefit somewhat from continuing to reach out to new doctors and patients still not converted to the H_2-antagonist technology, Zantac detailers also had strong incentives to persuade physicians already in the H_2-antagonist market to begin prescribing Zantac instead of Tagamet, emphasizing the alleged Zantac advantages of lower-frequency dosing and fewer adverse drug interactions. Unlike the monopoly case, in this duopoly situation the marketing efforts of firms may have both market-expanding and rivalrous (product-positioning) aspects.

Moreover, to the extent that Zantac would reap some of the benefits of Tagamet's market-expanding efforts to persuade physicians to adopt the H_2-antagonist drugs, and that Tagamet might similarly benefit somewhat from Zantac's market-expanding promotions, each firm's market-expanding promotional effort exerts a positive externality (spillover) on the other firm's sales. Similarly, we might consider rivalrous marketing to exert negative inter-firm externalities. When the number of products in the market increases, ceteris paribus, we would expect a decrease in firms' incentives to engage in market-expanding promotional efforts, and correspondingly greater incentives to engage in marketing with a more rivalrous content.[21] The practical implication of this hypothesis is that in a duopoly, ceteris paribus, one would expect the product marketing of the two participants to have a smaller impact on industry demand than would be the case if this advertising had occurred in a monopoly market structure, for some of the duopolists' advertising would primarily impact market share, not overall industry demand; similarly, ceteris paribus, for a given amount of cumulative marketing stocks, one might plausibly expect that in a triopoly the effects of marketing on industry demand would be less than in a duopoly.

In this paper we examine this hypothesis empirically by inferring econometrically the proportion-

ate impact (relative to a monopolist) that marketing efforts have under varying market structures. To this end, we distinguish cumulative marketing efforts according to the market structure in which such expenditures originally occurred. Let $M_{1,t}$ be the marketing stock at end of month t that accumulated in the monopoly market environment, let $M_{2,t}$ be the marketing stock at end of month t that accumulated in the duopoly market environment, and let $M_{k,t}$ be the marketing stock at end of month t that accumulated in a market environment consisting of K products. Define the "effective industry marketing" stock M_t as the weighted sum of the cumulative marketing efforts distinguished by market structure, *i.e.*,

$$\bar{M}_t = \mu_1 M_{1,t} + \mu_2 M_{2,t} + \mu_3 M_{3,t} + \ldots + \mu_k M_{k,t} \tag{2}$$

where the $M_{k,t}$, k = 1,....K, are each defined as in (1). Ceteris paribus, we therefore might plausibly expect that

$$\mu_1 > \mu_2 > \mu_3 > \ldots > \mu_k, \tag{3}$$

reflecting the fact that in terms of affecting overall industry demand, participants' market-expanding effects decline as the number of products in the industry increases.[22] Since in a monopoly all marketing efforts affect industry demand, we normalize the μ_k's by setting $\mu_1 = 1$.

It is worth noting that two other hypotheses might be proposed involving the μ_k's. First, if the effectiveness of firms' marketing on industry sales is independent of market structure, then $\mu_2 = \mu_3 = \mu_4 = 1$. Second and alternatively, if $\mu_2 = \mu_3 = \mu_4 = 0$, then in the presence of any competition all marketing efforts are rivalrous and affect only market shares. Note that in such a case of possibly but not necessarily socially "wasteful" marketing, firms' marketing efforts generate a zero-sum change in industry sales. In our empirical analysis, we will estimate the remaining μ_k's in Eq. (2) and assess whether the

evidence is consistent with any of these hypotheses.

We begin with some definitions of variables. Let Q_t be total units of sales for all products (a Fisher-Ideal quantity index), let PR_t be the corresponding real price index (deflated by the CPI), let $D_{k,t}$ be the stock of minutes detailed by product k at the end of time period t, let $J_{k,t}$ be the stock of pages advertised in medical journals by product k at time t, and let $GERD_t$ be the above-noted GERD dummy variable.

In terms of a mathematical formulation, we specify a traditional log-linear demand equation, where, however, the use of identities (1) and (2) necessitates estimation by nonlinear least squares (NLS) procedures. In particular, let

$$LNQ_t = \beta_0 + \beta_1 LNPR_t + \beta_2 LN\bar{D}_t + \beta_3 LN\bar{J}_t + \beta_4 GERD_t + \epsilon_t \tag{4}$$

where ϵ is an identically normally distributed random error term, and where LND_t and LNJ_t are natural logarithms of the "effective industry marketing" stocks of number of minutes detailed and pages of medical journal advertisements,[23] respectively, defined as

$$\bar{D}_t = D_{1,t} + \mu_2 D_{2,t} + \mu_3 D_{3,t} + \mu_4 D_{4,t} \tag{5}$$

and

$$\bar{J}_t = J_{1,t} + \mu_2 J_{2,t} + \mu_3 J_{3,t} + \mu_4 J_{4,t} \tag{6}$$

In turn, following Eq. (1), define the effective stock of minutes at end of month t for a market structure consisting of k products as

(7) $$D_{k,t} = (1 - \delta_M)D_{k,t-1} + MIN_{k,t}$$

where δ_M is the constant rate of depreciation for the detailing minutes stock, and MIN is the number of minutes detailed during month t, where month t was one in which the market structure consisted of k products. The construction of effective stocks of journal pages $J_{k,t}$ by type of market structure is analogous to that in Eq. (7). Since Eqs. (5) - (7) are nonlinear in the μ's and δ's, for convenience we will constrain $\mu_k^M = \mu_k^J$ and $\delta_M = \delta_J$, but of course the μ_k (equal for minutes and journal pages) will still be permitted to differ with industry structure k in order that the hypothesized inequality in Eq. (1) might emerge.

There is one other issue that merits attention. At the industry level, one would expect price to be simultaneously determined with quantity. Moreover, as has been emphasized by, among others, Dorfman-Steiner [1954] and Schmalensee [1972], advertising efforts are also likely to be jointly determined with price and quantity. In terms of stochastic specification, therefore, it may well be the case that LNPR, LND and LNJ are correlated with ϵ, in which case estimation by nonlinear least squares would provide inconsistent estimates of the parameters. In the next section, we therefore report results of a Hausman test for this possible endogeneity, and since we find the correlation to be significant, we also estimate and report results using the nonlinear two-stage least squares (NL-2SLS) estimator.

IV.2. Results of Econometric Analysis

Our data set consists of 189 monthly observations beginning in September 1977. We proceed using two alternative definitions of the market, one comprised of the two dominant products, Zantac and Tagamet, and the other consisting of all four H_2-antagonists. In each case, we begin by setting the depreciation rate $\delta = 0$; we then examine and choose among several possible alternative specifications. Given reasonable regression equations, we perform a grid search for the best-fit value of δ by

re-estimating the models assuming a variety of depreciation rates, where $0 \leq \delta \leq 1$. We choose as our final set of parameter estimates that value of δ and the other parameters for which the sum of squared residuals is minimized (the sample likelihood function is maximized). Our findings are summarized in Table 1; the top half is that for the two-product market, while the bottom is that of the four-product market.

First, as seen in the top row of Table 1, the iterative NLS procedure yielded an optimum when δ is very small (0.2% per month), and is not significantly different from zero.[24] While we expected a low value for this depreciation rate since knowledge and information about a product is very durable, that we obtained such a very low rate of depreciation is somewhat surprising. It is worth noting, however, that in an inter-industry productivity study estimating the depreciation rate of R&D capital (another good whose use involves potential spillovers, and for which information plays a central role), Griliches and Lichtenberg [1984] reported an estimated depreciation rate of zero.

Second, the estimate of μ_2 is about 0.69, and with a standard error estimate of about 0.07, it is significantly different both from unity and from zero. Since μ_1 has been normalized to unity, this estimate of μ_2 implies that, ceteris paribus, observed marketing stocks of detailing minutes and journal pages are only about 70% as effective in changing *industry* sales when they occur in a duopoly (Tagamet and Zantac), relative to when they take place in a monopoly (Tagamet). This is a plausible result, for anecdotal evidence suggests to us that much of the Zantac-Tagamet duopoly era contained highly competitive marketing aimed at securing market share, rather than focused on increasing overall industry growth.[25] Nonetheless, as was shown in Figure 1, during this duopoly industry sales grew rapidly.

Third, in terms of marketing effectiveness, as is seen in the top row of Table 1, the elasticity of sales with respect to effective cumulative industry detailing minutes (LND) is slightly greater than 0.5,

and is about two and one-half times as large as that for effective cumulative industry journal pages (LNJ), whose value is about 0.2.

Fourth, each of these two marketing elasticities is estimated to be considerably smaller in absolute magnitude than the market price elasticity, which is slightly less than unity (-0.90).

Finally, although we have some hesitations concerning its reliability in tracking physician awareness, the coefficient on GERD (a dummy variable equal to one during the time period in which the FDA approved an H_2-antagonist drug for the GERD indication) is positive and significant; the estimate implies that, ceteris paribus, FDA approval for GERD increased the market size by about 15%.

These NLS results are based on the assumption that the regressors are uncorrelated with the disturbance term (in our context, that the regressors are all exogenous). We have tested for this assumption using a Hausman specification test, based on instruments that will be discussed below. We find that the joint null hypothesis of no correlation between ϵ and LNPR, ϵ and LND, and ϵ and LNJ is soundly rejected:[26] the likelihood ratio test statistic is 49.2, while the 0.01 critical value for the five restrictions is 15.1.[27] This implies that NLS generates inconsistent parameter estimates, and suggests that we instead employ the NL-2SLS estimator.

We utilize two groups of exogenous variables to form the instruments. One group is common to both firms: the log of the producer price index for intermediate materials, the log of the wage rate for production workers in the pharmaceutical industry, the GERD dummy variable, and a time counter. The other set incorporates firm-specific variation, but aggregates them to the industry level: the number of details by firms for their products other than those in the H_2-antagonist market, and the number of real dollars of medical journal advertisements for the firms' non H_2-antagonist products. To make these variables comparable to the components of the regressors LND and LNJ (see Eqs. (5) and (6) above), we construct stocks separately by type of industry structure, and then cumulate them assuming $\delta = 0$.

The results of the NL-2SLS estimation are presented in the second row of the top panel in Table 1. Relative to the NLS findings, a number of results are worth noting. First, with NL-2SLS the criterion function is optimized when $\delta = 0$. This estimate is low, but as noted above, it is not without precedent in a related context. Second, under NL-2SLS estimation, the estimate of μ_2 increases from 0.69 to about 0.89, and now is no longer significantly different from unity. It is, however, significantly different from zero. Third, the price elasticity estimate under NL-2SLS is slightly larger in absolute value (-1.07 vs. -0.90), unlike estimates of the detailing minute elasticity (0.41 vs. 0.53). Fourth, for the journal page elasticity, under NL-2SLS estimation the estimate increases from 0.21 to 0.28. Hence with NL-2SLS as well as NLS estimation, the estimates of the journal page and detailing elasticities are much smaller in absolute value than is the price elasticity. Finally, under either estimation method, the R^2 is above 0.99, and the Durbin-Watson test statistics are very close to 2.0.

We now turn to a discussion of findings obtained under a four-product market definition; results are given in the bottom panel of Table 1. As shown in the table, under either estimation method the goodness of fit is above 0.99, and the Durbin-Watson test statistic is again quite close to 2.0. For both NLS and NL-2SLS, the estimated δ at the optimum was 0.00. Hence, the very low depreciation estimate results for marketing efforts of detailing minutes and pages of medical journal carries over from the two-product to the four-product market context. Also, the Hausman test for exogeneity is again clearly rejected, although not as decisively as in the two-firm analysis; here the likelihood ratio test statistic is 41.3, while the 0.01 critical value for the nine restrictions is 21.7. This suggests again that the NLS estimates may be inconsistent, and that we instead employ the NL-2SLS estimator.

The NL-2SLS estimate for the market price elasticity in this four-product market is slightly smaller (in absolute value) than in the two-product case, around -0.74 vs. -1.07. The estimate of the sales elasticity with respect to cumulative detailing minutes is somewhat larger here (0.57 vs. 0.41), while that

with respect to journal pages is slightly smaller (0.17 vs. 0.28). Moreover, with the larger four-firm market definition the GERD coefficient declines slightly, from about 15% to 12%.

Of particular interest, however, are the estimates of μ_2, μ_3 and μ_4. Recall from the discussion surrounding Eq. 3 that, ceteris paribus, we hypothesized that $1 > \mu_2 > \mu_3 > \mu_4$. As is seen in the bottom panel of Table 1, this pattern is largely, but not completely borne out; although less than unity, typical estimates of these three parameters are 0.6, 0.8 and 0.5, respectively. Why it is that marketing efforts in the triopoly epoch were more effective in generating industry sales than during the two- and four-product eras is an issue meriting further examination. Moreover, the joint null hypothesis that these μ's are all unity (that the effectiveness of marketing efforts on sales is independent of market structure) is decisively rejected, as is the joint hypothesis that $\mu_2 = \mu_3 = \mu_4 = 0$, the latter indicating that market-expansion spillovers do not entirely disappear when competition begins. While these spillovers are considerably lower in the duopoly period than would be the case in a monopoly, and are lower when there are four products on the market than two, in this market the relationship between μ_k and the number of products in the market is not completely monotonic.

V. ECONOMETRIC ANALYSIS OF FACTORS AFFECTING MARKET SHARES

To this point our analysis has focused on overall market demand, with alternative definitions of the market. We now report on an exploratory effort at modelling the factors that affect individual market shares earned by each of the products. The results reported here are those from our initial research; we intend to extend this analysis in future research. As in Section IV, we begin with a discussion of considerations drawn from economic theory, and then report on statistical findings.

V.1. Theoretical and Econometric Considerations

The specification of market share or relative demand functions traditionally draws on the economic theory of consumer behavior. As noted earlier, however, principal-agent problems and wedges

between marginal relative prices paid and received imply that one cannot directly employ the economic theory framework of consumers maximizing utility, given prices and budget constraints.

Consistent with traditional economic specifications, however, we would expect that relative rather than level prices affect market shares. Moreover, within the marketing literature, there is ample precedent for specifying that relative values (ratios) of product characteristics, and relative marketing efforts, affect market shares. In addition, both the economic and marketing literatures suggest that order of entry can be expected to be a significant determinant of market shares.[28] Following Urban et al. [1986], we employ a market share specification of the general form:

$$(8) \qquad \frac{Q_{jt}}{Q_{1t}} = f\left(\frac{p_{jt}}{p_{1t}}, \frac{MIN_{jt}}{MIN_{1t}}, \frac{PJL_{jt}}{PJL_{1t}}, X_{jst}, ENT_{jt}\right)$$

where Q_{jt}/Q_{1t} is the sales of product j relative to product 1 (the first or pioneer entrant, in this case, Tagamet) in month t, P_{jt}/P_{1t} are the corresponding relative prices per day of therapy, MIN_{jt}/MIN_{1t} and PJL_{jt}/PJL_{1t} are relative cumulative stocks of minutes of product detailing and cumulative pages of medical journal advertisements (defined as in Eq. 1), X_{jst} are a set of s variables measuring the quality of product j relative to the pioneer (e.g., dosage frequency, number of (adverse) drug interactions reported to the FDA, whether product j has a GERD indication advantage relative to the pioneer, etc.), and ENT_{jt} is the order of entry of product j (i.e., 2 for Zantac, 3 for Pepcid and 4 for Axid.).

In our context, the pioneer product is Tagamet, and thus all variables in Eq. (8) are measured for product j relative to Tagamet. Since market shares are 100% for Tagamet during its monopoly epoch (September 1977 through July 1983), the data set for which market share analysis is appropriate commences in August 1983; data prior to this are not employed. In the case of a two-product market definition, the data therefore consist of Zantac/Tagamet relative quantities beginning with August 1983, a total

of 118 observations. For the four-product (H_2-antagonist) market definition, however, the data set is expanded to incorporate relative Pepcid/Tagamet data points (December 1986 onwards), as well as relative Axid-Tagamet observations (beginning with June 1988), giving us a total of 255 observations. Note that in this four-product model the data take the form of an unbalanced panel.

Finally, in terms of econometric considerations, one would expect that relative market shares, relative marketing efforts, and relative prices are jointly determined. For this reason, we compare the OLS and NLS results with those based 2SLS and NL-2SLS.

In terms of mathematical formulation, we specify a relative demand equation as in Eq. (8), where variables are logarithmically transformed:

$$LN\left(\frac{Q_{jt}}{Q_{1t}}\right) = \beta_1 ENTRY_{jt} + \beta_2 LN\left(\frac{p_{jt}}{p_{1t}}\right) + \beta_3 LN\left(\frac{MIN_{jt}}{MIN_{1t}}\right) + \beta_4 DGERD_{jt} + \beta_5 LN\left(\frac{FREQ_{jt}}{FREQ_{1t}}\right) + \beta_6 LN\left(\frac{INT_{jt}}{INT_{1t}}\right) + \beta_7 AGE_{jt} + \epsilon_{jt} \quad (9)$$

where $ENTRY_{jt}$ takes on the value 2 for all Zantac observations, 3 for Pepcid and 4 for AXID, $FREQ_{jt}$ is the recommended daily dosage frequency of drug j, INT_{jt} is the number of (adverse) drug indications of drug j reported to the FDA as of time t,[29] $DGERD_{jt}$ is a variable indicating whether product j has a GERD indication advantage relative to Tagamet (1 if an advantage, zero if no advantage, -1 if a disadvantage), and AGE_{jt} is the number of months product j has been in the marketplace. Notice that if the relative price, relative detailing minutes, relative adverse interaction and relative dosing frequency variables were all unity, and if the products had no GERD advantage, then at age zero, the relative quantities would depend solely on order of entry effects. Thus the coefficient on ENTRY reflects disadvantages confronting later entrants into the market, other things held equal. The coefficient on AGE reflects

the impact of marketplace experience on sales, holding ENTRY (and other variables) fixed. A priori, we expect that $\beta_2 < 0$, $\beta_3 > 0$, $\beta_4 > 0$, $\beta_5 < 0$, $\beta_6 < 0$ and $\beta_7 > 0$.[30]

As noted earlier, the data set for this market share model begins when the Tagamet monopoly period ends and Zantac enters. To implement the model empirically, we must make an assumption concerning the "starting value" of the Tagamet stock of detailing minutes. Since the results of our industry analysis suggested depreciation rates for effective industry marketing stocks were zero, we begin the duopoly era using Tagamet's end of monopoly era value for MIN_{it}, assuming $\delta = 0$. However, we will permit δ, the depreciation rate for these stocks, to differ from zero now that competition has emerged, reflecting in part the fact that the content of marketing may now become more susceptible to counter-claims, and therefore, become less long-lived. Although we have not yet developed a formal model describing optimal behavior in this context, we would not be surprised if the depreciation rate δ in the rivalrous context were larger than it was in the industry-expanding environment.

V.2. Results of Econometric Analysis

We begin with a market share analysis for the two-product market, Tagamet and Zantac. Conditional on any given rate of depreciation, the market share model of Eq. (9) is linear in the parameters. We proceed by estimating parameters in Eq. (9) by ordinary least squares (OLS) under different rates of depreciation and then choose as our preferred model that set of δ and the other parameters that minimizes the sum of squared residuals (maximizes the sample likelihood function). Results from preliminary analysis suggested that it was difficult to obtain precise estimates of both marketing instruments -- minutes of details and pages of medical journal advertising, reflecting in part the fact that the simple correlation between MIN_{jt}/MIN_{1t} and PJL_{jt}/PJL_{1t} was 0.98. In the results presented in the top two rows of Table 2 below, the LNPJL variable was therefore deleted. Several points are worth noting.

First, as in the two-product industry equation, the likelihood function is maximized at the point where $\delta = 0$. A second somewhat unexpected result is that the coefficient on the relative frequency of dosage variable ($LNRFRQ_t \equiv LN(FREQ_{jt}/FREQ_{1t})$), though negative, is insignificantly different from zero. We therefore set this parameter to zero, and re-estimate the model. As is seen in the second row of Table 2, the logarithm of the relative quantities of Zantac to Tagamet ($LN(Q_{jt}/Q_{1t})$, the dependent variable) is significantly negatively affected by relative price ($LNRPR \equiv LN(P_{jt}/P_{1t})$) -- the own-price elasticity is about -0.8, and is very substantially affected by the relative stocks of cumulative detailing minutes ($LNRMIN \equiv LN(MIN_{jt}/MIN_{1t})$) -- this elasticity estimate is about 1.0. As hypothesized, the coefficient on the GERD advantage variable is positive (0.08) and significant , while that on LNRINT $\equiv LN[(INT_{jt}+1)/(INT_{1t}+1)]$, where INT is the number of (adverse) drug interactions reported to the FDA, is negative (-0.09) and significant. Finally, while the order of entry coefficient (in this 2-firm model, essentially just the intercept term) is negative, its standard error is quite large. By contrast, the coefficient on the AGE variable is positive and highly significant.

We then perform a Hausman test to check for possible endogeneity of LNRPR and LNRMIN. The exogenous variables used here are the same as those noted in Section IV above, except now the firm-specific number of details and dollars of medical journal advertising for products other than those in the H_2-antagonist market are employed, as are dummy variables for whether the product has received FDA approval for duodenal maintenance therapy, gastric ulcers, GERD, and stress ulcer prevention. These latter variables are particularly useful as instruments, since they represent "shocks" and new information for marketing efforts. The results of the Hausman test are not as clear as in the overall market analysis; here the likelihood ratio test for exogeneity of LNRPR and LNRMIN is 6.67, while the 0.01 chi-square critical value for the two restrictions is 6.63. As a sensitivity check, we proceed with 2SLS estimation. Our 2SLS results are presented in the bottom two rows of the top panel in Table 2.

With 2SLS estimation, the fitting optimum is again reached with the depreciation rate $\delta = 0$. Essentially, the results are the same as those obtained under OLS estimation. In particular, the own-price elasticity estimate is about -0.9, about the same in absolute value as the elasticity of sales with respect to cumulative detailing. The DGERD advantage is significant and equal to about 10%, AGE is significant and about 1% per month, while both ENTRY and LNRFRQ are negative but insignificantly different from zero. Finally, Zantac's relative market share is significantly negatively affected by its number of drug interactions relative to Tagamet. At the end of the sample, incidentally, values of INT are 12 for Tagamet and 1 for Zantac. Hence, the INT product quality variable is particularly important in explaining the growth in Zantac's market share and the corresponding decline of Tagamet.

In summary, in the two-product market, relative Zantac-Tagamet quantities demanded are systematically related to relative product prices, relative cumulative detailing efforts, relative product quality (relative adverse interactions and GERD, but not, apparently, by dosing frequency), and by the length of time the product has been on the market. Moreover, for both OLS and 2SLS estimation, the goodness of fit is above 0.99.[31]

We now turn to the broader market definition, one encompassing all four H_2-antagonist products (Tagamet, Zantac, Pepcid and Axid). The results of this analysis are given in the bottom panel of Table 2. First, we now uncover evidence suggesting that in the rivalrous market context, depreciation rates on detailing minutes differ substantially from zero. Specifically, with OLS estimation, the sample log-likelihood function is maximized when $\delta = 0.039$; this monthly rate of 3.9% corresponds with an annual rate of about 38%. Second, with this expanded market definition, order of entry effects (no longer just an intercept term) become very large and significant; the -0.492 estimate corresponds with about a 39% disadvantage accruing to each later entrant, ceteris paribus, and is remarkably close to the "consensus" estimate of order of entry effects (-0.5) in numerous other markets surveyed by Robinset et al.

[1994]. Third, although the price elasticity estimate is slightly smaller in absolute value in this four-firm market than in the two-firm context (-0.7 vs. -0.9), the standard error estimates are much smaller, and the t-statistics are therefore larger. Further, the elasticity of relative sales with respect to relative cumulative detailing minutes is slightly larger in absolute value than the price elasticity (0.73 vs. -0.64), and is also highly significant. Finally, as hypothesized, the coefficient on the relative number of (adverse) drug interactions variable (LNRINT) is negative and significant (-0.25, t-statistic of 12), and that on GERD is positive (0.03), but the latter coefficient is of only marginal statistical significance (t-statistic of 1.9). The AGE coefficient is again slightly greater than 1%, indicating that length of time in the marketplace affects relative sales in a positive manner. Goodness of fit is again about 0.99.[32]

To check on the possible endogeneity of relative prices and relative detailing stocks, we again perform a Hausman specification test. The null hypothesis of exogeneity of LNRPR and LNRMIN is decisively rejected; the likelihood ratio test statistic is 8.53, while the 0.01 chi-squared critical value for the two restrictions is 6.63.

Parameter estimates under 2SLS estimation are given in the bottom row of Table 2. Several findings are of particular interest. First, the estimate of δ at the fitting optimum is 0.042, and is significantly different from zero; this monthly depreciation rate of 4.2% implies an annual rate of about 40%. Hence, these results suggest that in the four-product anti-ulcer market, relative detailing efforts have a long-lived rivalrous impact that depreciates at about 40% per year. Second, order of entry effects are very substantial and statistically significant (-0.51, t-statistic of 59), and again conform remarkably closely to the -0.5 consensus estimate reported by Robinson et al. [1994] for numerous other packaged goods type products. Third, the absolute values of the price and advertising elasticities are roughly the same -- 0.7, and each is significantly different from zero. Thus the evidence suggests that in the four-firm market, relative shares garnered by the four products vary systematically and significantly with order of entry, relative

prices and relative cumulative detailing minutes. In terms of product quality variables, increases in the relative number of adverse drug interactions reported to the FDA negatively impact relative sales, whereas having a GERD approval advantage relative to Tagamet positively affects relative sales.

In summary, this exploratory four-firm market share analysis suggests that order of entry, pricing behavior, marketing behavior and product quality all affect relative sales quantities in the hypothesized manner. Moreover, rivalrous detailing appears to depreciate at about 40% per year.

Before leaving this discussion, however, we believe it is of interest to report estimates of total price elasticities. The price elasticity estimates reported in Table 2 focus only on relative quantities (market shares), but leave fixed the size of total industry demand at, say Q; denote these price elasticities by ϵ^{*}_{jj}. A total price elasticity also captures the impact of a product's price change on total industry demand; denote such a price elasticity by ϵ_{jj} (no asterisk). As has been shown by, inter alia, Berndt-Wood [1979], the relationship between ϵ^{*}_{jj} and ϵ_{jj} is as follows:

$$\epsilon_{jj} = \epsilon^{*}_{jj}|_{Q=\bar{Q}} + \left(\frac{\partial \ln Q_j}{\partial \ln Q}\right)\left(\frac{\partial \ln Q}{\partial \ln P}\right)\left(\frac{\partial \ln P}{\partial \ln P_j}\right) \tag{10}$$

where Q_j is quantity demanded of product j, Q is total industry demand, and P is industry price. The first partial derivative in Eq. (10) can be assumed to equal unity (other things equal, demand for product j grows equiproportionally with market demand, i.e., according to its market share), while the second partial derivative is the industry or market price elasticity (estimated values of which are given in Table 1). The last partial derivative in Eq. (10) indicates the impact of a change in product j's price on the overall industry price index; it can be approximated by the revenue share of product j in total industry revenues.

Alternative OLS and 2SLS estimates of the ϵ^{*}_{jj} are given in Table 2, while NLS and NL-2SLS

estimates of the industry price elasticity are presented in Table 1. For the two-product market, 1993 drug-store revenue shares for Tagamet and Zantac are approximately 0.25 and 0.75. For the four-product market, these shares are approximately 0.19 (Tagamet), 0.60 (Zantac), 0.12 (Pepcid) and 0.09 (Axid). Together, these relationships imply that in the two-market context, the 2SLS estimate of the total own-price demand elasticities for Tagamet and Zantac are approximately -1.154 and -1.690, respectively, while in the four-product market, the 2SLS estimated total own-price demand elasticity is -0.909 for Tagamet, -1.153 for Zantac, -0.820 for Pepcid, and -0.799 for Axid. Note that while these point estimates imply that some of the demand elasticities are less than one in absolute magnitude, the associated standard errors may well imply that reasonable confidence intervals include values of one and above (in absolute value).

VI. CONCLUDING REMARKS

In this paper we have attempted to explain the phenomenal growth of the H_2-antagonist anti-ulcer drug industry in the U.S., as well as changes in the market shares garnered by the various products over time. Although we have examined the roles of product quality, order of entry and price, we have focussed particular attention on the role of various marketing efforts. Our framework and results can be summarized as follows.

First, marketing efforts such as detailing and medical journal advertising have long-lived impacts. Thus in explaining current period sales, a stock of cumulative detailing or cumulative medical journal advertising is a more appropriate measure of marketing impacts than is current monthly expenditures. In the context of industry demand, we distinguish investments of firms in these marketing activities by the industry structure prevailing when the expenditures originally occurred. In a monopoly market structure, all marketing expenditures are market-expanding, for the monopolist has 100% market share. In a market structure with k products, however, marketing activities become more rivalrous, and as k be-

comes large, we expect relatively little "spillover" of a firm's marketing efforts in affecting industry demand. We have hypothesized, therefore, that in terms of affecting industry demand, the relative effects of marketing expenditures originally made when k products were in the market will tend to decline as k increases. In other words, we hypothesize that the effectiveness of marketing in generating industry sales depends on market structure in a systematic manner.

In our empirical analysis of the anti-ulcer drug market, we obtained considerable but not quite unanimous support for this hypothesis. In particular, normalizing the impact of a monopolist's marketing investments on current sales to unity, we estimated the impact in a duopoly to be 0.6, in a three-product industry to be 0.8, and in a four-product market to be 0.5; these last three numbers are all statistically significantly different from unity (implying that we reject the hypothesis that the effectiveness of marketing efforts is independent of market structure), and from zero (indicating that we reject the hypothesis that once there is competition, the only impact of marketing is on market share, and none on overall market size). Thus our results suggest that in the anti-ulcer drug market there is clear evidence of spillovers, and that these spillovers are considerably less than 100% effective. Moreover, for the most part, these spillovers decline as the number of products in the industry increases.

Second, we find that at the industry level, both cumulative minutes of detailing and cumulative pages of medical journal advertising affect sales; typical estimates of these elasticities are 0.5 and 0.2, respectively. At the market share level, relative sales of products are also positively related to relative cumulative minutes of detailing; this elasticity is typically in the range of 0.7 to 0.9. Together these results imply that the marketing efforts of firms in the anti-ulcer drug market had substantial effects, both in terms of affecting market shares and the size of the overall industry.

Third, a somewhat unexpected result we obtained is that at the industry level, the rate of depreciation of stocks of both minutes of detailing and medical journal advertising was estimated to be zero. We

believe that this result reflects the fact that market-expanding marketing primarily involves informing physicians about the usefulness of this class of drugs, and that once a physician begins prescribing these drugs, he/she is not likely to forget about their existence and stop prescribing them. By contrast, at the level of market shares a rather different picture emerges. In particular, in the four-product market (Tagamet, Zantac, Pepcid and Axid), we find that the market share impact of the stock of detailing minutes deteriorated at an annual rate of around 40%, reflecting perhaps a more rivalrous content of marketing efforts.

The remarkable growth in the market share of Zantac over time can be partially explained, then, by the very substantial marketing efforts undertaken by Glaxo. However, pricing policies also had an impact. Zantac increased share over Tagamet in part because the price premium commanded by Zantac declined from about 56% in 1983 to only about 25% in 1993. Our estimates of industry price elasticities range from about -0.7 to -0.9, while estimates of cross-price elasticities between any pair of the four products are about 0.7.

Another set of important factors affecting sales of anti-ulcer drugs concerns product quality attributes. At the industry level, the evidence suggests that the size of the market was enlarged considerably when the FDA granted approval for the GERD indication -- a condition that occurs in a relatively large population. At the market share level, we find that when a product had a GERD approval advantage relative to other products, its market share increased. Thus another reason why Zantac fared so well in the marketplace is that for quite some time it was the only product having received FDA approval for the treatment of GERD. Another variable affecting market share significantly is the number of adverse interactions with other drugs reported to the FDA. Relative to its competitors, on this account Tagamet fared relatively badly (by 1993, Tagamet had 12 drug interactions, Zantac and Axid had only one, and Pepcid had none). Thus Zantac also enjoyed advantages from this product quality characteristic.

An unexpected result we obtained, however, was that dosing frequency did not appear to affect market shares in a statistically significant manner.

Finally, we found that, as in many other markets, order of entry effects are very substantial. In particular, holding price, marketing efforts and product quality constant, relative to the n^{th} product, the $(n+1)^{th}$ entrant can expect about 40% lower sales.

The results of this paper are of considerable interest in the current health care reform debate. Critics of the pharmaceutical industry have argued that much detailing is merely aimed at market share, and is socially wasteful. Some have suggested placing ceilings on the marketing activities of pharmaceutical firms, but our findings demonstrate that this could have negative social welfare impacts. The findings in this paper suggest that marketing efforts also play a very important role in the diffusion of information to physicians, although the degree to which this is true probably declines somewhat as the number of products in a market increases. Moreover, our results suggest that in order to overcome pioneer product advantages, later entrants have found it necessary to advertise more intensively. An implication of these results is that if all pharmaceutical firms were constrained in their marketing activities, it is possible that the benefits would accrue primarily to the pioneer firms, at the expense of later entrants who would be prevented from trying to overcome pioneer product advantages. Thus, such a policy could have anti-competitive impacts, although it would be consistent with a patent system that rewards innovation.

The research reported in this paper should be extended in a number of ways. First, although the industry and market share equations are plausible and provide important initial evidence on the roles of marketing, price and product quality competition in the anti-ulcer market, the underlying models could be modified in a number of useful ways. The most obvious extension is to reformulate the models within an explicitly dynamic diffusion framework, such as those involving the Gompertz, logistic or other more

general diffusion curve formulations. In such a framework, marketing and pricing policies might not only affect the long-run or equilibrium level of demand, but they might also affect the speed at which a long-run equilibrium level is approached.

A second useful extension would involve incorporating data on direct-to-consumer marketing. In 1988 SKB experimented with a "Tommy Tummy" television advertising campaign that was aimed directly at consumers but did not mention Tagamet by name. More recently, Glaxo has advertised in magazines and on television, suggesting that patients with heartburn and acid discomfort should see their physician. These ads are sponsored by the Glaxo Research Institute, and, consistent with FDA regulations on direct-to-consumer advertising, do not mention the Zantac product by name unless the requisite warning and other product information is also fully disclosed. Since these advertisements typically do not mention product name, their impact is more likely to be on industry demand than on market share. Moreover, direct-to-consumer advertising may change the physician-patient information sharing relationship, and therefore could modify the diffusion process. It would be useful to examine whether such effects have actually occurred, and by extension, how effective is direct-to-consumer marketing in the anti-ulcer marketplace.

Third, and perhaps most importantly, the findings of this paper suggest interesting topics in the theory of industrial organization. What is the optimal marketing strategy for firms when there are spillovers and marketing activities have long-lived impacts? What is the correspondingly optimal pricing behavior? How does this optimal behavior vary with market structure? How is the optimal behavior affected by federal tax provisions that allow the expensing (rather than amortizing) of long-lived marketing investments? What are the implications for social welfare?

Obviously, much remains to be done. We believe we have demonstrated quite clearly that marketing efforts are very important in understanding the diffusion and economic success of new products.

Product quality and pricing behavior have also been shown to play important roles in the diffusion process. We hope the results of this paper contribute to this and other related research projects that enrich our understanding of the economics of new products.

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ENDNOTES

1. MedAdNews, "One Hundred Powerhouse Drugs", Special Supplement, May 1993, Vol. 12, No. 6. Incidentally, Tagamet is seventh, Pepcid ranks 17, Prilosec 25 and Axid 61 in terms of US sales. In terms of world sales, Tagamet is 7, Pepcid is 22, Prilosec is 49 and Axid is 67.

2. The material that follows is taken in large part from Scouler [1993] and the references cited therein. Also see Fine et al. [1988] and McKenzie et al. [1990].

3. See Fine et al. [1988].

4. Tagamet was introduced into the U.K. one year earlier, in 1976.

5. By June 1983, Tagamet had registered ten adverse interactions at the FDA. Zantac recorded its first adverse interaction in January 1992.

6. Discussions with industry officials suggest that Glaxo actually invented the GERD indication at the FDA.

7. McKenzie et al. [1990], p. 58.

8. Ibid.

9. Merck obtained the rights to market Prilosec in the US from AB Astra of Sweden. Prilosec was originally named Losec; however, its name was changed because of confusion surrounding the similarity of the name Losec to that of Lasix, a common diuretic.

10. IMS America, 660 W. Germantown Pike, Plymouth Meeting, Pennsylvania 19462 (215-834-5000).

11. Information on IMS is taken from the IMS Pharmaceutical Database Manual.

12. This sample size has increased with time. The 3500 number refers to 1993. In the mid 1980's, the sample size was about 2800.

13. Cearnal [1992], p. 23.

14. See New York Times [November 9, 1993].

15. For a discussion of the possible social welfare impacts of a pioneer raising its price in response to the introduction of a competitive product by a second entrant, see Perloff and Suslow [1994]. Related literature is found in Bresnahan-Reiss [1990], Cocks [1975], Cocks-Virts [1974], and Reekie [1978].

16. As Bond-Lean [1977, p. vi] state, "Neither heavy promotion nor low price appears to have been sufficient to persuade prescribing physicians to select in great volume the substitute brand of late entrants...When other things are equal, physicians appear to prefer the brands of existing sellers to those of new sellers."

17. On first mover advantages, see, for example, the surveys and references in Kalyanaram-Urban [1992], Robinson [1988], Robinson-Fornell [1985], Robinson-Kalyanaram-Urban [1994], Samuelson-Zeckhauser [1988], Schmalensee [1982], and Urban-Carter-Gaskin-Mucha [1986]. For an alternative interpretation, see Golder-Tellis [1992].

18. Industry sources say that this is not only true for Axid, but for all of Lilly's products. Lilly's corporate strategy has been to use a much higher percentage of detailing over journal advertising in their marketing efforts. Lilly's mix of detailing to advertising is approximately 90%-10%, whereas the industry average is 75%-25%.

19. Specifically, the Fisher-Ideal price is the geometric mean of the Laspeyres and Paasche price indexes, where each of them is computed using updated weights. New products are incorporated as soon as feasible (i.e., in the second period of their existence, so that their first difference is calculated). For further details concerning the Fisher-Ideal price index, see W. Erwin Diewert [1981,1992].

20. See, for example, Schmalensee [1972]. There is a considerable body of literature on a related, but distinct, approach that decomposes advertising into its "information" and "persuasive" components. For examples in the context of the pharmaceutical industry, see Leffler [1981], and Hurwitz and Caves [1988].

21. This also implies that incentives to advertise, and perhaps the content of advertising messages, can be expected to vary with industry structure. For further discussion of these issues, see Reiley [1994].

22. Note that the μ's do not deal at all with the effects of marketing stocks on the market shares garnered by the various firms in the market. We discuss determinants of market shares further in Section V below.

23. Two possible measures of medical journal advertising are current dollar expenditures divided by a BLS price index for advertising in professional journals, and the number of pages of medical journal advertising. An exploratory examination of the BLS price index suggested to us that in the 1980's and early 1990's it increased much less rapidly than advertising rates in the New England Journal of Medicine and the Journal of the American Medical Association. On the other hand, the page measure does not account well for variations in copy quality, or in journal circulation. Results from preliminary regression estimation suggested that the page measure provided more plausible parameter estimates.

24. The implicit standard error estimates in Table 1 are conditional on the value of δ. The t-statistic for δ was computed by comparing the likelihood function at $\delta = 0$ with that at $\delta = 0.0020$, and then computing the implied test statistic.

25. For a journalist's account of Glaxo's marketing activities and their success in the marketplace, see Lynn [1991].

26. More precisely, the null hypothesis involves testing that the various component (monopoly, duopoly) stocks of MIN and PJL are uncorrelated with ϵ. Hence under the alternative hypothesis there are five endogenous variables, monopoly stocks of MIN and PJL, duopoly stocks of MIN and PJL, and price.

27. Coefficients on each of the marketing stock variables, and on the price variable, were significantly different from zero as well.

28. See, for example, Schmalensee [1982], Kalyanaram-Urban [1992] and Urban et al. [1986].

29. Data on INT_{it} are taken from annual issues of the Physicians Desk Reference.

30. Note that if one insisted, this logarithmic functional form could be rationalized as deriving from the relative demand equations based on a constant elasticity of substitution (CES) indirect utility function augmented by marketing and product characteristic variables.

31. Durbin-Watson test statistics in the two OLS equations are 1.646 and 1.624, while in the two 2SLS equations they equal 1.627 and 1.608.

32. Since the data set now consists of an unbalanced panel, the traditional Durbin-Watson test statistic is no longer appropriate.

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DATA APPENDIX: DATA SOURCES FROM IMS AMERICA

We hope that this discussion will serve as a useful reference for economists who will be using IMS sales data on pharmaceuticals in the future, as there are a number of important issues and quirks to the data which are not well documented in IMS literature.

A. U.S. DRUGSTORES AUDIT (USD) AND U.S. HOSPITALS AUDIT (USH):

A panel of pharmaceutical wholesalers report to IMS each month on the sales of each presentational form (unit dose syringes, bottles of 100 tablets, etc.) of each drug product (Tagamet, Zantac, etc.) to drugstores and hospitals in the United States. From the sales reports they obtain in this audit, IMS computes national projections of the number of units and the dollars of revenue of each presentational form of each product sold each month in the United States, separately for drugstores and for hospitals. In recent years, the panel has grown to encompass nearly the entire universe of pharmaceutical wholesalers, according to IMS, making the audit nearly a full census, and the projections therefore quite accurate.

One interesting feature of all of the IMS data used in this study is that although IMS has been collecting such data for decades, the company keeps computer records of only the immediate past six years, on a rolling basis. In order to have the opportunity to study the anti-ulcer market since its very inception, which dates back over fifteen years, we chose to type in numbers by hand from archived monthly IMS publications. The sales data from January 1986 through December 1981 comes directly from IMS computer records, but all other IMS data used in this study was hand-typed.

Because the sales data contained so many different numbers (quantities and revenues each month for each presentational form of each drug for a total of over 5200 hand-typed numbers in the fifteen-year sample, above and beyond the 8000 numbers provided by IMS in computer format), and because the original copies of the published data were often very difficult to read (often the numbers were available

only on poor-quality microfilm, where a 3 was indistinguishable from an 8), we deemed the possibility for error to be very high. We therefore chose to invest several months in ensuring the integrity of the hand-typed data by carefully checking it for typographical errors. It turns out that there is a reasonable degree of variation from month to month in the sales quantities and revenues for each individual drug presentation (variation often on the order of 10% or more), but the prices of the drug presentations (IMS-reported revenues divided by IMS-reported units) are relatively stable. Therefore, our method of error correction was to sort the data by presentational form of each drug, and then print separate graphs of the drugstore and hospital prices of each presentation as a function of time. We were easily able to spot potential typographical errors as outliers on these graphs, at which point we were able to correct the errors by checking them against copies of the original published data. (Unfortunately, we had to make more than one trip back to Philadelphia in order to obtain copies of data pages which were missing from our collection! It was easy to lose a page, or miss it in the first place, because our data was obtained from dozens of three-inch thick monthly volumes of printed data, or their microfilm equivalents, in which the data of interest was contained on just a page or three in the middle of each hefty tome.) In all, we corrected a few dozen serious errors on the approximately 100 graphs printed, but as a result we are now quite confident of the reliability of the data, to the extent that it accurately matches the data collected by IMS.

Neverthcless, additional manipulations remained to be performed on this data set in order to put it into a form that would be useful for this study. Details of those manipulations follow.

First, as noted earlier, there were multiple presentational forms of each drug sold. To obtain a single number describing the quantity of each brand of drug (e.g. Tagamet) sold in a given month, we summed up the total number of milligrams of the chemical sold that month. For example, if in August 1979 SmithKline sold 6200 bottles of 100 Tagamet 300mg tablets and 1600 packages of 10 unit-dose

containers of 10ml of Tagamet syrup at 5mg/ml concentration, then we would compute the total number of milligrams of Tagamet sold that month as:

$$(6200)(100)(300\text{mg}) + (1600)(10)(5\text{mg/ml}) = 1{,}868{,}000 \text{ mg.}$$

An alternative approach to constructing a single monthly sales series for each drug, and one which a number of other studies have adopted, would be merely to proxy a drug's total sales (units and revenues) by the sales of a single leading presentation. The advantage of this alternative approach is its computational simplicity; by contrast, our method required dozens of additional hours of data manipulation. However, there is a serious disadvantage to the simpler approach, especially in this ulcer market, which is that the leading presentation changes over time. For example, see Figure A1, which displays the sales of Tagamet over time, broken down by its four major product forms (note that even this is a simplification of the full sales data set, as for example, the portion of the graph corresponding to Tagamet 800mg tablets represents a sum of two different presentational forms: bottles of 30 tablets, and unit-dose packages of 100 tablets). From this graph, we see that although originally Tagamet was sold only in the 300mg form, by 1992 the 400mg form had become the "leading form," considerably overtaking the 300mg sales. Other drugs in the sample present similar problems, having more than one presentation which hold significant shares of the drug's total sales.

(Figure A1 somewhere near here)

Also, we chose to include only those presentational forms which were intended to be taken orally by patients: tablets, capsules, and oral liquids. Excluded were those forms packaged in vials, minibags, syringes, etc., for injection or intravenous administration. One reason for this decision is that we intended to concentrate our study mainly on the drugstore market, where the bulk of the anti-ulcer sales occur, and where detailing to physicians is most salient. By contrast, the non-oral preparations are

developed mainly for hospitals, although some non-oral sales also show up in the drugstore market, presumably with the end consumers being patients either in nursing homes or under hospice care. (For the twelve-month period ending in May 1993, drugstore sales revenues for non-oral presentations of H_2-antagonist s were less than one thousandth as much as revenues for oral presentations. Even in the hospital market, non-oral presentations brought in less than half as much revenue as the oral presentations during that time period.) A second, very substantive reason for including only the oral preparations is that we learned, from conversations with doctors and pharmaceutical marketing professionals, that the non-oral preparations are generally used for very different purposes: instead of healing painful ulcers in otherwise healthy people, as the tablets and capsules are intended, the intravenous administration of anti-ulcer medication is used mainly for the prevention of ulcers in emergency-room patients at risk for ulcers due to the increased acid secretion brought on by trauma, for example, and in patients who are at risk for ulcers due to regimens of large doses of non- .eroidal painkillers. Anti-ulcer medication may also be injected as part of a complete anesthesiology for surgery. These uses require very different numbers of milligrams of drug than do the standard therapies (DU, GU, DU maintenance, and GERD) that are usually administered orally, and the price per milligram of drug tends to be an order of magnitude higher for the intravenous preparations (likely a combination of two effects: price discriminations, and the more complicated packaging and storage requirements of the IV preparations). So rather than confound the two types of uses, we have chosen to define our market of interest to be the orally-administered anti-ulcer drugs.

Next, we had to find a way to make the quantity units comparable across drugs. Milligrams were not an appropriate unit for comparison, because, for example, treatment of an active duodenal ulcer with Tagamet requires 800mg of drug to be ingested per day, but an equivalent therapy with Pepcid requires only 40mg of drug. Each drug is a different chemical entity, with different molecular weights, different

rates of absorption, and different rates of binding to bioactive sites in the body, which combine to cause wide variation in the amounts of mass of drug that must be consumed to achieve the same desired effect. Because marginal manufacturing costs in the pharmaceutical industry are generally much lower than prices, we have chosen to concentrate on the demand side of the market in our choice of quantity units: patient-days of therapy. (This may have some concordance with the producer side as well, for although the different chemicals may not have the exact same marginal costs of synthesis, it is at least plausible to assume that packaging the drug into tablets, and the tablets into bottles, should have approximately the same marginal cost per tablet, regardless of the chemical being so packaged.) This choice of quantity units considers 800mg of Tagamet to be the same mount of drug as 40mg of Pepcid, for purposes of computing sales levels and market shares, since these quantities are therapeutically equivalent.

The quantity of patient-days of therapy of a drug sold in a given month is equal to the total number of milligrams sold divided by the number of milligrams per day of active duodenal ulcer therapy for that particular drug (in the case of Cytotec, which is not indicated for active DU therapy, we instead used the daily recommended doser for NSAID-induced ulcer prevention). Thus, continuing our earlier example, we would find that in our hypothetical month, there were sold:

$$(1{,}868{,}000\text{mg})/(800\text{mg/day}) = 233{,}500 \text{ patient-days of therapy.}$$

The number of milligrams per day of therapy used for our quantity conversions were as follows for each drug:

(Table A1 somewhere near here)

Defining our quantity unit to be the total number of milligrams divided by the standard dosage in milligrams per day is, unfortunately not without problems. First, the same drug may be used for slightly different therapies, and it may be taken in different dosages for the different purposes. For

example, Zantac may be prescribed at a dosage of 300mg per day (either 300mg once daily, or 150mg twice daily) for active duodenal ulcer, gastric ulcer, or GERD, but its recommended dosage for duodenal maintenance therapy is only 150mg per day, half of that required for the other therapies. Each of the H_2-antagonist s has a similar prescribing regimen for those four different indications. Therefore, our quantity measures are not literally the number of patient-days of therapy being consumed, but rather the number of patient-days of therapy which would be consumed of all of the sales were for treatment of active DU. Second, while we have assumed that the milligram dosage required for DU therapy remained constant over time, this was not the case for Tagamet. At the time of its introduction in 1977, the recommended dosage for DU therapy was 1200mg per day (300mg, for times daily), but subsequent experimentation showed that lower doses could be just as effective for ulcer healing, and by 1988 the recommended dosage was only 800mg per day (either 800mg once daily or 400mg twice daily). We have taken the approach that a milligram of Tagamet in 1977 is the same quantity as a milligram of Tagamet in 1990, despite the fact that people may have been consuming fewer milligrams on average in the later years for the same length of treatment. Since we have no way of knowing how many DU patients were taking 1200mg of Tagamet versus 800mg of Tagamet at any point in time (the choice between the two depended upon the vagaries of individual doctors' prescribing habits), we feel that we have chosen the most appropriate way to proceed.

A final modification which needed to be made to the sales data concerns the fact that the data collection from pharmaceutical warehouse invoices has, at different times during the sample, been rather lumpy. This problem introduces seasonal noise into the data, which can be eliminated by rescaling the sales and revenue figures. For purposes of rescaling, there are three distinct periods in our sample. Until December of 1980, the sales audit was actually conducted at a sample of pharmacies rather than at warehouses, and there was no lumpiness to the data, so no rescaling was required. From January 1981

of detailing in different periods).

A second change occurred in January 1993, when IMS significantly increased the breadth of coverage of detailing data. Under the newly created Integrated Promotional Services, there exist a wide variety of reports, including the Office Contact Report, which is the most directly related to the now-defunct National Detailing Audit. In the Office Contact Report, there are now reported many more *types* of details, including sample drops, educational visits, service visits, and telephone calls, than it did before, so the data on details and minutes are not easily comparable.

We were able to construct a measure of the number of details for 1993 which would be comparable to the pre-1993 years, by looking at the new breakdown of details into the various new IMS categories, and counting as details only those visits which were either "full discussion" details or "brief mention" details, which is what IMS considers to be the "traditional" details that doctors were intended to include in their reports for the NDA prior to 1993. Although similarly disaggregated information on minutes of detailing are not readily available in IMS's printed reports, we were able to match up 1993 on minutes of detailing with the pre-1993 data on minutes by special arrangement with IMS, who provided us with computer-generated reports from their database on the number of minutes of detailing in 1993 devoted to full discussions and brief mentions.

C. NATIONAL JOURNAL AUDIT (NJA)

In this audit, IMS performs a complete census of advertising in medical journals. They subscribe to every known medical journal and examine every advertisement in every issue of each journal. They note the number of whole and partial pages, the number of colors used in printing the ads, the location of the advertisement in the journal (for example, if it was found at the very front, or if it was printed on the back cover, in either case getting more exposure than an ad buried in the middle of the publication), and other attributes that affect the cost of placing an advertisement. Then, using standard rate sheets,

they compute the cost of each of the advertisements placed. Reported in the NJA monthly report are the total number of pages of advertising published for each product in that month (weighting all journals equally, regardless of circulation or professional influence), as well as the total estimated cost of all medical journal ads for that product.

We consider the cost figure to be the most accurate single measure of the amount of medical journal advertising done for a particular product, because (assuming that medical journal advertising is close to being a competitive industry), the prices of the ads reflect the reach of the advertisements, in terms of number of doctors reached, visual impact of the advertisement (through color, for example), etc. These cost figures are reported in nominal dollars, so to obtain a real measure of medical journal advertising effort, we deflate these series by the PPI for Advertising in Professional and Institutional Periodicals (BLS product code 2721-415).

As with the detailing data, the series we collected from the NJA include monthly series for each drug product in our sample, as well as monthly series on total monthly advertising for each manufacturer producing one of the products in our sample and the total monthly advertising by the pharmaceutical industry as a whole.

to December 1989, the data were apparently (according to the best information we could obtain from IMS, whose data specialists are not accustomed to answering questions about historical data) reported from warehouses on the bases of full weeks, so some months could contain four weeks of data, while others contained five. This causes large month-to-month variations in the sales data, which is obviously inappropriate for a detailed monthly analysis of the competitive effects of price and advertising on sales. A lengthy investigation has failed to reveal an appropriate way to rescale the data to correct for these fluctuations. (Based on conversations with IMS representatives, we tried several possibilities, such as rescaling the data by the number of Wednesdays in each month, but none turned out to be correct.) Thus our best approximation to the truth is that the sales data for this period of time contain a component of stochastic measurement error. In the third period of the sample, from January 1990 to the present, the number of reporting weeks per month were standardized so that the first four weeks of the year were designated as January, the next four weeks as February, the next five weeks as March, and repeated in a 4-4-5 pattern each quarter. (The single exception is December 1991, which for accounting purposes - there are not exactly 52 weeks in each year - was designated as a month of 6 weeks rather than 5.) To rescale the data for our purposes, we divided the IMS sales figures in each month from January 1990 to the end of the sample by the number of reporting weeks in that month, and then multiplied by 4.33 in order to retain the same normalization of physical units as in the original IMS data.

Finally, in order to transform the nominal prices from the IMS data into real prices, we deflated by the Consumer Price Index (1982-84 base years).

B. NATIONAL DETAILING AUDIT (NDA)

The National Detailing Audit (which as of 1993 has been subsumed by the Integrated Promotional Services, Office Contact Report) is a service that collects data from a nationwide panel of doctors about the visits which have bee paid to them by pharmaceutical sales representatives. The doctors participating

in the panel keep a log of the number of minutes they spend talking to detailers on each detail visit. If the detailer talks to the doctor about more than one product (for example, a Lilly detailer might discuss both Axid, an ulcer drug, and Ceclor, an antibiotic, with a family doctor), the physician makes an estimate of how many minutes were devoted to each product. From this panel, IMS then reports nationally projected estimates of the number of details and the number of minutes spent detailing each product, each month.

The detailing data series, unlike the sales data series, consist of only one observation per month, since detailing is performed at the level of the drug brand, rather than at the level of the presentational form. This fact made typographical errors much less of a problem than in the sales data, despite the fact that we had to manually enter the monthly detailing data for every month in the more than fifteen years of our sample. We collected monthly data on details and minutes for our seven drugs of interest, as well as for the total number of details and minutes done by each of the manufacturers producing these drugs (across all of their products) and for the total number of details and minutes in the entire U.S. pharmaceutical industry. These last two types of data are intended to be used as instruments for brand detailing, which is a potentially endogenous variable.

Beyond typographical errors, there were still some corrections to be made. In 1986, IMS expanded its panel of doctors from 1400 physicians reporting two weeks of every month to 2800 physicians reporting full months. Concurrently, they changed their projection methodology, and it turns out that a scaling factor of 0.74 must be applied to the data for all months prior to January 1986 in order to make it comparable to the data for January 1986 through December 1992. (In suggesting this scaling factor, IMS cautions that it is much more confident in its ability to measure the relative shares of detailing by different products than its ability to measure absolute levels. Nevertheless, we assume that after applying the recommended transformations, we can make reasonably accurate comparisons of the levels

TABLE A1

NUMBER OF MILLIGRAMS PER DAY OF THERAPY USED FOR QUANTITY CONVERSIONS

DRUG	MILLIGRAMS PER DAY OF THERAPY
TAGAMET	800
ZANTAC	300
PEPCID	40
AXID	300
PRILOSEC	20
CARAFATE	400
CYTOTEC	0.2

TABLE I

PARAMETER ESTIMATES IN THE TWO AND FOUR PRODUCT INDUSTRY MODELS

$$LNQ_t = \beta_0 + \beta_1 LNPR_t + \beta_2 LN\bar{D}_t + \beta_3 LN\bar{J}_t + \beta_4 GERD_t + \epsilon_t, \quad where$$

$$\bar{D}_t = D_{1,t} + \mu_2 D_{2,t} + \mu_3 D_{3,t} + \ldots + \mu_k D_{k,t} \; where$$

$$D_{i,t} = (1 - \delta) D_{k,t} + MIN_{k,t} \; and$$

$$\bar{J}_t = J_{1,t} + \mu_2 J_{2,t} + \mu_3 J_{3,t} + \ldots + \mu_k J_{k,t}, \; where$$

$$J_{i,t} = (1 - \delta) J_{k,t-1} + PAGES_{k,t}.$$

METHOD	NLS	NL-2SLS	NLS	NL-2SLS
MARKET	T-Z	T-Z	T-Z-P-A	T-Z-P-A
β_0	-6.574*	-5.165*	-7.291*	-7.110*
	(-0.46)	(-0.54)	(-0.58)	(-0.68)
β_1	-0.901*	-1.072*	-0.737*	-0.737*
	(-0.11)	(-0.14)	(-0.14)	(-0.20)
β_2	0.534*	0.413*	0.574*	0.574*
	(0.06)	(0.08)	(0.06)	(0.08)
β_3	0.210*	0.275*	0.166*	0.174*
	(0.06)	(0.08)	(0.06)	(0.07)
β_4	0.157*	0.164*	0.117*	0.118*
	(0.03)	(0.03)	(0.03)	(0.03)
μ_2	0.688*	0.892*	0.577*	0.600*
	(0.07)	(0.12)	(0.08)	(0.11)
μ_3			0.812*	0.848*
			(0.14)	(0.18)
μ_4			0.464*	0.491*
			(0.09)	(0.13)
δ	0.002	0.000	0.000	0.000
	(0.00)			
R^2	0.992	0.992	0.994	0.994
D-W	1.767	1.729	1.909	1.907
N	189	189	189	189

Note: T-Z: Tagamet-Zantac. T-Z-P-A: Tagamet-Zantac-Pepcid-Axid. Standard errors reported in parentheses.
* denotes significance at the 95 percent level.

TABLE II

PARAMETER ESTIMATES IN THE TWO AND FOUR PRODUCT MARKET SHARE MODELS

$$LN\left(\frac{Q_{jt}}{Q_{1t}}\right) = \beta_1 ENTRY_{jt} + \beta_2 LN\left(\frac{p_{jt}}{p_{1t}}\right) + \beta_3 LN\left(\frac{MIN_{jt}}{MIN_{1t}}\right) + \beta_4 DGERD_{jt}$$

$$+ \beta_5 LN\left(\frac{FREQ_{jt}}{FREQ_{1t}}\right) + \beta_6 LN\left(\frac{INT_{jt}}{INT_{1t}}\right) + \beta_7 AGE_{jt} + \epsilon_{jt}$$

METHOD	OLS	OLS	2SLS	2SLS	OLS	2SLS
MARKET	T-Z	T-Z	T-Z	T-Z	T-Z-P-A	T-Z-P-A
β_1	-0.054 (-0.17)	-0.116 (-0.17)	-0.147 (-0.20)	-0.181 (-0.17)	-0.492* (-0.01)	-0.507* (0.04)
β_2	-0.862* (0.24)	-0.840* (-0.24)	-0.885* (0.24)	-0.886* (-0.24)	-0.643* (-0.06)	-0.693* (-0.07)
β_3	1.003* (0.06)	0.950* (0.05)	0.922* (0.10)	0.893* (0.06)	0.731* (0.02)	0.673* (0.04)
β_4	0.087* (0.02)	0.085* (0.02)	0.093* (0.02)	0.094* (0.02)	0.032 (0.02)	0.046* (0.02)
β_5	-0.066 (-0.05)		-0.023 (0.06)			
β_6	-0.090* (-0.04)	-0.093* (-0.04)	-0.097* (-0.04)	-0.099* (-0.04)	-0.251* (0.02)	-0.232* (0.03)
β_7	0.010* (0.00)	0.010* (0.00)	0.011* (0.00)	0.011* (0.00)	0.012* (0.00)	0.013* (0.00)
δ	0.000	0.000	0.000	0.000	0.039* (0.00)	0.042* (0.01)
R^2	0.993	0.993	0.993	0.993	0.990	0.989
N	118	118	118	118	255	255

Note: T-Z: Tagamet-Zantac. T-Z-P-A: Tagamet-Zantac-Pepcid-Axid. Standard errors reported in parentheses.
* denotes significance at the 95 percent level.

Figure 1. Drug Store and Hospital Sales

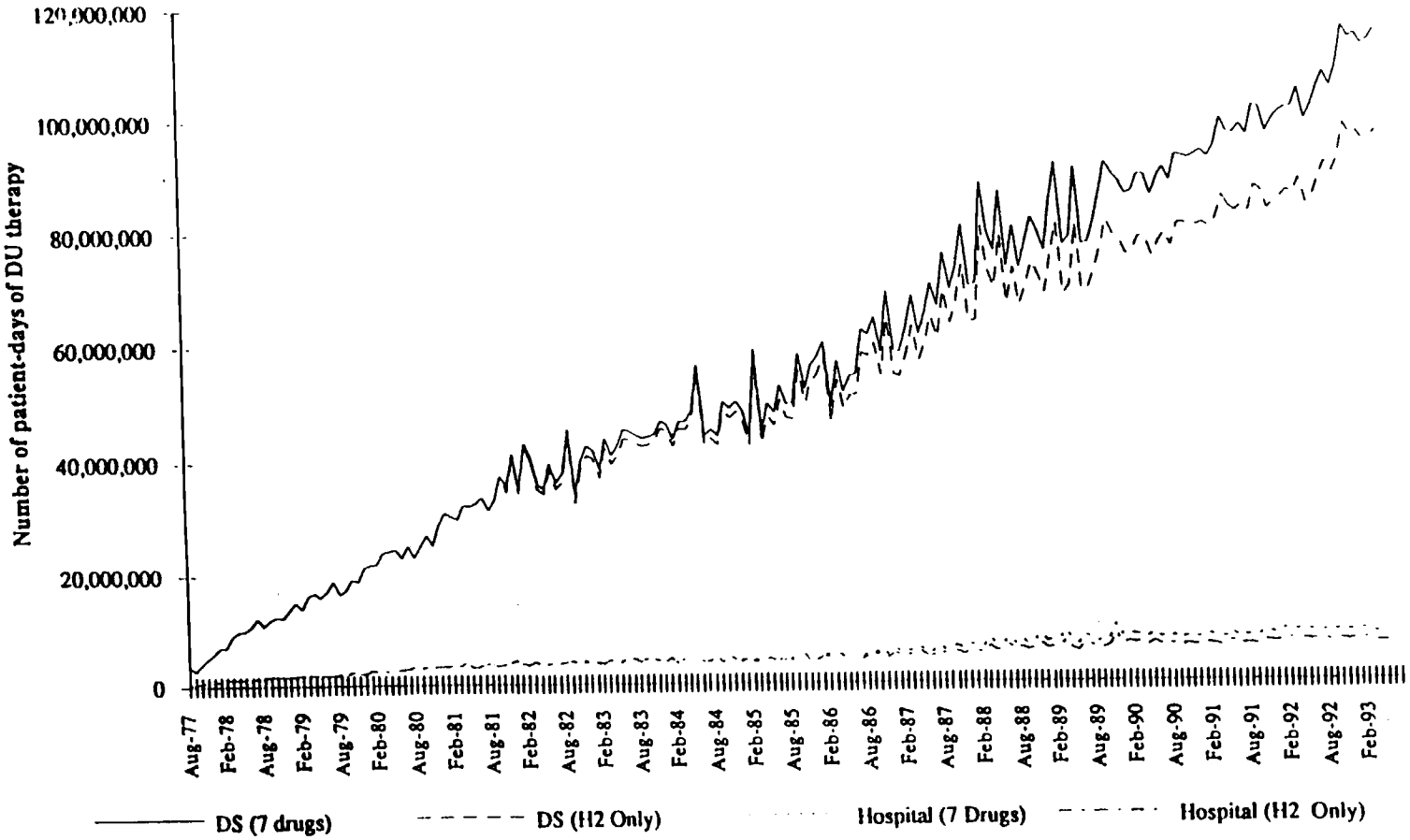

Figure 2. Drug Store Market Shares

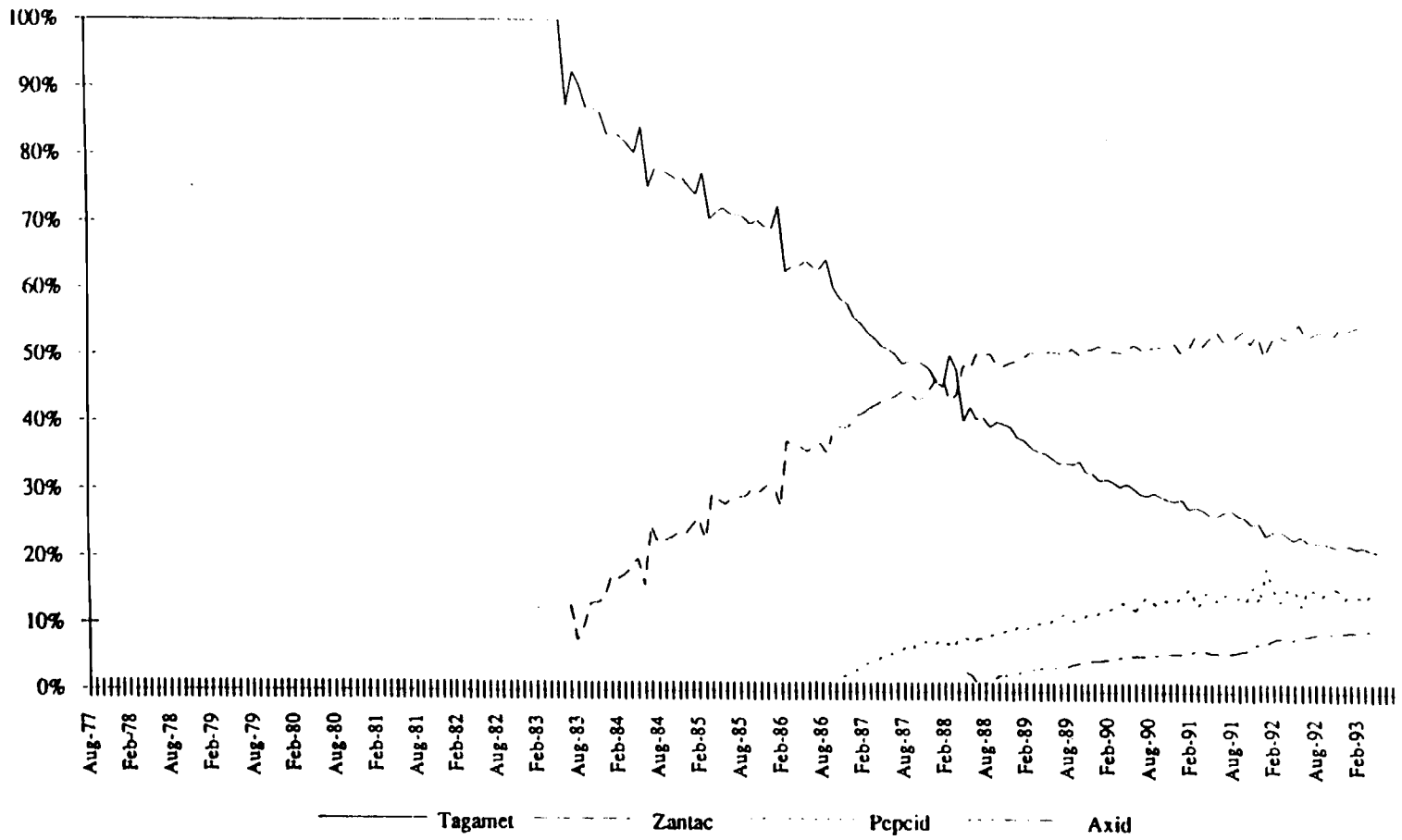

Figure 3. Drug Store Sales

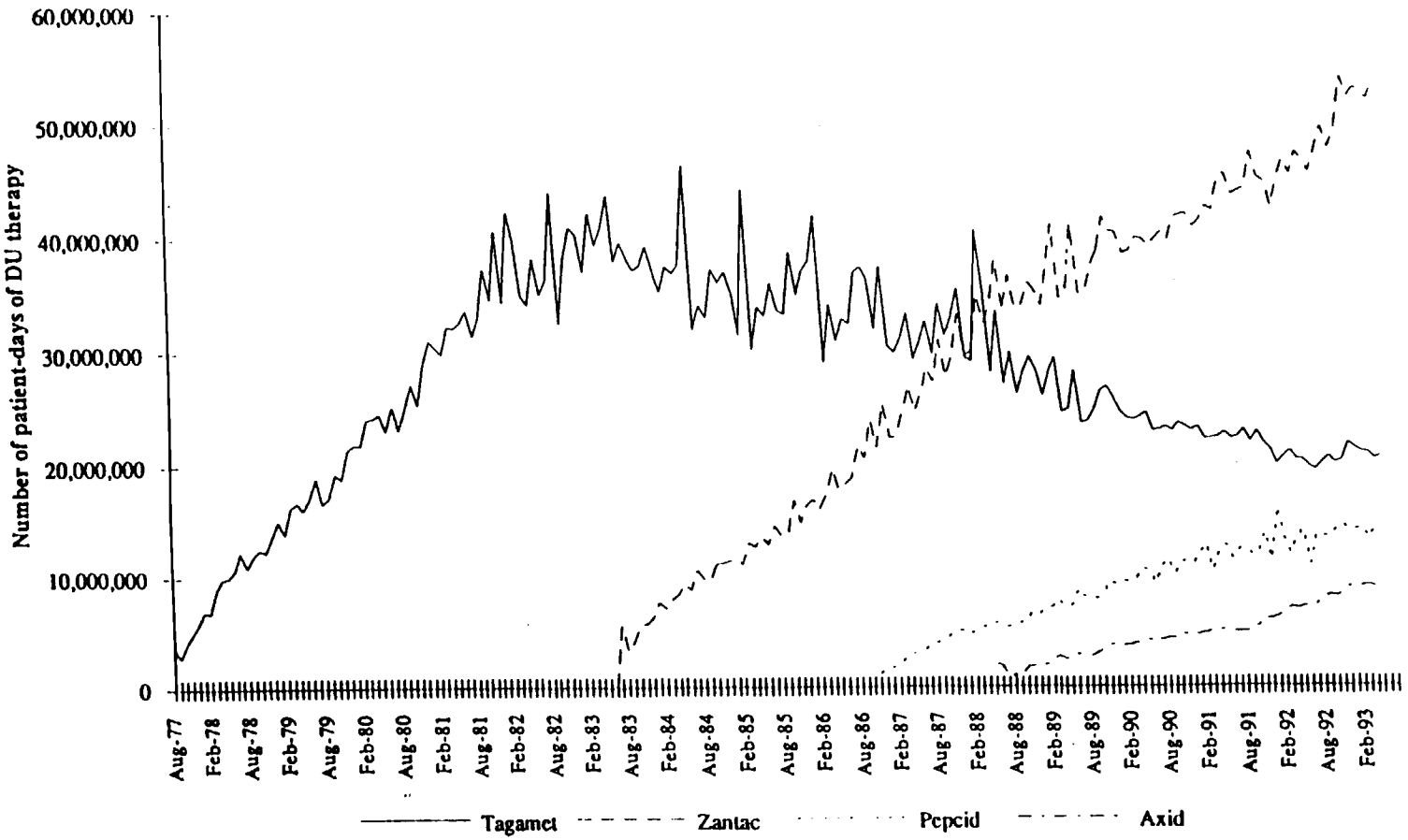

Figure 4. Real Drug Store Prices

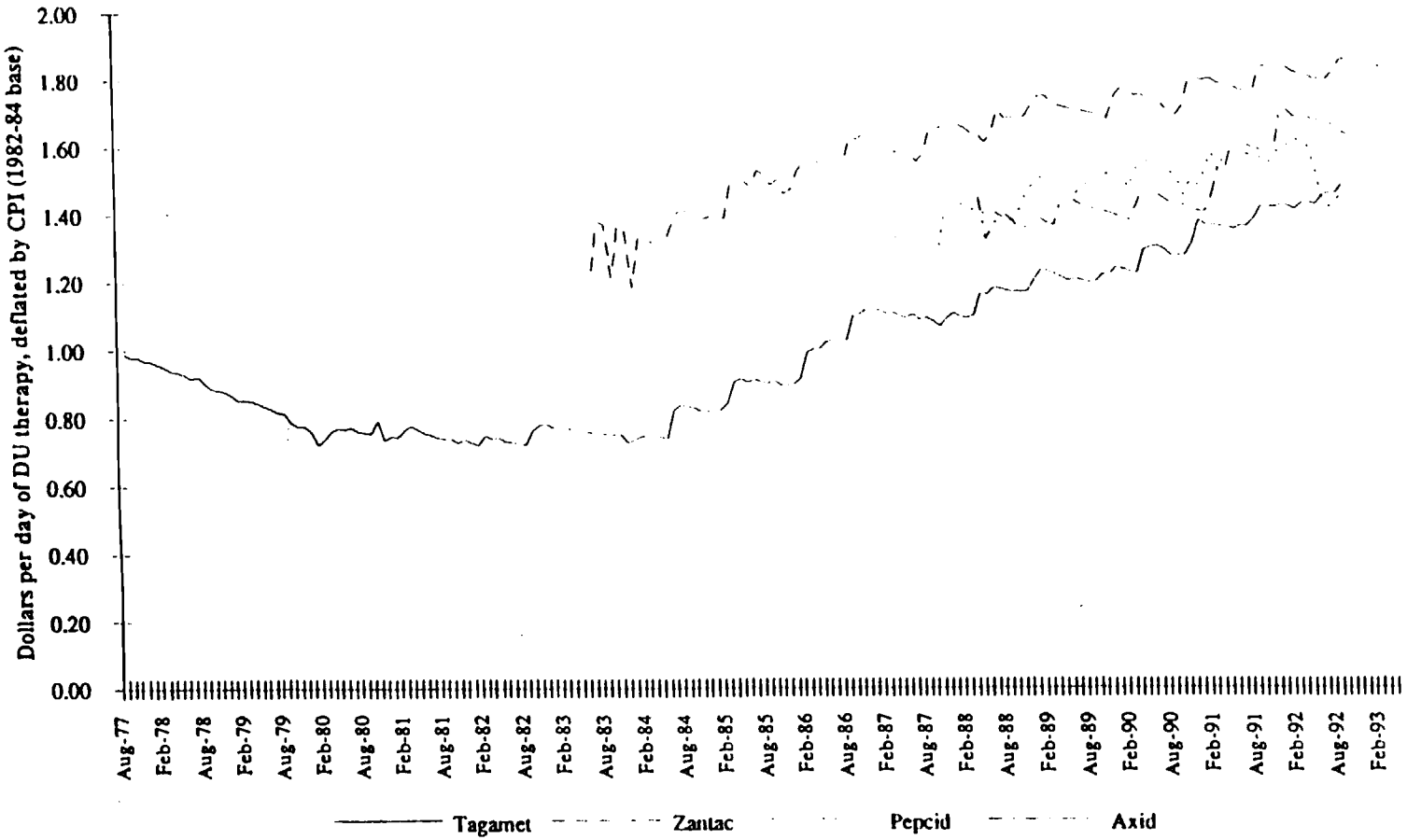

Figure 5. Tagamet and Zantac Minutes of Detailing

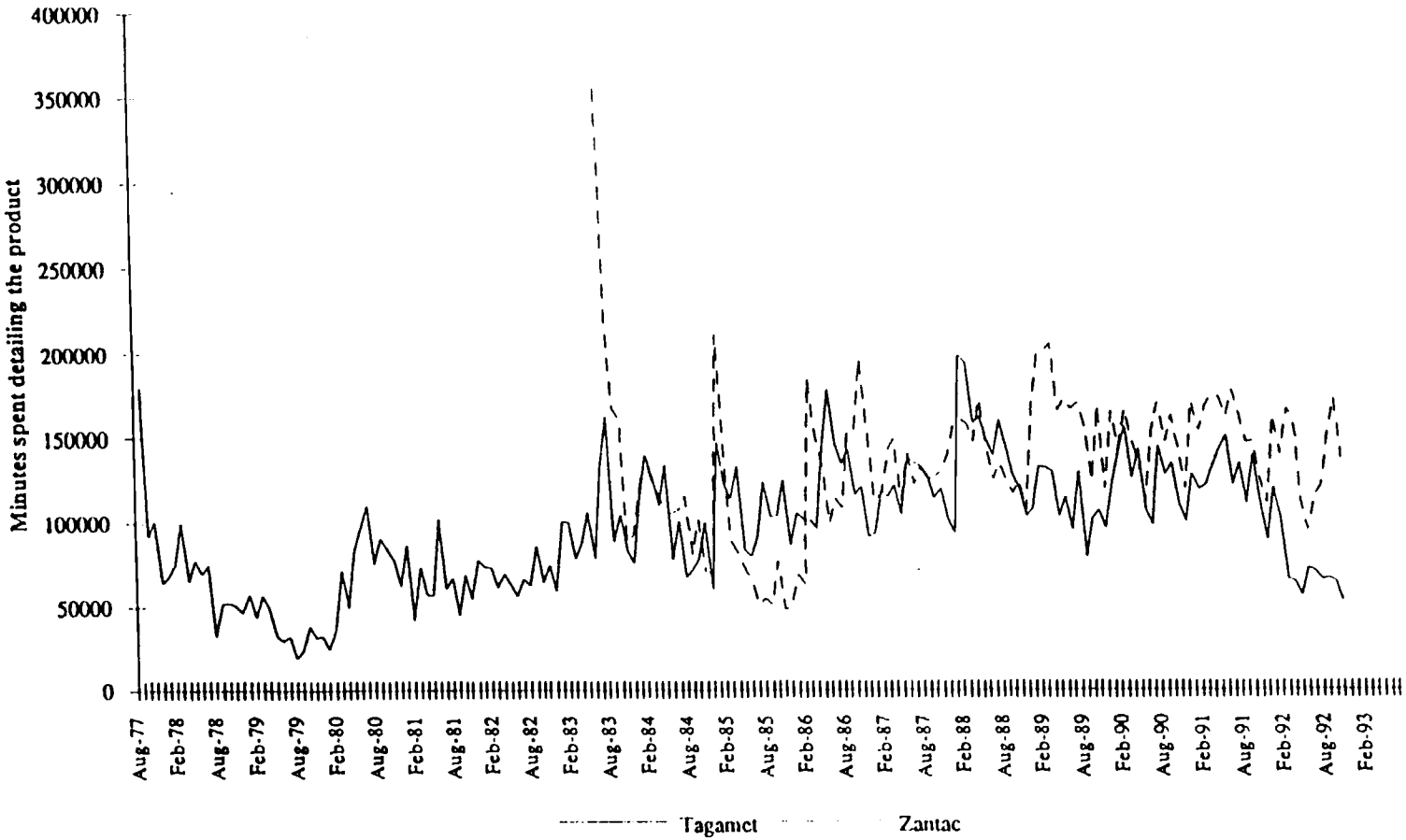

Figure 6. Cumulative Minutes of Detailing

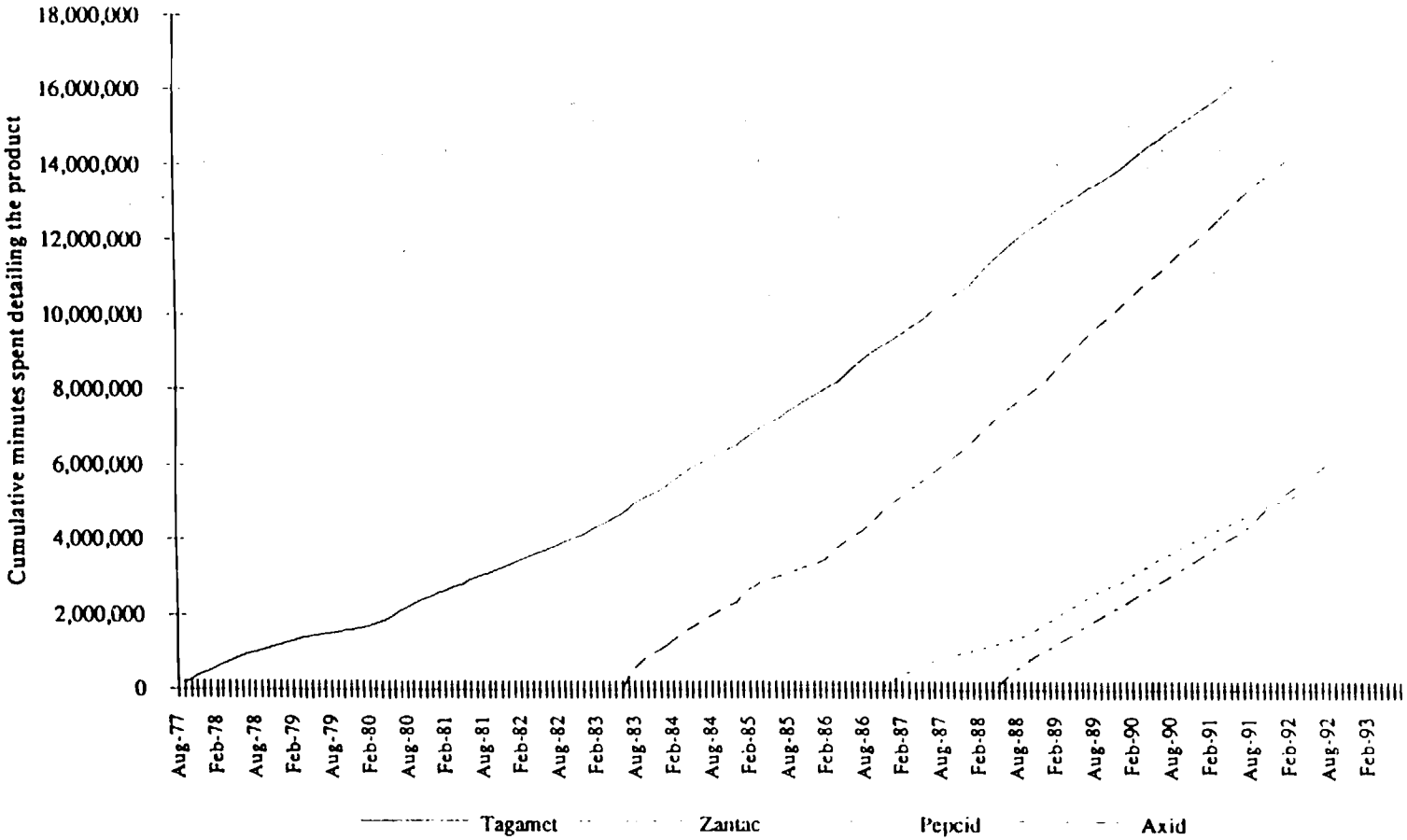

Figure 7. Cumulative Detailing/Sales Ratios

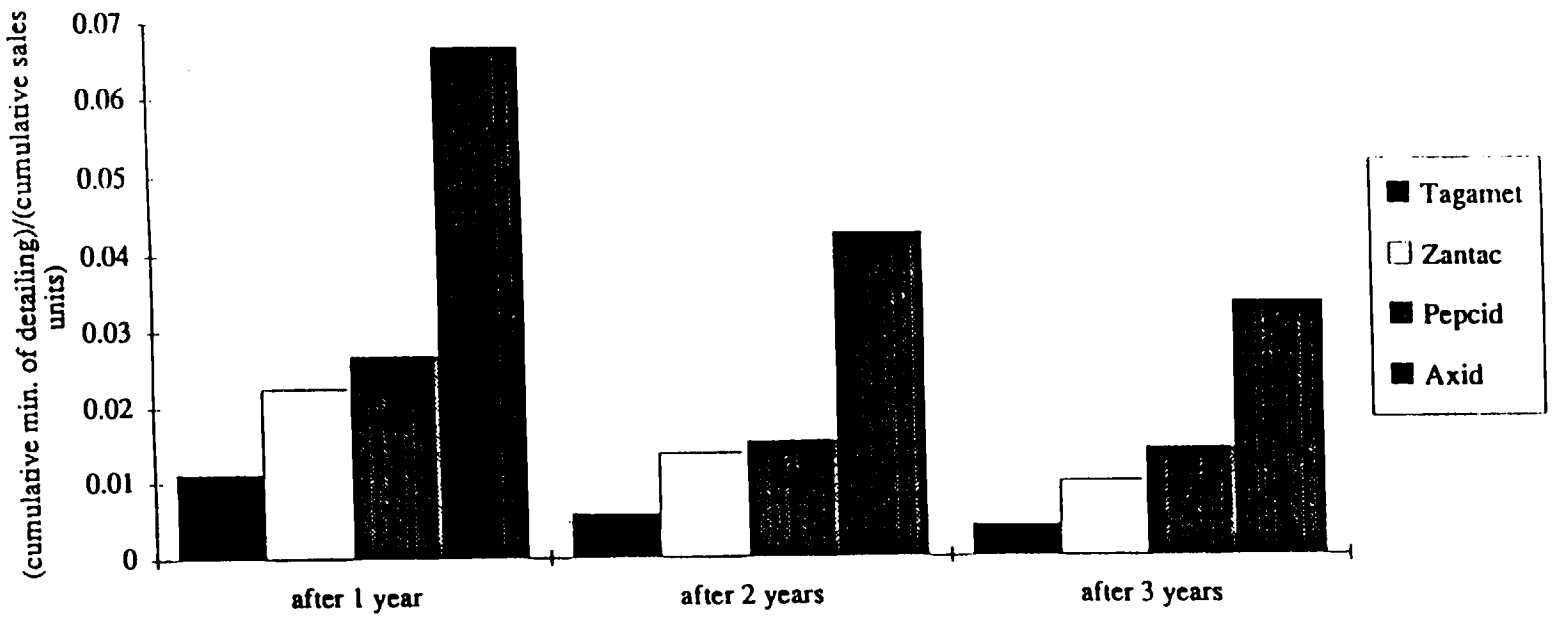

Figure 8. Cumulative Real Journal Advertising

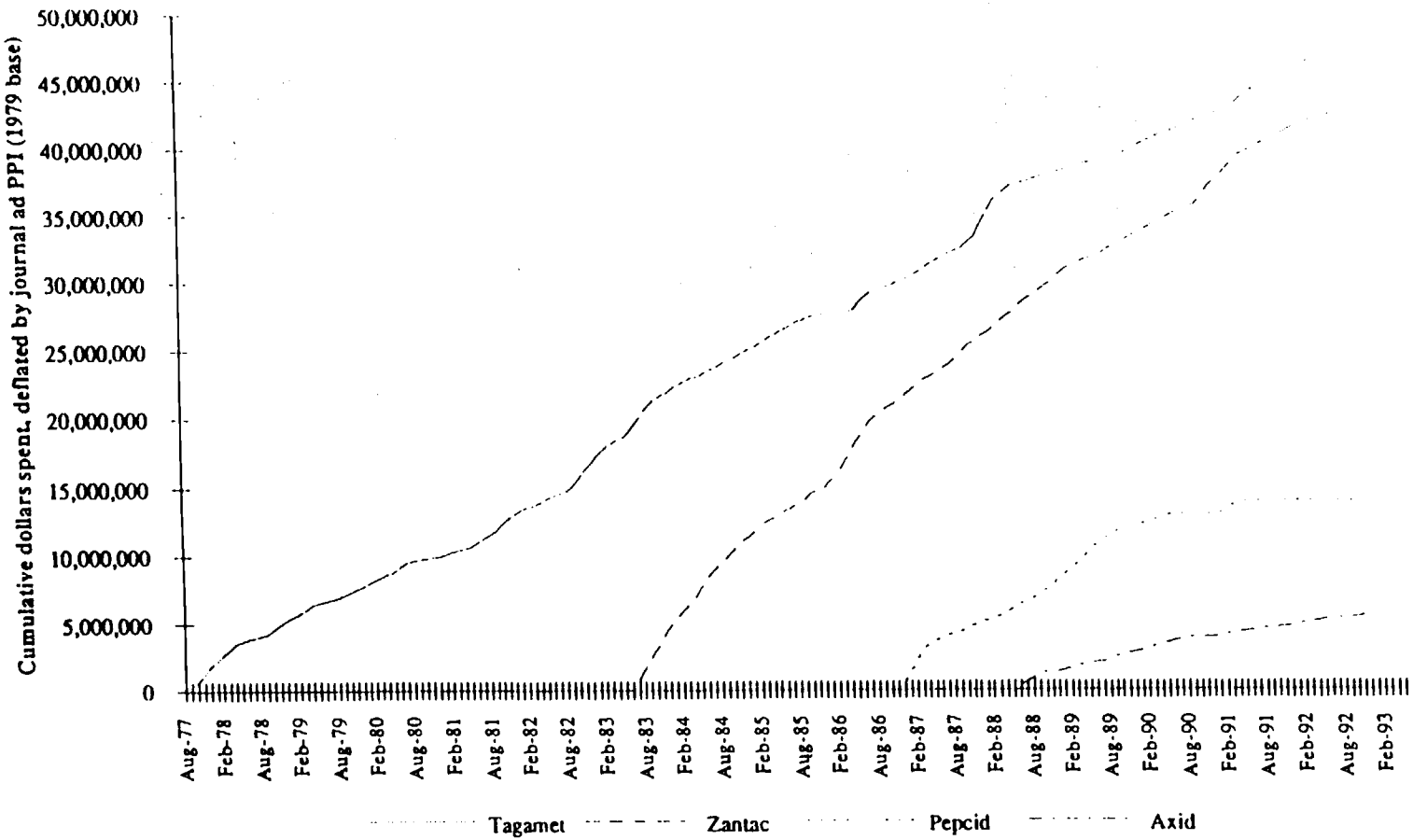

Figure A1. Tagamet Drug Store Sales