THE LONG SHADOW OF PATENT EXPIRATION:

GENERIC ENTRY AND RX TO OTC SWITCHES

by

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I. **INTRODUCTION**

In 2001 and 2002, a number of the US's best selling prescription pharmaceuticals -- Prilosec, Prozac, Pepcid, and Claritin, for example -- faced patent expiration. What should we expect to happen as these products approach the end of their patent product life cycle? Will switches from prescription to non-prescription over-the-counter (“Rx to OTC”) status occur, and if so, what will be their effects on average prices and utilization? Does the Rx to OTC switch significantly mitigate the effects of Rx patent expiration on branded pharmaceutical sales?

In this paper we address a number of issues surrounding the economic behavior of pioneer branded pharmaceutical firms facing Rx patent expiration and the consequences of generic Rx entry. We integrate retail scanner transactions data with wholesale sales records, and data on marketing efforts. We focus on three main sets of issues: (i) pricing and marketing strategies by branded pioneer drug manufacturers on their Rx drugs pre- and post-patent expiration; (ii) the impact of generic Rx entry on the price, utilization, and revenues of the Rx molecule post-patent expiration; and (iii) the effects of Rx to OTC switches on cannibalization of same-brand Rx sales, and on total (Rx plus OTC) brand sales. Although the first two sets of issues can be addressed using traditional data sources for pharmaceuticals, the third set of issues requires use of OTC data, data now available from scanned retail transactions.

To assess the more general impacts of generic Rx entry and Rx to OTC switches on prices and utilization, it is necessary to construct aggregate price indexes that incorporate these new good introductions. In this context, alternative ways of introducing new goods into price
indexes have been proposed by Feenstra [1994, 1997] and by Griliches and Cockburn [1994]. In this paper we compare these two price index approaches in terms of their data and modeling requirements, robustness of empirical results, and plausibility of empirical findings.

As best we can determine, the research we report here is the first systematic empirical examination of the interactions between Rx and OTC versions of "sunset" branded pharmaceuticals as they face Rx patent expiration.¹ In this study we focus on the US market segments for antiulcer and heartburn drugs, which are large and in the last decade have experienced both patent expiration and extensive OTC introductions. We examine how the various product life cycle forces have operated in this market segment over the last decade. Our research integrates data from various sources, such as prescription drug sales data from IMS Health, as well as scanner OTC retail transactions data from Information Resources Inc. (IRI).

II. BACKGROUND

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

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

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

The H₂s revolutionized medical treatments for gastrointestinal disorders. But they soon faced forces of creative destruction in the form of a new and sometimes superior generation of drugs for the treatment of ulcers and GERD, namely the proton pump inhibitors (PPIs).³ The more potent PPIs suppress acid secretion by directly inhibiting the acid producing pump system of the parietal cell, have very few side effects, and have convenient once-a-day dosing.

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

Although the H$_2$s provide effective treatments for many individuals, in some cases the PPIs are even better. For example, at the time of its obtaining initial marketing approval in May 1995, the manufacturer of Prevacid was permitted by the FDA to claim superiority over ranitidine (then the most prescribed H$_2$) for the treatment of heartburn.$^4$

With long-term safety issues settled, and superiority over the H$_2$s established, the PPIs were marketed intensively beginning in the mid-1990s. Remarkably, sales of the PPIs exceeded even those of the record-setting H$_2$s. By 1997, for example, Prilosec had overtaken Zantac as the US's (and the world's) largest revenue prescription drug, and by 1999, Prevacid ranked not far behind.$^5$

In addition to intense rivalry from the next generation PPIs, the H$_2$s also faced imminent loss of patent protection. Tagamet's patent was the first to expire on May 17, 1994, and after considerable litigation, Zantac's market exclusivity was terminated in late July 1997.

In this context, one specific provision of the Waxman-Hatch Act of 1984 was particularly important to the H$_2$ prescription drug manufacturers in the 1990s. This provision granted pioneer manufacturers an additional three years of limited market exclusivity, if they obtained FDA approval for a new presentation and indication for the chemical entity.$^6$ As early as a decade before its anticipated patent expiration, SmithKline discussed with the FDA the possibility of it seeking and gaining approval for an OTC version of Tagamet for the treatment of heartburn.$^7$ By timing the OTC launch to coincide approximately with the pioneer Rx patent expiration date, SmithKline could potentially benefit from an additional three years of market exclusivity on the OTC version of Tagamet, thereby offsetting somewhat its loss of post-patent expiration Rx sales.
Consumers, not just branded manufacturers, might also enjoy welfare gains from Rx to OTC switches. Specifically, provided the OTC drug is safe, consumers could benefit by having access to an effective medication without incurring the time and dollar costs of obtaining a physician's prescription (Rx).\(^8\)

This provision of the Waxman-Hatch Act created clear incentives for SmithKline, the manufacturer of the pioneer \(\text{H}_2\) Tagamet, to be the first to switch from Rx to OTC. But the later \(\text{H}_2\) Rx entrants (Zantac, Pepcid, and Axid) also had incentives to launch OTC versions of their Rx products, particularly if late OTC entry meant foregoing potentially large OTC sales. For the later Rx entrants, OTC entry could possibly occur even prior to their own Rx patent expiration. All \(\text{H}_2\) manufacturers realized that the order of exit from patent protection in the Rx market need not be the same as the order of entry into the OTC market, nor would first mover advantages in the Rx market necessarily transfer to the OTC environment.\(^9\)

Moreover, in implementing an Rx to OTC switch, pharmaceutical firms had to consider two possible offsetting forces. Branded Rx manufacturers needed to account for the possible cannibalization of sales of their branded Rx product that could result by introducing a same-brand OTC variant. On the other hand, positive spillovers could result from increased brand awareness when both OTC and Rx same-brand products were marketed simultaneously. Would positive spillover or negative cannibalization effects dominate?\(^{10}\)

Two of the four \(\text{H}_2\) brands (Tagamet and Zantac) lost patent protection in the 1990s, while the other two brands (Axid and Pepcid) lost patent protection in 2001. All four have implemented Rx to OTC switches. Thus the variation among the \(\text{H}_2\)s, and over time, should enable us to quantify the importance of the various factors affecting sales of these molecules. Moreover, Prilosec, currently the best-selling drug in the world is scheduled to lose U.S. market
exclusivity and face generic competition sometime in 2002, although ongoing litigation currently leaves the precise date of Prilosec patent expiration uncertain. Thus an examination of the recent historical record involving the $H_2$s could yield insights into what developments to expect in the market for the PPIs as patent protection ends, and possibly, as Rx to OTC switches occur for the PPIs as well.

The remainder of this chapter continues as follows. In Section III we review conceptual bases that provide hypotheses involving pricing and marketing as Rx brands face Rx generic competition. Then in Section IV we describe alternative methodologies for incorporating generic and OTC products (“new goods”) into various aggregate price indexes. In Section V we discuss data sources and the construction and interpretation of various price and quantity measures, first for prescription drugs, and then for OTCs. With this as background, in Section VI we present a number of stylistic facts that appear to characterize these markets in anticipation of and following Rx patent protection, and provide some preliminary evidence on our hypotheses. We discuss our price index results in Section VII. Finally, in Section VIII we summarize and conclude.

III. CONCEPTUAL FOUNDATIONS AND TESTABLE HYPOTHESES

The existing literature in economics and marketing provides a conceptual basis for a number of hypotheses. We first address pricing by branded Rx firms in response to generic competition. Frank and Salkever [1992,1997] demonstrate that under certain conditions, a profit-maximizing branded pioneer may not lower (and might even increase) price in response to generic competition. The branded firm must be able to segment its market into sets of brand-loyal consumers, who will continue to purchase the product, and price-sensitive consumers, who will migrate to the lower cost generics. Other things equal, the larger the brand-loyal segment
is relative to the price-sensitive segment, the greater the branded pioneer's post-patent expiration price. The magnitude and speed of the price response by the branded pioneer following patent expiration is, however, an empirical issue. We hypothesize that branded firms will not lower Rx prices following patent expiration.\textsuperscript{12}

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

\[
(1) \quad \frac{\text{Marketing}}{\text{Sales}} = \frac{\varepsilon_M}{|\varepsilon_P|},
\]

where $\varepsilon_M$ is the elasticity of demand with respect to marketing efforts, and $|\varepsilon_P|$ is the absolute value of the price elasticity of demand.\textsuperscript{13}

There is considerable evidence that early in the product life cycle pharmaceutical marketing efforts involving physician detailing and medical journal advertising provide long-lived benefits in the form of additional current and future sales, i.e., evidence suggests that up to the mature phase of the product life cycle $\varepsilon_M$ is positive and significant. Moreover, $\varepsilon_M$ is larger in the long run than over the short term. The substantial amount of marketing commonly observed at the time of initial product launch is of course consistent with large and long-lived sales impacts from such marketing efforts.\textsuperscript{14}

However, as patent expiration approaches, one expects that branded manufacturers anticipate a decline in $\varepsilon_M$, as lower-priced generic entrants could instead capture a large portion of sales from additional marketing. If true, branded manufacturers would reduce their current marketing-to-sales ratio in anticipation of patent expiration. Notice that if marketing efforts were
not long-lived, one might instead expect them to occur unabated until the day of patent
expiration. Once patent expiration actually occurs, not only would $\varepsilon_M$ likely fall further, but it is
also reasonable to expect that price competition would intensify, increasing $\varepsilon_P$, the denominator
of the right side of Eq. (1), and thereby further reducing the marketing-to-sales ratio. We
hypothesize, therefore, that the pioneer's marketing-to-sales ratio will fall as patent expiration
approaches, and may even approach zero after patent expiration occurs. Because any single
generic entrant finds it difficult to appropriate any sales benefits from marketing of the molecule,
for generic firms we expect $\varepsilon_M$ to be very small. The intense price competition among generics
implies a large $\varepsilon_P$. Hence, we hypothesize that generic manufacturers will have marketing-to-
sales ratios close to zero, where marketing efforts consist of physician detailing and medical
journal advertising.\(^{15}\)

IV. ALTERNATIVE PROCEDURES FOR INCORPORATING NEW GOODS INTO
PRICE INDEXES

For the purpose of assessing impacts of generic Rx entry and Rx-to-OTC new product
introductions, it is useful to construct price indexes aggregated up to the level of a molecule
(including both generic and brand Rx), and/or a brand level (including both Rx and OTC
versions). Theoretical and empirical discussions of alternative methodologies for constructing an
aggregate price index over generic and brand Rx drugs are found in Feenstra [1997] and in
Griliches-Cockburn [1994] (hereafter, GC).\(^{16}\) GC assume a uniform distribution of reservation
prices across heterogeneous consumers between the brand and generic prices at the time of
patent expiration, and thereby obtain an average reservation price midway between the brand and
generic price. Their price index method employs post-generic entry data only. Feenstra's
method involves inferring the elasticity of substitution from aggregate expenditure variations
pre- and post-patent expiration, and has the benefit of not requiring estimation of a reservation price. In this chapter, in addition to examining these issues in the more general context of Rx-to-OTC switches (not just brand-generic drugs after patent expiration), we will assess the sensitivity of alternative price index calculations to the choice of functional form, to the complexity of modeling requirements, and to the inclusion of non-price regressors.

Both the Feenstra and GC procedures are based on the economic theory of consumer demand. In the context of the Rx drug market, principal-agent issues involving physicians and patients, as well as moral hazard considerations resulting from the presence of insurance coverage, complicate matters considerably. Price comparisons between OTC and Rx versions of the same molecule are also more complex to interpret when the Rx version is covered by insurance whereas the OTC is not. Thus, although we make no attempt to incorporate such complications here, we caution that many of the traditional relationships between welfare calculations and price index movements are unlikely to hold in the Rx and OTC markets.

Following Feenstra’s notation, we denote total expenditures on a molecule by $E$, price by $P$, the change operator by $\Delta$, and the positive price elasticity of demand by $\eta$. Since $\Delta E = -(\eta - 1) \Delta P$, it follows that

$$\Delta P = -\Delta E / (\eta - 1),$$

where $\eta > 0$. Feenstra's insight is that if data on $\Delta E$ were available and if $\eta$ were known, then one could simply use Eq. (2) to obtain an estimate of $\Delta P$ consistent with consumer preferences, without requiring knowledge of the reservation price of the generic drug. Feenstra suggests estimating $\eta$ simultaneously with parameters of the price index $P$, as described below.

Assuming that different molecules are imperfect substitutes, Feenstra specifies a simple log-log demand equation for molecule $i$ having the form
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(3) \[ \ln Q_i^t = \alpha_i - \eta_i \ln P_i^t + \sum_{i \neq j} \beta_j \ln P_j^t + \delta_i \ln I^t + \epsilon_i^t, \]

for periods \( t=0, 1, \ldots, T \), where \( Q_i \) and \( P_i \) are quantity (in grams) and price per gram of the \( i \)th molecule, \( P_j \) is the price of imperfect substitutes for the \( i \)th molecule, \( I \) is total expenditures across the various molecules, and \( \epsilon_i \) is a random disturbance term. When \( i \) and \( j \) are substitutes, the \( \beta_j \) are positive. Also, as long as \( i \) is not an inferior good, we expect the \( \delta_i \) to be positive.

To incorporate brand-generic substitutability within a given molecule, Feenstra assumes the existence of a unit expenditure function that is weakly separable from other molecules (and other goods), and that is consistent with aggregation of tastes over heterogeneous consumers. When a constant-elasticity-of-substitution (CES) unit expenditure assumption is assumed (which can be derived from a linear random utility model where each consumer has differing additive utility over the varieties available), Feenstra shows that the exact price index in period \( t \) (after the generic is introduced) relative to time period 0 (just prior to the generic introduction) is

(4) \[ P_i^t = \left( \frac{p_{ib}^t}{p_{ig}^t} \right)^{1/(\sigma_i - 1)} \]

where \( p_{ib}^t \) is the per gram price of the branded version of molecule \( i \), \( s_{ig} \) is the revenue share of the generic, and \( \sigma_i \) is the elasticity of substitution between generic and branded versions of molecule \( i \), with \( \sigma_i > 1 \). The elasticity of substitution \( \sigma_i \) is obtained by estimating parameters in the equation

(5) \[ \ln \left( \frac{s_{ig}^t}{s_{ib}^t} \right) = \alpha_i + (\sigma_i - 1) \ln \left( \frac{p_{ib}^t}{p_{ig}^t} \right) + u_i^t \]

where \( s_{ib} \) is the brand revenue share, \( p_{ig} \) is the per gram price of the generic version of molecule \( i \), and \( u_i \) is a random disturbance term. Feenstra also derives estimating equations in the case of a
translog unit expenditure functional form. To save on space, we do not discuss translog forms further here; their extension is straightforward.

Notice that in order that the area above price but under the demand curve (consumers’ surplus) be finite, it is required that the \( \sigma_i \) elasticities of substitution between brand and generic versions of a molecule be greater than one. In the current context, since there are only two goods (brand and generic drugs) and quantity demanded is homogeneous of degree zero in prices, this elasticity of substitution restriction is tantamount to requiring demands to be own-price elastic. Intuitively, when the price of good \( i \) increases with \( p_j \) fixed, eventually as quantity demanded of good \( i \) approaches zero, the proportional decline in quantity of good \( i \) must be greater than its price increase, else the demand curve would not intersect the vertical price axis (the reservation price would not be finite). When \( \sigma_i > 1 \), the CES function satisfies this condition globally. However, if any of the elasticities of substitution \( \sigma_i \) are less than or equal to unity, at any positive price the amount of consumers’ surplus (and the reservation price) will be infinite. It is worth emphasizing that both the GC and Feenstra approaches to aggregate price index construction in the context of the introduction of a new good share this substitution elasticity constraint.

To implement the CES framework empirically, Feenstra substitutes Eq. (4) into Eq. (3), normalizes a "real" expenditure index relative to the price of the branded drug,

\[
\tilde{Q}_i = \frac{\frac{E_i}{E_i^0}}{\frac{p_{ib}^i}{p_{ib}^0}},
\]

and then obtains an estimating equation nonlinear in the parameters, of the form
\[
\ln \tilde{Q}_i' = \alpha_i - \eta_i \ln \frac{p_{ib}^i}{p_{ib}^0} + \left(\frac{1-\eta_i}{\sigma_i-1}\right) \ln \left(1-s^i_{ig}\right) + \\
\sum_{i\neq j} \beta_{ij} \left[\ln \frac{p_{jb}^j}{p_{jb}^0} + \frac{\ln \left(1-s^j_{ig}\right)}{\sigma_j-1}\right] + \delta_i \ln I' + \varepsilon_i',
\]

where \(i \neq j\). Notice that estimation of the within molecule and between molecule substitution elasticities is accomplished using data from both the pre- and post-generic entry time periods.

The alternative, simpler methodology suggested by GC is to estimate within-molecule brand-generic substitutability employing only post-generic entry data, using data on, for example, the CES revenue share Eq. (5). These elasticity estimates are then inserted into Eq. (4) to obtain exact price indexes.

Feenstra [1997] argues that his approach has two advantages over that of GC. First, it makes use of a longer time series of data, and second, it is more robust empirically to the choice of functional form when applied to monthly 1984:10-1990:9 U.S. data on two anti-infective drugs. We assess both procedures here in a rather different context -- the H2 market for two types of new goods, generic and OTC drugs, based on data primarily from the 1990s. Specifically, we first consider construction of aggregate price indexes with generic entry into the Rx H2 market, and then we aggregate further to consider the impacts of OTC entry in the total H2 market (Rx brand, Rx generic and OTC), using monthly 1989:1-1998:12 data.

A. Rx H2 MARKET ONLY, BRANDS, AND GENERIC ENTRY

Of the four molecules in the Rx H2 market, two (cimetidine and ranitidine) experienced generic entry during the 1989-1999 time period analyzed. We therefore specify two estimable equations embodying both within (brand-generic) and between molecule (cimetidine, ranitidine, Pepcid and Axid) substitutability, based on a CES unit expenditure function. We also experiment with introducing additional explanatory variables into the molecule demand
equations (e.g., marketing efforts), but only in a preliminary way, for an extensive demand analysis is beyond the scope of the current study.

The relatively simple equations take the form

\[
\ln \tilde{Q}_i = \alpha_i - \eta_i \ln \frac{p_{ib}^i}{p_{0b}^i} + \left( \frac{1 - \eta_i}{\sigma_i} \right) \ln(1 - \frac{s_{ig}^i}{s_{0g}^i}) + \beta_i \left[ \ln \frac{p_{jb}^i}{p_{0b}^i} + \frac{\ln(1 - s_{ig}^i)}{\sigma_j} \right] + 
\]

\[
\beta_{ik} \ln \left( \frac{p_{kb}^i}{p_{0b}^i} \right) + \beta_{il} \ln \left( \frac{p_{lb}^i}{p_{0b}^i} \right) + \delta_i \ln I^i + \varepsilon_i^i
\]

where \( i = \) cimetidine (brand name Tagamet) or ranitidine (brand name Zantac); \( j, k, \) and \( l \) denote the other H\(_2\)-antagonist molecules; and \( I^i \) is total expenditures on all four molecules (both brand and generic, where applicable).

Assuming a CES unit expenditure assumption, for the GC framework the two estimating equations have the considerably simpler form:

\[
\ln \left( \frac{s_{ig}^i}{s_{0g}^i} \right) = \alpha_i + (\sigma_i - 1) \ln \left( \frac{p_{ib}^i}{p_{ig}^i} \right) + u_i^i
\]

where \( i = \) cimetidine or ranitidine, \( b \) refers to the Rx brand, and \( g \) refers to the Rx generic. Although in principle Eqn. (8) could be generalized to incorporate data on relative brand-generic marketing efforts, in fact generics’ traditional marketing efforts are essentially zero.

**B. TOTAL H\(_2\) MARKET WITH OTC ENTRY**

The exact price indexes obtained for the cimetidine and ranitidine Rx H\(_2\) molecules can now be employed in a larger context in which aggregate molecule price indexes are constructed consistent with imperfect substitutability between OTC and Rx versions of the same H\(_2\) molecule. Recall that during our 1989-99 sample period, all four H\(_2\) Rx drugs implemented same-brand introductions of OTC versions.

With a CES unit expenditure function defined over Rx and OTC versions of the same H\(_2\)
molecule in the Feenstra approach, the four estimating equations take the form

\[ \ln \tilde{Q}_i = \alpha_i - \eta_i \frac{p_{ir}^i}{p_{ir}} \left[ \frac{1}{\sigma_i} - 1 \right] \ln (1 - \sigma_i) + \sum_{j \neq i} \beta_{ij} \left[ \ln \frac{p_{jr}^j}{p_{jr}^0} + \ln \left( \frac{1 - s_{jc}^j}{s_{jc}^j} \right) \right] + \delta_i \ln I_{rc} + \epsilon_i. \]

Here, \( p_{ir} \) is the estimated price index of the Rx version of the molecule i (as calculated in Section V-A below) when \( i= \) cimetidine or ranitidine, but \( p_{ir} \) is the price index of the branded Rx version of molecule i when \( i= \) Pepcid or Axid, since Rx Pepcid and Rx Axid did not lose patent protection and thus did not face generic entry during the 1989-98 time period of our study. \( s_{ic} \) is the revenue share of the OTC version of the molecule i, and in this broader context \( \sigma_i \) is the elasticity of substitution between Rx and OTC versions of molecule i, \( \sigma_i > 1 \). The index j denotes the imperfect substitutes for molecule i. Hence, \( p_{jr} \) is the estimated price index of the Rx version of the molecule j, as calculated in Section V-A below, when \( j= \) cimetidine or ranitidine. But \( p_{ir} \) is the price index of the branded Rx version of molecule j if \( j= \) Pepcid or Axid. \( s_{jc} \) is the revenue share of the OTC version of molecule j, and \( \sigma_j \) is the elasticity of substitution between Rx and OTC versions of molecule j. \( I_{rc} \) is the total expenditure across the Rx and OTC versions of the molecules, and \( \epsilon_i \) is a random disturbance term. These four equations are nonlinear in the parameters and contain numerous cross-equation restrictions.

With the GC approach based on the CES unit expenditure function, the four estimating equations take the relatively simple form:

\[ \ln \left( \frac{s_{ic}^i}{s_{ir}^i} \right) = \alpha_i + (\sigma_i - 1) \ln \left( \frac{p_{ir}^i}{p_{ic}^i} \right) + u_i, \]

where the notation is the same as above. Below we undertake empirical analyses of Eqns. (9) and (10), adding measures of relative cumulative marketing efforts as additional demand-shifters.
V. DATA SOURCES, DESCRIPTIONS AND INTERPRETATIONS

Our framework requires integrating data from a number of diverse sources, which we now briefly summarize. We begin with prescription drugs, and then discuss the OTCs.

A. PRESCRIPTION DRUG MARKETS

Quantity shipped, revenue, and marketing data for antiulcer and heartburn prescription drugs are taken from IMS Health, monthly from January 1988 through June 1999. IMS' Retail Perspective™ tracks monthly shipments from manufacturers and wholesalers to retail warehouses and outlets. The data on revenues includes those to manufacturers and wholesalers, but not to the retail outlets (who add retail margins). Although revenues are net of chargebacks (discounts given purchasers and channeled through wholesalers), rebates (payments made to providers who often do not take title to the pharmaceuticals, e.g., managed care organizations) are not included in the IMS revenue data, nor are prompt payment discounts. The exclusion of rebates from the revenue data implies an overstatement of manufacturers’ Rx revenues and prices. The extent of this bias is unknown, for data on rebates tend to be highly proprietary. In spite of this drawback in the IMS data, however, most branded and generic pharmaceutical companies purchase and utilize the IMS data for their internal research. Industry officials have indicated to us that while the absolute prices and revenues are likely to be upward biased, there is no reason to believe any bias carries over to relative prices and revenues.

Quantity shipped and revenue information is at the level of presentation, e.g., 30 tablet bottles of 150 milligram (mg) strength tablets. We convert these presentational sales measures into quantity or unit data by using the recommended daily dosage for active duodenal ulcer treatment as the transformation factor. The resulting quantity data can then be interpreted as the hypothetical patient days of therapy per month were all patients taking the recommended active
duodenal ulcer daily dosage.\textsuperscript{17} Data on recommended daily dosages are taken from Physicians' Desk Reference \cite{2000}. Price per day of therapy is then computed as revenues divided by the quantity of therapy days in that month. Further details on price, quantity, and revenue measurement are found in the Data Appendix of Berndt, Bui, Lucking-Reiley and Urban \cite{1997}.

The price and quantity data we employ only cover sales into drug stores. Drug store sales constitute on average about 70-80\% of sales in all outlets, but exclude sales to hospitals, long-term care facilities, and mail order distributors.\textsuperscript{18} Since hospital usage and marketing differ considerably from the outpatient environment, we confine our attention here to transactions occurring in the traditional retail sector.

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

Medical journal advertising pages and expenditures are estimated by IMS in their National Journal Audit\textsuperscript{™}. This audit includes journal pharmaceutical advertising directed to practitioners in all types of medical practice, including pharmacists, nurses, podiatrists, and dentists, as well as medical and osteopathic practitioners. Based on circulation, the number of square inches, pages of advertisements, copy characteristics such as premium positioning and the number of colors in each advertisement, IMS uses standard rate sheets from over 300 major medical journals to estimate total dollars of journal advertising, monthly, by drug. Further details on these marketing measures can be found in the Data Appendix of Berndt, Bui, Lucking-
Reiley and Urban [1997], and in IMS Health [1998].

The Rx H\textsubscript{2} antagonists have been marketed not only to physicians, but also more directly to consumers (DTC). In the context of Rx to OTC switches, DTC marketing of Rx products permits manufacturers to build up consumer brand awareness in anticipation of the future launch of OTC variants. In the mid-1980s Tagamet Rx had a "Tommy Tummy" direct to consumer (DTC) marketing campaign, and later in the early 1990s Glaxo launched an extensive TV and print DTC campaign for Zantac. In 1997 the FDA clarified regulations on the content of DTC ads. Increases in DTC marketing of Rx drugs have been steady during the 1990s.\textsuperscript{19}

Data on DTC marketing of Rx brands from Leading National Advertisers (LNA)/Media Watch Multi-Media Service is published on a quarterly basis by Competitive Media Reporting. This service reports Rx brand advertising expenditure estimates in ten major media: consumer magazines, Sunday magazines, newspapers, outdoor, network television, spot television, syndicated television, cable television, network radio, and national spot radio. The LNA/Media Watch Multi-Media Service includes only brands of companies spending a total of $25,000 or more year-to-date in the ten media measured. The data we employ are taken from Class D21X, which reports advertising expenditures by company, and then lists brands for each company. Currently our DTC data are available only through 1998Q4. To transform the quarterly data into monthly periodicity, we employ the STATA command "ipolate".\textsuperscript{20} The monthly expenditure data are then deflated by the Bureau of Labor Statistics' Advertising Agency Producer Price Index to convert them into constant-dollar figures.\textsuperscript{21}

B. OVER-THE-COUNTER DRUG MARKETS

Quantity and revenue data for the OTC H\textsubscript{2} market are taken from InfoScan\textsuperscript{TM}, based on store-level optical scanner data purchased and collected from multiple retail outlets by
Information Resources, Inc. (IRI). These scanner data are collected weekly from more than 29,000 chain drug stores, mass merchandisers, food stores, and chain convenience stores located in major metropolitan areas and rural areas. They are then projected to national levels for these chains. The IRI data provide detailed information on sales, pricing, and promotion on a stock-keeping unit basis. The volume of sales is recorded for each package size of each brand on an average weekly basis. The weekly data is aggregated to the monthly level.

To establish comparable units of consumption for Rx and OTC products, we aggregate the data for each OTC brand across presentations and regional outlets so that the quantity measure reflects the total milligrams sold each month nationally. For instance, if 5,000 packages of Tagamet HB each with 25 tablets of 200 mg cimetidine are sold, we compute the total number of mg of Tagamet HB sold that month as $5000 \cdot 25 \cdot 200 = 25$ million mg. Unlike the IMS Health data on Rx sales to drug stores, the IRI data record sales from drug stores, mass merchandisers and foodstores to consumers, so the IRI data include both wholesale and retail margins. Moreover, while the IMS data reflect inventory stocking behavior by, for example, chain drug store warehouses, the IRI data only include actual transactions to final consumers.

To make the quantity units of the various OTC H$_2$ brands comparable with each other, we normalize the total number of milligrams per brand sold each month by the daily dosage recommended to treat active duodenal ulcers. Although we describe our quantity measure as patient days of therapy, in fact this is not literally true. Both the Rx and OTC versions are used for the treatment of a number of related disorders, often at varying dosages, and by individuals having different body masses. Rather, the quantity measures should be interpreted as the number of patient days of therapy that would be consumed were all the OTC H$_2$s used for the treatment of active duodenal ulcers at recommended Rx dosages. It is worth emphasizing that
we do not wish to imply or suggest here that any or all patients actually (mis)use the OTC H$_2$s to treat active duodenal ulcers.$^{25}$ We make this transformation solely for the purpose of standardizing units of active ingredient.

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

OTC medications have been marketed intensively to consumers. For example, between 1990-1996 for the seven largest-selling antacid OTC products in 1994, the median real advertising to retail sales ratio was approximately 34%.$^{26}$ To obtain measures of monthly advertising of the OTC H$_2$s, we employ data from Leading National Advertisers/Media Watch Multi-Media Service. LNA distinguishes consumer-oriented OTC brand advertising from that for Rx brands. Quarterly data on media advertising over the ten media mentioned earlier for the H$_2$ OTC brands are taken from Class D213, Over-the-counter Digestive Aids and Antacids. Currently these data are only available to us through 1998Q4. The "ipolate" command in STATA is again employed to convert expenditure data from quarterly to monthly. Monthly advertising expenditures in current dollars are then deflated by the BLS' Producer Price Index for Advertising Agencies, as discussed above.

VI. OBSERVED PATTERNS NEAR THE END OF THE PATENTED PRODUCT LIFE CYCLE

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

We now turn to a description and preliminary analysis of marketing and pricing developments as the Rx H$_2$ manufacturers anticipated and accommodated loss of patent
protection of their own products or those of their competitors. We also examine the impacts of the pre-emptive launch of OTC H₂ variants and the effects of competition from generic Rx H₂ producers.

A. MARKETING INTENSITY NEAR PATENT EXPIRATION

We begin by examining how branded pioneer firms changed their marketing behavior in anticipation of, and following loss of patent protection. To assess the hypotheses advanced in Section III, we examine marketing efforts for the two H₂-antagonists losing patent expiration, Tagamet (May 1994) and Zantac (August 1997). We compare average marketing efforts when the date of patent expiration is quite some time away (between 25 and 48 months ahead), as it becomes much closer (between 1 and 24 months ahead), and has passed (0 to 23 months after). For each time frame, we compute average monthly minutes of detailing and average journal pages, as well as the Dorfman-Steiner dollar ratio of average marketing expenditures to average sales revenues. Differences between the 1 - 24 vs. 25 - 48 months prior to patent expiration periods are called "near vs. far away", while those between 0 - 23 months after vs. 25 - 48 months before are called "after vs. far away". The results of these calculations are given in Table 1, the top panel in terms of marketing quantity levels, and the bottom in dollar marketing to sales ratios.

For Tagamet, average monthly minutes of detailing fell by 30% as its patent expiration approached (May 1992 - April 1994 vs. May 1990 - April 1992), and by 87% following its patent expiration in May 1994 (May 1994 - April 1996 vs. May 1990 - April 1992). Journal page advertising fell even more sharply, by 55% and 97%, respectively. The total marketing (detailing plus medical journal advertising) expenditures to total sales revenue ratio (bottom two rows of Table 1) fell by 43% as Tagamet patent expiration approached, and then subsequently by
a smaller amount, -30%, after patent expiration. The post-patent smaller decline in the ratio reflects in part the sharp decrease in the denominator – brand revenues – after patent expiration.

For Zantac, the decline in marketing efforts was even more dramatic. Average monthly minutes of detailing fell by 59% as Zantac patent expiration approached (August 1995 - July 1997 vs. August 1993 - July 1995), and by 94% following Zantac patent expiration in August 1997 (August 1997 - July 1999 vs. August 1995 - July 1997). As with Tagamet, journal page advertising fell even more sharply than detailing minutes, at 99% and 100%, respectively. The total marketing-to-sales ratio fell by almost 60%, and by an additional 13% after patent expiration.

It is also of interest to examine how the competitors of Zantac, then the leading selling H₂, reacted when they observed Zantac cutting back on marketing in anticipation of and following Zantac’s patent expiration. Since the entire H₂ prescription drug market was in decline during this time due to competition from the more potent PPIs and the introduction of OTC versions that potentially cannibalized H₂ Rx sales, would Pepcid and Axid Rx also cut back on marketing efforts? Or would they capitalize on a strategic opportunity to fill a void created by the dramatic cutbacks by Tagamet and Zantac, and instead increase their marketing efforts?28 The marketing responses of Pepcid and Axid surrounding the time of Zantac's patent expiration are summarized in the last two columns of Table 1.

Pepcid and Axid had rather different responses. For Axid, average minutes of detailing fell by about 36% as Zantac's patent expiration approached, and they fell another 13% following expiration. The journal advertising cutback was more varied: -16% as Zantac's patent expiration approached and -95% following it. For Pepcid, however, the decline in minutes of detailing was much more modest -- only 20% in the time leading up to Zantac patent expiration, and an
additional 8% following it. Journal page advertising for Pepcid actually increased by 258% (from rather low levels) as Zantac patent expiration approached, and after patent expiration fell to 16% less than that 25 – 48 months before Zantac patent expiration occurred. Though the responses of Pepcid and Axid as Zantac cut back on its levels of marketing efforts differed, they were quite similar in terms of total marketing-to-sales ratios. Both reduced these ratios by about 33-36% as Zantac patent expiration approached, and then maintained them at approximately those values after Zantac’s patent expiration.

Finally, IMS data indicate zero recorded detailing efforts by generic manufacturers. However, for about 12-18 months following patent expiration, generic manufacturers of cimetidine and ranitidine did a very modest amount of medical journal advertising.\(^\text{29}\) While the generic firms' medical journal advertisements announced the new availability of cimetidine or ranitidine, frequently these ads also noted the portfolio of other generic products offered by the manufacturer rather than focusing on their specific H\(_2\) products.

**B. PRICING OF RX DRUGS IN ANTICIPATION OF AND FOLLOWING PATENT EXPIRATION**

Next we analyze pricing behavior prior to and following patent expiration. Figure 1 plots prices per day of therapy for Rx Tagamet and generic Rx cimetidine from January 1988 through December 1998, while Figure 2 presents those for Rx Zantac and generic Rx ranitidine over the same period. Both figures include the average price per day of therapy over all Rx and OTC forms for each molecule ("Total Molecule") and the average price over branded Rx and generic Rx ("Total Rx"). All prices are in current (not deflated) dollars.

As is seen in Figure 1, Tagamet's Rx price continued to increase following patent expiration in May 1994, and by June 1999 it was about 10% greater than five years earlier when
it lost patent protection. The price of generic cimetidine has fallen considerably since 1994, but has remained fairly constant since about mid-1997. By mid-1999, the Tagamet Rx brand price was about eight times that of generic Rx cimetidine. Instead of meeting price competition from the generics, Tagamet Rx maintained and even slightly increased its price.

Patent expiration provided considerable benefits for cimetidine consumers who switched to generic versions. In particular, the total Rx price of cimetidine (a sales-weighted average over Tagamet Rx and generic cimetidine Rx) has fallen to about 20% of its level at the time of patent expiration in May 1994. The total Rx price at mid-1999 was about a sixth that of the Tagamet Rx brand price.

Figure 2 presents the comparable price paths for Zantac Rx and generic Rx ranitidine. Following loss of market exclusivity in July 1997, the Zantac brand price increased steadily, and by mid-1999 it was about 20% higher than at patent expiration. The rate of price decline for generic ranitidine immediately following patent expiration appears to be greater than that of cimetidine (compare Figures 1 and 2). This difference could reflect greater entry incentives for ranitidine since at the time of patent expiration, the branded Zantac Rx was a larger dollar and unit sales market than was branded Tagamet Rx. In June 1999 the price of generic ranitidine was about a quarter that of Zantac at the time of its patent expiration, and a fifth of the current Zantac price. Zantac pricing in the post-patent expiration era does not appear to differ in any dramatic way from the patent-protected time period, although its prices have increased more sharply than has Tagamet Rx post-patent expiration.

Just as with cimetidine, consumers have realized far lower average prices for ranitidine following Zantac’s patent expiration. By mid-1999 the average ranitidine Rx price (a sales-weighted average over Zantac Rx and generic ranitidine Rx) was about 65% lower than it was at
the time of Zantac patent expiration in July 1997.

In summary, neither Tagamet Rx nor Zantac Rx adopted a policy of competing with generics on price following patent expiration, and instead increased prices. As a consequence they lost very substantial market share, but retained sales to a small, relatively price-insensitive segment of brand-loyal customers.

C. MOLECULE RX VOLUME BEFORE AND AFTER PATENT EXPIRATION

Next we examine quantity (patient days of Rx therapy) data for cimetidine and ranitidine before and after patent expiration. For branded Tagamet, as seen in Figure 3, sales were relatively flat during the four years preceding patent expiration in May 1994, but plummeted afterwards as generic entrants flourished. By mid-1999, generic cimetidine had more than 95% market share of the prescription cimetidine market. Total quantity of brand plus generic Rx cimetidine sales (labeled "Total Rx" in Figure 3) has shrunk by about one third since Tagamet lost patent protection, even though the average price per day of therapy for the Rx cimetidine molecule (over its brand and generic Rx versions) declined precipitously (see Figure 1). This cimetidine Rx sales decline reflects the combined impacts of new competition from generic ranitidine following Zantac Rx patent expiration, increased rivalry from the PPIs, cannibalization from the introduction of the OTC variant Tagamet HB, and sharply curtailed Rx marketing efforts.

For Rx ranitidine the picture is slightly different, as is seen in Figure 4. In particular, branded Zantac Rx sales appear to have fallen steadily since early 1995 (around the time Pepcid AC, the first OTC H₂, came on the market), preceding its patent expiration by more than two years. Reflecting perhaps the effects of OTC cannibalization, branded Zantac Rx sales continued a steady decline until August 1997, when Rx patent expiration took place. Thereafter, as with
branded Tagamet Rx, branded Zantac Rx quantity units fell dramatically, and by June 1999 Zantac Rx unit sales were less than 10% of their 1994-95 peak levels. Total ranitidine Rx sales ("Total Rx" in Figure 4) also experienced a continued decline following patent expiration. The post-patent expiration decline in total Rx sales for ranitidine is smaller than that for cimetidine (compare Figures 3 and 4), but the fall in average Rx price for ranitidine from the time of patent expiration is also smaller for ranitidine Rx than with cimetidine Rx (compare Figures 1 and 2).

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

Next we turn to an exploratory empirical assessment of the impact of a brand's OTC introduction on its own Rx sales. In theory, this impact could be either positive or negative. If cannibalization is extensive, then patients taking Rx versions will switch to the OTC product, and the trend of overall OTC plus Rx sales for that brand will be largely unaffected. Alternatively, non-users exposed to marketing for OTC products might seek advice from their physicians and be prescribed the stronger Rx version (whether as medically appropriate or as a consequence of insurance coverage), generating positive spillovers. If these spillovers are sufficiently large, overall OTC plus Rx sales for that brand could increase. Whether cannibalization or positive spillovers dominate is therefore an empirical issue.

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

First, we compare Rx and OTC prices. Recall that for comparability, the OTC price per day of therapy assumes twice the recommended daily OTC dosage, so that the Rx and OTC versions have the same amount of mg strength each day. By June 1999 the OTC Tagamet HB
price per day of therapy is about 45% the Rx Tagamet price, but slightly more than three times the Rx generic cimetididine price, as shown in Figure 1. Figure 2 shows that by mid-1999, on a per patient day of therapy basis, the price of OTC Zantac 75 is about one and a half times that of Rx generic ranitidine, but only about a third that of Zantac Rx. These estimates of the difference between the branded Rx and OTC versions are a lower bound of the true differential magnitude, since the Rx generic price does not include the retail margin, which is often larger than that for the branded Rx product, while the OTC price is gross of the retail margin. In spite of this OTC relative price overstatement, for consumers paying cash, purchasing a day of therapy is much less expensive with the OTC versions of Tagamet and Zantac than with their branded Rx variants. The OTC purchase also avoids the time and other costs of obtaining a physician’s prescription.

Although to save on space we do not present comparable figures here for Pepcid and Axid, prices per day of therapy for Pepcid Rx and Axid Rx were about two and a half times their comparable OTC price in mid-1999.

The quantity of OTC Tagamet sold in mid-1999 is about 7-8 times larger than Rx Tagamet. In 1995 OTC sales resuscitated overall brand sales following the 1994 loss of Tagamet patent protection. Tagamet’s OTC introduction was a clear spillover winner: because its brand Rx sales had fallen so sharply following patent expiration, there were few Rx sales left to cannibalize. But by mid-1998, total Rx plus OTC Tagamet sales were again falling, and by mid-1999 they reached levels about the same as just prior to patent expiration. Through its OTC launch, Tagamet averted and postponed the gradual brand franchise death, but only temporarily.

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

Tagamet OTC revenues (not shown) were about three and a half times greater than those for Tagamet Rx in mid-1999, while OTC Zantac 75 revenues were approximately the same as those from Zantac Rx. Summed over both OTC and Rx versions, however, Zantac revenues were about 3-4 times larger than those for Tagamet. Hence, while on a relative basis the OTC introductions appear to have benefited Tagamet more than Zantac, on an absolute revenue basis over both OTC and Rx forms, Zantac gained more.

VII. PRICE INDEX CONSTRUCTION WITH GENERIC AND OTC “NEW GOOD” ENTRY

Constructing price and quantity measures on the basis of simple summed up milligram units for a given molecule implicitly assumes that, for example, generic versions of cimetidine are perfectly substitutable with Tagamet (branded cimetidine). Similarly, aggregating milligrams of the OTC version of Zantac to milligrams of the Zantac Rx and generic Rx ranitidine, then obtaining price per milligram by dividing total revenue by these summed milligrams, also assumes perfect substitutability among OTC and Rx versions of ranitidine. Since perfect substitutability is clearly an unrealistic assumption (witness, for example, continued sales of Rx
Zantac after much lower priced generic Rx ranitidine enters, it is useful to examine alternative methods for creating aggregate price indexes that allow for imperfect substitutability.

Recall from our earlier discussion in Section IV that in the context of medical care, we believe the traditional theory of consumer demand is best employed with great caution. In particular, principal-agent issues involving relationships between patients and their physicians, and the role of moral hazard and insurance in creating wedges between insurers' and consumers' marginal prices for covered Rx drugs, seriously compromise and constrain one's ability to draw any consumer welfare implications from observed aggregate price index trends.

We have implemented the methodologies of Feenstra and GC, as outlined in Section IV. Specifically, to implement the Feenstra procedure using nonlinear estimation procedures, we have estimated parameters in the normalized quantity Eq. (6) derived from the CES brand-generic demand equations, using monthly data from both pre- and post-patent expiration for Tagamet and Zantac; an analogous equation system based on the translog unit expenditure function was also estimated. In each case, the two-equation system (cimetidine and ranitidine) is estimated by maximum likelihood, allowing for contemporaneous correlation amongst residuals in the two equations.

To implement the GC methodology, single equation least squares procedures are employed in estimating the CES parameters in Eq. (5), using only post-patent expiration data for the cimetidine and ranitidine equations.

For both the Feenstra and GC procedures, aggregate CES price indexes for the cimetidine and ranitidine molecules are then constructed by inserting parameter estimates into Eq. (4). In the GC method, the assumed reservation price just prior to the time of initial generic entry is midway between the brand and generic price. Aggregate molecule price indexes incorporating
the introduction of OTCs as new goods are calculated in an analogous manner. Notice that in the GC method these aggregate price indexes depend only on brand-generic substitutability within each molecule, and not on own-price elasticities for the molecule in aggregate.

Before proceeding with a discussion of results comparing the GC and Feenstra procedures, we emphasize that with both the GC and Feenstra procedures, our simplest demand specification is quite restrictive in that no account is taken of other, non-price factors affecting demands, such as marketing efforts. In the GC specification that only employs post-patent expiration data, this restrictiveness may not be that undesirable, for only brand-generic substitutability within a given molecule is being modeled, and as we observed earlier, in practice very little marketing efforts occur post-patent expiration. On the other hand, in the Feenstra specification, because pre-patent expiration data is included, excluding non-price factors as regressors in the total molecule demand Eq. (3), such as measures of relative brand marketing efforts could well be expected to have a much larger impact. Moreover, although brand marketing variables could be introduced as additional regressors, since patent expiration could involve a regime shift, we would not be surprised if parameters on these price and marketing variables would differ in the pre- and post-patent expiration environments. It is possible that regime shifts are less evident in the Rx to OTC context than in the patent expiration and brand-generic entry environment.

A. CIMETIDINE AND RANITIDINE PRICE INDEXES WITH GENERIC ENTRY

Despite a substantial amount of experimentation with alternative time periods, functional forms, and the incorporation of measures of marketing efforts, we were unable to obtain satisfactory estimates of the crucial within-molecule substitution elasticity estimates using the Feenstra procedure.

More specifically, with marketing effort measures excluded, and using data from the
1989:01-1999:06 time frame, for both the CES and translog specifications we obtained reasonable estimates for the cimetidine and ranitidine aggregate molecule own-price elasticities of demand; these ranged from around -2.2 to -2.4 for the CES form for cimetidine and ranitidine, respectively, while the corresponding estimates based on the translog were about -2.6 and -2.3. However, estimates of the within-molecule brand-generic substitution elasticity were either of the wrong sign or of an unreasonable magnitude. For example, for cimetidine and ranitidine, based on the CES form, the estimates of $\sigma$ were about -1.6 and 140, respectively; assuming generic revenue shares of 67%, the comparable translog-based substitution elasticity estimates were about -0.6 and 70.

To check on the robustness of these unsatisfactory $\sigma$ estimates, we systematically shortened the pre-patent expiration time period that ended first in May 1994 for Tagamet, sequentially dropping all observations in 1990, 1990-1991, 1990-1992, and then 1990-1993; although estimates of both the own-price and cross brand-generic substitution elasticity varied considerably with the choice of time period, in no case did satisfactory estimates of the $\sigma$'s result. We also experimented with a number of specifications that incorporated measures of marketing efforts; for each molecule, we cumulated physician-oriented detailing data over the previous 12 months, and included in each of the molecule equations both own and others' cumulative marketing efforts. While estimates of parameters on own-molecule cumulative marketing efforts were typically positive and significant, estimates on others' cumulative marketing efforts were negative and only occasionally significant. More importantly, however, inclusion of these additional Rx marketing effort measures did not entirely overcome our inability to obtain satisfactory estimates of the $\sigma$ within-molecule elasticity of substitution between brand and generic. Unlike the situation with marketing efforts excluded, when
marketing effort measures were included the molecule whose elasticity of substitution estimate was typically of the wrong sign was ranitidine (estimates ranged from -6.1 to -4443), while elasticity of substitution estimates for cimetidine ranged from 1.02 (using 1991:01-1998:12 data) to 3.26 (1994:01-1998:12).

If one instead implements the GC method using only post-patent expiration observations, own-price elasticity estimates for the aggregate molecule are not needed, and estimates of the brand-generic elasticities of substitution for the CES turn out to be plausible at 1.44 (standard error of 0.11) and 1.96 (0.18). For the translog, assuming generic revenue shares of 0.67, the GC parameter estimates imply elasticity of substitution estimates of 1.42 and 1.99 for cimetidine and ranitidine, respectively. Since only a very modest amount of medical journal advertising was conducted by generic entrants post-patent expiration, and since generic physician detailing efforts were essentially zero, it is not surprising that incorporating brand-generic relative marketing efforts into the revenue share equations as an additional regressor did not change these results in any material manner.

B. PRICE INDEXES FOR ALL FOUR MOLECULES ACCOUNTING FOR OTC ENTRY

OTC entry occurred for Tagamet HB in August 1995, about 15 months after Rx Tagamet lost patent expiration. In contrast, the OTC entry of Zantac 75 took place in April 1996, about 18 months before the August 1997 loss of patent expiration for Rx Zantac. The Tagamet-Zantac OTC launch date experience is very different from that of both Pepcid AC (June 1995) and Axid AR (July 1996) who launched their OTC version years before their patent expiration occurred (in 2001). We now examine aggregate price indexes for each of the four molecules, where the aggregate is over Rx brand, Rx generic (only in the case of cimetidine and ranitidine), and OTC
brand versions.

We begin by constructing, for cimetidine and ranitidine, a price index over brand and generic Rx versions. Since, as discussed in the preceding sub-section, our modeling efforts to construct price indexes over brand and generic versions were generally unable to yield satisfactory brand-generic substitution elasticity estimates, we use the non-parametric Divisia index procedure instead.

With the Feenstra method, we then model total generalized quantity for each molecule (Rx and OTC) using both pre- and post-OTC launch data, while with the GC method we employ only the post-OTC launch data. Measures of total marketing for each molecule include that for Rx marketing for each molecule (the sum of constant dollar expenditures for physician-oriented detailing, physician-oriented journal advertising, and direct to consumer marketing (DTC) of the Rx brand), plus the OTC measure of Rx marketing for each molecule (only DTC marketing of the OTC brand). We then cumulated total marketing efforts for each molecule over the preceding 12 months. We also constructed a relative Rx/OTC marketing measure as the ratio of the Rx cumulative marketing efforts to OTC cumulative marketing efforts, where the cumulation encompasses the preceding 12 months. Since the DTC data available to us ended in 1998:12, we utilize data over the ten year time period, 1989:01 - 1998:12, yielding cumulative marketing effort measures for each molecule for the nine-year period 1990:01-1998:12.

The Feenstra method involves maximum likelihood estimation of a four-equation system with cross-equation parameter restrictions and a balanced panel, while for the GC method single equation OLS estimation is carried out using each molecule's post-OTC launch data only. In both the Feenstra and GC methods, for price index construction the crucial parameter is the Rx vs. OTC substitution elasticity, which differs of course for each of the four molecules.
Using the Feenstra procedure and excluding marketing variables, we experienced considerable numerical convergence issues, with typically two or so of the within molecule Rx-OTC elasticity estimates being very large in absolute value (sometimes positive, sometimes negative). Matters improved considerably, however, when we incorporated into each of the CES generalized quantity equations both that molecule's own total marketing efforts, as well as the total marketing efforts summed over the other three molecules, where both marketing measures are logarithmically transformed. Specifically, estimates of the within molecule Rx-OTC elasticity of substitution were 2.00 (standard error of 0.20) for famotidine (Pepcid), 1.42 (0.10) for ranitidine (Zantac), and 1.80 (0.25) for nizaditine (Axid). For cimetidine (Tagamet), however, the point estimate was an unreasonably large 9069, with a standard error almost 100 times as large. Interestingly, for each of the four molecules the own (log) total marketing elasticity estimate was positive and significant (ranging from a low of 0.057 for famotidine to a high of 0.136 for ranitidine, with respective standard errors of 0.027 and 0.023), while those for the (log) of the sum of the other molecules' marketing efforts was negative, albeit only in the case of nizaditine was the -0.391 estimate significant (standard error of 0.106). Except for cimetidine, estimates of the own-price total molecule demand price elasticity were negative, significant and plausible, while that for cimetidine was very imprecisely estimated.

Given the very large standard error estimates on the cimetidine own-price and within-molecule Rx-OTC elasticity of substitution estimates, we constrained the $\sigma$ elasticity of substitution estimate for cimetidine to be 1.74, the mean of the corresponding $\sigma$ estimates over famotidine, ranitidine, and nizaditine. We then substituted these $\sigma$ estimates into Eq. (4) and computed exact price indexes for each of the four molecules, where these price indexes are an aggregate over Rx and OTC versions. These molecule-specific four aggregate price indexes are
Graphed in Figure 5, where for each molecule the price index is 1.000 in 1989:01. A number of points are worth noting.

First, for all four molecules, prices generally increase during the first five years from 1989:01 to 1994:01, and in the second half of the sample they take on different time paths.

The cimetidine price falls in early 1994 following patent expiration and generic entry, and experiences another sharp fall in mid-1995 as OTC entry occurs. At the end of 1998, the cimetidine price index had fallen to a level of 0.548, about 42% of its 1994:04 peak of 1.312.

For famotidine, the fall in price is also substantial, but because it had not lost patent protection by end 1998, its price decline reflects only the impact of OTC entry. As seen in Figure 5, there is a sharp decline in the famotidine price in mid-1995 as Pepcid AC enters, and thereafter prices are roughly stable, ending at 0.793 in 1998:12, about 29% less than its 1.112 value in May 1995 just prior to the OTC launch of Pepcid AC.

In contrast to both cimetidine and famotidine, for nizaditine the molecule price increases steadily from 1989:01 through 1996:06, it then drops about 15% to 1.04-1.06 in late 1996, and thereafter it experiences a steady increase, ending up at 1.147 in 1998:12, down about 11% from the 1.289 level in 1996:06 just prior to launch of the OTC Axid AR product. The Rx version of Axid did not lose patent protection until 2001, beyond the 1998:12 last observation in this study.

For ranitidine, however, the combination of lost patent protection, very substantial low-priced generic entry, and substantial growth of the OTC Zantac 75 product resulted in by far the largest price decline among the four molecules. As seen in Figure 5, the ranitidine molecule experienced about a 25% price decline in May 1996 as OTC entry of Zantac 75 occurred, and then another sharp price decline of about 25% between August and December 1997 as generic ranitidine initially entered the market, and continuing declines during 1998 with further generic
ranitidine entry. At 1998:12, the ranitidine molecule price index was 0.313, about 30% of its level just prior to the OTC launch of Zantac 75, and about 50% of its level just prior to entry of generic ranitidine.

These molecule price indexes are based on the Feenstra methodology that includes observations for each molecule both pre- and post-OTC entry. Following Griliches-Cockburn (GC), we have also estimated the Rx-OTC elasticity of substitution using Eq. (8) and, for each molecule, only the data following OTC launch. These results were somewhat disappointing. For all four molecules, GC-CES estimates of $\sigma$ were less than 1.0, violating a necessary condition of the model that $\sigma > 1$. With relative Rx/OTC marketing variables excluded, the estimated $\sigma$ (standard error) was 0.802 (0.215) for cimetidine, 0.892 (0.164) for famotidine, -0.400 (0.581) for ranitidine, and -0.399 (0.186) for nizatidine. When a cumulative (log) relative Rx/OTC marketing variable was included as an additional regressor in Eq. (8), the relative marketing variable was typically significant and of the right sign, but all of the $\sigma$ estimates remained below unity. These $\sigma$ estimates were 0.848 (0.210) for cimetidine, 0.535 (0.134) for famotidine, -0.105 (0.312) for ranitidine, and -0.222 (0.273) for nizatidine. Since measures of consumer surplus are infinite when $\sigma < 1.0$, conditions for the validity of the CES exact price index are violated, and thus we do not report the corresponding price indexes.

VIII. **SUMMARY AND CONCLUSIONS**

In this paper we have reported results of our research examining the "sunset" H$_2$'s up to and following their Rx patent expiration, as they encountered cannibalization from their own and competitors' OTC introductions, and as they faced forces of creative destruction from the next generation of more potent antiulcer and heartburn Rx drugs, the proton pump inhibitors (PPIs). Although the looming prospect of patent expiration had significant impacts on the
behavior of the H2 manufacturers in terms of their pricing and marketing behavior, it was more than the shadow of patent expiration that dimmed the H2 prospects -- undoubtedly, the forces of dynamic competition in the form of the newly dominant PPI products were equally foreboding.

Within this larger context, consumers appear to have benefited from generic entry and the introduction of OTC versions of previously prescription-only H2's. One way to characterize these developments is to employ the exact aggregate price and quantity measures based on the CES function within the Feenstra framework (an aggregate over Rx and OTC versions for each molecule), and then construct aggregate Divisia price and quantity indexes encompassing all four molecules. These aggregate H2 price and quantity measures, denoted PH2TOT and QH2TOT, are graphed in Figure 6, with each indexed to 1.000 in 1989:01. As is seen in Figure 6, the aggregate H2 price series increased steadily from 1989:01 to about 1992:01, was flat at about 1.15 for several years until early 1995, and then began to fall, with a particularly large decline in early 1996 (following OTC entry by several brands), and another substantial decline in late 1997 following Zantac loss of patent protection and Rx generic ranitidine entry. By the end of our sample in 1998:12, the aggregate H2 price index was 0.57, roughly 50% lower than in early 1995 just prior to the first OTC entry.

In terms of quantity of H2s consumed, from 1989:01 to early 1995 the quantity index increased from 1.00 to about 1.33, it then grew more rapidly to about 1.86 by November 1996, and then it began falling again, ending up at about 1.41 in 1998:12.

It is worth emphasizing again, however, that how one interprets these price and quantity trends is somewhat ambiguous, given principal-agent relationships between physicians and patients, and the moral hazard arising from insurance coverage of Rx, but typically not OTC versions of these products.
As expected, we find that the branded H₂ manufacturers have not competed on price with generic entrants following Rx patent expiration, but instead have maintained or even slightly increased brand prices, losing market share and retaining sales to a small but relatively price-insensitive segment of brand-loyal customers.

We also find evidence strongly supporting the notion of protracted effects from marketing. In particular, we find very substantial declines in marketing efforts by branded firms as Rx patent expiration approaches, a phenomenon suggesting long- rather than short-lived anticipated sales impacts from marketing.

Even though generic entry results in average molecule prices (weighted over brand and generic) falling 65%-80% of their pre-patent expiration levels, for both cimetidine and ranitidine the combined brand plus generic quantity sales following patent expiration has also fallen considerably. This utilization decline could reflect the impacts of decreased marketing efforts, competition from the more potent PPIs, and/or cannibalization of Rx sales by the introduction and marketing of a same-brand OTC product. The relative importance of these various factors in explaining the post-patent expiration decline in sales is a topic worthy of further research.

On a per patient day basis, we find that in mid-1999 brand OTC prices were 30%-50% of their brand Rx prices, but brand OTC prices were still several times larger than same molecule generic Rx prices. These price ratios should be interpreted somewhat cautiously, however, since the Rx prices do not reflect retail margins, unlike the OTC prices based on scanner transaction data.

Since Zantac executed the OTC switch prior to its 1997 patent expiration, it suffered considerably from OTC cannibalization of Rx sales, but ultimately the substantial amount of OTC Zantac 75 sales has partially resuscitated the Zantac brand franchise. Because Tagamet lost
patent protection prior to its OTC switch, it had the least to lose by going OTC, and in fact on a relative basis, its OTC/Rx sales ratio has grown, though levels of both OTC Tagamet HB and Tagamet Rx are small.

Finally, we have compared two different approaches to incorporating the generic and OTC new goods into aggregate price indexes. The Griliches-Cockburn (GC) method yielded reasonably plausible elasticity of substitution estimates in the context of Rx generics being the "new good" relative to Rx brands. However, in this brand-generic context, the Feenstra method did not fare as well, yielding estimates of the within-molecule elasticity of substitution that were either of the wrong sign or of an unreasonable magnitude. Matters did not improve much for the Feenstra method when demand equations were augmented by own and others' measures of cumulative marketing efforts. We note that in Feenstra [1997], the Feenstra method yielded plausible substitution elasticity estimates for cephalexin, but not so for cephradine.

The Feenstra and GC methods reversed roles when the "new good" was instead defined to be an OTC version of the branded Rx drug. With the GC method, estimates of the elasticity of substitution were all less than unity, violating an integrability condition that requires \( \sigma > 1 \). In contrast, with the Feenstra method, in the Rx to OTC context three of the four estimates of \( \sigma \) were plausible and reasonably precisely estimated, whereas only one had an implausibly large value (and standard error). The addition of marketing variables to the molecule demand equation was particularly important in the Feenstra methodology, for there it greatly facilitated numerical convergence to plausible parameter estimates. Although detailed results were not presented in the paper, it is worth noting that the relative performance of the GC and Feenstra methods was unchanged when the CES functional form was replaced by a translog expenditure function.

Together, these results suggest that use of econometric methods in constructing price
indexes that incorporate the effects of new goods requires considerably more experimentation, perhaps with other data sets and families of products, and with specifications that include non-price factors affecting demand functions, such as measures of marketing efforts. Future research should focus on the conditions under which the Feenstra, the GC or some other method is more likely to yield robust and plausible findings. Particular attention needs to be focused on the feasibility of integrating scanner price, quantity and promotional data with more complete measures of marketing efforts from other publicly available data sources. Until more progress is made on these fronts, and reasonably robust findings are reported by a number of independent researchers, government statisticians may be understandably cautious in publishing price indexes based on econometrically estimated reservation prices, or on econometric estimation of expenditure formulations that obviate the need for estimation of reservation prices. Apparently, the "new goods" problem is not simply solved by mechanical implementation of econometric estimation methods.

In terms of other future research, the impact of Rx to OTC switches on prices paid by consumers, after allowing for insurance coverage and patient copays, is a most interesting research topic, as is the more general issue of the effects of such switches on patient health and consumer welfare. The availability of scanner data helps make such research feasible. It would also be useful to exploit econometric procedures that allow for preference estimation even when the number of available products changes over time.\textsuperscript{30} The existence of principal-agent and moral hazard issues, particularly important in the Rx market, however, makes such research very challenging.

A number of top-selling prescription drugs are scheduled to lose patent protection in 2001 and 2002 -- Prilosec, Prozac, Claritin, and Mevacor, for example. Whether the long
shadows of imminent patent protection for these drugs will display similar pricing, marketing, and Rx-OTC switching patterns as we have observed in the H₂ market remains to be seen.
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FOOTNOTES

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

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

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

4 Electronic Orange Book [2000].

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


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

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


10 It is interesting to note that when joining up with or creating joint ventures with the more retail-oriented consumer product companies, the Rx drug manufacturers also created cannibalization possibilities for the traditional antacids used to treat heartburn. For example, for SmithKline Beecham, OTC Tagamet competed with its antacid products, Tums and Gaviscon. For Glaxo Wellcome, pairing with Warner-Lambert meant that OTC Zantac would compete with Rolaids. Finally, for the J&J•Merck joint venture, the OTC Pepcid would compete with Mylanta and Imodium. Ling [1999] provides an empirical analysis of the interactions among the incumbent
antacid and the newer H$_2$ OTC products.

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


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

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

15Generic firms may, however, engage in other marketing efforts for which the benefits are more easily internalized. Generic firms market very differently from brand firms. Instead of engaging in detailing and journal advertising, generic firms tend to have home office major account representatives for particular customers, such as drug store chains, staff model managed care organizations, and mass merchandisers such as Walmart. Unfortunately, we have no data on these types of marketing efforts.


17The transformation factors are: Tagamet (cimetidine), 800 mg/day; Zantac (ranitidine), 300 mg/day; Pepcid, 40 mg/day; Axic, 300 mg/day; Prilosec, 20 mg/day; Prevacid, 30 mg/day; and Propulsid, 40 mg/day. Since Propulsid never had FDA approval for active duodenal ulcer treatment, we use the recommended daily dosage for treatment of nocturnal GERD.

18IMS Health [1998].

19On this, see Rosenthal, Berndt, Donohue et al. [2002].


21For July 1995 onward (when the deflators first became available), we construct this deflator as the arithmetic average of the Producer Price Index for "Advertising agencies, ad creation, billed separately", and "Advertising agencies, media placement, including ad creation not billed". For months prior to July 1995, we employ the Producer Price Index for All Finished Goods.

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

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

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

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

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

Note that the patents of Axid and Pepcid did not expire until 2001.

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

See, for example, Berry, Levinsohn and Pakes [1995], and Bresnahan, Stern and Trajtenberg [1997].
TABLE 1: CHANGES IN MARKETING EFFORTS IN ANTICIPATION OF AND FOLLOWING PATENT EXPIRATION, H₂-ANTAGONIST PRESCRIPTION DRUGS

<table>
<thead>
<tr>
<th></th>
<th>TAGAMET</th>
<th>ZANTAC</th>
<th>PEPCID</th>
<th>AXID</th>
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<tbody>
<tr>
<td></td>
<td>PATENT LOSS</td>
<td>PATENT LOSS</td>
<td>AT ZANTAC PATENT LOSS</td>
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</tr>
<tr>
<td>Minutes of Detailing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Near vs. Far Away</td>
<td>-30.2%</td>
<td>-59.3%</td>
<td>-19.6%</td>
<td>-36.0%</td>
</tr>
<tr>
<td>After vs. Far Away</td>
<td>-86.6%</td>
<td>-94.4%</td>
<td>-28.3%</td>
<td>-48.5%</td>
</tr>
<tr>
<td>Pages of Journal Advertising</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near vs. Far Away</td>
<td>-55.1%</td>
<td>-99.3%</td>
<td>257.7%</td>
<td>-16.1%</td>
</tr>
<tr>
<td>After vs. Far Away</td>
<td>-96.7%</td>
<td>-100.0%</td>
<td>-16.2%</td>
<td>-94.7%</td>
</tr>
<tr>
<td>DOLLAR MARKETING TO DOLLAR SALES RATIOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detailing Dollars to Sales Ratio</td>
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</tr>
<tr>
<td>Near vs. Far Away</td>
<td>-37.8%</td>
<td>-57.4%</td>
<td>-39.1%</td>
<td>-36.3%</td>
</tr>
<tr>
<td>After vs. Far Away</td>
<td>-32.3%</td>
<td>-71.2%</td>
<td>-36.7%</td>
<td>-35.1%</td>
</tr>
<tr>
<td>Total Detailing Plus Journal Advertising Dollars to Sales Ratio</td>
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<td></td>
<td></td>
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<td>Near vs. Far Away</td>
<td>-43.1%</td>
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<td>-33.3%</td>
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</tr>
<tr>
<td>After vs. Far Away</td>
<td>-30.1%</td>
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