Volume Title: Scanner Data and Price Indexes

Volume Author/Editor: Robert C. Feenstra and Matthew D. Shapiro, editors

Volume Publisher: University of Chicago Press

Volume ISBN: 0-226-23965-9

Volume URL: http://www.nber.org/books/feen03-1

Conference Date: September 15-16, 2000

Publication Date: January 2003

Title: The Long Shadow of Patent Expiration. Generic Entry and Rx-to-OTC Switches

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URL: http://www.nber.org/chapters/c9737

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The Long Shadow of Patent Expiration
Generic Entry and Rx-to-OTC Switches

Ernst R. Berndt, Margaret K. Kyle, and Davina C. Ling

8.1 Introduction

In 2001 and 2002, a number of the United States' 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 (Rx) to nonprescription over-the-counter (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: (a) pricing and marketing strategies by branded pioneer drug manufacturers on their Rx drugs before

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Research support from the National Science Foundation (to Berndt) and the MIT Program on the Pharmaceutical Industry (to Berndt and Kyle) is gratefully acknowledged, as is data support from Information Resources Inc., J&J•Merck Consumer Products, IMS Health, and Merck & Co. The authors thank Steve Morgan, Robert Feenstra, Richard Frank, Robert Pindyck, and an anonymous referee for comments on an earlier version of this paper. The views expressed in this paper are those of the authors only and do not necessarily reflect those of any institutions with which they are related, or of any research sponsor.

and after patent expiration; (b) the impact of generic Rx entry on the price, utilization, and revenues of the Rx molecule after patent expiration; and (c) 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 introductions of new goods. 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 U.S. 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).

8.2 Background

In 1977 SmithKline introduced a pharmaceutical product branded Tagamet (a histamine$_2$-receptor antagonist, chemical name cimetidine) into the U.S. 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, which had involved more costly hospitalizations and surgeries.

In the following years, a number of additional new histamine$_2$-receptor antagonist (hereafter, H_2) 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 H_2s have expanded medical uses far beyond just the treatment of existing ulcers. For example, over the last two decades the Food and

1. For earlier empirical research on Rx-to-OTC switches, see Temin (1992).

Drug Administration (FDA) has approved use of the H_2s for the treatment of hypersecretory conditions and gastroesophageal reflux disease ("GERD," a common but severe form of heartburn); for the prevention of stress ulcers; for 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 H_2s have also been often prescribed to offset stomach-related side effects from other medications, as well as from anesthesia and radiological and chemotherapy treatments.[2]

Aided by patent protection, the widespread utilization of the H_2s 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 United States, but Tagamet was typically in the top ten, and Pepcid and Axid were also usually among the fifty or so best-selling prescription drugs.

The H_2s revolutionized medical treatments for gastrointestinal disorders. However, 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 U.S. 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. However, after reviewing long-term use evidence, in March 1995 the FDA permitted Prilosec to remove the "black box" warning in its product labeling regarding possible risks from long-term use, and in June 1995 the FDA explicitly granted long-term maintenance use approval for Prilosec.

Although the H_2s 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 (Electronic Orange Book 2000).

With long-term safety issues settled, and superiority over the H_2s estab-

2. For more detailed discussions of the H_2 market up until 1994, see Berndt et al. (1995, 1997).

3. A London Business School case study dealing with how the H_2 manufacturers could respond to competition from the new PPIs is that by Dell'Osso (1990). Also see Perloff and Suslow (1994).

lished, the PPIs were marketed intensively beginning in the mid-1990s. Remarkably, sales of the PPIs exceeded even those of the record-setting H_2s. By 1997, for example, Prilosec had overtaken Zantac as the United States' (and the world's) largest revenue prescription drug, and by 1999, Prevacid ranked not far behind.[4]

In addition to intense rivalry from the next-generation PPIs, the H_2s also faced imminent loss of patent protection. Tagamet's patent was the first to expire, on 17 May 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.[5] As early as a decade before its anticipated patent expiration, SmithKline discussed with the FDA the possibility of its seeking and gaining approval for an OTC version of Tagamet for the treatment of heartburn.[6] 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).[7]

This provision of the Waxman-Hatch Act created clear incentives for SmithKline, the manufacturer of the pioneer H_2 Tagamet, to be the first to switch from Rx to OTC. However, the later H_2 Rx entrants (Zantac, Pepcid,

4. 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).

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

6. For a Harvard Business School case study discussion of the race to develop and launch the first OTC H_2 in the United States, see King et al. (2000).

7. For discussions of possible benefits and costs to consumers, manufacturers, and insurance providers from the Rx-to-OTC switch, see Hesselgrave ("Will Managed Care Embrace Rx-to-OTC Switches?" *Drug Topics,* 2 June 1997), Jaroff ("Fire in the Belly, Money in the Bank," *Time,* 6 November 1995, 56–58), McCarthy (1999), Tanou and Burton ("More Firms 'Switch' Prescription Drugs to Give Them Over-the-Counter Status," *Wall Street Journal,* 29 July 1993, B1), 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).

and Axid) also had incentives to launch OTC versions of their Rx products, particularly if late OTC entry meant forgoing potentially large OTC sales. For the later Rx entrants, OTC entry could possibly occur even *prior to* their own Rx patent expiration. All 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.[8]

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?[9]

Two of the four H_2 brands (Tagamet and Zantac) lost patent protection in the 1990s, and 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 H_2s, 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 some time 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_2s 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 8.3 we review conceptual bases that provide hypotheses involving pricing and marketing as Rx brands face Rx generic competition. Then in section 8.4 we describe alternative methodologies for incorporating generic and OTC products ("new goods") into various aggregate price indexes. In section 8.5 we discuss data sources and the construction and interpretation of various

8. On first-mover advantages and their rationale in the market for pharmaceuticals, see Bond and Lean (1977), Berndt et al. (1995, 1997), King (2000), and King et al. (2000). The theoretical foundations and empirical evidence on first-mover advantages in other markets are discussed in, among others, Robinson, Kalyanaram, and Urban (1994); Samuelson and Zeckhauser (1988); Schmalensee (1982); and Urban et al. (1986).

9. 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 OTC antacid products, Tums and Gaviscon. For Glaxo Wellcome, pairing with Warner-Lambert meant that OTC Zantac would compete with OTC Rolaids. Finally, for the J&J•Merck joint venture, the OTC Pepcid would compete with OTC Mylanta and Imodium. Ling (1999) provides an empirical analysis of the interactions among the incumbent OTC antacid and the newer OTC H_2 products.

price and quantity measures, first for prescription drugs and then for OTCs. With this as background, in section 8.6 we present a number of stylistic facts that appear to characterize these markets in anticipation of and following Rx patent protection, and we provide some preliminary evidence on our hypotheses. We discuss our price index results in section 8.7. Finally, in section 8.8 we summarize and conclude.

8.3 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 may 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.[10] Other things being 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.[11]

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; that is,

$$\frac{\$\ \text{Marketing}}{\$\ \text{Sales}} = \frac{\varepsilon_M}{\varepsilon_P}, \tag{1}$$

where ε_M is the elasticity of demand with respect to marketing efforts, and ε_P is the absolute value of the price elasticity of demand.[12]

There is considerable evidence that early in the product life cycle phar-

10. On this, also see Scherer (1993, 2000), Griliches and Cockburn (1994), and Ellison et al. (1997).

11. Empirical evidence presented in Frank and Salkever (1997) and Berndt, Cockburn, and Griliches (1996) is consistent with the Frank-Salkever segmented market hypothesis. Related econometric evidence from Berndt, Griliches, and Rosett (1993) suggests that over the 1986–91 time period, prices of older drugs increased more rapidly than those of newer products.

12. The 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).

maceutical marketing efforts involving physician detailing and medical journal advertising provide long-lived benefits in the form of additional current and future sales; that is, evidence suggests that up to the mature phase of the product life cycle, ε_M is positive and significant. Moreover, ε_M is larger in the long run than over the short term. The substantial amount of marketing commonly observed at the time of initial product launch is of course consistent with large and long-lived sales impacts from such marketing efforts (see, e.g., Berndt et al. 1995, 1997; Perloff and Suslow 1994; King 2000).

However, as patent expiration approaches, one expects that branded manufacturers anticipate a decline in ε_M, because lower-priced generic entrants could instead capture a large portion of sales from additional marketing (on this, see also Ellison and Ellison 2000). If this is 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 ε_M likely fall further, but it is also reasonable to expect that price competition would intensify, increasing ε_P, the denominator of the right side of equation (1), and thereby further reducing the ratio of marketing-to-sales. We hypothesize, therefore, that the pioneer's marketing-sales ratio will fall as patent expiration approaches, and it 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 ε_M to be very small. The intense price competition among generics implies a large ε_P. Hence, we hypothesize that generic manufacturers will have marketing-sales ratios close to zero, where marketing efforts consist of physician detailing and medical journal advertising.[13]

8.4 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), 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)

13. Generic 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 drugstore chains, staff model managed care organizations, and mass merchandisers such as Wal-Mart. Unfortunately, we have no data on these types of marketing efforts.

and in Griliches and Cockburn (1994; hereafter GC).[14] Griliches and Cockburn assume a uniform distribution of reservation prices across heterogeneous consumers between the brand and generic prices at the time of patent expiration, and they 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 it 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 nonprice 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 Δ, and the positive price elasticity of demand by η. Since $\Delta E = -(\eta - 1)\,\Delta P$, it follows that

$$\Delta P = \frac{-\Delta E}{(\eta - 1)}, \tag{2}$$

where $\eta > 0$. Feenstra's insight is that if data on ΔE were available and if η were known, then one could simply use equation (2) to obtain an estimate of ΔP consistent with consumer preferences, without requiring knowledge of the reservation price of the generic drug. Feenstra suggests estimating η 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

$$\ln Q_i^t = \alpha_i - \eta_i \ln P_i^t + \sum_{i \neq j} \beta_j \ln P_j^t + \delta_i \ln I^t + \varepsilon_i^t, \tag{3}$$

for periods $t = 0, 1, \ldots, T$, where Q_i and P_i are quantity (in grams) and price per gram of the ith molecule, P_j is the price of imperfect substitutes for the ith molecule, I is total expenditures across the various molecules, and ε_i is a

14. Feenstra's (1997) work builds on that in Feenstra (1994) and Feenstra and Shiells (1997).

random disturbance term. When i and j are substitutes, the β_j are positive. Also, as long as i is not an inferior good, we expect the δ_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 in which 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

$$P_i^t = \left(\frac{p_{ib}^t}{p_{ib}^0}\right)(1 - s_{ig}^t)^{1/(\sigma_i - 1)} \tag{4}$$

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

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

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 σ_i elasticities of substitution between brand and generic versions of a molecule be greater than 1. 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 σ_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

equation (4) into equation (3), normalizes a "real" expenditure index relative to the price of the branded drug,

$$\widetilde{Q}_i^t = \frac{E_i^t / E_i^0}{p_{ib}^t / p_{ib}^0},$$

and then obtains an estimating equation nonlinear in the parameters, of the form

$$\ln \widetilde{Q}_i^t = \alpha_i - \eta_i \ln \frac{p_{ib}^t}{p_{ib}^0} + \left(\frac{1-\eta_i}{\sigma_i - 1}\right) \ln(1 - s_{ig}^t) + \sum_{i \neq j} \beta_{ij} \left[\ln \frac{p_{jb}^t}{p_{jb}^0} + \frac{\ln(1 - s_{jg}^t)}{\sigma_j - 1} \right] + \delta_i \ln I^t + \varepsilon_i^t, \tag{6}$$

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 equation (5). These elasticity estimates are then inserted into equation (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 October 1984–September 1990 U.S. data on two anti-infective drugs. We assess both procedures here in a rather different context—the H_2 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 H_2 market, and then we aggregate further to consider the impacts of OTC entry in the total H_2 market (Rx brand, Rx generic, and OTC), using monthly data from the time period January 1989–December 1998.

8.4.1 Rx H_2 Market Only, Brands, and Generic Entry

Of the four molecules in the Rx H_2 market, two (cimetidine and ranitidine) experienced generic entry during the 1989–99 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, because an extensive demand analysis is beyond the scope of the current study.

The relatively simple equations take the form

$$(7)\quad \ln \tilde{Q}_i^t = \alpha_i - \eta_i \ln \frac{p_{ib}^t}{p_{ib}^0} + \left(\frac{1-\eta_i}{\sigma_i - 1}\right)\ln(1 - s_{ig}^t) + \beta_{ij}\left[\ln \frac{p_{jb}^t}{p_{jb}^0} + \frac{\ln(1-s_{jg}^t)}{\sigma_j - 1}\right] + \beta_{ik}\ln\left(\frac{p_{kb}^t}{p_{kb}^0}\right) + \beta_{il}\ln\left(\frac{p_{lb}^t}{p_{lb}^0}\right) + \delta_i \ln I^t + \varepsilon_i^t$$

where i = cimetidine (brand name Tagamet) or ranitidine (brand name Zantac); j, k, and l denote the other H_2-antagonist molecules; and I^t 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

$$(8)\quad \ln\left(\frac{s_{ig}^t}{s_{ib}^t}\right) = \alpha_i + (\sigma_i - 1)\ln\left(\frac{p_{ib}^t}{p_{ig}^t}\right) + u_i^t$$

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

8.4.2 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

$$(9)\quad \ln \tilde{Q}_i^t = \alpha_i - \eta_i \ln \frac{p_{ir}^t}{p_{ir}^0} + \left(\frac{1-\eta_i}{\sigma_i - 1}\right)\ln(1 - s_{ic}^t) + \sum_{i \neq j} \beta_{ij}\left[\ln \frac{p_{jr}^t}{p_{jr}^0} + \frac{\ln(1-s_{jc}^t)}{\sigma_j - 1}\right] + \delta_i \ln I_{rc}^t + \varepsilon_i^t.$$

Here, p_{ir} is the estimated price index of the Rx version of the molecule i (as calculated in section 8.5.1 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, because 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. The revenue share of the OTC version of the molecule i is s_{ic}, and in this broader context σ_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 8.5.1, when *j* = cimetidine or ranitidine. However, p_{ir} is the price index of the branded Rx version of molecule *j* if *j* = Pepcid or Axid. The revenue share of the OTC version of molecule *j* is s_{jc}, and σ_j is the elasticity of substitution between Rx and OTC versions of molecule *j*. The total expenditure across the Rx and OTC versions of the molecules is I_{rc}, and ε_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

$$\ln\left(\frac{s_{ic}^t}{s_{ir}^t}\right) = \alpha_i + (\sigma_i - 1)\ln\left(\frac{p_{ir}^t}{p_{ic}^t}\right) + u_i^t, \tag{10}$$

where the notation is the same as above. Below we undertake empirical analyses of equations (9) and (10), adding measures of relative cumulative marketing efforts as additional demand-shifters.

8.5 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.

8.5.1 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 Health's Retail Perspective™ tracks monthly shipments from manufacturers and wholesalers to retail warehouses and outlets. The data on revenues include those to manufacturers and wholesalers but not to the retail outlets (which 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, because 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 although 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.

Information on quantity shipped and revenue is at the level of presenta-

tion, for example, thirty-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.[15] Data on recommended daily dosages are taken from the *Physicians' Desk Reference* (2000). Price per day of therapy is then computed as revenues divided by the quantity of therapy days in that month. Further details on price, quantity, and revenue measurement are found in the data appendix of Berndt et al. (1997).

The price and quantity data we employ only cover Rx sales into drugstores. Drugstore sales constitute on average about 70–80 percent of sales in all outlets but exclude sales to hospitals, long-term care facilities, and mail-order distributors (IMS Health 1998). Because 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 its Office Contact Report™. Basing its data on a panel of about 3,800 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 its National Journal Audit™. 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, and 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 et al. (1997) and in IMS Health (1998).

The Rx H_2 antagonists have been marketed not only to physicians but also, more directly, to consumers. In the context of Rx-to-OTC switches, direct-to-consumer (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"

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

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 were steady during the 1990s.[16]

Data on DTC marketing of Rx brands from Leading National Advertisers (LNA)/Media Watch Multi-Media Service is published on a quarterly basis by Competititve Media Reporting. This service reports Rx brand advertising expenditure estimates in ten major media: consumer magazines, Sunday magazines, newspapers, outdoor advertising, 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 1998:4. To transform the quarterly data into monthly periodicity, we employ the Stata command "ipolate."[17] 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.[18]

8.5.2 Over-the-Counter Drug Markets

Quantity and revenue data for the OTC H_2 market are taken from InfoScan™, based on store-level optical scanner data purchased and collected from multiple retail outlets by IRI.[19] These scanner data are collected weekly from more than 29,000 chain drugstores, 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 are 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 twenty-five tablets of 200 mg cimetidine are sold, we compute the to-

16. On this, see Rosenthal et al. (2002).

17. See Stata Corporation (1999).

18. For 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.

19. See Information Resources Inc. (1997), Guadagni and Little (1983), and Bucklin and Gupta (1999). The IRI website is [http://www.infores.com].

tal number of mg of Tagamet HB sold that month as $5000 \times 25 \times 200 = 25$ million mg. Unlike the IMS Health data on Rx sales to drugstores, the IRI data record sales from drugstores, mass merchandisers, and food stores to consumers, so the IRI data include both wholesale and retail margins. Moreover, whereas the IMS data reflect inventory stocking behavior by, for example, chain drugstore 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.[20] 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.[21] Rather, the quantity measures should be interpreted as the number of patient days of therapy that would be consumed were all the OTC H_2s 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_2s to treat active duodenal ulcers.[22] 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.

Over-the-counter medications have been marketed intensively to consumers. For example, between 1990 and 1996 for the seven largest-selling antacid OTC products in 1994, the median real ratio of advertising to retail sales was approximately 34 percent.[23] To obtain measures of monthly advertising of the OTC H_2s, we employ data from Leading National Advertisers/Media Watch Multi-Media Service. Leading National Advertisers 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 1998:4. The "ipolate" command in Stata is again employed to con-

20. This follows procedures utilized by Ling (1999) and Berndt et al. (1995, 1997).

21. Recommended dosages vary by indication. For example, whereas 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.

22. For each of the four OTC H_2s, the transformation of OTC to Rx involves using twice the maximum daily recommended OTC dosages.

23. Ling (1999). The seven brands are Tums, Mylanta, Gaviscon, Maalox, Alka-Seltzer, Rolaids, and Pepto-Bismol.

vert 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.

8.6 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 preemptive launch of OTC H_2 variants and the effects of competition from generic Rx H_2 producers.

8.6.1 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 8.3, we examine marketing efforts for the two H_2 antagonists losing patent expiration, Tagamet (May 1994) and Zantac (August 1997).[24] 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 periods 1–24 and 25–48 months prior to patent expiration are called "near versus far away," and those between the periods 0–23 months after and 25–48 months before are called "after versus far away." The results of these calculations are given in table 8.1, the top panel in terms of marketing quantity levels, and the bottom in ratios of dollar marketing to sales.

For Tagamet, average monthly minutes of detailing fell by 30 percent as its patent expiration approached (May 1992–April 1994 vs. May 1990–April 1992) and by 87 percent 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 percent and 97 percent, respectively. The ratio of total marketing (detailing plus medical journal advertising) expenditures to total sales revenue (bottom two rows of table 8.1) fell by 43 percent as Tagamet patent expiration approached, and then it subsequently fell by a smaller amount, 30, after patent expiration. The post-patent smaller decline

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

Table 8.1 **Changes in Marketing Efforts in Anticipation of and Following Patent Expiration, H_2-Antagonist Prescription Drugs (%)**

	Tagamet Patent Loss	Zantac Patent Loss	Pepcid at Zantac Patent Loss	Axid at Zantac Patent Loss
Minutes of detailing				
Near vs. far away	–30.2	–59.3	–19.6	–36.0
After vs. far away	–86.6	–94.4	–28.3	–48.5
Pages of journal advertising				
Near vs. far away	–55.1	–99.3	257.7	–16.1
After vs. far away	–96.7	–100.0	–16.2	–94.7
Dollar Marketing to Dollar Sales Ratios				
Detailing dollars to sales ratio				
Near vs. far away	–37.8	–57.4	–39.1	–36.3
After vs. far away	–32.3	–71.2	–36.7	–35.1
Total detailing plus journal advertisingdollars to sales ratio				
Near vs. far away	–43.1	–59.8	–33.3	–36.0
After vs. far away	–30.1	–72.8	–35.3	–35.5

Notes: For Tagamet, "far away" is May 1990–April 1992, "near" is May 1992–April 1994, and "after" is May 1994–April 1996. For Zantac, Pepcid, and Axid, "far away" is August 1993–July 1995, "near" is August 1995–July 1997, and "after" is August 1997–July 1999.

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 percent as Zantac patent expiration approached (August 1995–July 1997 vs. August 1993–July 1995), and by 94 percent 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 percent and 100 percent, respectively. The total marketing-sales ratio fell by almost 60 percent, and it fell by an additional 13 percent after patent expiration.

It is also of interest to examine how the competitors of Zantac, then the leading selling H_2, reacted when they observed Zantac cutting back on marketing in anticipation of and following Zantac's patent expiration. Because the entire H_2 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 H_2 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?[25] The marketing responses of Pepcid and Axid surrounding the time of Zantac's patent expiration are summarized in the last two columns of table 8.1.

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

Pepcid and Axid had rather different responses. For Axid, average minutes of detailing fell by about 36 percent as Zantac's patent expiration approached, and they fell another 13 percent following expiration. The journal advertising cutback was more varied: 16 percent as Zantac's patent expiration approached and 95 percent following it. For Pepcid, however, the decline in minutes of detailing was much more modest—only 20 percent in the time leading up to Zantac patent expiration, and an additional 8 percent following it. Journal page advertising for Pepcid actually increased by 258 percent (from rather low levels) as Zantac patent expiration approached, and after patent expiration it fell to 16 percent less than that 25–48 months before Zantac patent expiration occurred. Although 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-sales ratios. Both reduced these ratios by about 33–36 percent 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 twelve to eighteen months following patent expiration, generic manufacturers of cimetidine and ranitidine did a very modest amount of medical journal advertising.[26] Although 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.

8.6.2 Pricing of Rx Drugs in Anticipation of and Following Patent Expiration

Next we analyze pricing behavior prior to and following patent expiration. Figure 8.1 plots prices per day of therapy for Rx Tagamet and generic Rx cimetidine from January 1989 through December 1998, whereas figure 8.2 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.

26. For cimetidine, medical journal pages with generic cimetidine advertisements in the eighteen months following Tagamet patent expiration were only about 14 percent of the corresponding Tagamet pages in the eighteen months prior to its patent expiration. For ranitidine, in the eighteen 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 eighteen months following Zantac patent expiration was only about 17 percent of Tagamet's pages in the eighteen months prior to Tagamet's patent expiration. For both generic cimetidine and ranitidine, journal page advertising beyond eighteen months following the brand's patent expiration date is essentially zero.

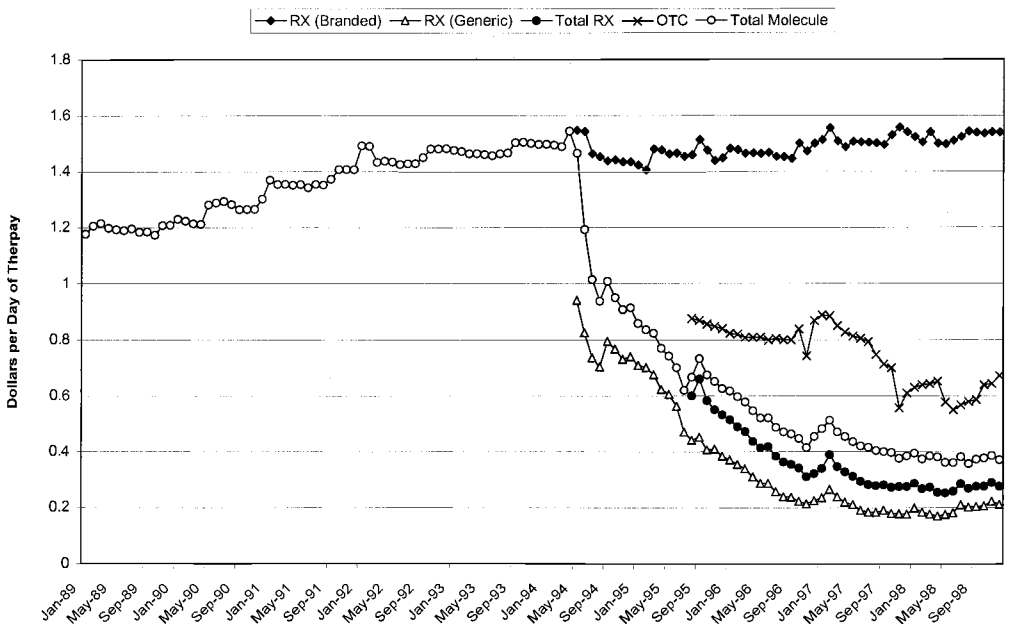

Fig. 8.1 Cimetidine price

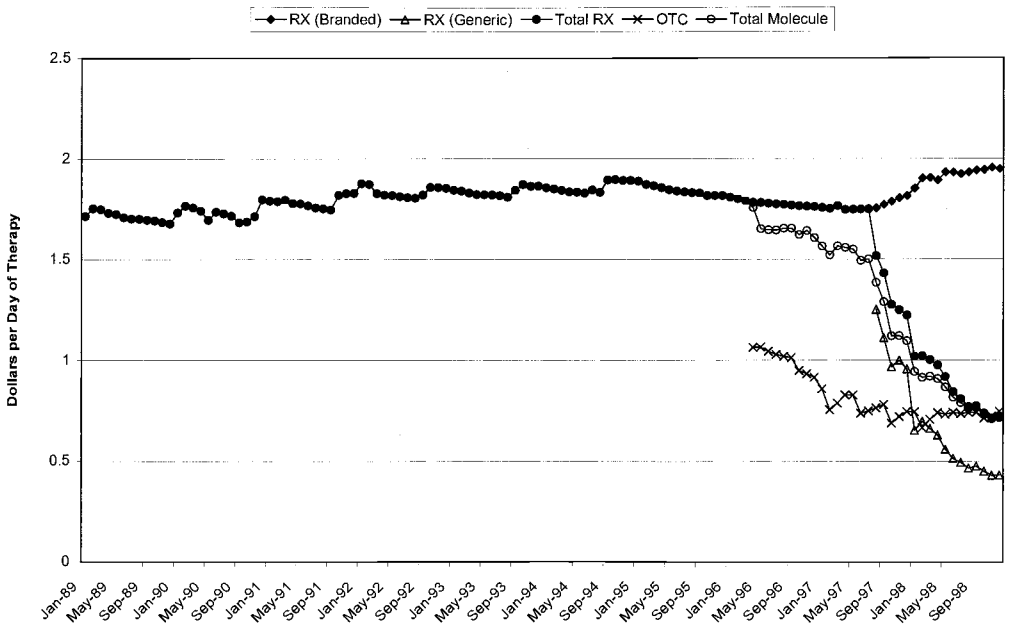

Fig. 8.2 Ranitidine price

As is seen in figure 8.1, Tagamet's Rx price continued to increase following patent expiration in May 1994, and by December 1998 it was about 5 percent 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 late 1998, the Tagamet Rx brand price was almost 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 percent of its level at the time of patent expiration in May 1994. The total Rx price at late 1998 was about one-sixth that of the Tagamet Rx brand price.

Figure 8.2 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 late 1998 it was about 10 percent 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 8.1 and 8.2). This difference could reflect greater entry incentives for ranitidine, because at the time of patent expiration the branded Zantac Rx was a larger dollar and unit sales market than was branded Tagamet Rx. In December 1998 the price of generic ranitidine was about one-quarter that of Zantac at the time of its patent expiration and one-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 since patent expiration.

Just as with cimetidine, consumers have realized far lower average prices for ranitidine following Zantac's patent expiration. By late 1998 the average ranitidine Rx price (a sales-weighted average over Zantac Rx and generic ranitidine Rx) was about 65 percent 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 they increased prices. As a consequence, they lost a very substantial market share but retained sales to a small, relatively price-insensitive segment of brand-loyal customers.

8.6.3 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 is seen in figure 8.3, sales were relatively flat during the four years preceding patent expiration in May 1994 but plummeted afterward as

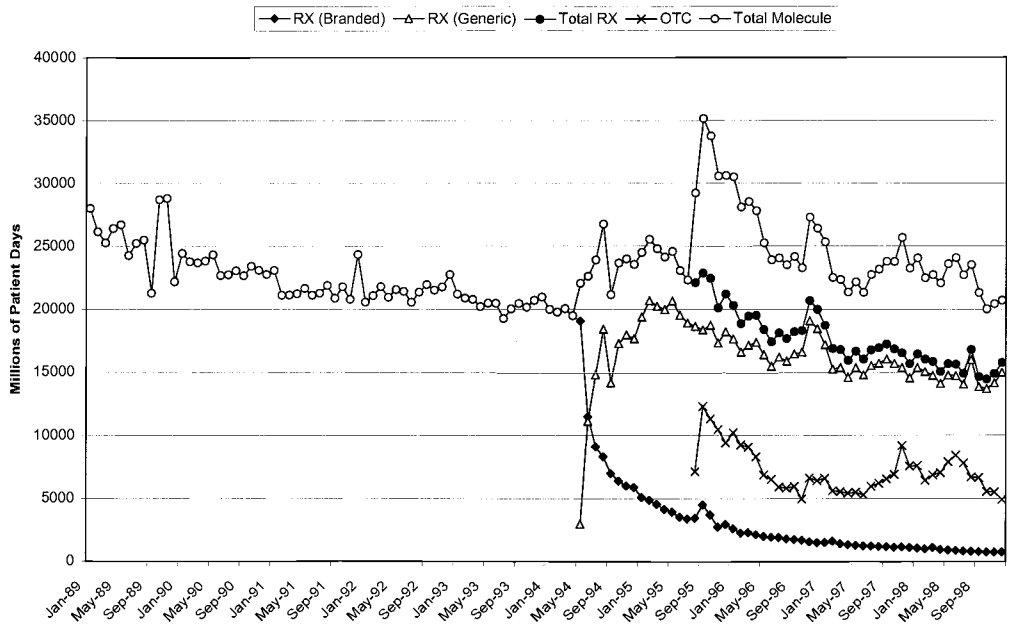

Fig. 8.3 Cimetidine units

generic entrants flourished. By late 1998, generic cimetidine had more than 95 percent market share of the prescription cimetidine market. Total quantity of brand plus generic Rx cimetidine sales (labeled "Total Rx" in figure 8.3) 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 8.1). 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 8.4. In particular, branded Zantac Rx sales appear to have fallen steadily since early 1995 (around the time Pepcid AC, the first OTC H_2, came on the market), 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 December 1998 Zantac Rx unit sales were about 10 percent of their 1994–95 peak levels. Total ranitidine Rx sales ("Total Rx" in figure 8.4) 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 8.3 and 8.4), 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 8.1 and 8.2).

8.6.4 L(a)unching with Cannibals: Effects of OTCs 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, nonusers 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 because 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.

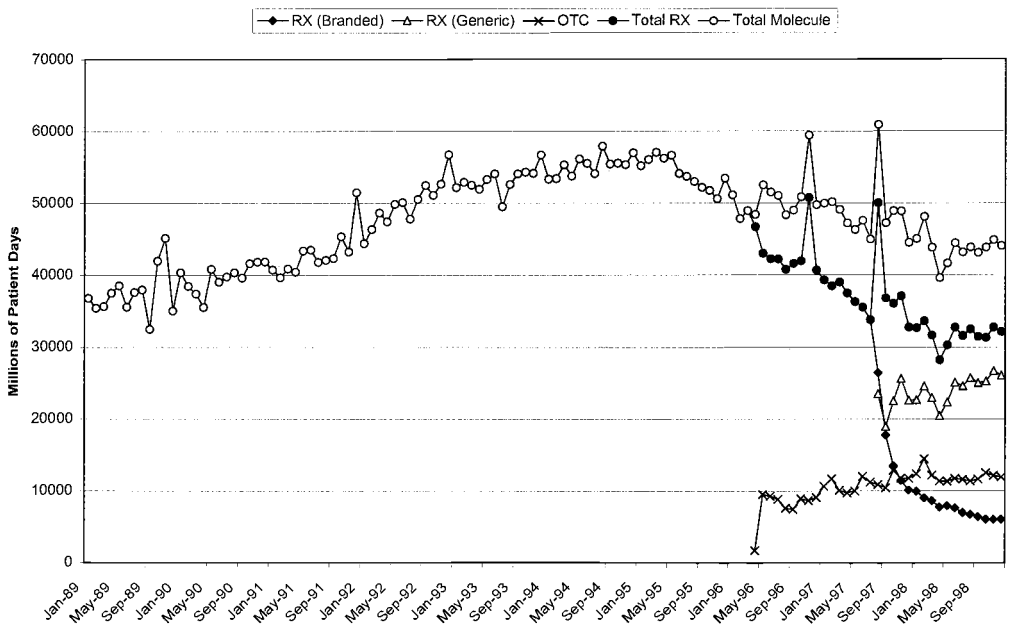

Fig. 8.4 Ranitidine units

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 December 1998 the OTC Tagamet HB price per day of therapy is about 45 percent the Rx Tagamet price, but slightly more than three times the Rx generic cimetidine price, as shown in figure 8.1. Figure 8.2 shows that by late 1998, on a per-patient day of therapy basis, the price of OTC Zantac 75 is about one and one-half times that of Rx generic ranitidine, but only about 40 percent 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, whereas 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 one-half times their comparable OTC price in late 1998.

The quantity of OTC Tagamet sold in late 1998 is about seven to eight 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. By mid-1998, however, total Rx plus OTC Tagamet sales were again falling, and by late 1998 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 8.4, 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 late 1998 patient days of Zantac OTC were twice 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 that 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 times greater than those for Tagamet Rx in late 1998, whereas OTC Zantac 75 revenues

were only slightly less than those from Zantac Rx. Summed over both OTC and Rx versions, however, Zantac revenues were about four to five times larger than those for Tagamet. Hence, although 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.

8.7 Price Index Construction with Generic and Over-the-Counter "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. Because 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 8.4 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 8.4. Specifically, to implement the Feenstra procedure using nonlinear estimation procedures, we have estimated parameters in the normalized quantity equation (6) derived from the CES brand-generic demand equations, using monthly data from both before and after 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 among residuals in the two equations.

To implement the GC methodology, single equation least squares procedures are employed in estimating the CES parameters in equation (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 equation (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, nonprice 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, because only brand-generic substitutability within a given molecule is being modeled, and, as we observed earlier, in practice very few marketing efforts occur after patent expiration. On the other hand, in the Feenstra specification, because pre–patent expiration data are included, excluding nonprice factors as regressors in the total molecule demand equation (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.

8.7.1 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 January 1989–June 1999 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, whereas 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 σ were about –1.6 and 140, respectively;

assuming generic revenue shares of 67 percent, the comparable translog-based substitution elasticity estimates were about –0.6 and 70.

To check on the robustness of these unsatisfactory σ estimates, we systematically shortened the pre–patent expiration time period that ended first in May 1994 for Tagamet, sequentially dropping all observations in 1990, 1990–91, 1990–92, and then 1990–93; 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 σ estimates 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 twelve months and included in each of the molecule equations both own and others' cumulative marketing efforts. Although 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 σ 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 –4,443), whereas elasticity of substitution estimates for cimitedine ranged from 1.02 (using January 1991–December 1998 data) to 3.26 (January 1994–December 1998).

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 after 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.

8.7.2 Price Indexes for All Four Molecules Accounting for Over-the-Counter Entry

OTC entry occurred for Tagamet HB in August 1995, about fifteen months after Rx Tagamet lost patent expiration. In contrast, the OTC entry of Zantac 75 took place in April 1996, about eighteen 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 subsection, 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 nonparametric 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, whereas 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 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 twelve 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 twelve months. Because the DTC data available to us ended in December 1998, we utilize data over the ten-year time period January 1989–December 1998, yielding cumulative marketing effort measures for each molecule for the nine-year period January 1990–December 1998.

The Feenstra method involves maximum likelihood estimation of a four-equation system with cross-equation parameter restrictions and a balanced panel, whereas for the GC method single equation ordinary least squares (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 versus OTC substitution elasticity, which of course differs 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 and 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 9,069, 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), whereas 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, whereas 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 σ elasticity of substitution estimate for cimetidine to be 1.74, the mean of the corresponding σ estimates over famotidine, ranitidine, and nizaditine. We then substituted these σ estimates into equation (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 8.5, where for each molecule the price index is 1.000 in January 1989. A number of points are worth noting.

First, for all four molecules, prices generally increase during the first five years from January 1989 to January 1994, 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 percent of its April 1994 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 8.5, 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 December 1998, about 29 percent 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 January 1989 through June 1996; it then drops about 15 percent to 1.04–1.06 in late 1996, and thereafter it experiences a steady increase, ending up at 1.147 in December 1998, down about 11 percent from the 1.289 level in June 1996 just prior to launch of the OTC Axid AR product. The Rx version of Axid did not lose patent protection until 2001, beyond the December 1998 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

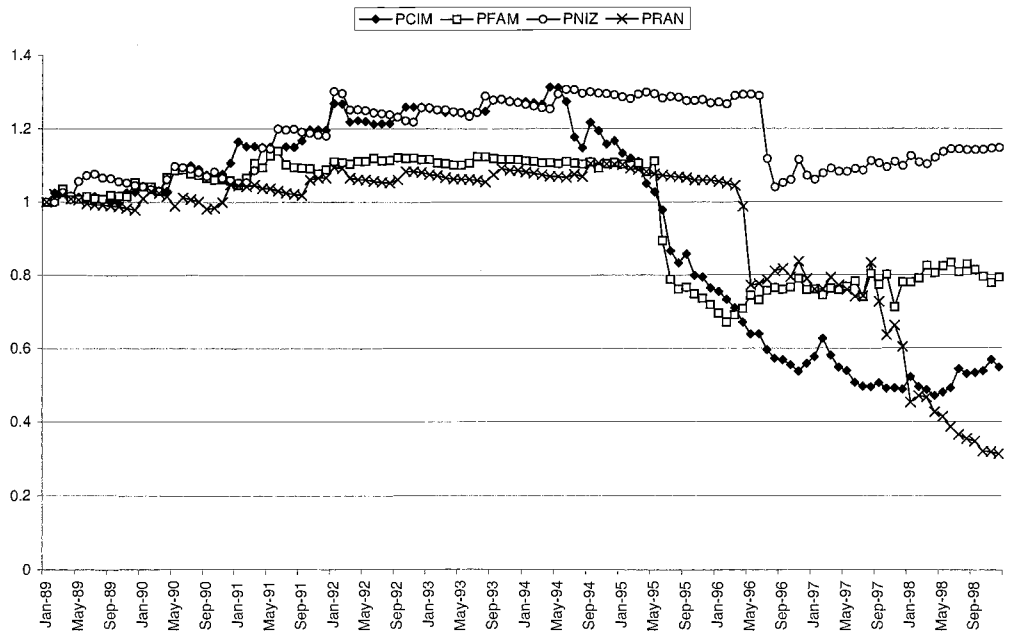

Fig. 8.5 Aggregate molecule price indexes

Zantac 75 product resulted in by far the largest price decline among the four molecules. As seen in figure 8.5, the ranitidine molecule experienced about a 25 percent price decline in May 1996 as OTC entry of Zantac 75 occurred, then another sharp price decline of about 25 percent between August and December 1997 as generic ranitidine initially entered the market, and continuing declines during 1998 with further generic ranitidine entry. In December 1998, the ranitidine molecule price index was 0.313, about 30 percent of its level just prior to the OTC launch of Zantac 75 and about 50 percent 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 before and after OTC entry. Following GC, we have also estimated the Rx-OTC elasticity of substitution using equation (8) and, for each molecule, only the data following OTC launch. These results were somewhat disappointing. For all four molecules, GC-CES estimates of σ were less than 1.0, violating a necessary condition of the model that $\sigma > 1$. With relative Rx/OTC marketing variables excluded, the estimated σ (standard error follows in parentheses) 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 equation (8), the relative marketing variable was typically significant and of the right sign, but all of the σ estimates remained below unity. These σ 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.

8.8 Summary and Conclusions

In this paper we have reported results of our research examining the "sunset" H_2s 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 PPIs. Although the looming prospect of patent expiration had significant impacts on the behavior of the H_2 manufacturers in terms of their pricing and marketing behavior, it was more than the shadow of patent expiration that dimmed the H_2 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 H_2s. 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 H_2 price and quantity measures, denoted PH2TOT and QH2TOT, are graphed in figure 8.6, with each indexed to 1.000 in January 1989. As is seen in figure 8.6, the aggregate H_2 price series increased steadily from January 1989 to about January 1992, 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 December 1998, the aggregate H_2 price index was 0.57, roughly 50 percent lower than in early 1995 just prior to the first OTC entry.

In terms of quantity of H_2s consumed, from January 1989 to early 1995 the quantity index increased from 1.00 to about 1.33, then grew more rapidly to about 1.86 by November 1996, and then began falling again, ending up at about 1.41 in December 1998.

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 H_2 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 percent of their pre–patent expiration levels, for both cimetidine and ranitidine the combined brand and generic quantity sales following patent expiration have also fallen considerably. This utilization decline could reflect the impacts of decreased marketing efforts, competition from the more potent PPIs, 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 late 1998 brand OTC prices were 35–45 percent of their brand Rx prices, but brand OTC prices were still several times larger than same molecule generic Rx prices. These price

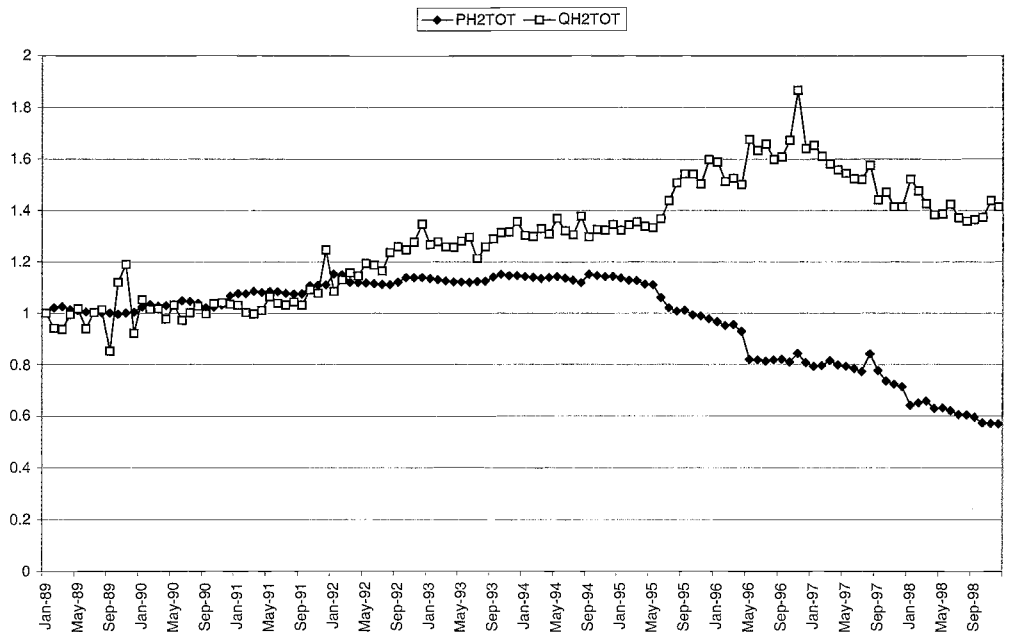

Fig. 8.6 Aggregate H_2 price and quantity indexes

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, although 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 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 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 σ 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 nonprice 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 (see, e.g., Berry, Levinsohn, and Pakes 1995; Bresnahan, Stern, and Trajtenberg 1997). The existence of principal-agent and moral hazard issues, particularly important in the Rx market, however, makes such research very challenging.

Pepcid, Prozac, and Mevacor all lost patent protection and faced generic entry in 2001, and Prilosec could face generic entry in 2002, pending the outcome of patent litigation. Whether the long shadows of imminent patent protection for these drugs will display similar pricing, marketing, and Rx-OTC switching patterns to what we have observed in the H_2 market remains to be seen.

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Comment

Steve Morgan

In "The Long Shadow of Patent Expiration: Generic Entry and Rx-to-OTC Switches" Ernst R. Berndt, Margaret K. Kyle, and Davina C. Ling tackle two problems: one concerning producer theory, the other concerning price measurement based on consumer theory. In both regards, their focus is on the strategies used by manufactures of "sunset" branded pharmaceutical products—products for which patent expiry is imminent. They aptly illustrate how manufacturers can tailor marketing, pricing, and product lines to protect the profitability of their brands at this stage of the product life. Understanding the strategies of sunset brands is important because many leading pharmaceutical products are due to lose their patented status soon.

It is also of policy interest to assess the welfare impact of market dynamics associated with patent loss. This leads to the second problem addressed by Berndt, Kyle, and Ling: price measurement in the changing market environments of sunset branded drug products. In view of the theme of the conference, my comments focus on these measurement issues; they draw, however, on the practical realities of the pharmaceutical sector that make profitable the corporate strategies identified in the first half of their paper.

Berndt, Kyle, and Ling contrast two approaches to measuring the "new goods" effects of generic entry and the launch of over-the-counter versions of brand name products among a class of acid suppression drugs, histamine$_2$-receptor antagonists. They implement a reservation price estimation technique advocated by Griliches and Cockburn (1994, 1996) and a demand system estimation technique advocated by Feenstra (1997). Both methods have been use to address the generic drug problem elsewhere, but not the over-the-counter question.

The method advocated by Griliches and Cockburn is to use postentry market observations to estimate a reservation price for a generic entrant. Griliches and Cockburn simplify the task by assuming that consumers have a uniform distribution of reservation prices over the interval between the

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launch price of the generic and price of the brand at patent expiration. Berndt, Kyle, and Ling implement the approach using least squares procedures for estimating intraproduct class elasticity of substitution, upon which reservation price estimates are based.

The results gleaned from the Griliches and Cockburn method are intuitive for the prescription-only submarket. Indexes accounting for the price effect of generics fall upon their entry. Consumers, it would appear, are better off from increased competition among chemically equivalent prescription-only products. The econometric results pertaining to the over-the-counter availability of like-branded histamine$_2$-receptor antagonists, however, fail to meet necessary assumptions concerning the own-price elasticity when the Griliches and Cockburn method is employed. Postentry data generate unduly low elasticities.

The index method advocated by Feenstra is based on the estimation of the elasticity of substitution within and across products using both pre- and postentry data. It does not require the estimation of a reservation price and has been applied by Feenstra in other consumer product submarkets as well as on two classes of prescription drug products (Feenstra 1994). Others have advocated such a method as a generalized means of addressing substitution biases in product classes where the number of goods fluctuates over time (Balk 1999).

When Berndt, Kyle, and Ling implement this approach in the absence of marketing data, the parameter estimates are unstable and the implied indexes are counter-intuitive. As presented at the conference, their findings indicated that those price indexes went up after generic entry, implying that consumers are made worse off. Indexes that incorporate the impact of over-the-counter availability of like-branded products also produced inconsistent results in the absence of advertising data. When data on the marketing efforts are incorporated into the analysis, however, Feenstra-method findings related to the over-the-counter availability of like-molecule products were much improved. Three of four elasticity estimates converged at expected signs, and the implied price indexes showed substantial declines following the launch of over-the-counter versions of same-brand products.

Interpreting the index results—based on either Griliches and Cockburn's methods or Feenstra's method—that pertain to launch of over-the-counter products is particularly challenging due to a number of limitations in the data and the nature of the product class being analyzed.

The wholesale-level prescription data and the retail-level nonprescription data are not particularly comparable. This is because wholesale prices do not closely resemble the actual prices paid by large buyers of pharmaceuticals in the United States. Few but the uninsured pay list (wholesale plus markup) prices for pharmaceuticals. Instead, price-volume discounts and rebates are typically negotiated between manufacturers and pharmacy benefit providers (insurers, government agencies, or managed care corpo-

rations). The value of these negotiated discounts was substantial in the 1990s—sufficient to provoke the Health Care Financing Administration to revise its expenditure estimates to account for average discounts of approximately 24 percent (Genuardi and Stiller 1996). Moreover, discounts are achieved by pitting competing manufacturers' price offers against each other, which sets off a bidding war—the winner of which gets on, or receives preferential treatment within, the drug benefit provider's formulary. However important these pricing dynamics may be, they remain hidden.

Further challenges to the comparability of over-the-counter and prescription-only market segments come from the nature of the products being sold—including the nature of the information about those products contained in advertising. The prescription-only and over-the-counter products are marketed for quite different indications, even though they are comprised of the same active chemical ingredients.[1] As Berndt, Kyle, and Ling acknowledge, over-the-counter histamine$_2$-receptor antagonists are marketed and labeled for the prevention of minor heartburn, acid indigestion, and sour stomach. The packages of both Zantac 75 and Tagamet HB explain the dosing regimen for treating or avoiding heartburn due to acid indigestion or sour stomach, and warn patient not to use the drug for more than fourteen days unless directed to by a physician. Manufacturers cannot legally suggest that these nonprescription products be used for other purposes—neither in their packaging, nor in their advertising. However, to treat an ulcer with these over-the-counter drugs, patients must take twice the recommended dose for thirty to sixty days—two to four times the recommended duration of over-the-counter therapy. There is little doubt that some consumers do treat ulcers with the over-the-counter products—many, I suspect, do so on the advice of their physician. A vast majority of consumers in the over-the-counter market, however, are probably taking the drugs in small doses to ward off the annoyance of heartburn (e.g., as induced by eating spicy foods), not for the treatment of active ulcers. In light of these comparability issues, the index results concerning over-the-counter product launches are probably insufficient grounds to endorse one methodology over the other. With either the Feenstra or the Griliches and Cockburn method, it is unclear that one is comparing apples with apples.

On the other hand, the anomalous results found with Feenstra's preferred method of accounting for the impact of generic availability do provoke questions that may lead one to prefer the method of reservation-price estimation. In their presentation at the conference, Berndt, Kyle, and Ling

1. It is not uncommon for a single chemical to be marked for different indications. Two examples illustrate. Glaxo Wellcome markets *bupropion hydrochloride* as "Wellbutrin" for the treatment of depression and attention deficit disorder and as "Zyban" to help patients quit smoking. Merck markets *finasteride* as "Propecia" for male pattern baldness and as "Proscar" for the treatment of benign prostatic hyperplasia (non-cancerous enlargement of the prostate gland).

offer several possible reasons for the prescription-only price index discrepancies. One of these conjectured sources of inconsistency deserves elaboration, because it seems to point toward much-needed future research.

Feenstra's method requires the stability of parameters within the unit expenditure functions defined over equivalent brand and generic products (or over prescription and over-the-counter products) as well as the separability of these unit expenditure functions from the remainder of the consumer's utility function. Berndt, Kyle, and Ling remind us that their data span a period of more than ten years, raising a caution against the assumption of parameter stability (and possibly even separablility). In fact, the particular ten years for the particular products being analyzed may be less stable than might be the case in other commodity markets, including other classes of pharmaceuticals.

The nature of the demand for Histamine$_2$-receptor antagonists has been nothing if not unstable over the past two decades. These antiulcer drugs were the defining blockbuster drugs of the 1980s—their marketing hype and cash-box success earning them the Hollywood analogy. Soon after the stellar rise of this product class, the premise upon which much of its success was based came under scrutiny. Beginning in the early 1980s, clinical scientists began a protracted debate about the ulcer-causing role of bacteria known as Helicobacter-pylori. By 1994, evidence indicating that the presence of the bacteria was a causal factor in gastritis, duodenal ulcer, and some gastric ulcers had convinced even those who were outspoken critics of the Helicobacter-pylori theory (Therapeutics Initiative 1994). Combined with imminent patent expiration and serious prescription-only competition from the proton pump inhibitors, the widespread acceptance of the Helicobacter-pylori theory forced manufactures of Histamine$_2$-receptor antagonists to define and expand other uses of these acid suppressors.

One would hope that consumers' (or more specifically, physicians') appraisals of the prescription versions of Histamine$_2$-receptor antagonists changed over the 1990s. If so, the unit expenditure functions for antiulcer products would neither be stable nor separable from the remainder of consumers' utility functions. Consider, for example, the interaction between the marginal utility of Histamine$_2$-receptor antagonists and the antibiotic products used to eradicate the Helicobacter-pylori bacteria.

Notwithstanding changes unique to the antiulcer market, the availability of a generic alternative in a subclass can have several impacts on that class and others. The fact that branded products can "cream-skim" by raising prices following generic entry implies that the market is somehow segmented. It is quite possible that the most important segmentation is not with respect to tastes for branded versus generic products, but segmentation along financial incentives. Not only is there a distinction between the insured and uninsured, but many insured consumers now face forms of incentive pricing aimed at encouraging them to consider low-cost generics.

Knowing the financial incentives of the consumers in question is essential to understanding what is revealed by their consumption patterns.

Consider patients covered under the British Columbia Pharmacare Plan A. Plan A, which accounts for about 30 percent of drug spending in this Canadian province, is a tax-financed plan offering drug benefits for all residents in British Columbia who are sixty-five years of age and older. The plan covers ingredient costs of prescribed drugs; beneficiaries must pay associated pharmacists' dispensing fees. Before 1994, Plan A beneficiaries could obtain equivalent branded and generic drugs at the same cost: whatever the pharmacist charged for dispensing. Generic utilization under these incentives was understandably low (Grootendorst et al. 1996). Starting in April 1994, the government began an incentive pricing policy wherein the brand-name product was fully covered only for consumers who had medical reasons for obtaining the brand over generic alternatives. All other consumers who preferred the brand to the generic would have to pay the price difference—Pharmacare paying a share equal to the cost of the generic.

Figure 8C.1 illustrates how this simple change in financial incentives altered utilization patterns. The figure plots the average market share held by all (272) brand-name products that existed in 1988 and were subject to generic competition before 1998, grouped by the year of generic entry. The average price of brand-name drugs exceeded that of generics by approximately 40 percent in 1993. Although generics gradually penetrated markets before the incentive pricing policy was implemented, the process was slow and seldom complete. When the policy change took place in 1994:2, few brand-name firms matched generic prices, and the rate of generic drug utilization rose to the neighborhood of 80 to 90 percent.

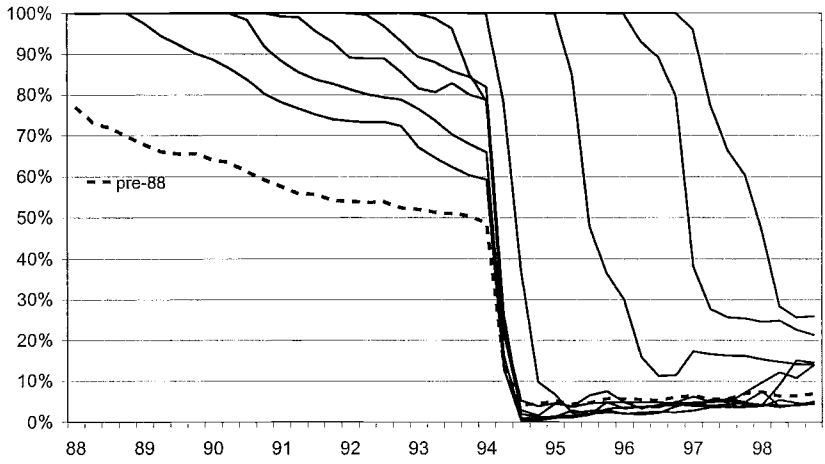

Fig. 8C.1 Average of brand's share of markets grouped by year subject to generic competition

A reservation price technique for capturing the impact of generics is probably better suited to deal with the discontinuity of financial incentives that occurs under an incentive pricing policy. For purchases made without such incentives (e.g., prior to the Pharmacare policy change), would the real revealed preferences be revealed under either the Feenstra or the Griliches and Cockburn method? Probably not.

An increasing number of insurance companies, pharmacy benefits managers, and health maintenance organizations in the United States are using incentive pricing policies to encourage generic drug utilization (Aventis 2000; Scott-Levin 2001). However, it is not clear if uninsured individuals are always aware of the generic option. In a recent survey of American consumers, 87 percent said they would choose a generic drug if it would save them money, yet fewer than half reported having been presented with the choice when purchasing drugs (Flemming 1999). Given the mix of financial incentives and product knowledge at the individual level, aggregate price and quantity observations are difficult—if not impossible—to interpret.

Berndt, Kyle, and Ling offer us an important, detailed description of firm behaviors when products are in their sunset phase, as well as a thought-provoking comparison of the indexes that economists might otherwise use to measure the impact of firm behaviors. Four times they caution readers about the difficulty of interpreting cost-of-living measures in the pharmaceutical sector due to the nonstandard financial incentives of consumers and potential imperfections in the physicians' agency role. Unfortunately, most readers, even trained economists, beg the welfare-theoretic question when they read price index results. Berndt, Kyle, and Ling rightfully (I believe) conclude that for measurement theorists and statistical agencies to address the welfare-theoretic question head-on, we do not necessarily need more sophisticated econometric techniques; we require better models of the principal agent relationships in the pharmaceutical sector and better sources of data. Even the detailed data sources employed by Berndt, Kyle, and Ling suffer from the fact that financial incentives are a dog's breakfast in the market as a whole. I believe the best future research in this area will probably come from drug-plan specific databases. With such databases, one can be (more) certain of consumers' financial incentives and tailor the price indexes accordingly.

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