Do Pharmaceutical Sales Respond to Scientific Evidence?

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I investigate how different sources of information influence the diffusion of pharmaceutical innovations. In prescription-drug markets, both advertising and scientific information stemming from clinical trials can affect physicians' prescription choices. Using novel indices of clinical-research output, I find that both marketing and scientific evidence directly influence the diffusion process in the antiulcer-drug market, with marketing having a more pronounced influence. I also find evidence that clinical outputs are important drivers of firms' marketing efforts, affecting sales indirectly. Taken together, the direct and indirect effects of science on demand imply strong private incentives for clinical research. I conclude that product-market competition in the pharmaceutical industry is shaped by both advertising rivalries and scientific rivalries. Moreover, drug advertising may perform an important informative function.

1. Introduction

How do different types of information influence the diffusion of pharmaceutical innovation? The spread of technological advances is limited by the extent to which relevant information is available among potential adopters. Furthermore, the information necessary for the diffusion of pioneer products may be different from that required for the market penetration of subsequent innovations.

In most industries, one would expect underinvestment in the production of knowledge to limit the availability of objective sources of information about product characteristics, safety, and efficacy (Arrow, 1962). However, in prescription-drug markets, two features of the institutional environment—extensive, government-mandated

For useful suggestions and support, I would like to thank audience participants at the MIT IO Lunch and the NBER Productivity Lunch, as well as Dan Ackerberg, Richard Caves, Peter Davis, John DeFigueiredo, Sara Ellison, Stan Finkelstein, Jeff Furman, David Genesove, Jerry Hausman, David Hsu, Rebecca Henderson, Kip King, Bob Pindyck, Robert Rubin, Otto Toivanen, and especially Scott Stern and Ernie Berndt. The usual disclaimer applies.

Journal of Economics & Management Strategy, Volume 11, Number 4, Winter 2002, 551–594

testing requirements, and the structure of incentives in academic medicine—provide a context in which privately valuable information is made publicly available through the publication of clinical studies in medical journals. In addition, pharmaceutical companies promote their products extensively, though disagreements remain among economists and policy makers concerning the role of drug advertising. For some, marketing activities foster the rapid dissemination of product information about potentially life-saving products, while others emphasize its strategic use by sellers of incumbent brands to jam information channels that could be used by new entrants (Leffler, 1981; Hurwitz and Caves, 1988).

A finding that pharmaceutical sales do not respond to scientific information (holding advertising intensity constant) would be consistent with the jamming hypothesis. In contrast, a positive science elasticity of demand would imply that a more nuanced view of the relationships between advertising, scientific information, and demand is needed. Moreover, boundaries between science and advertising in pharmaceutical markets are blurry, since much advertising refers explicitly to clinical results. Thus, the pharmaceutical industry provides a unusual setting in which to compare the informative as well as persuasive functions of advertising: Are firms' promotion efforts sensitive to changes in the supply of objective, scientific information contained in published clinical studies?

I explore these questions using data pertaining to a particular subset of the antiulcer-drug market: the therapeutic class of histamine2-receptor antagonists, commonly referred to as H_2 antagonists or simply H_2 blockers. It enjoyed explosive growth from 1977, the year of the pioneer drug's introduction, until the early 1990s, when there were four related molecules in this class vying for market dominance.[1] Importantly, product-market competition in this therapeutic market was marked by the overthrow of an established monopolist (Tagamet) by a subsequent entrant (Zantac). As noted by Suslow (1997), this change in market dominance could be the result of intense price competition, advertising rivalry (both persuasive and informative), or a battle to offer the most attractive package of nonprice attributes. In this paper, I argue that among these nonprice attributes, published clinical results contributed significantly to this turnover in market leadership.

1. During the time spanned by the dataset, none of these drugs went off patent or moved to the over-the-counter (OTC) market. Therefore, I can safely ignore important issues such as substitution with generics and market segmentation between distribution channels.

Using a brand-level, discrete-choice model of product differentiation, I examine the impact of scientific information embodied in randomized controlled trials (RCTs) on the sales of these four drugs. I attempt to use the fact that RCTs can use either a placebo or a competing drug as a control group to isolate the effects of these two types of scientific information on drug sales, contingent on market structure. The results show that both marketing and science directly influence the diffusion process, with marketing having a more pronounced influence. I also examine the possibility of an indirect influence of scientific information on demand by estimating advertising response functions, and I find some evidence that clinical-research outputs indeed drive firms' marketing expenditures. Plugging back the advertising equation into the demand system, the sum of the direct and indirect effects yields total demand elasticities of science of between 0.3 and 0.5 for the pioneer drug and its challenger.

Overall, these results are consistent with a view that sees product-market competition outcomes in the pharmaceutical industry as the result of firms' rivalrous efforts in marketing and applied science. They cast doubt on the validity of the belief, widespread in the medical community, that drug advertising totally jams other conduits of professionally sanctioned information, such as the results of RCTs (Wade et al., 1989). Finally, these findings help explain the growing involvement of industry in the conduct and funding of clinical research. Not only do clinical expenditures contribute to meet safety and efficacy requirements (thereby securing regulatory approval for entry), they also constitute investments marked by long-lived and direct economic payoffs on the product market.

The remainder of the paper proceeds as follows. Section 2 reviews the literature on drug advertising and the diffusion of pharmaceutical innovations. Section 3 provides a short background on the antiulcer-drug market, in addition to describing the dataset and constructing clinical-output variables. Section 4 presents the econometric results for the discrete-choice model, while Section 5 provides estimates of advertising response functions. I offer some concluding remarks and suggestions for future research in Section 6.

2. Literature Review

The diffusion of pharmaceutical innovations is a complex social process and is subject to multiple influences. Because drugs are experience goods, the impact of entry is limited by physicians' switching costs and herding around the most popular products in a given therapeutic class (Coscelli, 2000; Berndt et al., 2000). As a result,

diffusion is rooted in learning, word-of-mouth, and other dynamic phenomena occurring within the population of potential adopters. In their landmark study of tetracycline's diffusion, Coleman et al. (1966) emphasized these *demand-pull* forces by documenting the heterogeneity of the physician population with regard to patterns of information consumption, and highlighted the role of "medical opinion leaders" who were both among the early adopters of this novel antibiotic and closely tied with the academic medical community. On the other hand, diffusion paths are also influenced by *technology-push* forces, in particular the approval by the Food and Drug Administration of additional indications for existing drugs (or of additional therapies within a given therapeutic market). These decisions result in the fall of quality-adjusted prices over time, triggering the adoption of inframarginal consumers.

While there exists numerous sources of information that might influence the adoption of pharmaceutical innovations at the individual physician level, at a more aggregate level information regarding product quality is made available to potential adopters through two primary information channels: advertising by pharmaceutical firms and published clinical results regarding the safety and efficacy of drug therapies.[2]

Beginning with Bond and Lean's (1977) FTC study, economists have extensively studied the role of drug advertising. In experience-goods markets, the mere fact that a product is advertised can signal to customers that it is of high quality (Nelson, 1974; Milgrom and Roberts, 1986). In this perspective, advertising can be interpreted as performing mostly a persuasive role, since it conveys information only implicitly. The medical literature has further argued that advertising swamps the effect of professionally sanctioned sources of information (Avorn et al., 1982; Manning and Denson, 1980) and has deleterious effects on medical practice (Wade et al., 1989). Pharmaceutical firms promote their products heavily, with advertising expenditures typically amounting to between 12% and 15% of sales. The most heavily used form of promotion—known as *detailing*—consists of visits to physicians by the sales representatives of the producers of branded pharmaceuticals. Another instrument for bringing product information to the attention of prescribing physicians is medical-journal advertising. Relative to detailing, journal advertising expenditures are modest, although the mix of promotion methods varies substantially across products and firms (Berndt et al., 1997).

2. At least, this was the situation during the period examined in this paper. The lifting of the ban on direct-to-consumer advertising and the advent of the World Wide Web in the mid-1990s have further expanded the number of relevant information sources.

Despite the intensity of promotion, the overall concern and distrust for commercial messages is surprising, since the advertising of ethical drugs is quite stringently regulated by the FDA.[3] Comanor (1986) observes that the hypothesis of wasteful or jamming advertising is insufficiently formalized, and that evidence on its behalf is largely impressionistic, relying on comments, letters and editorials of a self-appointed group of physicians and health professionals. Indeed, other scholars have claimed that drug advertising performs an eminently informative function. Peltzman (1975) proposes that advertising helps to achieve an efficient rate of diffusion—where the benefit from increasing the rate just pays the costs required to do so. Leffler (1981) shows that product promotion has a significant positive effect on the entry success of new drugs yielding important therapeutic gains. However, this evidence must be pitted against results demonstrating the role of advertising outlays in building up *brand-name recall* effects that favor established products facing new competition by generic entrants (Hurwitz and Caves, 1988). In a similar vein, Stern and Trajtenberg (1998) find that physicians who prescribe a narrow set of therapies for a given condition are more likely to prescribe highly advertised drugs.

In one of the most detailed studies of pharmaceutical advertising, Berndt et al. (1997) examine the effect of marketing investments on the growth and changing composition of the antiulcer-drug market.[4] The authors find that the effect of these investments was substantial and long-lived, although it partly spilled over to competing drugs. They also show that the second entrant's intense promotion efforts were instrumental in overthrowing the market-share leadership of the incumbent. Finally, they hint—but do not explicitly test empirically—that advertising was more effective when it interacted with a superior bundle of product-quality attributes, such as lower dosage or fewer side effects.

Market power in prescription-drug markets seems to rest as much upon habit persistence as upon fears that serious adverse consequences (such as a malpractice lawsuit) will follow an inappropriate

3. Any material distributed by pharmaceutical companies must carry the "full package insert," i.e., the complete product information reviewed by the agency as part of the drug approval process. Also, the advertising of drugs for nonapproved indications is prohibited, and comparative advertising must be supported by well-controlled clinical studies. Finally, comparison of side-effect profiles is not allowed, because most drug studies are not designed to assess the incidence of adverse interactions (Kessler and Pines, 1990).

4. I am indebted to Ernie Berndt for providing their data, which is used in this paper.

choice. However, this power may be diminished when objective information about the quality of competing products is available (Scherer, 1990). In the pharmaceutical industry, government-mandated testing requirements coalesce with the incentives of academic clinicians to assist in the production of impartial information—through the publication of clinical-trial results in medical journals. While many studies have sought to inform the debate between the persuasive and informative nature of pharmaceutical advertising, none has explicitly considered published clinical trials as an alternative information conduit. This paper is the first to use both advertising data and clinical-research output measures to examine the effect of advertising and science on diffusion, as well as the complex relationship between promotion efforts and scientific sources of information.

3. The Antiulcer-Drug Market

3.1 History

The antiulcer-drug market has been extensively studied by applied economists over the past five years, so I will provide only a brief review here. The interested reader should refer to Berndt et al. (1997) and Suslow (1996) for a more complete exposition. H_2 antagonists heal ulcers by reducing the secretion of acids in the stomach, and are effective in several contexts. Originally approved to cure gastric ulcers (located in the stomach), and subsequently for the treatment of peptic and duodenal ulcers, their introduction (starting in 1977 with cimetidine) suppressed the need for costly surgeries, allowing treatment on an outpatient basis. Later, the FDA approved H_2 antagonists as preventive treatments, and most importantly, for the treatment of gastroesophageal reflux disease (GERD)—a nonulcerous condition whose mild manifestation is more commonly known as heartburn. Finally, the liquid formulation of these drugs is also used by hospitals for the treatment of patients severely burned or bleeding.

The antiulcer-drug market can be segmented into three distinct submarkets: antacids, H_2 antagonists, and proton-pump inhibitors. Antacids (Mylanta, Maalox) were the first drugs introduced on the market, and are still considered good pain relievers (they relieve symptoms within minutes). They do not, however, inhibit acid secretion, and are therefore poor substitutes for the therapeutic class considered here.

Beginning in 1989, a new generation of drugs, known as proton-pump inhibitors, appeared on the market. Proton-pump inhibitors operate by completely shutting down acid secretion, and seem to provide an improvement on the performance of H_2 antagonists. Today,

TABLE I.
H_2-ANTAGONIST DRUGS

Drug	Molecule	Firm	Entry Date	FDA Indications: Duodenal Ulcer	Duod. Ulcer Maintenance	Gastric Ulcer	GERD
Tagamet	Cimetidine	SmithKline	Aug. 77	Aug. 77	Apr. 80	Dec. 82	Mar. 91
Zantac	Ranitidine	Glaxo	June 83	June 83	May 86	June 85	May 86
Pepcid	Famotidine	Merck	Nov. 86	Aug. 86	Oct. 86	Oct. 88	Dec. 91
Axid	Nizatidine	Eli Lilly	May 88	May 88	Apr. 88		July 91

H_2 antagonists are available over the counter, and Prilosec has become the main prescription drug for the treatment of infections of the gastrointestinal tract.[5]

3.2 Overview of the Data

Given the competitive history described above, the empirical exercise will be limited to the period beginning in August 1977 (date of entry on the US market for the pioneer drug), and ending in May 1993 (before Prilosec's rise to market dominance and Tagamet's imminent patent expiration). The first H_2 antagonist, Tagamet, was launched by SmithKline in 1977, and soon became one of the most popular prescription drug ever sold. Since then, three alternative H_2-blocker medications have entered the market: Zantac (Glaxo) in 1983, Pepcid (Merck) in 1986, and Axid (Eli Lilly) in 1988. A brief synthesis of the main product characteristics for these four drugs appears in Table I. The date for a specific indication corresponds to the time of FDA approval.

The dataset draws upon two distinct sources of information. First, product-level data on monthly sales, prices, advertising levels, and other product characteristics originates with the market research firm IMS (Philadelphia, Pennsylvania) and is discussed at greater length in Section 3.4.[6] Second, product-level indices of clinical

5. Three other forms of treatment deserve brief mention. Carafate was introduced in 1981, after Tagamet but before all the other H_2 antagonists. Because the required dosage is four times a day, it has remained a marginal player. Reglan entered the market in 1984, but is only approved for GERD. Finally, Cytotec entered in 1988, but is only indicated for the prevention of ulcers induced by nonsteroidal antiinflammatory drugs (NSAIDs).

6. This data is also described extensively in Azoulay (2001) and in Berndt et al. (1997), both in Section 7.3 (pp. 282–295) and in the appendix (pp. 314–321). Although both drugstore and hospital markets are covered by IMS audits, the analysis below will

TABLE II.
DESCRIPTION OF VARIABLES IN SAMPLE

Variable	Definition
Q_{it}	Number of monthly patient-days for drug i, in millions
SHARE_{it}	Market share of drug i (total market includes outside good)
INTERACTIONS_{it}	Number of adverse drug interactions for drug i
INDICATIONS_{it}	Number of approved FDA indications for drug i
DOSAGE_{it}	Daily frequency of administration for drug i
p_{it}	Real price per daily dose of duodenal ulcer therapy for drug i
$\text{FLOWDETAILING}_{it}$	Flow of monthly detailing minutes for drug i, in millions
$\text{FLOWDETAILING\_}_{it}$	Flow of monthly detailing minutes for competitors of drug i, in millions
$\text{FLOWDETAILINGCO}_{it}$	Flow of monthly detailing minutes for firm selling drug i, in millions
STKDETAILING_{it}	Stock of monthly detailing minutes for drug i, in millions ($\delta = 5\%$)
FLOWJOURNAL_{it}	Flow of monthly journal advertising expenditures for drug i, in millions of real dollars
FLOWJOURNAL__{it}	Flow of monthly journal advertising expenditures for competitors of drug i, in millions
$\text{FLOWJOURNALCO}_{it}$	Flow of monthly journal advertising expenditures for firm selling drug i, in millions
STKJOURNAL_{it}	Stock of monthly journal advertising expenditures for drug i, in millions ($\delta = 5\%$)
SCIENCE1_{it}	Stock of market-expanding citations for drug i, in hundreds ($\delta = 0\%$)
SCIENCE2_{it}	Stock of comparative citations for drug i, in hundreds ($\delta = 0\%$)
SCIENCE__{it}	Total stock of citations for competitors of drug i, in hundreds ($\delta = 0\%$)

research output are constructed in Section 3.3 below, using abstracts of clinical studies published in the medical literature. The complete list of variables and their definitions can be found in Table II. Descriptive statistics are displayed in Table III.

3.3 Measuring Clinical-Research Output

In order to study the response of sales to scientific information, as well as the sensitivity of promotion efforts to published clinical results, it is necessary to construct measures of relevant scientific activity. In the Data Appendix, I describe in detail the construction of indices measuring the flows and stocks of scientific information in

rely exclusively on the drugstore-market data, since it accounts for 90% of total dollar sales, and hospital use is very different from outpatient use, both in purpose and in presentation.

TABLE III.
DESCRIPTIVE STATISTICS

(A) For Tagamet ($T = 188$)

Variable	Mean	Std. Dev.	Min.	Max.
Q_{it}	27.685	8.904	3.923	46.424
SHARE_{it}	0.142	0.047	0.021	0.244
INTERACTIONS_{it}	7.096	3.617	0.000	10.000
INDICATIONS_{it}	2.745	1.089	1.000	5.000
DOSAGE_{it}	2.516	1.416	1.000	4.000
p_{it}	1.057	0.328	0.672	1.700
$\text{FLOWDETAILING}_{it}$	0.094	0.036	0.019	0.199
$\text{FLOWDETAILING\_}_{it}$	0.155	0.149	0.000	0.464
$\text{FLOWDETAILINGCO}_{it}$	0.254	0.095	0.128	0.732
STKDETAILING_{it}	1.727	0.656	0.263	2.576
FLOWJOURNAL_{it}	0.253	0.161	0.010	1.019
FLOWJOURNAL__{it}	0.337	0.335	0.000	1.386
$\text{FLOWJOURNALCO}_{it}$	0.623	0.248	0.146	1.317
STKJOURNAL_{it}	4.749	1.149	0.701	7.230
SCIENCE1_{it}	24.929	4.291	12.220	31.490
SCIENCE2_{it}	−2.071	1.973	−4.720	0.000
SCIENCE__{it}	7.301	6.477	0.000	21.600

Correlation Matrix

	SCIENCE1_{it}	SCIENCE2_{it}
SCIENCE1_{it}	1.000	
SCIENCE2_{it}	−0.903	1.000
STKDETAILING_{it}	0.947	−0.856
STKJOURNAL_{it}	0.533	−0.227

(B) For Zantac ($T = 117$)

Variable	Mean	Std. Dev.	Min.	Max.
Q_{it}	30.477	14.241	4.190	54.271
SHARE_{it}	0.150	0.068	0.022	0.276
INTERACTIONS_{it}	0.145	0.354	0.000	1.000
INDICATIONS_{it}	3.248	1.231	1.000	4.000
DOSAGE_{it}	1.342	0.476	1.000	2.000
p_{it}	1.771	0.238	1.309	2.129
$\text{FLOWDETAILING}_{it}$	0.133	0.036	0.048	0.212
$\text{FLOWDETAILING\_}_{it}$	0.221	0.098	0.060	0.456
$\text{FLOWDETAILINGCO}_{it}$	0.166	0.038	0.065	0.299
STKDETAILING_{it}	2.233	0.739	0.378	3.046
FLOWJOURNAL_{it}	0.361	0.195	0.056	0.940
FLOWJOURNAL__{it}	0.405	0.258	0.010	1.179
$\text{FLOWJOURNALCO}_{it}$	0.661	0.376	0.057	1.696
STKJOURNAL_{it}	6.618	1.256	1.558	8.621
SCIENCE1_{it}	6.381	2.479	2.030	13.070
SCIENCE2_{it}	2.962	1.209	0.040	3.970
SCIENCE__{it}	−3.150	3.891	−8.650	3.300

Correlation Matrix

	SCIENCE1_{it}	SCIENCE2_{it}
SCIENCE1_{it}	1.000	
SCIENCE2_{it}	0.842	1.000
STKDETAILING_{it}	0.911	0.778
STKJOURNAL_{it}	0.231	0.406

Continued

TABLE III.
CONTINUED

(C) For Pepcid ($T = 77$)

Variable	Mean	Std. Dev.	Min.	Max.
Q_{it}	9.157	3.739	1.729	16.134
SHARE_{it}	0.045	0.018	0.009	0.076
INTERACTIONS_{it}	0.000	0.000	0.000	0.000
INDICATIONS_{it}	2.961	0.715	2.000	4.000
DOSAGE_{it}	1.000	0.000	1.000	1.000
p_{it}	1.620	0.114	1.402	1.851
$\text{FLOWDETAILING}_{it}$	0.075	0.023	0.031	0.131
$\text{FLOWDETAILING}\_{it}$	0.348	0.069	0.205	0.505
$\text{FLOWDETAILINGCO}_{it}$	0.506	0.126	0.053	0.797
STKDETAILING_{it}	1.193	0.406	0.226	1.641
FLOWJOURNAL_{it}	0.173	0.198	0.000	0.906
FLOWJOURNAL_{it}	0.600	0.240	0.124	1.310
$\text{FLOWJOURNALCO}_{it}$	1.404	0.735	0.253	3.023
STKJOURNAL_{it}	3.360	1.275	1.021	5.532
SCIENCE1_{it}	1.978	0.470	0.350	2.590
SCIENCE2_{it}	0.876	0.459	0.000	1.390
SCIENCE_{it}	0.283	5.121	−5.800	9.710

Correlation Matrix

	SCIENCE1_{it}	SCIENCE2_{it}
SCIENCE1_{it}	1.000	
SCIENCE2_{it}	0.894	1.000
STKDETAILING_{it}	0.828	0.784
STKJOURNAL_{it}	−0.304	−0.487

(D) For Axid ($T = 59$)

Variable	Mean	Std. Dev.	Min.	Max.
Q_{it}	4.935	2.337	0.715	9.207
SHARE_{it}	0.024	0.011	0.004	0.047
INTERACTIONS_{it}	1.000	0.000	1.000	1.000
INDICATIONS_{it}	2.390	0.492	2.000	3.000
DOSAGE_{it}	1.000	0.000	1.000	1.000
p_{it}	1.683	0.165	1.484	1.943
$\text{FLOWDETAILING}_{it}$	0.114	0.024	0.069	0.217
$\text{FLOWDETAILING}\_{it}$	0.332	0.065	0.199	0.441
$\text{FLOWDETAILINGCO}_{it}$	0.310	0.056	0.200	0.476
STKDETAILING_{it}	1.611	0.546	0.316	2.268
FLOWJOURNAL_{it}	0.091	0.067	0.000	0.308
FLOWJOURNAL_{it}	0.579	0.244	0.117	1.099
$\text{FLOWJOURNALCO}_{it}$	0.176	0.067	0.071	0.372
STKJOURNAL_{it}	1.531	0.284	0.583	2.036
SCIENCE1_{it}	0.815	0.181	0.720	1.220
SCIENCE2_{it}	−0.428	0.240	−0.640	0.000
SCIENCE_{it}	−1.811	4.024	−6.410	6.760

Correlation Matrix

	SCIENCE1_{it}	SCIENCE2_{it}
SCIENCE1_{it}	1.000	
SCIENCE2_{it}	−0.461	1.000
STKDETAILING_{it}	0.581	−0.941
STKJOURNAL_{it}	−0.283	−0.302

pharmaceutical markets, an original methodological contribution of this paper. I briefly summarize the process below.

I select 483 randomized controlled trials (RCTs) pertaining to the four H_2-antagonist drugs published in 16 prominent general medicine and gastroenterology academic journals (these journals are listed in the Data Appendix). I examine the control group used in the trial. If a placebo or any active substance other than the four H_2 blockers is used, I assign to the article the label *market-expanding science.* In the case of a comparative drug study between two or more of the H_2 antagonists, the label *comparative science* is assigned. Conditional on the label, I score each RCT using a three-step Likert scale $(+1, 0, -1)$ to assess the negative, neutral, or positive impact of the article: $+1$ (respectively -1) is assigned if the treatment effect is significant and favors (respectively does not favor) the drug studied. A score of 0 is assigned if the treatment effect fails to reach statistical significance. In order to capture variation in quality across clinical studies, I weight the treatment effect score by the cumulative number of forward citations to the original article as of May 2001.

3.3.1 Flows and Stocks of Scientific Information. The final step is to define the variables characterizing the monthly flows and stocks of scientific information in the H_2-blockers therapeutic class. For each market-expanding (respectively comparative) study s, pertaining to drug i, published during month t, I define FLOW1_{it} (respectively FLOW2_{it}) as $\text{FLOW1}_{it} = \sum_s w_s \cdot \text{TE}_{sit}$, where TE_{sit} is the score received by drug i in trial s published during month t, and w_s is the weight assigned to study s. The variable $\text{FLOW}_{it} = \text{FLOW1}_{it} + \text{FLOW2}_{it}$ lumps together market-expanding and comparative science for each drug.

However, one would not expect the monthly flow of scientific information to have an effect on sales. Figure 1 graphs FLOW_{it} for Tagamet and Zantac. Except for the spikes, which correspond to large-scale trials published in prestigious journals, it is difficult to discern a trend by studying month-to-month variations. Since RCTs provide information about the existence and/or usefulness of a molecule, one would expect their effect to be long-lived, decaying slowly until better evidence appears in the literature. Hence, the effect of scientific information on sales is likely to be better proxied by a stock rather than a flow variable. Since clinical results start to accumulate before entry on the product market and do not diffuse instantaneously, the origin on the time axis was set at $m_0 - 36$ (where m_0 denotes the month of entry).

Finally, I allow for the possibility that the stock of clinical output decays over time with monthly depreciation rate δ (to be estimated

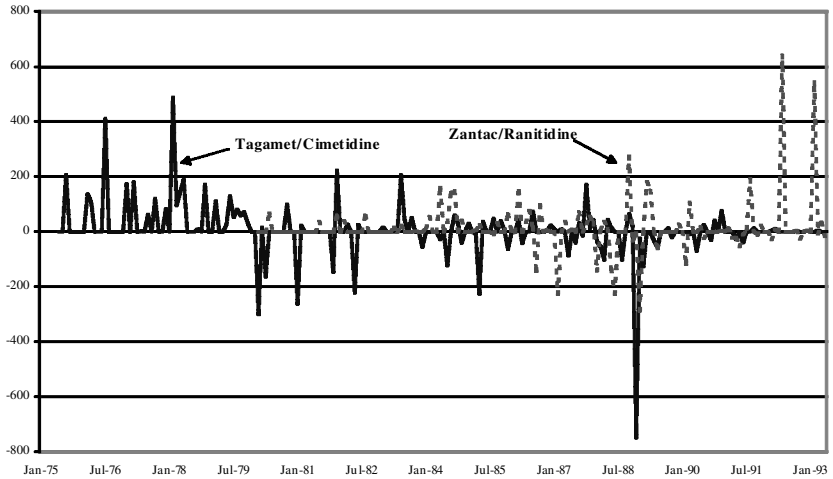

FIGURE 1. CIMETIDINE AND RANITIDINE FLOW OF SCIENTIFIC INFORMATION, 1975–1993

below). A perpetual inventory model is used to define stock variables corresponding to each flow variable defined above:

$$\text{SCIENCE}_{it} = (1-\delta)\text{SCIENCE}_{i,\,t-1} + \text{FLOW}_{it} = \sum_{\tau=m_0-36}^{t} (1-\delta)^{t-\tau}\ \text{FLOW}_{i\tau}.$$

3.3.2 QUALITY OF THE SCIENCE VARIABLES. Several issues can be raised regarding the method used to compute the SCIENCE indices. First, one could have designed many alternative scoring and weighting schemes. One such alternative would have been to choose a measure of efficacy (such as the treatment effect itself) as the grade. For example, Cockburn and Anis (2001) use clinical studies to build regressors in the construction of hedonic price indices for arthritis drugs. They collect measures of efficacy, toxicity, and side effects for each study and use them to build variables measuring quality changes. However, it is difficult to replicate this approach in the context of the antiulcer-drug market because no homogeneous efficacy measure is available for the three conditions studied. For instance, ulcer treatment studies refer to healing rates, ulcer maintenance studies refer to relapse rates, and GERD studies most often record the percentage of patients for whom the symptoms disappeared. Measurement devices (endoscopes, pH meters) vary across articles. Though the Likert-scale approach is a simplification, it circumvents these issues.

Second, are the articles selected authentically scientific? This is a concern in light of the evidence that industry is funding clinical trials, and that frontiers between advertising and research have become blurred. Bero and Rennie (1996) document the growing prominence of industry sponsorship of clinical studies concurrent with the relative shrinking of government support for research.[7] This trend is alleged to result in a growing distrust of academic medicine by practitioners. To examine the relevance of this claim in the data, I reviewed funding sources for a subsample of 21 studies included in this analysis. Eight articles did not report their funding. The remainder of the studies either were totally industry-funded (14%), were partially industry-funded (14%), or benefited from some form of industry support (38%), for example, through the supply of drugs, placebo tablets, advice on experimental design, or help with the statistical analysis. It is difficult to ascertain the precise effect of industry funding on the quality of clinical trials. The imposition of rigid selection criteria for the journals and articles alleviates the concern that SCIENCE only represents different measures of advertising: all included studies report the results of randomized, controlled trials, and are published by peer-reviewed journals with good standing in their field.

Third, is the weighting scheme adopted justifiable? Adams and Griliches note that the flow of ideas is in general difficult to quantify. Nevertheless, they assert that "the best that can be done at the moment is to count papers and patents and adjust them for the wide dispersion in their quality by using measures of citation frequency" (1996, p. 12664). This is accomplished here through the use of forward-citation weights. This method implicitly assumes that the academic clinical community acts as a catalyst of the diffusion process. If one believed instead that physicians make prescription choices on the basis of their individual reading of the clinical literature, then a better alternative would have been to weight studies by journal circulation. Unfortunately, time-series circulation data is regarded as proprietary by publishing houses and is not available.

3.4 Descriptive Statistics

In Figure 2, I plot the quantity of US drugstore sales (in patient days) over time for the four H_2 antagonists. Starting from 0 in 1977, total

7. Between 1980 and 1989, 61% of the clinical trials conducted in the US were fully funded by the pharmaceutical industry, whereas this practice was unheard of between 1945 and 1969. Furthermore, in 1992, the $10.9 billion in research expenditures reported by the drug industry exceeded the entire NIH budget of $10.1 billion (the industry figure includes drug discovery research).

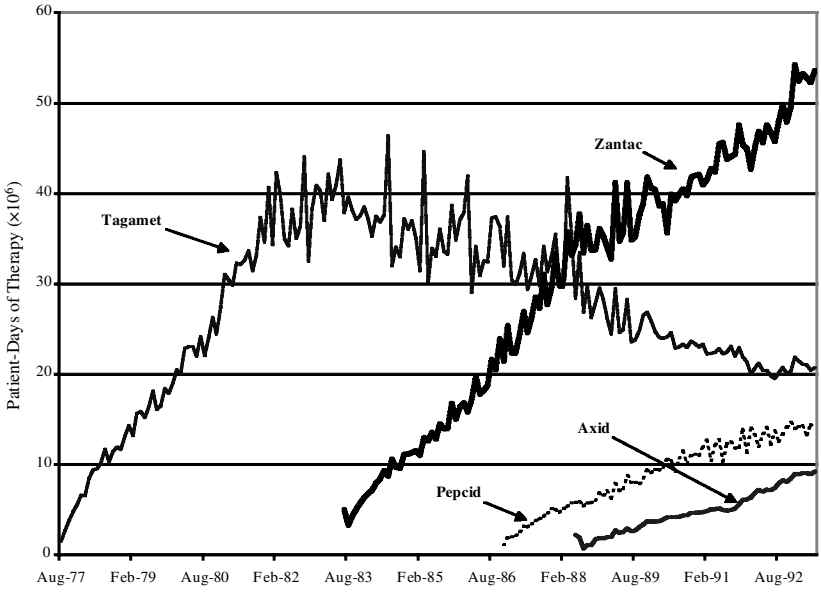

FIGURE 2. MONTHLY SALES FOR H_2 BLOCKERS, 1977–1993

monthly sales reached almost 98 million by May 1993.[8] Figure 3 shows the evolution of market shares for Tagamet, Zantac, Pepcid and Axid. Although Tagamet was the pioneer, Zantac entered in June 1983, and within a year had seized a 25% market share.

Nominal price series for these four drugs reveal infrequent price changes. The price per day of duodenal therapy (based on recommended dosage, and adjusted for inflation using the producer price index for finished goods with 1982 = 1.00) is displayed for the four products in Figure 4. Except for the break in the price trend coinciding with Zantac's entry (which resulted in the incumbent *increasing* rather than decreasing its price, consistent with theories of price discrimination), there does not appear to be substantial pricing responses by incumbents to the entry of new competitors into the H_2-blocker market.

Pricing behavior, however, is not the only strategic instrument of competing pharmaceutical firms: marketing plays a significant role. The introduction of Tagamet coincided with a large detailing effort, which gradually diminished after entry. When Zantac entered with

8. This represented 84% of total sales for the antiulcer market (defined as the four H_2 blockers plus Carafate, Cytotec, and Prilosec). Because of this market dominance, it seems legitimate to confine the analysis to the H_2-antagonist therapeutic class.

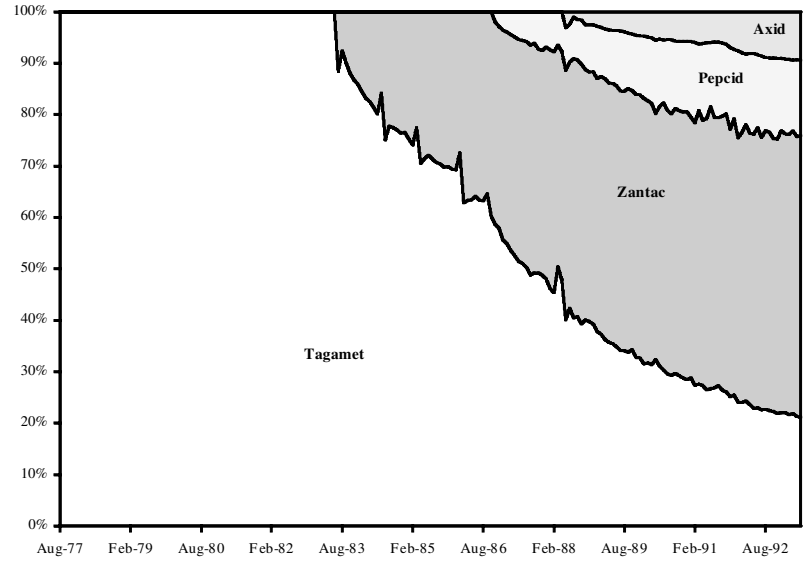

FIGURE 3. MARKET SHARES OF H_2 BLOCKERS, 1977–1993

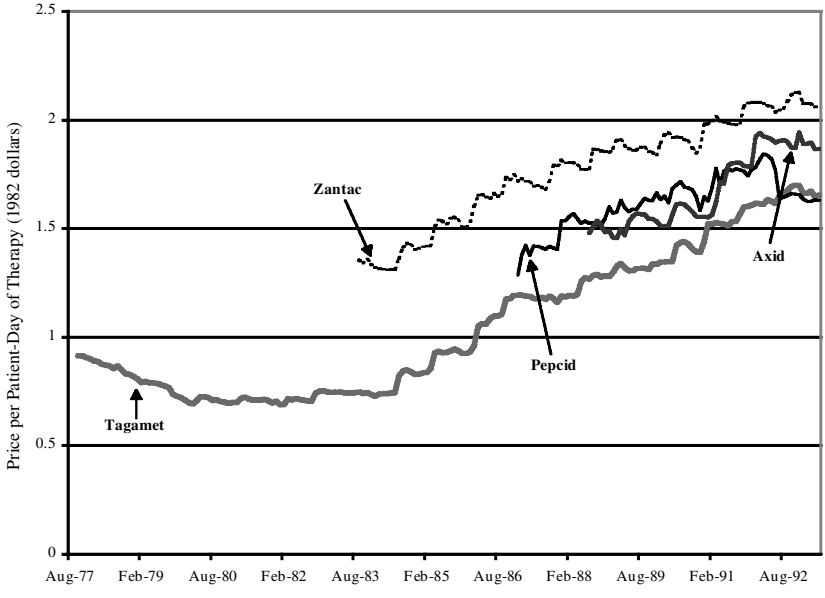

FIGURE 4. REAL PRICES OF H_2 BLOCKERS, 1977–1993

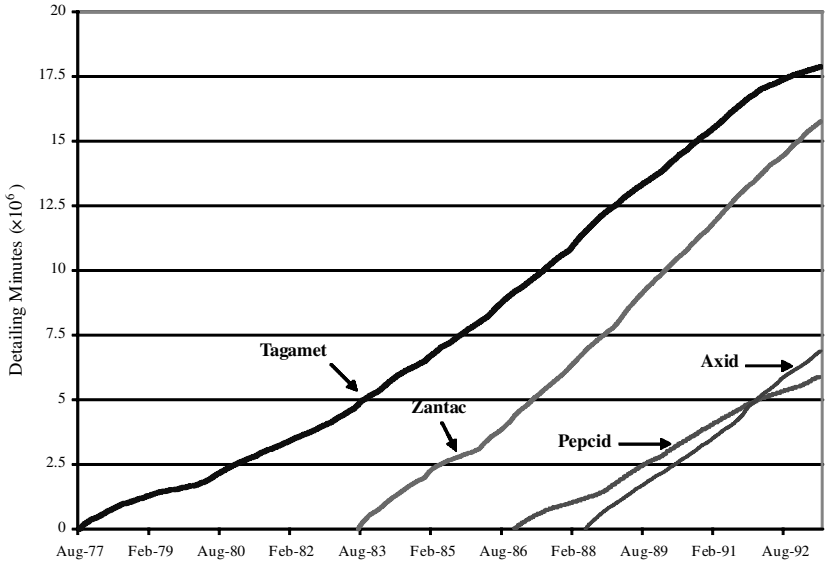

FIGURE 5. CUMULATIVE DETAILING STOCKS FOR H_2 BLOCKERS, 1977–1993

a very aggressive detailing effort in July 1983 (over 350,000 minutes), SmithKline responded with a 50% increase of its own. Figure 5 graphs the cumulative stock of detailing minutes over the sample period for Tagamet, Zantac, Pepcid, and Axid. Up to 1993, Tagamet has outdetailed Zantac. However, in detailing minutes per year, Zantac has notably exceeded Tagamet.

Medical-journal advertising is another source of marketing rivalry. I measure associated expenditures with time series from the IMS National Journal Audit [see Berndt et al. (1997, p. 320) for details]. To convert nominal to real dollars, I use the BLS price index for scientific and professional journals. Figure 6 plots cumulative journal-advertising real dollars for each of the four H_2 blockers.

The peculiar feature of this therapeutic market is that despite the pioneer's lead time of six years, the second entrant managed to overcome Tagamet's first-mover advantage. The proposition of this paper is that the scientific nature of the rivalry between these drugs sheds additional light on the process that led to the market leader's overthrow. From Figure 1—which plots the flow of scientific information for Tagamet (cimetidine) and Zantac (ranitidine)—it is evident that little scientific information is available before entry. Negative studies appear relatively late in the patent life of the molecules.

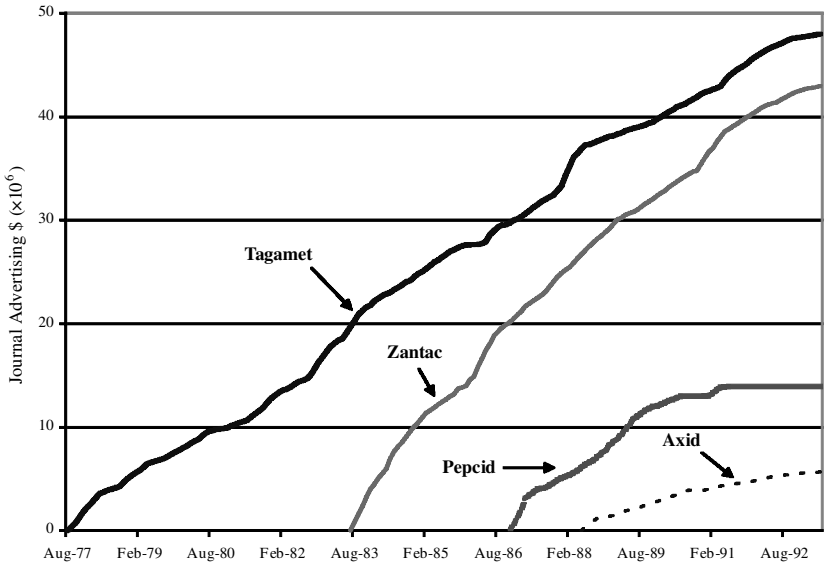

FIGURE 6. CUMULATIVE JOURNAL-ADVERTISING STOCKS FOR H_2 BLOCKERS, 1977–1993

Drugs generally appear in a less and less favorable light in clinical trials as time goes by, since side effects and adverse interactions are only discovered gradually. Furthermore, "me too" drugs enter, providing incremental improvement on pioneer drugs' performance. This is the case for Tagamet after Zantac's entry. The situation recurs with Prilosec in the role of the late innovator, engaged in a scientific contest against the incumbent Zantac.

Figure 7 displays the cumulative stock of science for the four H_2 blockers. As Tagamet is the therapeutic pioneer, most of the increase for it can be accounted for by market-expanding science. In contrast, Zantac owes much of its increase to comparative trials. For both drugs, there is a noticeable decrease once trials comparing Prilosec and the two main H_2 blockers are published. In comparison, Pepcid and Axid's stocks remain unaffected. As less-utilized drugs, they do not provide an attractive platform on which to compare the effects of H_2 antagonists and proton-pump inhibitors.

A more detailed analysis of the science stocks for Tagamet and Zantac reveals that the scientific rivalry does not mirror the marketing war between these two drugs. Tagamet has by far "outscienced" Zantac over the sample period, with a higher yearly average except for the last two years. However, from 1983 onwards, Tagamet experienced a

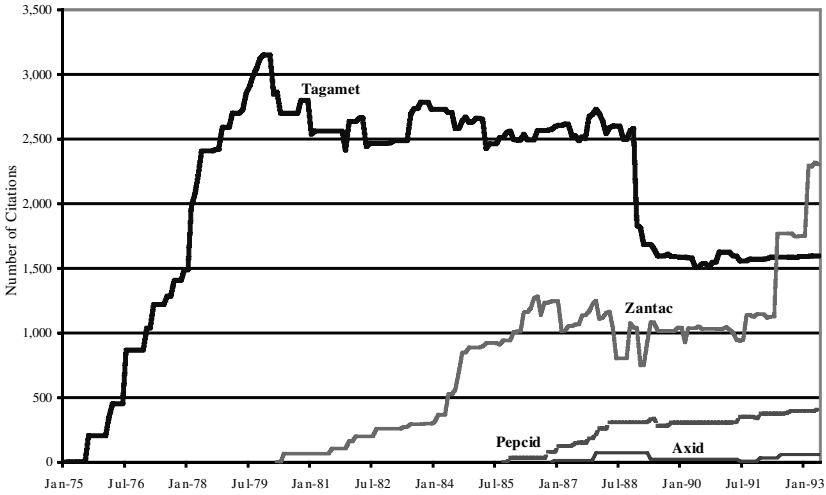

FIGURE 7. CUMULATIVE STOCK OF FORWARD CITATIONS FOR H_2 BLOCKERS, 1975–1993

steady erosion of its science stock, which resembles the time path of its sales. This reflects the disadvantage faced by the pioneer drug vis-à-vis the other H_2 blockers, especially Zantac. For these two drugs, comparative scientific outputs (the SCIENCE2_{it} variables) are highly negatively correlated subsequent to Zantac's entry ($\rho = -0.986$ for the stocks, $\rho = -0.951$ for the flows).

From this preliminary analysis, I conclude that studying the scientific rivalry in combination with the advertising rivalry emphasized by Berndt et al. seems a promising approach to explain diffusion and product-market competition outcomes in the H_2-antagonist therapeutic class. After this overview of sales, price, advertising, and scientific trends, I now turn my attention to modeling the evolution of market shares earned by the four products, and later explore the informational drivers of advertising.

4. Econometric Analysis of Competition and Diffusion

In this section, I estimate a simple discrete-choice model of product differentiation to examine the effect of advertising and scientific information on the outcome of product-market competition in the H_2-antagonist therapeutic market. I choose to treat information about drugs as product characteristics, whether or not it is privately supplied. This allows me to investigate, using brand-level data, how

low-search-cost sources of information (i.e., advertising) and high-search-cost sources of information (i.e., clinical studies) directly influence diffusion and rivalry.

This approach involves a number of simplifications. First, I ignore various insurance and copayment schemes that drive wedges between marginal prices paid by patients and revenues received by dispensing pharmacies. Second, I abstract away from the patient-doctor agency relationship and consider the population of physicians as the pool of potential adopters. Third, I neglect intertemporal aspects of demand, which are relevant for pharmaceutical products. A more complete model of demand would incorporate these aspects into the analysis.

This paper's main goal is more modest: to estimate the average sensitivity of market shares to different sources of product information. Consequently, I estimate a static demand system that relates the evolution of market shares to prices and other product characteristics. Among a variety of static demand frameworks used by previous researchers, I favor the discrete-choice approach of Berry (1994) for several reasons. First, it is uniquely suited to the examination of the role of product characteristics on demand. In contrast, *almost ideal demand systems* might be more appropriate when researchers take a keen interest in estimating the full matrix of price and cross-price elasticities (Ellison et al., 1997). Another route is that chosen by Berndt et al. (1997), who use an ad hoc specification in their study of pharmaceutical advertising. While the logit specification proposed here is no less ad hoc, it has the distinct advantage of incorporating the monopoly period naturally into the estimation framework.[9] However, since the simple economic theory of consumer demand from which it is drawn clearly does not apply for the reasons given above, I will refrain from structural interpretations, referring loosely to the model as the "diffusion equation."

Let SHARE_{it} denote the market share of product i in month t, and SHAREO_t denote the share of the outside good that same month (one might think of the outside good as the choice of not undergoing treatment or as purchasing antacids, which are available OTC). Let p_{it} represent the price of drug i in month t, X_{it} represent a vector of observable product characteristics, and ξ_{it} summarize the effects of attributes observed by market participants, but not by the econometrician.

9. This modeling approach has been employed by King (2000) in the H_2-blocker market, but his analysis focuses only on advertising.

Following the notation of Berry (1994), I estimate the following logit demand equation:

$$\ln\left(\frac{\text{SHARE}_{it}}{\text{SHARE0}_t}\right) = X'_{it}\beta - \alpha p_{it} + \xi_{it}. \quad (1)$$

As a result, an instrumental variable regression of the differences in log market shares on $(\mathbf{X}, \mathbf{p})$ allows the recovery of consistent estimates for (α, β).[10]

4.1 Data and Specification

Estimating (1) requires information about market shares, total market size M, prices p_i, and product characteristics X_i (including detailing, journal advertising, and scientific stocks). The dataset records monthly observations for the variables listed in Table II, corresponding to the four H_2 antagonists Tagamet, Zantac, Pepcid, and Axid. Each drug is a unique chemical entity endowed with specific characteristics. A few of them are particularly important to prescribing physicians, such as the recommended dosage frequency (DOSAGE), the number of FDA-approved indications (INDICATIONS), the number of adverse drug interactions (INTERACTIONS), and the number of months the drug has been on the market (AGE).

Since the dependent variable involves market shares, one needs to know the size of the total available market for ulcer drugs, M_t. Following King (2000), I set M_t exogenously at 2.7% of the total US population in month t, as defined by the US Census Bureau. The share of the outside good, SHARE0$_t$, is defined as $1 - Q_t/M_t$, where Q_t is total sales for the entire H_2-antagonist therapeutic class. Finally, the dataset provides—along with the SCIENCE variables described above—the detailing and journal-advertising expenditure stocks for the four drugs (STKDETAILING and STKJOURNAL), which are computed using a perpetual-inventory model and depreciated at a monthly rate of 5%.[11]

10. That the logit model produces unreasonable substitution patterns has been well documented (McFadden, 1984). The problem is known as the *independence of irrelevant alternatives*: any pair of products (i_1, i_2) with identical market shares (S_{i_1}, S_{i_2}) will have the same cross-price elasticity with any given third product. I do not adopt more sophisticated approaches here, because the total number of products in the market is small $(N = 4)$.

11. The depreciation rate was set at 5% because this is the approximate value estimated by both Berndt et al. (1997) and King (2000).

I am now in a position to estimate a fixed-effects, panel-data version of (1). The estimated equation becomes

$$\begin{aligned}\ln\left(\frac{\text{SHARE}_{it}}{\text{SHARE0}_t}\right) = {} & \beta_0 + \beta_1 \text{AGE}_{it} + \beta_2 \text{INDICATIONS}_{it} + \beta_3 \text{DOSAGE}_{it} \\ & + \beta_4 \text{INTERACTIONS}_{it} + \beta_5 p_{it} + \beta_6 \text{STKDETAILING}_{it} \\ & + \beta_7 \text{STKJOURNAL}_{it} + \beta_8 \text{SCIENCE1}_{i,\,t-k} + \beta_9 \text{SCIENCE2}_{i,\,t-k} \\ & + \beta_{10} \text{ZANTAC}_i + \beta_{11} \text{PEPCID}_i + \beta_{12} \text{AXID}_i + \Delta\xi_{it}. \qquad (2)\end{aligned}$$

The error term ξ_i in (1) has been split into two parts, $\xi_{it} = \bar{\xi}_i + \Delta\xi_{it}$. Here $\bar{\xi}_i$ denotes the mean utility to consumers accruing from the unobserved characteristics of product i, averaged over the length of the sample.[12] It is now picked up by the fixed effects. The second term, $\Delta\xi_{it}$, represents changes over time about this mean and is the stochastic disturbance in (2). Moreover, market-wide trends are soaked up by year and quarter fixed effects (unreported in the results below).[13]

4.2 Instrumental Variables

Since p_{it} may be correlated with month-to-month variations in unobserved product characteristics, fixed-effects estimates of (2) may be inconsistent. Moreover, as has been emphasized by Schmalensee (1972), advertising efforts are also likely to be jointly determined with price and quantity. As a result, a set of instrumental variables is needed to allow consistent estimation of the diffusion model. The dataset provides many potential instruments. Some vary over time, but not across firms: the log of the wage rate in the pharmaceutical industry, the producer price index for intermediate goods, the producer price indices for three distinct pharmaceutical markets (cardiovascular, hypertensive, and antidepressant therapies), and the stock of detailing minutes, detailing visits, and journal advertising expenditures for the entire pharmaceutical industry spent on the promotion of other products than antiulcer drugs.

To generate instrumental variables that vary across time *and* firms, I find it useful to examine price and advertising data from other therapeutic markets. In the context of the H_2-antagonist therapeutic

12. Since each of the four drugs in the H_2-blocker market is sold by only one firm, fixed unobserved variation in drug characteristics cannot be separately identified from similar variation at the firm level. As a result, the "drug fixed effects" in fact pick up both types of effects.

13. Note that (2) assumes that it takes a fixed lag k for published clinical results to diffuse in the population of adopters; k will be estimated below, along with the depreciation rate δ.

class, the hospital and drugstore segments can plausibly be considered independent. Hospitals administer these drugs intravenously to emergency-room patients in order to reduce acid secretion induced by severe trauma. On the other hand, drugstores sell oral preparations to outpatients suffering from a wide range of ulcerous conditions. Since both markets experience the same manufacturing-cost shocks, hospital price changes provide a rich experiment in supply uncorrelated with $\Delta\xi$. Lastly, I use the cumulative stocks of detailing minutes, detailing visits, and journal-advertising expenditures performed by the four firms on all their other products as instruments for the firms' promotion efforts in the H_2-antagonist market.[14] These will be valid instrumental variables if pharmaceutical companies set an overall advertising budget, and then use rules of thumb—such as percentage of last year's sales—to allocate advertising expenditures across their product portfolio.[15] The fit of the first stage for the three endogenous variables is good.

4.3 Is Science Exogenous?

Science and sales might also be simultaneously determined. This may be the case if clinical investigators have a propensity to study drugs with high sales or high expected sales. While this source of endogeneity would be worrisome if I were studying the effect of published clinical results on demand across therapeutic fields, it is less of a concern in the present study, where I focus on a single, narrowly defined therapeutic area. A more serious concern is that science might be a strategic instrument of the four firms in this market, because of corporate funding of clinical studies. As Rosenberg points out, scientific research is a costly activity, and "it can be directed in ways that may yield large economic rewards" (Rosenberg, 1982, p. 159). Indeed, according to NIH estimates, the share of industry support for health R&D grew from 37.8% in 1986 to 52.1% in 1995.

Moreover, because of implementation and publication lags, clinical research output reflects decisions by academic clinicians or marketing executives taken in the distant past. While certainly not exogenous in some broad economic sense, it might be reasonable to assume that science is predetermined in the diffusion model.

14. These stocks are constructed in the same manner as STKDETAILING and STKJOURNAL (following a perpetual-inventory model, allowing for a 5% monthly rate of decay).

15. This assumption may be hazardous in the case of Glaxo: Zantac was the company's star product, representing its main source of revenues and accounting for the bulk of its advertising effort.

In what follows, I make the identifying assumption that clinical-research outputs and (SCIENCE1 and SCIENCE2) are uncorrelated with month-to-month *changes* to these unobserved characteristics ($\Delta\xi$).[16]

4.4 RESULTS

This section reports the empirical results on the *direct* competitive effects of advertising and science (Section 5 below estimates the magnitude of the *indirect* effect of scientific information on demand—through the promotion efforts induced by scientific activity). The findings suggest that the levels of both variables drive diffusion and performance on the product market, with marketing activities having a more pronounced effect. Because of the semilog functional form of the logit model, coefficient estimates are not immediately interpretable as elasticities.

Turning to the results of Table IV, model (1) presents OLS estimates of the diffusion equation ignoring the effect of scientific information ($\beta_8 = \beta_9 = 0$). The coefficient on STKDETAILING and STKJOURNAL are positive and significant, and the demand curve is downward sloping, as anticipated. Other product characteristics contribute significantly to the model fit, with signs conforming to priors, except for DOSAGE and INTERACTIONS.[17]

Model (2) adds the effect of science. In this specification, β_5 decreases by about 10%, and both SCIENCE1 and SCIENCE2 obtain positive and significant coefficients. A likelihood-ratio test between models (1) and (2) easily rejects the former (LR $= 62.334$, df $= 2$). Interestingly, including the SCIENCE measures causes the DOSAGE coefficient to flip sign, while the coefficient on INTERACTIONS is not statistically significant.

Model (3) addresses the issue of endogeneity by presenting 2SLS estimates. The results are similar, except that the STKDETAILING coefficient drops substantially.[18] Because serial correlation is present

16. I gain additional insight into this issue by examining whether variation in the flow of scientific information can be explained by differences in the characteristics of the firms selling these drugs. I report the results of specifications that regress FLOW (and also the count of published clinical studies) on a constant, the log of the US revenues of the firm outside the gastrointestinal therapeutic area, its stock of detailing minutes on all its other products, and its stock of journal advertising expenditures on all its other products. I observe no systematic relationship between these variables. See Azoulay (2001) for further details.

17. One would expect consumers to prefer drugs with the lowest dosage frequency, *ceteris paribus*. Tagamet entered the market with a requirement of four daily doses, but was able to match Zantac's twice-a-day dosage within a year of the new drug's entry.

18. The Hausman specification test decisively rejects the null hypothesis of exogenous regressors ($\chi^2 = 2065.144$, df $= 7$).

TABLE IV.
LOGIT DISCRETE CHOICE MODEL ($NT = 441$)

	(1) OLS	(2) OLS	(3) 2SLS	(4) GMM
CONSTANT	−3.348	−2.446	−1.116	−1.815
	(−15.816)	(−7.094)	(−2.555)	(−4.817)
AGE_{it}	0.030	0.029	0.035	0.031
	(3.358)	(3.549)	(3.812)	(5.190)
$INDICATIONS_{it}$	0.098	0.055	−0.001	0.032
	(4.974)	(2.887)	(−0.028)	(1.130)
$DOSAGE_{it}$	0.141	−0.226	−0.501	−0.350
	(3.752)	(−2.724)	(−4.976)	(−3.794)
$INTERACTIONS_{it}$	0.049	−0.003	−0.014	−0.019
	(1.760)	(−0.125)	(−0.488)	(−0.533)
p_{it}	−1.336	−0.759	−1.035	−0.959
	(−9.816)	(−4.832)	(−3.987)	(−4.346)
$STKDETAILING_{it}$	1.081	0.904	0.582	0.654
	(28.184)	(17.200)	(9.984)	(10.170)
$STKJOURNAL_{it}$	0.031	0.043	0.148	0.112
	(2.192)	(3.153)	(4.452)	(4.753)
$SCIENCE1_{it}$	—	0.009	0.011	0.013
		(2.620)	(2.462)	(3.183)
$SCIENCE2_{it}$	—	0.142	0.228	0.181
		(4.548)	(6.368)	(5.288)
$ZANTAC_i$	3.118	1.472	1.253	1.307
	(4.543)	(2.068)	(1.488)	(2.009)
$PEPCID_i$	4.228	2.875	2.894	2.729
	(4.149)	(2.928)	(2.557)	(3.477)
$AXID_i$	3.789	2.704	3.198	2.831
	(3.226)	(2.454)	(2.514)	(3.324)
R^2	0.971	0.975	0.967	0.970

Robust t-statistics in parentheses. All specifications include year and quarter fixed effects. Dependent variable: $\ln(SHARE_{it}/SHARE0_t)$, where $SHARE_{it}$ is the market share of drug i in month t, and $SHARE0_t$ is the market share of the outside good in month t.

in the data (the Durbin-Watson statistic is around 0.5), 2SLS estimates are consistent, but not efficient.

Model (4) presents the estimates from a generalized method of moments (GMM) estimation procedure, which allows for an ARMA(2,2) error structure: the resulting t-statistics are robust to both heteroskedasticity and serial correlation.[19] In this preferred specification, both SCIENCE1 and SCIENCE2 enter with positive and significant

19. Experimenting with longer lag structures did not alter the results. The test of overidentifying restrictions rejects the null (TOR = 21.225, df = 10).

TABLE V.
MEAN-PRICE, DETAILING, JOURNAL-ADVERTISING, AND SCIENCE ELASTICITIES IMPLIED BY MODEL (4)

	Tagamet	Zantac	Pepcid	Axid
p_{it}	−0.869	−1.443	−1.484	−1.570
	(−4.346)	(−4.346)	(−4.346)	(−4.346)
STKDETAILING$_{it}$	0.969	1.242	0.746	1.010
	(10.170)	(10.170)	(10.170)	(10.170)
STKJOURNAL$_{it}$	0.454	0.627	0.358	0.168
	(4.753)	(4.753)	(4.753)	(4.753)
SCIENCE1$_{it}$	0.287	0.073	0.025	0.011
	(3.183)	(3.183)	(3.183)	(3.183)
SCIENCE2$_{it}$	−0.322	0.457	0.152	−0.071
	(−5.288)	(5.288)	(5.288)	(−5.288)

t-statistics in parentheses.

coefficients. The effect of AGE is small but significant; but this variable imperfectly captures order-of-entry effects, since the specification also includes a set of drug fixed effects.[20]

Table V computes price, detailing, and science elasticities of demand at the mean of the data for each drug, based on the results of model (4). The demand for Tagamet is the most price-inelastic, reflecting the seven years of monopoly enjoyed by SmithKline's pioneer drug. Zantac's detailing and journal advertising elasticities are the highest, illustrating the effectiveness of the advertising campaign that accompanied Zantac's entry. Finally, the science elasticities are of smaller magnitude than the detailing and journal-advertising elasticities. Tagamet's market-expanding science elasticity of demand is 0.287, and its comparative science elasticity is −0.322 (vs. 0.457 for Zantac). Taken together, these results suggest that placebo-controlled studies were an important driver of diffusion, but that their effect waned soon after the end of Tagamet's monopoly period. Conversely, Tagamet sales responded negatively, and Zantac's positively, to the

20. These results were obtained while allowing the stocks of science to be lagged k months and decay at monthly rate δ. I performed a grid search for the best-fit values of δ and k by reestimating the models assuming a variety of depreciation rates and lags. I chose as parameters the values of δ and k that minimized the GMM objective function ($E'HH'E$). This iterative procedure yielded an optimum when $\delta = 0.00$ and $k = 4$. The high stickiness of science implied by this value for δ may seem surprising. However, one must recall that, by construction, incoming scientific information "endogenously" depreciates these variables when clinical results are negative. I also note that, in an interindustry productivity study estimating the depreciation rate of R&D capital (another measure of innovation and scientific output), Griliches and Lichtenberg (1984) report an estimated depreciation rate of 0.

large amount of comparative science published after the entry of Zantac on the market.

Another interesting finding is the relevance of the distinction between market-expanding and comparative science. The estimates above suggest that physicians respond to both types of published clinical results differently, and that this effect is mediated by market structure. It is plausible that market-expanding science is mostly a by-product of the regulatory approval process, while comparative science tends to originate in firms' marketing departments. One could surmise that the latter type of studies lack the seal of legitimacy bestowed upon placebo-controlled trials by the prestige of public research institutions or the scientific aura of academic clinicians working hand-in-hand with corporate clinical staff. The results, however, belie such an interpretation. Comparative trials may be viewed by physicians as a sophisticated form of advertising; nonetheless, they shape competitive dynamics. The evidence suggests that comparative science constitutes a potent business-stealing weapon.[21]

These findings leave open the possibility that detailing efforts are more effective when they can build on a high level of positive clinical information. The relationship between advertising and science is explored in more detail in the next section.

5. Estimation of an Advertising Response Function

Two related features of the pharmaceutical industry make the question of the relationship between science and advertising a relevant one for business and public policy. First, final consumers must hire expert services to access the industry's products. Second, the pace of technological change is particularly rapid. Since drugs are experience goods, patients employ prescribing physicians as their agents to solve the information market failure resulting from the wealth of therapies and scientific information available about them (Arrow, 1963).[22] What the

21. In Azoulay (2001), I examine whether these results are robust to the use of a different weighting scheme to adjust the SCIENCE variables for differences in quality. Instead of citation weights, this alternative scheme uses journal impact factors published by ISI, as well as the number of patients enrolled in each study. The two sets of weights yield results that are quite similar, although the magnitudes of the SCIENCE estimates are smaller when using forward-citation weights.

22. Scherer (2000) notes that "the prescription system implies that patients are unable to make well-informed decisions about their own welfare, so physicians must act *in loco parentis*." In the absence of this intermediary, the need for publication of clinical studies would not arise, and there would be no scientific dimension along which prescription drugs compete: products would simply be advertised directly to consumers. There is

information channels are that enable these agents to become informed about alternative treatment options is therefore an important question. Below, I investigate the possibility that advertising levels respond to their own and competitors' clinical-research outputs, thereby reducing the differences across physicians by lowering the costs of acquiring nonprice information.

In addition to scrutinizing the relationship between advertising and other variables, I examine the dependence of advertising intensity on competitors' promotion outlays. Game-theoretic models of vertical product differentiation often have the feature that investments in quality improvements (of which advertising expenses are a special case) are strategic substitutes (Shaked and Sutton, 1982; Athey and Schmutzler, 2001), although the literature has identified other cases where strategic complementarity obtains (Ronnen, 1991). As a result, theory does not deliver strong predictions with regard to the slope of advertising reaction functions in the H_2-antagonist market. I tackle this issue below.

5.1 Econometric Considerations

The estimation of advertising decision rules has a long history in economics; they are generally estimated with demand as a system of simultaneous equations (Schmalensee, 1972). Here, I depart from the marketing-literature denomination by estimating the parameters of an *advertising response function*, which relates advertising levels to potential information drivers. One could expect decisions regarding the level of advertising at the brand level to respond to the quantity and quality of information available on the firm's own brand and on competing brands. In pharmaceutical markets, the observed information sources on a given drug are the intensity of promotion for competing drugs, the scientific capital of the drug, and the scientific capital of its competitors. The preceding section highlighted the significance of the scientific rivalry for competition in the H_2-blocker market. An additional finding of a positive relationship between advertising and science would establish that advertising and scientific rivalries not only coexist, but also interact in more complex ways than have been recognized in the public-policy debate.

The empirical strategy is to estimate a panel-data regression model relating detailing flows (respectively, journal-advertising flows) to detailing flows of competitors (respectively, journal-advertising

evidence that pharmaceutical advertising targeting consumers directly is on the rise. Examining the motivations behind this recent phenomenon is beyond the scope of this paper.

flows of competitors), changes in own market-expanding stock of science, changes in own comparative stock of science, and changes in competitors' overall stock of science. Since detailing messages are constrained by law to relate only to approved FDA indications, the number of new indications enters as a control variable, along with drug-specific time trends (AGE), changes in recommended daily dosage (ΔDOSAGE), changes in the number of adverse interactions (ΔINTERACTIONS), and the flow of marketing for the firm as a whole (FLOWDETAILINGCO or FLOWJOURNALCO).[23] This leads to the following specification:

$$\begin{aligned}\text{FLOWDETAILING}_{it} = {} & \gamma_0 + \gamma_1 \text{AGE}_{it} + \gamma_2 \Delta\text{INDICATIONS}_{it} \\ & + \gamma_3 \Delta\text{DOSAGE}_{it} + \gamma_4 \Delta\text{INTERACTIONS}_{it} \\ & + \gamma_5 \text{FLOWDETAILING}_{-i,t} + \gamma_6 \text{FLOWDETAILINGCO}_{it} \\ & + \gamma_7 \Delta\text{SCIENCE}_{-i,t} + \gamma_8 \Delta\text{SCIENCE1}_{it} + \gamma_9 \Delta\text{SCIENCE2}_{it} \\ & + \gamma_{10} \text{ZANTAC}_i + \gamma_{11} \text{PEPCID}_i + \gamma_{12} \text{AXID}_i + \eta_{it}. \quad (3A)\end{aligned}$$

A similar specification (3B) is estimated for the determinants of journal-advertising expenditures (the estimated coefficients will be denoted λ below). In both cases, I adopt a linear functional form—as opposed to a constant-elasticity formulation—for three reasons. First, the linear model allows the use of the monopoly-period data (1977–1983), during which advertising and science for competitors are 0. Second, it enables discrimination between the effect of market-expanding and comparative science: since SCIENCE2 can take on negative values, this is an advantage over the log-linear functional form. Finally, a linear specification eases considerably the computation of science elasticities of demand that account for the indirect effect of science through the advertising it induces.

Joint determination of advertising levels across firms is a potential problem, which I address with instrumental variables. The instrument set is similar to the one used in Section 4: the flow of detailing minutes (respectively, journal-advertising expenditures) performed by competitors on all their other products, and the flow of detailing minutes (respectively, journal-advertising expenditures) for the entire

23. In discussions with practitioners, I discovered that fully incorporating novel clinical results into marketing communication materials could take up to a year because of the FDA's cumbersome vetting process. As a result, $\Delta\text{SCIENCE1}_{it}$ refers to changes in the stock of market-expanding science for drug i between month t and month $t - 12$, while $\Delta\text{INDICATIONS}_{it}$ refers to the number of new indications approved by the FDA during the same period. Other change variables are similarly defined using this 12-month time window.

pharmaceutical industry for all other products. Rivals' detailing and journal-advertising intensity in other therapeutic markets is likely to be correlated with their promotion outlays in the H_2-antagonist class (because advertising requires sunk investments above the therapeutic-market level, such as setting up a network of trained detail persons and maintaining relationships with prescribing physicians), but uncorrelated with conditions specific to the H_2-blocker market.

Since the conduct of clinical trials is a lengthy endeavor, it is assumed that the SCIENCE variables are mean-independent from the disturbance η_{it}. This assumption is made less problematic by the inclusion of drug fixed effects, which control for unobserved product characteristics that might lead drugs to be both heavily advertised and extensively studied in clinical trials.

5.1.1 DETAILING. Tables VI and VII present the estimation results. Model (1) displays OLS estimates, but omits the scientific variables. The results indicate that detailing responds only weakly to changes in the number of approved indications and negatively to increases in detailing expenditures on other products sold by these firms. They also point to product life-cycle effects whereby drugs are heavily detailed upon entry, with detailing intensity gradually decreasing over time. However, this last result turns out to be sensitive to small changes in the econometric specification.

Model (2) adds the influence of SCIENCE1, SCIENCE2, and SCIENCE of others. Model (1) is misspecified: a likelihood-ratio test decisively rejects the restriction $\gamma_5 = \gamma_6 = \gamma_7 = 0$ (LR= 29.994, df = 3). The flow of detailing minutes is increasing in changes to the stock of competitors' scientific information and also reacts positively to changes in own market-expanding stock of citations. However, the direction of the effect is reversed for changes in the comparative stock of science. While it is useful to remember that comparative claims are not authorized by the FDA, one interpretation of this counterintuitive result is that well-cited comparative studies constitute a sophisticated form of advertising that can partly substitute for detailing effort. A subsidiary finding is that the flow of detailing minutes appears to decrease after adverse drug interactions come to light.[24]

Model (3) presents 2SLS estimates, correcting for the bias engendered by the joint determination of detailing flows across competing brands. Whereas OLS estimates indicated that detailing levels are strategic substitutes, IV estimates show that detailing reaction curves

24. This is not surprising, since FDA regulations require that adverse findings figure in the fine print of promotional documents.

TABLE VI.
DETAILING RESPONSE FUNCTION ($NT = 441$)

Variable	(1) OLS	(2) OLS	(3) 2SLS	(4) GMM
CONSTANT	0.083	0.072	0.084	0.083
	(6.754)	(5.357)	(5.069)	(6.352)
AGE_{it}	−0.005	−0.005	−0.001	−0.002
	(−3.306)	(−3.237)	(−0.438)	(−0.758)
$NEW\text{-}INDICATIONS_{it}$	0.003	0.003	0.000	−0.000
	(1.222)	(1.488)	(0.028)	(−0.121)
$NEW\text{-}DOSAGE_{it}$	−0.020	−0.009	−0.012	−0.012
	(−3.527)	(−1.411)	(−1.434)	(−1.211)
$NEW\text{-}INTERACTIONS_{it}$	−0.008	−0.009	−0.013	−0.011
	(−2.738)	(−2.665)	(−2.778)	(−1.983)
$FLOWDETAILING_{-it}$	0.023	0.039	0.544	0.469
	(0.748)	(1.374)	(2.810)	(2.636)
$FLOWDETAILINGCO_{it}$	−0.096	−0.083	−0.123	−0.118
	(−5.317)	(−4.572)	(−4.531)	(−3.725)
$\Delta SCIENCE_{-it}$	—	0.002	0.003	0.003
		(2.540)	(2.827)	(2.343)
$\Delta SCIENCE1_{it}$	—	0.002	0.002	0.003
		(1.904)	(2.082)	(1.990)
$\Delta SCIENCE2_{it}$	—	−0.008	−0.012	−0.010
		(−2.565)	(−2.786)	(−2.070)
$ZANTAC_i$	−0.329	−0.309	−0.047	−0.082
	(−3.170)	(−3.003)	(−0.258)	(−0.565)
$PEPCID_i$	−0.551	−0.532	−0.144	−0.189
	(−3.407)	(−3.338)	(−0.516)	(−0.857)
$AXID_i$	−0.625	−0.603	−0.147	−0.204
	(−3.325)	(−3.257)	(−0.449)	(−0.789)
R^2	0.626	0.645	0.446	0.479

Dependent variable is $FLOWDETAILING_{it}$. Robust t-statistics in parentheses. All specifications include year and quarter fixed effects.

slope up (corresponding elasticities, computed at the mean of the data for each drug, can be found in Table VII).

Using a GMM routine similar to the one used in Section 4, model (4) produces estimates of γ for which t-statistics are robust to heteroskedasticity and serial correlation. This does not alter the results substantially.[25]

25. The test of overidentifying restrictions cannot reject the null ($\chi^2 = 4.085$, df $= 3$).

TABLE VII.
MEAN DETAILING RESPONSE ELASTICITIES IMPLIED BY (4)

Variable	Tagamet	Zantac	Pepcid	Axid
FLOWDETAILING$_{-it}$	0.772	0.781	2.180	1.366
	(2.636)	(2.636)	(2.636)	(2.636)
ΔSCIENCE1$_{it}$	0.018	0.009	0.011	0.004
	(1.990)	(1.990)	(1.990)	(1.990)
ΔSCIENCE2$_{it}$	0.029	−0.028	−0.027	0.010
	(2.070)	(−2.070)	(−2.070)	(2.070)

t-statistics in parentheses.

In conclusion, I find some evidence that detailing diffuses product information (the results of randomized clinical trials) to potential adopters (in this case doctors), but the magnitude of this effect is modest, as documented in Table VII.[26]

5.1.2 JOURNAL ADVERTISING. The analysis above is repeated using journal-advertising expenditures as the dependent variable. Estimation results can be found in Tables VIII and IX. In general, the results are consistent with those obtained in the case of detailing. Without the scientific variables, OLS estimates indicate that reaction curves are downward sloping. Detailing flows are positively correlated across products of a given company's portfolio (in the sense that the FLOWJOURNALCO coefficient is positive and marginally significant). Finally, journal-advertising expenditures increase with the number of indications recently approved by the FDA.

Model (2) adds the effects of changes in SCIENCE1, SCIENCE2, and SCIENCE of others, and, as above, these variables improve the fit of the model significantly (a likelihood-ratio test rejects the null $\lambda_5 = \lambda_6 = \lambda_7 = 0$). Similarly to detailing, addressing the endogeneity of FLOWJOURNALOTHERS changes the strategic substitution result into one of strategic complementarity. However, the slope is less steep than in the case of detailing (this can be seen by comparing elasticities in Tables VII and IX). This finding can be explained by reference to the longer planning horizon for journal advertisements—pharmaceutical firms and academic publishers usually sign long-term contracts to govern the release of promotional material in scientific journals.

26. Because the signs of the stocks of comparative science differ across brands, I investigated (in an unreported regression) the possibility of asymmetric firm responses to SCIENCE2 by interacting this variable with drug dummies. The results were not substantially affected.

TABLE VIII.
ADVERTISING RESPONSE FUNCTION ($NT = 441$)

Variable	(1) OLS	(2) OLS	(3) 2SLS	(4) GMM
CONSTANT	0.545	0.448	0.305	0.304
	(6.135)	(4.989)	(3.453)	(3.993)
AGE_{it}	0.005	0.005	−0.004	−0.004
	(0.643)	(0.646)	(−0.401)	(−0.568)
$NEW\text{-}INDICATIONS_{it}$	0.044	0.049	0.081	0.082
	(3.485)	(3.875)	(5.085)	(3.825)
$NEW\text{-}DOSAGE_{it}$	−0.002	0.021	0.028	0.028
	(−0.090)	(0.563)	(0.635)	(0.469)
$NEW\text{-}INTERACTIONS_{it}$	−0.041	−0.030	−0.042	−0.043
	(−2.652)	(−1.912)	(−2.094)	(−1.583)
$FLOWJOURNAL_{-it}$	−0.200	−0.204	0.366	0.362
	(−3.733)	(−4.012)	(4.847)	(4.494)
$FLOWJOURNALCO_{it}$	0.046	0.048	0.049	0.051
	(2.115)	(2.134)	(1.486)	(1.131)
$\Delta SCIENCE_{-it}$	—	0.009	0.007	0.007
		(3.218)	(1.828)	(1.502)
$\Delta SCIENCE1_{it}$	—	0.016	0.014	0.014
		(2.687)	(2.779)	(2.252)
$\Delta SCIENCE2_{it}$	—	−0.015	−0.021	−0.022
		(−0.971)	(−1.114)	(−0.873)
$ZANTAC_i$	0.467	0.467	−0.094	−0.095
	(0.836)	(0.850)	(−0.141)	(−0.200)
$PEPCID_i$	0.481	0.469	−0.534	−0.539
	(0.553)	(0.547)	(−0.516)	(−0.728)
$AXID_i$	0.580	0.551	−0.628	−0.634
	(0.572)	(0.552)	(−0.521)	(−0.734)
R^2	0.529	0.549	0.332	0.334

Dependent variable is $FLOWJOURNAL_{it}$. Robust t-statistics in parentheses. All specifications include year and quarter fixed effects.

The science variables enter the model with coefficients similar in magnitude to those obtained in the estimation of the detailing response function, although λ_9, the coefficient of SCIENCE2, does not reach statistical significance. These results obtain even with serial-correlation robust t-statistics [model (4), $\chi^2 = 0.656$, df $= 2$ for the test of overidentifying restrictions].

In summary, I find validation in this data for the idea that advertising was an important device to disseminate scientific information in the H_2-antagonist therapeutic class, although the modest magnitude

TABLE IX.
MEAN JOURNAL-ADVERTISING RESPONSE ELASTICITIES IMPLIED BY (4)

Variable	Tagamet	Zantac	Pepcid	Axid
FLOWDETAILING$_{-it}$	0.482	0.407	1.256	2.223
	(4.494)	(4.494)	(4.494)	(4.494)
ΔSCIENCE1$_{it}$	0.037	0.019	0.027	0.024
	(2.252)	(2.252)	(2.252)	(2.252)
ΔSCIENCE2$_{it}$	0.025	−0.024	−0.027	0.028
	(0.873)	(−0.873)	(−0.873)	(0.873)

t-statistics in parentheses.

of this effect stands somewhat in contrast to previous evidence (Ippolito and Mathios, 1990; Berndt et al., 2001). Nonetheless, combined with results pointing to advertising flows being strategic complements, the overall pattern of evidence appears more consistent with an "informative" view of pharmaceutical advertising than with a "persuasive" view. At the very least, the results indicate that, for the jamming hypothesis to hold, one would need to argue that the primary purpose of published clinical results is to *signal* product quality, rather than to provide relevant product information. Published clinical results shape the diffusion process primarily in a direct fashion, but their indirect role as drivers of advertising expenditures should not be ignored.

5.2 TOTAL SCIENCE ELASTICITIES OF DEMAND

I compute total science elasticities of demand, allowing both for the direct effect of scientific information on sales and for the (small or negative) indirect effect induced by the detailing and journal advertising response to science. Practically, I plug back equations (3A) and (3B) into the diffusion equation (2), taking into account that (3A) and (3B) use a flow specification for the advertising variables (FLOWDETAILING and FLOWJOURNAL), while (2) uses a stock formulation (STKDETAILING and STKJOURNAL).

ζ_{it}^{K}, the total market-expanding ($K = 1$) and comparative ($K = 2$) science elasticities of demand for drug i in month t, can be computed by the following formulas:

$$\zeta_{it}^{1} = (1 - \text{SHARE}_{it}) \cdot \text{SCIENCE1}_{it} \cdot (\beta_8 + \beta_6\gamma_8 + \beta_7\lambda_8), \tag{4}$$

$$\zeta_{it}^{2} = (1 - \text{SHARE}_{it}) \cdot \text{SCIENCE2}_{it} \cdot (\beta_9 + \beta_6\gamma_9 + \beta_7\lambda_9). \tag{5}$$

For computational ease, I form a stacked vector with the moment conditions implied by equations (2), (3A), and (3B), and perform a

TABLE X.

Total Science Elasticities of Demand Implied by Model (4) in Tables IV, VI, and VIII

	Mean of Sample				December 1992			
Variable	Tagamet	Zantac	Pepcid	Axid	Tagamet	Zantac	Pepcid	Axid
SCIENCE1_{it}	0.346	0.088	0.031	0.013	0.299	0.157	0.037	0.019
	(4.025)	(4.025)	(4.025)	(4.025)	(4.025)	(4.025)	(4.025)	(4.025)
SCIENCE2_{it}	−0.270	0.383	0.127	−0.064	−0.644	0.450	0.198	−0.093
	(−4.747)	(4.747)	(4.747)	(−4.747)	(−4.747)	(4.747)	(4.747)	(−4.747)

t-statistics in parentheses.

GMM estimation routine as in Sections 4 and 5. Then, I use the formulas above to calculate ζ^1 and ζ^2 for each drug, both at the mean of the data and near the end of the sample period (December 1992).[27] I compute similar total elasticities of demand for the other observable product characteristics that enter the specifications above: INDICATIONS, DOSAGE, INTERACTIONS.

The results are displayed in Table X and XI. The logit functional form, along with the coefficient estimates, implies that the direct effect accounts for about 80% of the total effect of information on demand. The magnitudes of these total elasticities is important for comparative scientific information, and somewhat less so for market-expanding scientific information (except in the case of the pioneer Tagamet, for which the reverse holds true). Interestingly, the market-expanding science total elasticity of demand approaches 0.35 at the mean of the data for the pioneer Tagamet, while the comparative science elasticity of demand is above 0.4 for Zantac. The magnitudes of these elasticities are more modest for Pepcid and Axid, but the total product-market effect of scientific information should not be neglected. As far as the effect of observable product characteristics is concerned, the results are mixed. One intriguing result is that adverse drug interactions do not appear to influence demand directly, but they do so indirectly by triggering a reduction in the flow of advertising.

Traditionally, clinical research represented one-half to two-thirds of pharmaceutical companies' overall R&D expenditures, and its primary role was to drive new molecules through a lengthy and bureaucratic regulatory approval process. I interpret my results as providing evidence for an important product-market function of clinical studies.

27. Although this procedure uses an optimal weighting matrix for the two moment conditions, the results are virtually unchanged from model (4) of Tables IV, VI, and VIII. For this reason, I do not report this new set of estimates.

TABLE XI.

Direct and Indirect Effect of Product Information Comparison of Elasticities Implied by Model (4) in Tables IV, VI, and VIII

	INDICATIONS		DOSAGE		INTERACTIONS		SCIENCE1		SCIENCE2	
Drug	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect
Tagamet	0.109	0.012	−0.638	−0.031	0.028	−0.107	0.281	0.065	−0.279	0.009
	(1.796)	(1.273)	(−3.369)	(−1.535)	(0.142)	(−3.433)	(3.222)	(2.546)	(−4.908)	(1.229)
Zantac	0.128	0.014	−0.337	−0.016	0.000	−0.002	0.071	0.017	0.395	−0.013
	(1.796)	(1.273)	(−3.369)	(−1.535)	(0.142)	(−3.433)	(3.222)	(2.546)	(4.908)	(−1.229)
Pepcid	0.131	0.014	−0.283	−0.014	0.000	0.000	0.025	0.006	0.131	−0.004
	(1.796)	(1.273)	(−3.369)	(−1.535)	—	—	(3.222)	(2.546)	(4.908)	(−1.229)
Axid	0.108	0.012	−0.289	−0.014	0.004	−0.017	0.010	0.002	−0.066	0.002
	(1.796)	(1.273)	(−3.369)	(−1.535)	(0.142)	(−3.433)	(3.222)	(2.546)	(−4.908)	(1.229)

t-statistics in parentheses.

Because advertising does not jam all other information channels available to reach the population of prescribing physicians, pharmaceutical firms face strong private incentives to perform clinical research.

6. Concluding Remarks

The results presented here demonstrate that product-market competition in the H_2-antagonist therapeutic class was shaped by rival firms' advertising efforts and the quality of the scientific information concerning the four drugs. The paper provides an original methodology for computing indices of quality-adjusted scientific outputs. I find that marketing had a more pronounced direct effect on demand than science, but the latter was still statistically and economically significant. I introduce the distinction between market-expanding and comparative science, demonstrating that the second type was a particularly effective business-stealing weapon for the second mover Zantac. In addition, I find evidence that clinical-research outputs were important drivers of firms' promotion efforts, although detailing and journal-advertising expenditures also responded positively to the intensity of competitors' marketing campaigns. Taken together, these results suggest that pharmaceutical advertising does not perform a purely persuasive function, nor does it jam professionally sanctioned information channels by preventing scientific results to get through to prescribing physicians.

I take into account both the direct and the indirect effect of science on demand to compute the appropriate elasticities. The sum of the direct and indirect effects yields a level for the total market-expanding science elasticities of demand around 0.4 for the pioneer drug and its challenger, and positive and significantly above zero for the two later entrants. These results imply strong private incentives for performing clinical research and suggest that controlled clinical trials do not accomplish the sole function of securing regulatory approval, but also represent investments whose effects on the product market are both substantial and long-lived. The results are consistent with long-run trends noted by industry practitioners (Carr, 1998). A growing number of drugs go into postapproval, so-called Phase IV trials. These are designed to extend the range of conditions for which a drug can be used, thereby making it more profitable. Such trials also satisfy the need to accumulate evidence for use in persuading physicians to favor new drugs over older ones.

The results of this paper are also of significant interest in the continuing debate surrounding pharmaceutical advertising. Numerous academic critics of the industry have argued that promotion

efforts create inherent conflicts of interest for prescribing physicians and have supported caps or new regulations on marketing activities by pharmaceutical firms (Wade et al., 1989). Indeed, given the informational imperfections that plague pharmaceutical markets, the issue of whether the privately optimal level of advertising coincides with the socially optimal level is a first-order policy question. Unfortunately, a more sophisticated model of demand (in particular one that takes account of the patient-physician agency relationship) along with a complete specification of the dynamic game played by these firms would be required to determine the share of advertising activities that is socially wasteful. While such a contribution falls outside the scope of this paper, the findings presented here indicate that there might be less cause for alarm than proponents of reform suspect.

Though derived from data on a single therapeutic class, these findings may also be relevant to markets for other kind of drugs. In the statins market, for example, Warner-Lambert's Lipitor became the leading molecule within a few years of its introduction on the strength of widely discussed clinical results indicating that it was as effective in lowering blood cholesterol levels despite its much lower dose than for Merck's Zocor and Bristol Myers-Squibb's Pravachol (Winslow, 2000). Similarly, in the antihypertensive market, Merck introduced its ACE Inhibitor Vasotec later than Squibb's Capoten. As recounted by Werth (1994, p. 58): "Merck had put scores of chemists on the task of improving [Capoten], then followed up with a withering sales campaign so effective that it ended up beating Squibb in the market even though Capoten was launched first and was much the same drug." The pharmaceutical industry also provides examples of second movers challenging pioneer products in cases where there is no clear-cut quality gap between the two products. In the antidepressant market, a late innovator (Zoloft) nearly caught up with the pioneer drug (Prozac) because its very distinct side-effect profile enabled physicians to better match patients with the appropriate treatment (Berndt et al., 2001). Advertising may leverage minute differences in efficacy into decisive advantage on the product market, or it may convey information on the quality of patient-molecule matches. I leave for future research the study of the mechanisms through which science and advertising interact to influence product-market competition.

These results also raise the interesting question of the extent to which science is a strategic instrument available to pharmaceutical companies. A major limitation of this paper is that it treats the production of clinical knowledge as exogenous to product-market competition outcomes, when in fact the results highlight the possible role of scientific information in shaping competitive dynamics. Do

pharmaceutical firms differ in the extent to which they stimulate the production of clinical knowledge about their drugs through ties with academic or nonacademic physicians? Do clinical-research outputs correlate systematically with firm-level choices regarding the management of clinical development? Closer examination of the funding and management of clinical trials may provide useful insights into the interaction of product-market competition and the production of scientific information.

Data Appendix. Indices of Clinical-Research Outputs

I describe in detail the construction of indices measuring the flows of scientific information in pharmaceutical markets. I address the following issues: the selection of the articles counting toward these measures of scientific information, the compilation of the list of relevant medical journals from which these studies are drawn, and the design of a scoring and weighting scheme to adjust them for quality.

A.1 Selecting the Articles

Since 1966, the medical literature has been indexed by MedLine, a free database available on the National Library of Medicine web site (http://www.nlm.nih.gov/). Each article contains the following records: author, journal, title, date, abstract, miscellaneous headings. A quick search reveals that a total of 8,267 article titles contain the name of one of the molecules studied here. Searching on abstracts instead of titles raises this figure to 15,564. In order to analyze this data, one has to design a procedure that has no built-in bias and is replicable in other therapeutic markets.

Articles were included in the index based on the following conditions: the availability of the abstract in English, a reference to the name of the molecule in the title or abstract, and the presence of the miscellaneous heading "clinical trial." My rationale is as follows: early in the sample, when cimetidine was the only molecule available, "H_2-receptor antagonist" and "cimetidine" might be used as synonyms, so that a search on the article title alone might leave out important studies that mention the molecule name only in the abstract. Moreover, limiting the search criteria to study titles may yield too few articles for the less prominent drugs (famotidine and nizatidine).[28]

28. I also substituted in the search MK-208 and LY-139037, the code names used early in the development of Pepcid and Axid by Merck and Eli Lilly, respectively.

I restrict myself to clinical trials for reasons of both convenience and principle. Coding review articles, meta-analyses, and cost-efficacy studies according to objective criteria is difficult. Moreover, results of RCTs are the primary inputs into the drug-approval process as well as academic debates regarding drugs' relative safety and efficacy.

I also found it necessary to select articles according to their date of publication. I used the following rule: if a drug entered the market in month m_0, I retained the articles that were published between month m_0–36 and May 1993. I elected to use a long lag period for several reasons. First, the FDA approval process for a new molecule is lengthy, and important clinical results might be published before the entry of the drug on the market. Second, the growth of scientific knowledge is cumulative (Rosenberg, 1982): clinical results get locked into the collective consciousness of the medical community until they are dislodged by more conclusive evidence. For each of the four drugs, this approach resulted in no left-censoring of information.

A.2 Selecting the Journals

While the above criteria narrow down the set of includable studies significantly, the number of journals in which they can be found is large, and it is unclear whether these journals are read by physicians or if their circulation warrants their inclusion in the index. For the purpose of providing a replicable routine for journal selection, I used the Journal Citation Reports, published yearly by the Institute for Scientific Information. ISI ranks journals by impact factor in different scientific fields. The impact factor is a measure of the frequency with which the "average article" in a journal has been cited in a particular year. Basically a ratio between citations and recent citable items published, it suffers from built-in biases: it tends to discount the advantage of large journals over small ones, of frequently issued journals over less frequently issued ones, and of older journals over newer ones. Nonetheless, it conveys quite effectively the idea that the *New England Journal of Medicine* (impact factor 23.223 in 1991) is a much more influential publication than the *Journal of General Internal Medicine* (impact factor 1.056 in 1991).[29] I identified two scientific fields from which to select relevant journals: gastroenterology/hepatology, and general/internal medicine. The JCRs rank 120 general medicine journals and 32 gastroenterology journals, some of which are very marginal publications (Garfield, 1986). I narrowed down the list to the

29. The JCR rankings change slightly over time, and I constructed three-year moving averages to smooth these time series.

journals that account for two-thirds of the aggregate impact factor of all journals published in the focal field. As a result, thirteen gastroenterology/hepatology journals and fourteen general medicine journals were initially included. Of those, seven general medicine journals and four gastroenterology/hepatology journals contained no articles that fulfilled the inclusion criteria above, and were dropped from the analysis.[30]

A.3 Filtering the Abstracts

I narrowed down the list of included studies further by screening the abstracts of each clinical trial. First, I required that the trial be randomized and controlled (I accepted both single-blind and double-blind designs). Second, I required that the focus of the study be an ulcer condition, GERD, the interaction of a drug with another substance (e.g., ethanol or NSAIDs), or some related gastrointestinal disease such as nonulcer dyspepsia. Trials pertaining to hospital intravenous use of H_2 blockers for severely burned or traumatized patients were included, even though I use only drugstore data in the econometric analysis. This choice was made on the grounds that the mode of administration (oral or intravenous) does not affect the clinical relevance of the study as long as entry criteria are clearly defined. This process resulted in the selection of 483 clinical studies. In Azoulay (2001), I break down the number of studies by drug for this sample and for the MedLine universe of studies from which they were selected. Reassuringly, the proportions appear to be roughly similar.

A.4 Weighting the Studies

I then defined a scoring and weighting procedure for the set of articles selected above. First, I examine the control group used in the trial. If a placebo or any other active substance than the four H_2 blockers was used, I assigned to the article the label *market-expanding science*. In the case of a comparative study between two or more of the H_2 antagonists, a label *comparative science* was assigned. Conditional on the label,

30. The seven general medicine and nine gastroenterology journals selected are: The *New England Journal of Medicine*, the *Lancet*, the *Annals of Internal Medicine, JAMA*, the *American Journal of Medicine*, the *British Medical Journal*, the *Archives of Internal Medicine, Gastroenterology, Gut, Gastrointestinal Endoscopy, Digestive Diseases and Science, Digestion*, the *Scandinavian Journal of Gastroenterology, Gastroentérologie Clinique et Biologique*, the *American Journal of Gastroenterology*, and the *Journal of Clinical Gastroenterology*. To validate this list, I searched the *Italian Journal of Gastroenterology* (whose impact factor was too low to justify its inclusion) for trials that otherwise met the inclusion criteria. While I found a number of such trials, they tended to garner a very small number of citations. This provides confidence that this arbitrary cutoff matters little for the results.

I used a simple Likert scale (+1, 0, −1) to assess the negative, neutral, or positive impact of the article: +1 (respectively, −1) was assigned if the treatment effect was significant and favored (respectively, did not favor) the drug studied. If a drug taken in combination with another treatment proved to be superior to the drug taken alone, I coded this outcome as favorable in that it potentially extended the range of situations in which this particular drug could be prescribed. In the case of three-way or four-way drug comparison studies, each dyad was entered as a different trial. The analysis and results presented in the paper are crucially dependent on this interpretative step. Ascribing a positive, neutral, or negative value to clinical studies depending on the sign and significance of treatment effects does seem reasonable, given that this same step is taken routinely by academic physicians engaging in meta-analyses of the clinical literature. Nonetheless, this scoring method means that the measures of scientific information presented here cannot be directly compared with more traditional proxies for knowledge, such as patent or patent-citation counts (Trajtenberg, 1990).

In order to capture variation in quality across clinical studies, I weighted the treatment effect score TE by the cumulative number of forward citations to the focal study, as of May 2001. This data was obtained by searching systematically the *Science Citation Index* (ISI, Philadelphia) on the Internet.[31] I illustrate the scoring and weighting scheme using the following study of ulcer relapse (Jorde et al., 1987):

> After healing of a gastric ulcer, 53 patients were randomly allocated to either 12 months maintenance treatment with ranitidine 150 mg at night or an identical placebo. Fifty patients completed the trial. The patients were interviewed every third month. If symptoms indicated a relapse, endoscopy was done; and if an ulcer was found the maintenance trial was terminated. All remaining patients were endoscoped after one year. The accumulated relapse rate in the ranitidine group (36%) was significantly lower (p less than 0.01) than in the placebo group (76%), as also was the antacid consumption (p less than 0.01). Four of the six ulcers found at the final one year endoscopy were asymptomatic. In all but two of the 26 patients with relapse of symptoms an ulcer was found at endoscopy. The patients that suffered a recurrence had significantly

31. Seven studies were authored by cooperative groups of investigators and could not be matched to the *Science Citation Index*. They were omitted from the analysis.

> (p less than 0.05) higher maximal acid output than those without ulcer recurrence. The time needed for healing of the relapse ulcers (four or eight weeks) corresponded to that needed for healing of the preinclusion ulcers. It is concluded that ranitidine 150 mg at night significantly reduces the gastric ulcer recurrence rate, and that relapsing ulcers are similar to the initial ones in healing response.

From this abstract, we learn that: (1) the control group received a placebo; (2) the treatment group received ranitidine; and (3) the difference between the outcomes in the treatment and control group was positive and significant ($p < 0.01$). Furthermore, the *Science Citation Index* indicates that this study had been cited 16 times since it was published. As a result, this study's contribution toward the flow of Zantac's market-expanding science is $+1 \times (1 + 16)$.

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