

The Economics of Commercial Success in Pharmaceutical Patent Litigation

By Rahul Guha, Jian Li, and Andrea L. Scott

Under the 1984 Hatch-Waxman Act, a generic drug manufacturer may seek FDA approval to enter a market before patents on the branded drug expire by claiming that the relevant patents are invalid or not infringed.¹ Since the Act's passage, the share of generic manufacturers' Abbreviated New Drug Applications (ANDAs) that make such claims has been increasing substantially.² The result has been an increase in patent infringement litigation by branded drug manufacturers against generic manufacturers.

When an accused infringer attacks a patent as invalid, the patent holder may need to establish that the patented invention is "nonobvious."³ The Supreme Court decision in *Graham v. John Deere Co.* first structured a three-part test for determining the nonobviousness of a patent.⁴ In addition to examining evidence on the intrinsic or scientific features of an invention, the Court in *Graham* also expressly approved the use of "secondary" considerations such as the commercial success of an invention in the nonobviousness determination.⁵ Other secondary considerations that have been considered by the courts include copying by competitors, fulfillment of a long-felt need, failures of others, and the extent of licensing of the patented invention.

From an economic perspective, commercial success supports a conclusion of nonobviousness because it suggests that an economic incentive existed to produce the invention. Thus, if the invention was obvious, it would have been brought to market sooner by some other party in response to that incentive.⁶ Some of the economic indicators that have traditionally been accepted by the courts as proof of commercial success include significant levels of and rapid growth in sales and market share of the patented product.

For evidence of commercial success to be probative on the issue of nonobviousness, the courts generally require the patent holder to show that there is a "nexus" between the claimed invention and the commercial success. The courts describe a nexus as "a legally and factually sufficient connection between the proven success and the patented invention."⁷ In pharmaceutical cases, medical and scientific experts will

often provide support for the claim that the therapeutic benefits of a drug flow from the patent and doctors prescribe the drug due to its therapeutic benefits. Economic analysis can be used to provide additional evidence that the commercial success is due to those benefits.

The Nexus Requirement

However, patent challengers often try to undermine the nexus argument by claiming that the commercial success is not due to the patented product features but due to other factors such as extensive marketing, superior distribution, general business acumen, and any nonpatented features. Such challenges to the nexus often arise in pharmaceutical patent cases because marketing plays an important role in the diffusion of new drugs. In several Federal Circuit cases, the courts have found that evidence of high marketing expenditures alone is not sufficient to undermine the nexus presumption.⁸ Rather, the courts also considered factors such as the typical advertising intensity for a particular drug class, the relative marketing intensity of the drug at issue compared to its competitors, and the information benefits of advertising to consumers.⁹

In this article, we discuss several economic analyses that are relevant for evaluating the reasons for a drug's commercial success. We begin by discussing appropriate indicators of commercial success for the pharmaceutical industry. Next we discuss economic analyses that can be used to evaluate the nexus between the patented drug's therapeutic benefits and the success. Then we discuss how to evaluate the contribution of marketing. We start by describing some key features of pharmaceutical marketing and appropriate measures of marketing intensity. Then we describe some important determinants of marketing intensity that must be considered when assessing whether the marketing effort was "excessive" and thus undermines the nexus.

We find that, when scientific evidence proves that the therapeutic benefits of a drug flow from the patent, several types of economic evidence can be used to demonstrate that the commercial success of a drug is driven by those benefits. In particular, sales that increase in response to new information about drug benefits, sales that increase due to a patented formulation improvement, and favorable coverage by prescription drug plans based on therapeutic considerations all reinforce the nexus between the patent and the commercial success. With respect to the contribution of marketing to the commercial success, high marketing intensity relative to other promoted competing substitutes does not necessarily undermine the nexus. In particular, marketing is normally higher earlier in the life cycle of a drug and for later drug entrants in a particular therapeutic category and may increase in response to new information about product quality. Perhaps

Rahul Guha, Ph.D., is a vice president in the Boston office of Cornerstone Research, which provides economic and financial consulting and analysis to attorneys in complex business litigation. Mr. Guha can be reached at rguha@cornerstone.com. **Jian Li**, Ph.D., is an associate and **Andrea L. Scott**, Ph.D., is a senior manager, both in the Menlo Park, California, office of Cornerstone Research. They can be reached at jili@cornerstone.com and ascott@cornerstone.com. The authors would like to thank Michael Keeley and Mary Woodford for helpful comments. The opinions expressed in this article are solely those of the authors and do not necessarily represent the views of Cornerstone Research.

⁸ Published in *Landslide*, Volume 1, Number 5, May/June 2009. © 2009 by the American Bar Association. Reproduced with permission. All rights reserved. This information or any portion thereof may not be copied or disseminated in any form or by any means or stored in an electronic database or retrieval system without the express written consent of the American Bar Association.

more importantly, the primary function of pharmaceutical marketing is to disseminate scientific information about the therapeutic attributes of the drug. Ultimately, the therapeutic benefits of a drug, and not marketing, are likely to determine whether or not it is a commercial success.

Indicators of Commercial Success

Commonly used indicators of commercial success include significant sales levels, significant sales growth, price premiums, and other indicators. Pharmaceutical sales can be measured by dollars of sales revenue, prescriptions, or daily doses. Because pharmaceuticals have low production costs, sales revenue is a good proxy for gross profitability.¹⁰ The level and growth of sales as a share of sales by competing drugs is another important indicator of commercial success because it speaks to the success of the product relative to its competitors. Courts consider sales data to be even more convincing if the patented invention has displaced or surpassed sales of competing drugs developed with prior art.¹¹

Pricing of the drug relative to competing drugs may also be a relevant indicator of commercial success. In particular, the ability to command a price premium over other competing drugs and still enjoy sales and share growth suggests that a drug provides unique therapeutic benefits. Other possible indicators of a drug's commercial success include rapid and widespread international diffusion and widespread favorable coverage for the drug in prescription drug plans.

The Nexus Between the Patent and the Commercial Success

In pharmaceutical patent disputes, the first step in establishing the nexus between the patent and commercial success commonly involves relying on medical and scientific experts to evaluate whether the therapeutic benefits of a drug flow from the invention claimed in the patent. When the therapeutic properties can be shown to flow from the patent, several economic analyses can also be conducted to assess the nexus between the patent and the commercial success. First, it can be helpful to examine the response of sales to favorable clinical trial results or approvals for new indications that flow from the patented drug features. Second, when the patent-at-issue covers a new formulation, such as an extended release or combination therapy, it is relevant to examine how the sales of the improved formulation compare to sales for the original formulation. Finally, it can be relevant to examine how and why the drug is covered by managed care providers in their prescription drug plans.

After a drug receives FDA approval, a pharmaceutical manufacturer may continue to undertake clinical research that reveals additional uses (indications) for the drug. This is known as Phase IV research and may be conducted for purposes including assessing long-term safety and effectiveness, comparing efficacy and cost-effectiveness to other drugs, and exploring new uses for the drug.¹² Academic scientists may also undertake

clinical trials and publish their findings. Thus, over time new information may become available about a drug's therapeutic properties. A study of anti-ulcer drugs found that sales respond to new scientific evidence in the form of published clinical trial results.¹³

Other studies have found that FDA approvals for more indications are also associated with increased sales and share.¹⁴ This was true for anti-ulcer drugs, for example. Tagamet was the first H₂-antagonist introduced with approval for the treatment of duodenal ulcers in 1977, and Zantac was subsequently introduced for the same indication in 1983. However, Zantac was the first to obtain FDA approval for an indication for gastroesophageal reflux disease (GERD) in 1986, while Tagamet did not receive approval for GERD until 1991. After its approval for the GERD indication, Zantac experienced substantial growth in sales and share compared to the leading drug, Tagamet, and other competitors. When a patented drug's sales increase in response to favorable trial outcomes or new indication approvals, which themselves flow from the patented drug features, this reinforces a conclusion of a nexus between the patent and the commercial success.

In addition, when the patent-at-issue covers a new formulation, such as an extended release or combination therapy, it may be relevant to examine how the sales of the improved formulation compare to sales for the original formulation. For example, Wyeth's patented extended release formulation of the antidepressant Effexor[®] (Effexor[®] XR) has achieved far greater sales and share among competing drugs than the immediate release formulation. The improved formulation has superior therapeutic properties in terms of efficacy and side effects. It is associated with better tolerability and therefore improved patient adherence.¹⁵ This translated into increased sales since depression is a chronic condition that requires ongoing treatment. A comparison of the sales of the new formulation with the old reinforces a conclusion that there is a nexus between the formulation patent and the commercial success.

Finally, the extent of and reasons for coverage for the drug by managed care providers in their prescription drug plans is another factor that can be examined to reinforce the nexus. In the United States, the majority of outpatient drugs are at least partially covered by health care plans. Insurers, managed care organizations, and pharmacy benefit managers (PBMs) use various strategies for controlling prescription drug costs including formularies.¹⁶ Drug formularies are lists of approved drugs and a common type uses a three-tier system of co-payments. Generic drugs are in Tier 1 with the lowest co-payment. Preferred branded drugs are in Tier 2. Nonpreferred branded drugs are in Tier 3 with the highest co-payment. After they face generic entry, branded drugs will almost always be placed in Tier 3 (or removed from the formulary altogether).¹⁷

The process of assigning branded drugs (without direct generic substitutes) to the middle or highest tier of a

formulary is usually based on both therapeutic and economic considerations. Most PBMs and managed care organizations follow a two-step process. First, a pharmacy and therapeutics committee will determine whether a new branded drug should be reimbursed on medical grounds, and if so, whether there are close therapeutic substitutes for this product. A drug that does not face such substitutes is likely to be placed in Tier 2. However, if a product does have what the committee deems to be close substitutes, then the decision on which of the substitute products should be placed in the preferred tier will generally be made on economic grounds (e.g., based on their cost, including rebates and discounts).¹⁸ Therefore, when a commercially successful drug achieves widespread Tier 2 placement on three-tier formularies due to the drug's characteristics (e.g., unique therapeutic benefits that flow from the patent), that placement provides evidence that the commercial success is due to the patented features.

The Role of Marketing

The data on the commercial success of a drug often show rapid growth in sales and share coincident with substantial marketing efforts. The patent challenger may use this observation to argue that it is "excessive" marketing, and not the patented invention, that explains the commercial success. In this section we discuss how to assess the role of marketing. We start by briefly describing the nature of pharmaceutical marketing activities. Then we discuss useful measures of marketing intensity. Next we show that marketing intensity varies based on factors including the stage in the product life cycle, order of entry effects, and the arrival of new information about the drug. All these factors must be accounted for in evaluating whether or not the marketing was "excessive" and therefore undermines the link between the patented features and the commercial success.

Background on Pharmaceutical Marketing

Pharmaceuticals are complex products that are usually sold to consumers after being prescribed by a physician. As a result, pharmaceutical companies promote their products primarily through physician-oriented activities such as "detailing," provision of free samples, and advertising in medical journals.¹⁹ Pharmaceutical companies also engage in direct-to-consumer advertising for some products, but on a smaller scale.²⁰ These marketing activities serve to convey scientific information about the drug, including the efficacy, side effects, adverse interactions and contraindications, pharmacokinetic properties, dosage information, and cost-effectiveness. Based on FDA regulations, the substance of the marketing must be based on scientific evidence as obtained through clinical trials.²¹

Marketing is important for pharmaceuticals because they are "experience goods." Experience goods are those whose quality and effectiveness cannot be assessed definitively prior to consumption, but can only be determined from direct experience. Since patients often have idiosyncratic responses in terms of efficacy, side effects, and adverse interactions to a particular drug, they need to try the drug before the doctor can determine its value to them. As a result, manufacturers need to advertise the existence and attributes of their drugs to

induce consumers (both physicians and patients) to try them. Academic research has found that marketing-to-sales ratios are higher for experience goods than other types of goods.²²

That finding is consistent with evidence that, when compared to other industries, pharmaceutical manufacturers have some of the highest marketing expenditures when compared to sales revenue. One industry benchmark comes from a 2004 study that estimated an aggregate annual marketing-to-sales ratio for all pharmaceutical products of approximately 14 to 15 percent.²³ This benchmark may underestimate the marketing-to-sales ratio for some branded drugs with no direct generic competition, such as those that would be at issue in these cases. The industry-wide estimates are based on data for not just branded drugs that are likely to be promoted, but also generic drugs and branded drugs facing direct generic substitutes, two classes of drugs that typically involve little, if any, marketing. In contrast, company-level data from other industries reveals much lower marketing intensities.²⁴

Marketing performs an important role in disseminating clinical and therapeutic information about a drug. Perhaps unsurprisingly, research finds that advertising is more effective for higher-quality drugs than for "me-too" drugs with little therapeutic advantage.²⁵ This stems from the fact that the responsiveness of physicians' prescribing decisions to marketing efforts depends on therapeutic benefits such as the effectiveness and side effects of a drug.²⁶ As a result, pharmaceutical companies are more likely to invest in substantial marketing efforts for drugs with superior therapeutic benefits. Therefore, the level of marketing effort a pharmaceutical company invests in a drug and the impact of marketing on its success typically depend on the underlying therapeutic benefits of the drug.²⁷ Ultimately, the therapeutic benefits of drugs are likely to determine whether or not it is a commercial success.

Measuring Marketing Intensity

A commonly used measure of marketing intensity is the marketing-to-sales ratio, which is usually calculated as total marketing expenditures divided by sales dollars for the drug. Industry data sources such as IMS Health are frequently used to construct such measures.²⁸ The marketing-to-sales ratio for the drug at issue should be compared to the marketing-to-sales ratios for drugs that are the key competing therapeutic substitutes that are also promoted. A drug with a marketing-to-sales ratio similar to the other promoted branded drugs with which it competes is unlikely to have marketed excessively.

The drug's marketing efforts can also be compared to competing drugs as a group. This involves constructing a drug's share-of-voice, which is measured as the drug's marketing expenditures divided by the total marketing expenditures of all the competing drugs. If a drug's share-of-voice is less than or equal to its share of sales, it is unlikely that the commercial success is driven solely by marketing.

Determinants of Marketing Intensity

Marketing intensity for different drugs varies for a number of reasons, including the stage in the product life cycle, order of entry effects, and the arrival of new information about the drug's benefits. Higher marketing intensity of a drug

compared to other promoted therapeutic substitutes under some circumstances is normal and is justified by economic reasons. Therefore, high marketing intensity may not always undermine the contribution of the patented features to the drug's commercial success.

Pharmaceutical marketing-to-sales ratios vary over the product life cycle. They are typically highest immediately following the launch of a new branded drug when the manufacturer must undertake a substantial effort to inform physicians of the existence and therapeutic benefits of the product. For example, academic research estimates that the average marketing-to-sales ratio for a new branded drug is 100 percent, 50 percent, and 25 percent in the first three years.²⁹ Therefore, high marketing intensity that coincides with a product's launch usually should not be considered excessive.

Marketing intensity also varies with order of entry into a drug class. Academic research has demonstrated that there can be significant first-mover advantages for pharmaceuticals.³⁰ First-mover advantage is a phenomenon whereby the company that first enters has a long-lived advantage over competitors that enter subsequently. Because pharmaceuticals are experience goods, once physicians and patients experience benefits from the use of a particular drug, they may be reluctant to experiment with alternatives. As a result, it is usually harder for later entrants to persuade consumers and physicians to learn about the drug's attributes than it was for the first brand. Later entrants may need to invest more heavily in marketing to overcome the incumbent's advantage.³¹ Empirical evidence has shown that for a given duration of time, the cumulative marketing-to-sales ratios are usually lowest for the pioneer, are larger for the second entrant, and increase further for later entrants.³² Therefore, more intensive marketing by subsequent entrants can be explained as necessary to overcome the first-mover advantage, which argues against a conclusion of excessive marketing.

Finally, marketing intensity of a drug may be explained by the arrival of new information that signals better quality for a drug. Academic studies have shown that marketing is most valuable for those drugs that have substantial therapeutic benefits (such as better efficacy and side-effect profiles). As a result, the arrival of new information that signals better quality, such as favorable clinical trial results published in medical journals or announced in the press, or the approval of new indications by FDA is likely to be associated with increased marketing intensity. The publication of new clinical trial results led to increased marketing efforts for anti-ulcer drugs, according to an academic study.³³ Another study on antidepressant drugs found that on average, when a selective serotonin reuptake inhibitor (SSRI) was approved for two or more additional indications other than depression therapy, the marketing effort for this drug nearly doubled.³⁴

In sum, pharmaceutical companies make decisions on how intensively to promote a drug based on a number of factors. Failing to properly control for these relevant factors in an economic analysis may erroneously lead to the conclusion that the marketing of a particular drug is excessive. Such conclusions cannot credibly undermine the link between the patented features and the commercial success of a drug.

Conclusion

In the presence of scientific evidence that the therapeutic attributes of a drug flow from the patent, several types of economic analyses can be conducted to support a conclusion that the commercial success is due to the patent's claimed invention. This includes sales that respond to new information about drug benefits, sales that respond to patented formulation improvements, and favorable formulary placement based on therapeutic considerations. When evaluating the contribution of marketing efforts to the success, it is important to account for several factors that drive marketing intensity. In particular, marketing intensity is normally higher early in the product life cycle and for later entrants and will increase in response to new information about product quality. Finally, marketing serves an important function in disseminating information about the therapeutic benefits of pharmaceuticals. Ultimately, those benefits, and not marketing, are likely to determine whether or not it is a commercial success. ■

Endnotes

1. This is known as a Paragraph IV certification. A manufacturer filing an Abbreviated New Drug Application (ANDA) must provide one of four possible certifications regarding each of the patents listed in the FDA's Orange Book for a given new drug application (NDA). Paragraph I certification states that no patents have been filed. Paragraph II certification indicates that the patents have already expired. Under paragraph III, the manufacturer certifies that it seeks approval after the patents expire. Paragraph IV certification states that the patent is invalid or will not be infringed. See FTC, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 5* (2002).

2. The percentage of ANDAs submitted for approval prior to patent expiration increased from 2% of all ANDAs filed between 1984 and 1989 to 20% from 1998 to 2000. *Id.* at 10.

3. Nonobviousness requires the patented invention to be a nontrivial extension of the prior art. See 35 U.S.C. § 103.

4. The three-part test requires a judge to: (1) determine the state of "prior art" before the invention; (2) assess the ordinary level of skills in the inventor's field; and (3) examine the differences between the invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

5. The Court ruled that secondary considerations such as commercial success *may* be relevant as indicia of nonobviousness. *Id.* "Secondary" refers to their temporal occurrence after the invention has been brought to market. The Federal Circuit refers to them as "objective evidence of non-obviousness." Federal Circuit decisions elevated them in importance, to be considered by the courts and the USPTO in all cases. The recent *Syntex (U.S.A.) LLC v. Apotex, Inc.* decision by the Federal Circuit may suggest a lessened role for these factors, for consideration only when the other factors imply a close determination. JOHN R. THOMAS, *PHARMACEUTICAL PATENT LAW* 167-68 (BNA Books 2005) and JOHN R. THOMAS, *PHARMACEUTICAL PATENT LAW* 45-46 (BNA Books, Supp. 2007).

6. THOMAS (2005), *supra* note 5, at 168.

7. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir. 1988). The Federal Circuit standard has also been described as follows: "[t]o be safe in proving nexus, the evidence must be marshaled to show that [sic] at least that the claimed features contributed significantly to the existence of the objective evidence. Second, the proponent of a nexus must show that any extraneous factors do not overshadow the claimed features." Edward P. Walker, *Objective Evidence of Nonobviousness: The Elusive Nexus Requirement (Part I)*, 69 J. PAT. & TRADEMARK OFF. SOC'Y 175, 182-83 (1987).

8. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), and *Merck & Co. v. Danbury Pharm. Inc.*, 694 F. Supp. 1, 21 (D. Del. 1988).

9. *Id.*

10. Some economists may propose using the return on invested capital required to discover and develop the drug as a measure of profitability.

However, this measure has limitations and has rarely been used in court decisions. First, an accurate measure of investment return for a particular drug may be difficult to obtain because R&D costs may be incurred over a long period of time and may not be easily allocated to a particular drug. In addition, a lack of positive return on capital investment should not necessarily undermine a conclusion of commercial success. A few “blockbuster” drugs generate the majority of profits for the drug companies. That means the majority of smaller drugs may not be profitable in the sense of recouping all the costs of their discovery and development, even if they have proven therapeutic value.

11. Walker, *supra* note 7, at 189.

12. Ernst R. Berndt, *The U.S. Pharmaceutical Industry: Why Major Growth in Times of Cost Containment?* 20 HEALTH AFFAIRS 100, 109 (2001).

13. Pierre Azoulay, *Do Pharmaceutical Sales Respond to Scientific Evidence?* 11 J. ECON. & MGMT. STRATEGY, (2002), at 551.

14. See, e.g., Ernst R. Berndt et al., *The Roles of Marketing, Product Quality and Price Competition in the Growth and Composition of the U.S. Anti-Ulcer Drug Industry*, in THE ECONOMICS OF NEW GOODS (T. Bresnahan and R. Gordon eds. 1997), at 277.

15. Charles B. Nemeroff, *Improving Antidepressant Adherence*, 64 J. CLINICAL PSYCHIATRY 25 (2003).

16. See FTC, PHARMACY BENEFIT MANAGERS: OWNERSHIP OF MAIL-ORDER PHARMACIES 10–15 (2005); Henry Grabowski et al., *Pharmacy Benefit Management, Cost-Effectiveness Analysis and Drug Formulary Decisions*, 45 SOC. SCI. & MED. 535, 535 (1997).

17. See FTC *supra* note 16, at 11. This will be the case unless the manufacturer of the branded drug provides rebates or discounts to match the price of the generics.

18. See Grabowski, *supra* note 16, at 535, 537–38.

19. Detailing activities consist of in-person visits or phone calls by sales representatives. According to a study based on IMS Health data, in 2000 the vast majority of marketing spending was on physician-oriented promotion (about 84%), of which detailing accounted for 30.6% and samples accounted for 50.6%. Meredith B. Rosenthal et al., *Demand Effects of Recent Changes in Prescription Drug Promotion*, 6 J. FOR HEALTH ECON. & POL'Y, 1, 9–10 (2003).

20. Consumer-oriented promotions for pharmaceutical products usually use print and electronic media. In the past decade, there has been an increase in consumer-oriented promotions because of the release of clarified FDA guidelines in 1997. By 2000, direct-to-consumer advertising comprised 15.7% of total promotion expenditures by the pharmaceutical industry. *Id.* at 10.

21. For example, any materials distributed by the detailing sales force are considered “labeling” and must carry the “full package insert,” *i.e.*, the complete product information reviewed by the agency as part of the drug approval process. See David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising and Promotion*, 264 J. AM. MED. ASS'N 2409, 2410 (1990).

22. See, e.g., Ernst R. Berndt et al., *An Analysis of the Diffusion of New Antidepressants: Variety, Quality, and Marketing Efforts*, 5 J. MENTAL HEALTH POL'Y & ECON. 3, 4 (2002).

23. See Rosenthal, *supra* note 19 at 9–10.

24. For example, in 1998, the marketing-to-sales ratio for Home Depot was 1.6%; Phillips Electronics, 2.4%; American Express, 3.2%; Circuit City, 4.5%; Sony Corporation, 4.7%; and Intel, 5.8%. Ernst R. Berndt, *Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price*, 16 J. ECON. PERSP. 45, 52 (2002).

25. See Hubert Gatignon, et al., *Brand Introduction Strategies and Competitive Environments*, 27 J. MARKETING RES. 390, 392 (1990).

26. Sriram Venkataraman et al., *The Debate on Influencing Doctors' Decisions: Are Drug Characteristics the Missing Link?* 53 MGMT. SCI. 1688 (2007).

27. See, e.g., Berndt et al., *supra* note 22.

28. IMS Health is an independent consulting company that provides data and analysis to the pharmaceutical industry, researchers, the FDA, and numerous state and federal agencies.

29. Henry Grabowski et al., *Returns to R & D on New Drug Introductions in the 1980s*, 13 J. HEALTH ECON., 383, 391–392 (1994).

30. Berndt et al., *supra* note 22, at 4.

31. *Id.*

32. For example, among H2-antagonists, the marketing-to-sales ratios in the 1990s were 0.32 for pioneer drug Pepcid AC, 0.34 for second entrant Tagamet HB, 0.35 for third entrant Zantac 75, and 0.36 for last entrant Axid AR. Davina C. Ling et al., *Deregulating Direct-to-Consumer Marketing of Prescription Drugs: Effects on Prescription and Over-the-Counter Product Sales*, 45 J.L. & Econ. 691, 704 (2002). Also, for antidepressants, the three-year cumulative marketing-to-sales ratios (from 1997–99) for physician-oriented marketing spending were 0.09 for Prozac (with FDA approval in 1987), 0.14 for Zoloft (with FDA approval in 1991), 0.16 for Paxil (with FDA approval in 1992), 0.21 for Effexor XR (with FDA approval in 1993), and even higher for later entrants. Rosenthal et al., *supra* note 19, at 4.

33. Azoulay, *supra* note 13.

34. Berndt et al., *supra* note 22 at 3, 14–15.