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Provigil: A Case Study of Anticompetitive Behavior

by MICHAEL A. CARRIER*

I. Introduction

Using the sleep-disorder drug Provigil as a case study, this article exposes a new type of anticompetitive harm that stems from the combination of two distinct activities. First, brand-name drug firms such as Cephalon, the developer of Provigil, have settled patent litigation by paying generic firms to delay entering the market. Second, brand firms, frequently at the end of a patent term, have engaged in “product hopping,” switching from one means of administering a drug (e.g., tablet) to another (e.g., capsule). The story of Provigil demonstrates the anticompetitive harm that can result from the combination of these two activities.

II. Provigil

Provigil is a sleep-disorder medication marketed by Cephalon. It was initially approved for excessive daytime sleepiness associated with narcolepsy and was subsequently used to treat obstructive sleep apnea and shift work sleep disorder.¹ United States soldiers, most famously those fighting in the Iraq War, have used it to stay awake for as long as 40 hours at a time.²

The drug offers significant benefits over other amphetamine-like stimulants. In particular, Provigil does not result in side effects such

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1. Complaint for Injunctive Relief ¶ 26, *FTC v. Cephalon, Inc.*, 551 F. Supp. 2d 21 (D.D.C. 2008) (No. 08-0244), 2008 WL 446785 [hereinafter *Cephalon Complaint*].

2. Tom Spears, *New Drug May Help Soldiers Stay Awake Doctors Unsure of Long-Term Effect*, OTTAWA CITIZEN (Oct. 11, 2003), <http://www.modafinil.com/article/soldiers.html>.

as addiction, feeling jittery, and crashing afterward.³ As a result, the drug is considered the “gold standard” for the treatment of the excessive sleepiness accompanying sleep disorders.⁴ United States sales of Provigil increased from \$25 million in 1999 to \$475 million in 2005 to \$800 million in 2007.⁵

The active ingredient in Provigil is a chemical compound called modafinil.⁶ Cephalon filed a New Drug Application for Provigil in 1996, which the FDA approved in 1998.⁷ The U.S. patent covering modafinil was issued in 1979 and expired in 2001.⁸

Cephalon obtained a second patent in 1997. This patent covered a formulation of modafinil that consisted of a specified distribution of small particles.⁹ This narrower patent lasts until October 2014, with Cephalon receiving an additional six months of pediatric exclusivity that extends protection until April 2015.¹⁰

Unlike the patent on the compound itself, generic firms could easily avoid this narrow formulation patent. As a consultant advised Cephalon in 2002: “[A]ll generic companies know [that the patent] may be easily circumvented” by manufacturing products to contain a different distribution of modafinil particle sizes.¹¹

Given the ease with which generic firms could circumvent the particle-size patent, it is no surprise they were eager to do so. In December 2002, four generic firms submitted Abbreviated New Drug Applications on the first day the FDA would accept them.¹² Teva, Ranbaxy, Mylan, and Barr each certified “that [their] version[s] of generic Provigil did not infringe . . . [the] [p]atent, that the patent was invalid, or both.”¹³

3. *Cephalon Complaint*, *supra* note 1, ¶ 27.

4. *Id.*

5. *Id.* ¶ 28.

6. *Id.* ¶ 24.

7. *Id.* ¶ 26.

8. *Id.* ¶ 32.

9. *Id.* ¶ 33.

10. *Cephalon Granted Six Months of Pediatric Exclusivity for Provigil(R)*, CEPHALON.COM (Mar. 28, 2006), <http://www.cephalon.com/media/news-releases.shtml?mode=year&filterval=2006> (noting that Cephalon “met the terms of a written request to provide data from clinical studies examining the effect of Provigil in pediatric patients”) (emphasis omitted).

11. *Cephalon Complaint*, *supra* note 1, ¶ 35.

12. *Id.* ¶ 36.

13. *Id.*

Cephalon “knew that generic Provigil entry would lead to substantial declines in the company’s revenues.”¹⁴ A company vice president projected a 75%-90% price reduction that would lower revenues by more than \$400 million (nearly 75% of the drug’s annual sales) within one year.¹⁵ Similarly, Teva projected that generic versions “would garner 90[%] of all modafinil prescriptions within a month” and that the price would fall to 10% of Provigil’s price within one year.¹⁶

The consensus in the industry supported these projections. Wall Street analysts projected generic entry in 2006.¹⁷ The four first-filing generic firms planned for a launch in June 2006 at the latest.¹⁸ Barr ordered significant quantities of the active ingredient in late 2005.¹⁹ And Cephalon asserted, in November 2005, that “generic versions of modafinil” would enter the market in the middle of 2006.²⁰

Cephalon fought back against these projections by seeking to maintain its market share through a successor product, Nuvigil.²¹ The longer-lasting Nuvigil was similar to Provigil in many ways, including chemical composition.²² It offered modest improvements by allowing patients to take a pill once a day instead of two times daily. Cephalon also sought to switch to Nuvigil to expand its customer base to cover other conditions.²³

The FDA, however, had not yet approved Nuvigil by the end of 2005.²⁴ And, as the FTC pointed out, “[T]here was considerable uncertainty as to whether the FDA would approve Nuvigil early

14. *Cephalon Complaint*, *supra* note 1, ¶ 39.

15. *Id.*

16. *Id.* ¶ 40.

17. *Id.* ¶ 51.

18. *Id.* ¶ 50.

19. *Id.*

20. *Id.* ¶ 48.

21. *Id.* ¶ 52.

22. *Cephalon Receives FDA Approval of NUVIGIL(TM) for the Treatment of Excessive Sleepiness Associated with Three Disorders*, CEPHALON.COM (June 18, 2007), <http://www.cephalon.com/media/news-releases.shtml?mode=year&filterval=2007> (pointing out that “[t]he active pharmaceutical ingredient in Nuvigil, armodafinil, is the longer-lived r-enantiomer [molecule’s mirror image] of modafinil, the active ingredient in Provigil”) (emphasis omitted).

23. Cephalon, Inc., Q1 2009 Earnings Call Transcript, SEEKINGALPHA.COM (May 5, 2009), <http://seekingalpha.com/article/135541-cephalon-inc-q1-2009-earnings-call-transcript?page=-1> (discussing clinical trials for jet-lag disorders, bipolar depression, sleep apnea, co-morbid major depressive disorder, and traumatic brain injury).

24. *Cephalon Complaint*, *supra* note 1, ¶ 52.

enough in 2006 to enable Cephalon to successfully migrate customers from Provigil to Nuvigil before the entry of a generic version of Provigil.”²⁵

Given this uncertainty, Cephalon decided to settle patent litigation with the four first-filing generic firms.²⁶ Cephalon paid more than \$200 million to the four generics to agree to forgo entry until April 2012.²⁷ The Cephalon CEO conceded that the settlements provided “six more years of patent protection[,]” which was “\$4 billion in sales that no one expected.”²⁸

Cephalon was able to attain this windfall by combining two activities, which are the focus of the next two Parts.

III. Settlements

The first activity involved patent settlements. In recent years, brand-name drug companies have paid generic firms to settle patent litigation and delay entering the market. The relevant statutory framework is the Hatch-Waxman Act, enacted by Congress to solve problems that existed in the drug industry in the 1980s.²⁹

Most relevant for our purposes, the legislature created a 180-day period of marketing exclusivity, reserved for the first generic to certify that the brand firm’s patent is invalid or not infringed. In contrast to the purpose of the provision, which was to encourage patent challenges, the 180-day period has been employed to allow brand firms to block challenges by settling with the first generic (known as a “Paragraph IV” generic) to challenge patent validity or claim noninfringement.³⁰

By paying the first-filer to delay entering the market, the brand firm can prevent entry not only by that generic but also by all other generics, who are prohibited from entering the market until 180 days after the first-filer’s entry.³¹ Such settlements are occurring with increasing frequency since each of the parties benefits from

25. *Cephalon Complaint*, *supra* note 1, ¶ 52.

26. *Id.* ¶ 53.

27. *Id.* ¶ 3.

28. *Id.* ¶ 4.

29. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.

30. The other three Paragraphs apply to generics challenging a drug where there is no patent on the drug, an expired patent, or a promise to wait until the patent expires. 21 U.S.C. § 355(j)(2)(A)(vii) (2006).

31. *See* 21 U.S.C. § 355(j)(5)(B)(iv) (2006).

settlement. The brand blocks challenges that could invalidate its patent, while the generic receives a subset of the brand's monopoly profits that could exceed what it would have gained by entering the market.

These settlements threaten severe anticompetitive dangers. They introduce a type of market division, with the brand firm blocking all competition for a period of time.³² These so-called "reverse payments"³³ are red flags that—given the complex nature of patent issues in antitrust litigation—frequently offer the best evidence of patent invalidity or noninfringement.³⁴ One central element of patent drug settlements has been the timing of generic entry. Most generally (and oversimplifying dramatically), the longer the generic firm agrees to refrain from entering the market, the greater the anticompetitive concern in some of the early reverse-payment settlements, the generic agreed to stay out of the market for all or nearly all of the patent term. For example, in *In re Tamoxifen Citrate Antitrust Litigation*, generic firm Barr agreed in 1993 not to enter the market with a generic breast cancer treatment until brand firm Zeneca's patent expired in 2002.³⁵ And in *In re Ciprofloxacin Hydrochloride Antitrust Litigation*, brand firm Bayer in 1997 paid generic firm Barr to stay out of the market until six months before Bayer's patent on Cipro, a drug treating bacterial illnesses, was set to expire in 2003.³⁶

In recent settlements, however, such as the one concerning Provigil, the parties have provided for generic entry for longer periods before the end of the term. They presumably have reached such arrangements to convince courts that several years of competition before expiration are procompetitive. Cephalon, for example, touted the "obvious benefits and efficiencies" of its Provigil settlement, which "permitted the [g]enerics to enter the market three

32. *In re Schering-Plough Corp.*, 2003 WL 22989651, Part II.A (F.T.C. 2003), *vacated* by *Schering-Plough Corp. v. FTC.*, 402 F.3d 1056, 1058 (11th Cir. 2005).

33. These agreements are called reverse payments since they differ from typical licensing payments that flow from challengers to patentees.

34. In addition, an analysis of the merits of the patent infringement case would be unreliable. After a case settles, the parties' interests become aligned, with a generic firm lacking the incentive to vigorously attack a patent's validity or an infringement claim. Michael A. Carrier, *Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality*, 108 MICH. L. REV. 37, 73 (2009).

35. 466 F.3d 187, 193–94 (2d Cir. 2006).

36. 544 F.3d 1323, 1329 (Fed. Cir. 2008), *aff'g*, 363 F. Supp. 2d 514, 519 (E.D.N.Y. 2005).

years prior to the expiration of the . . . patent.”³⁷ While such a position could conceivably apply in the context of the patent that is the focus of settlement, a closer look at a second activity uncovers flaws in the argument.

IV. Product Hopping

This second activity, known as “product hopping,” involves switching from one formulation of a drug (e.g., capsule) to another (e.g., tablet). While product-hopping could offer (frequently minor) benefits for innovation by increasing patient compliance, it also threatens adverse effects on generic competition.

A central reason for the adverse effects involves state drug product selection (DPS) laws. These laws, in effect in all 50 states today, allow—and in many cases require—pharmacists, absent a doctor’s contrary instructions, to substitute generic versions of brand-name prescriptions.

DPS laws are designed to address the disconnect in the industry between prescribing doctors, who are not directly responsive to drug pricing, and paying insurers and consumers, who do not directly select the prescribed drug.³⁸ In particular, DPS laws carve out a role for pharmacists, who are much more sensitive to prices than doctors.³⁹

Doctors are subject to a vast array of drug promotion, which includes detailing (sales calls to doctor’s offices), direct mailings, free drug samples, medical journal advertising, sponsored continuing medical education programs, and media advertising.⁴⁰ Pharmacists, in contrast, respond to consumer demand and compete with other pharmacies on price.⁴¹

Reformulation from one version to another eliminates both price and quality competition. It eliminates quality competition since the brand firm switches its promotion to the new product, leaving doctors unable to effectively compare quality between the reformulated

37. Defendant Cephalon, Inc.’s Memorandum of Points and Authorities in Support of Motion to Dismiss at 1, *FTC v. Cephalon, Inc.*, 551 F. Supp. 2d 21 (D.D.C. 2008) (No. 08-0244) 2008 WL 2047585.

38. BUREAU OF CONSUMER PROTECTION, *DRUG PRODUCT SELECTION: STAFF REPORT TO THE FTC* 2–3 (1979).

39. BUREAU OF ECONOMICS, *GENERIC SUBSTITUTION AND PRESCRIPTION DRUG PRICES: ECONOMIC EFFECTS OF STATE DRUG PRODUCT SELECTION LAWS* 7 (1985).

40. STUART O. SCHWEITZER, *PHARMACEUTICAL ECONOMICS AND POLICY* 87–93 (2d ed. 2007).

41. See BUREAU OF ECONOMICS, *supra* note 39, at 7.

brand drug and the old version.⁴² It also limits price competition by avoiding the DPS laws.⁴³

The DPS laws typically allow pharmacists to substitute generic versions of brand drugs only if they are “AB-rated” by the FDA. To receive an AB rating, a generic drug must be pharmaceutically equivalent to the brand drug (having the same active ingredient, form, dosage, strength, and safety and efficacy profile) and also bioequivalent (being absorbed in the body at roughly the same rate).⁴⁴

The concern when a brand reformulates its drug is that the generic version of the first product is not bioequivalent or pharmaceutically equivalent to the second product. And while the generic firm may eventually show equivalence, such a showing likely will not occur for years.⁴⁵

Compounding this problem, the brand typically will switch its promotion to the new drug, even highlighting the comparative advantages of the new product. At the same time, no other party has the incentive and ability to promote the old product, which leads to doctors receiving an “entirely one-sided presentation” of the relative merits of the products.⁴⁶

Product hopping is most successful when brand firms can not only avoid state DPS laws but also orchestrate effective timing. Stated most simply, the brand firm will be more successful if it can switch the market before generic entry.

Introducing the new product before the generic enters the market “adds the near-elimination of price competition to the near-elimination of quality competition.”⁴⁷ Brand firms offer the

42. See generally Steve D. Shadowen et al., *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 RUTGERS L.J. 1, 3 (2009) (“We examine the economic effect . . . with special emphasis on identifying the particular dimension of rivalry—price competition or quality comparisons—that is affected.”).

43. *Id.* at 13–18.

44. FDA CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, *Approved Drug Products with Therapeutic Equivalence Evaluations* (30th ed. 2010), <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>; Shadowen et al., *supra* note 42, at 5.

45. The delay stems from the generic manufacturer reformulating its product, the generic firm seeking FDA approval, and delays stemming from a Hatch-Waxman process that includes a brand firm’s automatic “30-month stay” of FDA approval.

46. Shadowen et al., *supra* note 42, at 46 (explaining that other brands lack the incentive to promote a competitor’s products and that generics will not promote the product because they do not have large sales forces and would worry about free-riding by other generics).

47. *Id.* at 51.

“uncontested message” of the new product’s superiority as the manufacturer’s detailers “extol the virtues of the new product” at a time when “no one is promoting the original.”⁴⁸ In addition, brand firms make the switch “when doctors do not have a generic alternative available and do not know that one may be on the way.”⁴⁹ And evidence shows that patients who switch to the new drug are unlikely to switch back.⁵⁰ For example, in a product-hopping case involving the cholesterol drug TriCor, brand firm Fournier switched from a once-daily tablet taken with food to one taken without food. It conceded that such a change would not have “an expansive effect [on sales] on its own” but would have “a substantial benefit in avoiding losses of sales due to generics.”⁵¹ Such a change would allow Fournier to “sell more than ten times as many TriCor tablets than if the reformulated product competed head-to-head with the generic with simultaneous market entry.”⁵²

In contrast, King Pharmaceuticals, anticipating generic entry on its ACE inhibitor capsules, switched to a tablet, but not before a generic brought its capsule to the market. As a result, King’s sales fell from \$646 million in 2007 to \$166 million in 2008.⁵³

V. Combination of Settlements and Product Hopping

In the case at issue here, Cephalon sought to switch the market from Provigil to Nuvigil before generic Provigil reached the market. But because the FDA had not yet approved Nuvigil by late 2005, the only way Cephalon could ensure the absence of generic competition was by paying the generics not to enter the market. This is exactly what it did, settling patent litigation with the four first-filing generic firms to delay entry for six years.⁵⁴

In its motion to dismiss the complaint (which the court denied), Cephalon noted that the settlement, which allowed entry in 2012, “resulted in generic entry *years earlier* than patent expiration” in

48. Shadowen et al., *supra* note 42, at 51.

49. *Id.*

50. *Id.* at 51-55 (explaining brand firms’ marketing of “superior” reformulated product, generics’ lack of marketing, and doctors’ “reluctan[ce] to authorize a second switch of the patient’s medication within a relatively short period of time”).

51. *Id.* at 52.

52. *Id.*

53. *Id.* at 50–51. For other examples of the effects discussed in this and the previous paragraph, *see id.* at 48–58.

54. *Cephalon Complaint*, *supra* note 1, ¶¶ 52, 53.

2015.⁵⁵ This is typical of arguments voiced by proponents of recent reverse-payment settlements, who justify the agreements by pointing to the guaranteed years of competition before the end of the patent term.

A bird's-eye view of the activity, however, shows how the various forms of anticompetitive behavior fit together. Cephalon had no intention of competing in a robust market with generics in 2012. The generics themselves, in obtaining more than \$200 million from Cephalon, did not expect vibrant competition in 2012.

Rather, by delaying the potential onset of generic competition until 2012, Cephalon bought itself a period of six years in which it was *guaranteed* that its weak Provigil patent would not be challenged. With that certainty in hand, Cephalon could enjoy the luxury of an extended period of switching the market to its new sleep disorder drug, Nuvigil. Nuvigil, which the FDA approved in 2007, enjoys patent protection until 2023.⁵⁶ A Cephalon spokesman conceded that after settlement “[t]he pressure is not what it was,” and that the company was not required “to make a quick transition from Provigil to Nuvigil.”⁵⁷ An industry analyst agreed that the delay would “allow Cephalon to seek to expand its wakefulness franchise” rather than treating Nuvigil “merely as a conversion opportunity . . . that would be under pressure to establish itself early.”⁵⁸

Cephalon's switching strategy had two simple components: making Provigil less desirable and making Nuvigil more desirable. Cephalon accomplished the first task by increasing the price of Provigil by 74 percent between 2004 and 2008 and ceasing promotion of the drug.⁵⁹ Cephalon officials explained that they “actually pulled all promotion from Provigil” after the first quarter of 2009 “in anticipation of the [Nuvigil] launch,” which occurred in June.⁶⁰

Having weakened the competitive position of Provigil, Cephalon set off on its second task: promoting Nuvigil. The CEO sang Nuvigil's

55. Defendant Cephalon, Inc.'s Motion to Dismiss, *supra* note 37, at 26.

56. *Cephalon Receives FDA Approval Of Nuvigil(TM) for the Treatment of Excessive Sleepiness Associated with Three Disorders*, MEDICALNEWTODAY.COM (June 19, 2007), <http://www.medicalnewstoday.com/articles/74585.php>.

57. Robert Steyer, *Cephalon Puts Worries to Rest*, THESTREET.COM (July 14, 2006), <http://www.thestreet.com/print/story/10268224.html>.

58. Cephalon, Q1 2009 Earnings Call Transcript, *supra* note 23.

59. Jonathan D. Rockoff, *How a Drug Maker Tries to Outwit Generics*, WALL ST. J., Nov. 17, 2008, at B1.

60. Cephalon, Q1 2009 Earnings Call Transcript, *supra* note 23.

praises: “With an extensive clinical program supporting Nuvigil, and a patent that extends to 2023, we believe that Nuvigil will be a very successful product that will ultimately benefit more patients than Provigil.”⁶¹ And the company brought out the heavy promotion artillery: “Our sales force is trained and performing all the necessary pre-launch activities to ensure a successful launch.”⁶² As soon as Cephalon brought Nuvigil to the market, “close to 800 salespeople [could] be out there” selling it.

Divulging little about its role in increasing Provigil’s price, Cephalon played coy, stating that it was “particularly pleased to offer Nuvigil at a discount to Provigil.”⁶³ Of course, given Provigil’s methodically increasing costs and the *guaranteed* lack of generic entry until 2012, it was only natural that insurers and health-plan managers would switch patients to Nuvigil.

The certainty, of course, pleased Cephalon shareholders, not to mention the four generics that were assured they would share in the bounty. But it flies in the face of the Hatch-Waxman Act, which was designed to encourage patent *challenges*, as opposed to agreements *not to challenge* patents.

VI. Conclusion

In 2006, Cephalon faced imminent generic entry on Provigil. The generics had a strong claim that they did not infringe Cephalon’s narrow formulation patent. And there was no guarantee that the FDA would approve its successor drug Nuvigil before generic versions of Provigil entered the market.

Cephalon knew that it would significantly benefit if it could switch the market before generic entry. And so it paid the generic companies not to enter the market. These settlements bought Cephalon enough time to switch the market to Nuvigil, comfortable in the certainty that the generic firms would not even attempt to defeat its patent in court.

Without these settlements, the generics would have flooded the market with their versions of Provigil and undermined Cephalon’s ability to switch the market from Provigil to Nuvigil. It was only

61. Cephalon, Inc., Q4 2008 Earnings Call Transcript, SEEKINGALPHA.COM (Feb. 13, 2009), <http://seekingalpha.com/article/120423-cephalon-inc-q4-2008-earnings-call-transcript?page=-1>.

62. Cephalon, Q1 2009 Earnings Call Transcript, *supra* note 23.

63. *Id.*

through the subtle combination of settlements and product hopping that Cephalon was able to subvert the purpose of the Hatch Waxman Act and achieve "\$4 billion in sales that no one expected."⁶⁴

64. *Cephalon Complaint*, *supra* note 1, ¶ 4.
