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I. INTRODUCTION

The Federal Trade Commission ("FTC"), as part of its ongoing enforcement of perceived anticompetitive abuse of the regulatory and legal structure in the pharmaceutical industry, has turned its gaze to branded pharmaceutical firms' refusal to sell samples of restricted distribution products to firms seeking approval to market generic versions.[2]

The types of restricted distribution arrangements that gave rise to these concerns are relatively new, dating from Food and Drug Administration Amendments Act of 2007 ("FDAAA"). The FDAAA granted the FDA powers to require branded firms to design and implement risk evaluation and mitigation strategies ("REMS") for drugs with potentially serious and significant side effects. REMS requirements include a virtual continuum of potential distribution restrictions including requirements to distribute medication guidelines to patients, monitoring and reporting of adverse events, communication plans to disseminate safety information to healthcare providers, certification and training of healthcare providers and pharmacies, and limited distribution to only registered cites of service.[3] The most severe restrictions include Elements to Assure Safe Use ("ETASU") and Implementation Systems.

REMS restrictions in one form or another became increasingly common in new drug approvals. However, more recently, the FDA has been reducing the number of products with REMS designations. There are currently 65 FDA approved individual REMS and an additional six shared system REMS.[4] While the number of REMS programs has been falling (142 drugs have been released from REMS programs), the severity of REMS restrictions has increased dramatically. Over half (40 of 71) of the existing REMS contains an ETASU requirement.[5] This is

[1] The authors are a Vice President and Associate Principal at Charles River Associates. The opinions expressed herein are those of the authors and do not necessarily reflect those of other individuals within Charles River Associates.

[2] Fed. Trade Comm'n Brief of Amicus Curiae, *Actelion Pharmaceuticals Ltd.*, No. 1:12-cv-05743 (D.N.J. March 13, 2013), *available at* http://www.ftc.gov/sites/default/files/documents/amicus_briefs/actelion-pharmaceuticals-ltd.et-al.v.apotex-inc./130311actelionamicusbrief.pdf.

[3] Doyle, et al., *REMS: The New Reality*, CAMPBELL ALLIANCE, http://www.campbellalliance.com/articles/campbell_alliance_REMS_article.pdf.

[4] http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm#information. Last accessed on April 23, 2014.

[5] *Id.*

a stark change from 2009, when nearly 75 percent of REMS programs required only medication guides.[6]

It is these highly restrictive ETASU and implementation system programs that have given rise to antitrust complaints. Highly restrictive REMS programs have resulted in situations where generic manufacturers have difficulty procuring sufficient quantities of samples for bioequivalence demonstration, as required under Hatch-Waxman. Generally, generic manufacturers have no difficulty obtaining samples of branded products through normal distribution channels. In the case of REMS programs with ETASU components, though, some generic firms have been unable to obtain samples through normal channels, such as drug wholesalers, and have requested samples from the branded manufacturers. Branded manufacturers have sometimes refused to provide these samples, citing REMS restrictions, and in at least three cases, generic firms have responded with Section 2 antitrust allegations alleging that the refusal to deal illegally prevents generic competition.[7]

The FTC joined the fray, filing an *Amicus* brief in one of these cases noting that the refusal to provide samples could be a violation of either Section 1 or Section 2 of the *Sherman Act*.[8] In summary, while the FTC acknowledges that the Hatch-Waxman Act sought to strike a balance between encouraging low-cost generic entry and protecting branded firms' incentives for continued innovation, the FTC has focused its attention on the potential for misuse of certain REMS programs to impede generic competition.

The FTC argues that a branded monopolist's refusal to sell drugs under REMS programs to rivals supports "a plausible theory of exclusionary conduct."[9] The FTC further asserts that, contrary to the branded manufacturers' position, anticompetitive refusal to deal does not require a prior course of dealing with competitors. The FTC instead focuses on a profit sacrifice test and essentially argues that because branded firms sell REMS restricted drugs at substantial profit, "refusal to sell to generic rivals may provide evidence of its willingness to sacrifice profitable sales in the short run in order to protect its long-term monopoly profits."[10]

In a companion piece to this one, Jan Rybnicek makes a similar argument that a prior course of dealing, while potentially relevant, is not the determinative factor in a refusal to deal inquiry.[11] Instead, he argues that a "no economic sense" test is a better approach to assessing whether a refusal to deal in the context of REMS restrictions is anticompetitive. In this paper, we discuss some of the economic factors that would come into play under such an approach. Those factors would include a balanced view of the costs and benefits of sharing samples with a generic firm—over and above the potential competition that such sharing could facilitate—as well as a

[6] Doyle, et al., *supra* note 3 at 4.

[7] Private antitrust actions have been brought against Celgene (2008) regarding Thalomid, against Actelion Pharmaceuticals (2012) regarding Tracleer, and against Accord Healthcare (2013) regarding Ampyra.

[8] Fed. Trade Comm'n Brief of Amicus Curiae, *Actelion Pharmaceuticals Ltd.*, No. 1:12-cv-05743 (D.N.J. March 13, 2013), *available at* http://www.ftc.gov/sites/default/files/documents/amicus_briefs/actelion-pharmaceuticals-ltd.et-al.v.apotex-inc./130311actelionamicusbrief.pdf.

[9] *Id.* at 9.

[10] *Id.* at 12.

[11] Jan Rybnicek, *When Does Sharing Make Sense?: Antitrust & Risk Evaluation and Mitigation Strategies*, 4(2) CPI ANTITRUST CHRON. (April, 2014).

balanced view of the role of Hatch-Waxman and antitrust policy in the dynamic competition to develop new drugs.

II. THE DYNAMIC COMPETITION TO DEVELOP NEW DRUGS

The FTC, in its *Amicus* brief, and others commenting on the antitrust claims brought by generic firms in the context of REMS restrictions have noted that the Hatch-Waxman Act sought to strike a balance between consumers' interests in the flow of new and improved products (though incentivizing innovation) and the consumers' interests in low prices through increased generic competition. Despite this acknowledgement that Hatch-Waxman was focused on balancing the incentive to develop new drugs with the interest in increased competition, the FTC (and other commenters) have focused exclusively on static measures of competition in terms of the price effects of generic entry and ignored the other half of the balance that Congress attempted to craft—incentivizing the development of new products and treatments. Indeed, the FTC takes the strong position that an antitrust policy that requires branded manufacturers with REMS restricted products to provide samples to generic competitors cannot alter branded firms' incentives to innovate, but only increase consumer welfare through increased generic competition:

> First, allowing potential generic competitors to purchase product samples from the brand would not undermine the incentive to invest; it would simply maintain the incentive structure Congress created in the Hatch-Waxman Act, under which Actelion retains the ability to exert its patent rights.[12]

This view ignores how REMS restrictions brought about by the FDAAA, which did not exist at the time the Hatch-Waxman Act became law, have affected incentives to innovate. In fact, evidence indicates that some product innovations that have been introduced to the market would likely not have existed but for the restrictive distribution mechanisms that REMS protocols instituted. One analysis of the REMS program notes, "[T]hrough its mandated program to improve drug safety, REMS has provided the ability for the FDA to approve products that likely would have never made it to market."[13]

A case in point is Thalomid, one of the products that has been subjected to antitrust litigation regarding the refusal of the branded seller (Celgene) to provide samples to certain manufacturers seeking FDA approval for generic versions.[14] The active ingredient in Thalomid is thalidomide, a compound with a notorious history around the world. In the 1950s and 1960s, thalidomide was used in a number of countries outside the United States (it was not approved by the FDA at that time) as a sedative and a treatment for morning sickness until it was discovered that it caused severe birth defects and was withdrawn from markets worldwide.

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[12] FTC's *Amicus Curiae* brief in *Actelion Pharmaceuticals, Ltd., et al. v. Apotex Inc., et al.*, p. 15. *See also*, Tucker, et al., *REMS: The Next Pharmaceutical Enforcement Priority*, ANTITRUST, 76 (Spring 2014), "Requiring sales of RLD samples would be unlikely to reduce the monopolist's incentive to innovate because generic access to product samples and, ultimately, generic competition was contemplated under the Hatch-Waxman Act."

[13] Doyle, et al., *supra* note 3 at 4.

[14] Complaint, Lannett Co. v. Celgene Corp., No. 2:08-cv-03920 (E.D. Pa. Aug. 15, 2008).

In 1998, the FDA approved Thalomid to relieve complications of leprosy, but only with strict protocols to monitor distribution and educate patients and healthcare providers.[15] Celgene's REMS protocol included restrictions that only registered physicians could prescribe the drug, and only for one-month intervals. Pharmacists were also required to be registered, women of childbearing age had to agree to mandatory pregnancy tests, and both male and female patients had to adhere to birth control methods.[16] Additionally, Celgene was required to develop and maintain a secure patient database to monitor and evaluate the implementation of the ETASU requirements. [17] Approved indications have since expanded to the treatments of multiple myeloma and inflammation. Without these rigid restrictions and monitoring programs, it is unlikely that the FDA would have approved Thalomid.

Importantly, REMS drugs have additional development and marketing costs that are not borne by non-REMS drugs. First, a REMS designation is inherently an indication that there are substantial risks associated with the product. These risks result in increased scrutiny during the FDA review process and the evidence indicates that it takes longer for REMS drugs to receive FDA approval than non-REMS drugs.[18] The detrimental impact on incentives to innovate due to loss of market time from FDA regulatory delays was a key element that the Hatch-Waxman Act sought to address prior to the REMS programs resulting from the FDAAA. To the extent that these delays are longer on average than for other products, the incentives to innovate are already diminished relative to the products envisioned under Hatch-Waxman. Further, rigorous REMS protocols likely limit product demand since they impose additional costs on patients and healthcare providers.

Finally, strict REMS protocols require additional costs to monitor patients and providers, raising the costs of selling these products relative to non-REMS drugs. The branded company would likely continue to shoulder a significant burden for these costs, even after generics entered (see below). These high selling costs also decrease the incentive to innovate, all things equal.

Others have also noted that the current regulatory and antitrust regime has altered the balance struck by Hatch-Waxman in favor of increased generic competition at the expense of incentives to innovate.[19] The Supreme Court has recognized that forcing companies to share "may lessen the incentive for the monopolist, rival, or both to invest in those economically beneficial facilities…"[20] To the extent that consumers benefit from the dynamic competition to develop new products and new uses for existing products (which they surely do), then an

[15] Although this approval predates the formal changes to the Food & Drug Act in 2007, the basic protocols used in the case of Thalomid are similar to ETASU protocols under REMS.

[16] Although this approval predates the formal changes to the Food & Drug Act in 2007, the basic protocols used in the case of Thalomid are similar to ETASU protocols under REMS.

[17] Risk Evaluation and Mitigation Strategy (REMS) Approval for Thalomid® (thalidomide), Modified November 2013, p. 7. *Available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM222649.pdf

[18] Doyle, et al., *supra* note 3 at 3.

[19] Richard A. Epstein, *Branded versus Generic Competition-A Kind Word for the Branded Drugs*, HASTINGS SCI. & TECH. L. J. 459-70 (2011).

[20] Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP, 540 U.S. 398, (2004), p. 407.

antitrust policy that reduces incentives to innovate can reduce consumer welfare unless the gain from the price reductions outweighs the reduction from a reduced flow of new products.

III. THE ECONOMICS OF EXCLUSIVE DEALING AND ITS APPLICATION TO REMS PRODUCTS

Standard economic theory has long recognized that unilateral refusals to deal with rivals and exclusive dealing relationships with distributors can be pro-competitive when such exclusivity is necessary to promote efficient levels of investment in training and reputations. In particular, economic theory has recognized that if one party can free-ride on the investments of another party in training sales staff or customers on product features, that firms would underinvest in such programs, even if those investments increase demand and yield gains in consumer welfare.[21]

The REMS restrictions that have been challenged by generic manufacturers are in many ways akin to exclusive dealing arrangements, where a manufacturer restricts access downstream to prevent free-riding on investments in expanding demand for the product. Establishing REMS protocols entail significant investments to design and implement. One source notes that it can cost manufacturers between $5,000 and $500,000 per month to setup and maintain a REMS protocol, and costs to distributors can range from $5,000 to $1 million.[22]

Branded firms have expressed concerns that, even after generic entry, they would bear the lion's share of the cost in setting up and maintaining REMS protocols that would inure largely to the benefit of generics due to automatic substitution laws. All things equal, the branded company's incentive to maintain such programs would diminish with generic approval, with potentially negative impacts on consumer welfare.

In some cases, the branded companies have patented some elements of the risk management programs and those patents are listed in the Orange Book.[23] In those cases, if those patents were found to be valid, the generic firm would have to either license the protocols or develop non-infringing versions before they could market the product. However, even if the generic manufacturers developed their own versions of the ETASU protocols, branded firms may still face liability, withdrawal of FDA approval, and negative impacts on the firm's reputation. Branded companies that have faced antitrust allegations over refusals to provide samples to generics have noted that generic assurances and even indemnification may not adequately protect them from some or all of these risks.[24]

In all these situations, it may make economic sense for a branded company to refuse to provide samples to a potential generic rival since additional generic sellers add risks and uncertainties, the costs of which are largely borne by the branded company. A review of the refusals to deal for a REMS product under a "no economic sense" test would need to address the

[21] CARLTON & PERLOFF, MODERN INDUSTRIAL ORGANIZATION, 4th ed., pp. 418-428.

[22] Briz, *How Effective are REMS Programs in Increasing Patient Safety?,* Kulkarni Law Firm Blog (October 31, 2012), *available at* https://www.conformlaw.com/blog/how-effective-are-rems-programs-in-increasing-patient-safety/.

[23] The FDA's list of approved drug products with therapeutic equivalence evaluations.

[24] *Lannet Company, Inc. v. Celgene Corporation,* 2011 U.S. Dist. LEXIS 32915, Decided March 29, 2011.

impact of a requirement to deal on the branded manufacturer's incentive to invest in these welfare-enhancing activities and weigh any loss against the gains from lower generic prices.

Finally, branded companies have claimed that their patent rights give them the right to refuse to deal, even if the impact is to delay generic entry. The FTC's response is to assert that this is not true because under amendments to the Hatch-Waxman Act, the generics' use of a patented product in the course of pursing FDA approval is not considered an act of infringement.[25] Even so, it is at least an open question whether an amendment that made the use of a patented product immune to infringement claims also was also intended to take away a fundamental right of the patent holder to determine how (and to whom) to sell its patented product.

IV. CONCLUSION

Branded companies' refusal to supply generic firms with samples of products subject to REMS restrictions is thought by many to be the next front in ongoing FTC efforts to prevent perceived anticompetitive attempts by branded companies to forestall generic competition. Even a monopolist's refusal to deal with a competitor, however, is not necessarily anticompetitive. As a matter of economics, there are pro-competitive, or at least competitively neutral, reasons for such a refusal.

In the context of the pharmaceutical industry, a blanket requirement that branded manufacturers deal with potential generic rivals can reduce consumer welfare by reducing the incentive to develop new products and the incentive to make investments that provide critical information to the marketplace and expand demand. A full investigation of whether these refusals to deal with generic rivals are anticompetitive would have to weigh the welfare-reducing effects of these reduced incentives against the welfare gain from earlier entry of lower-priced generic competitors.

[25] FTC's *Amicus Curiae* brief in *Actelion Pharmaceuticals, Ltd., et al. v. Apotex Inc., et al.*, pp. 17-18.