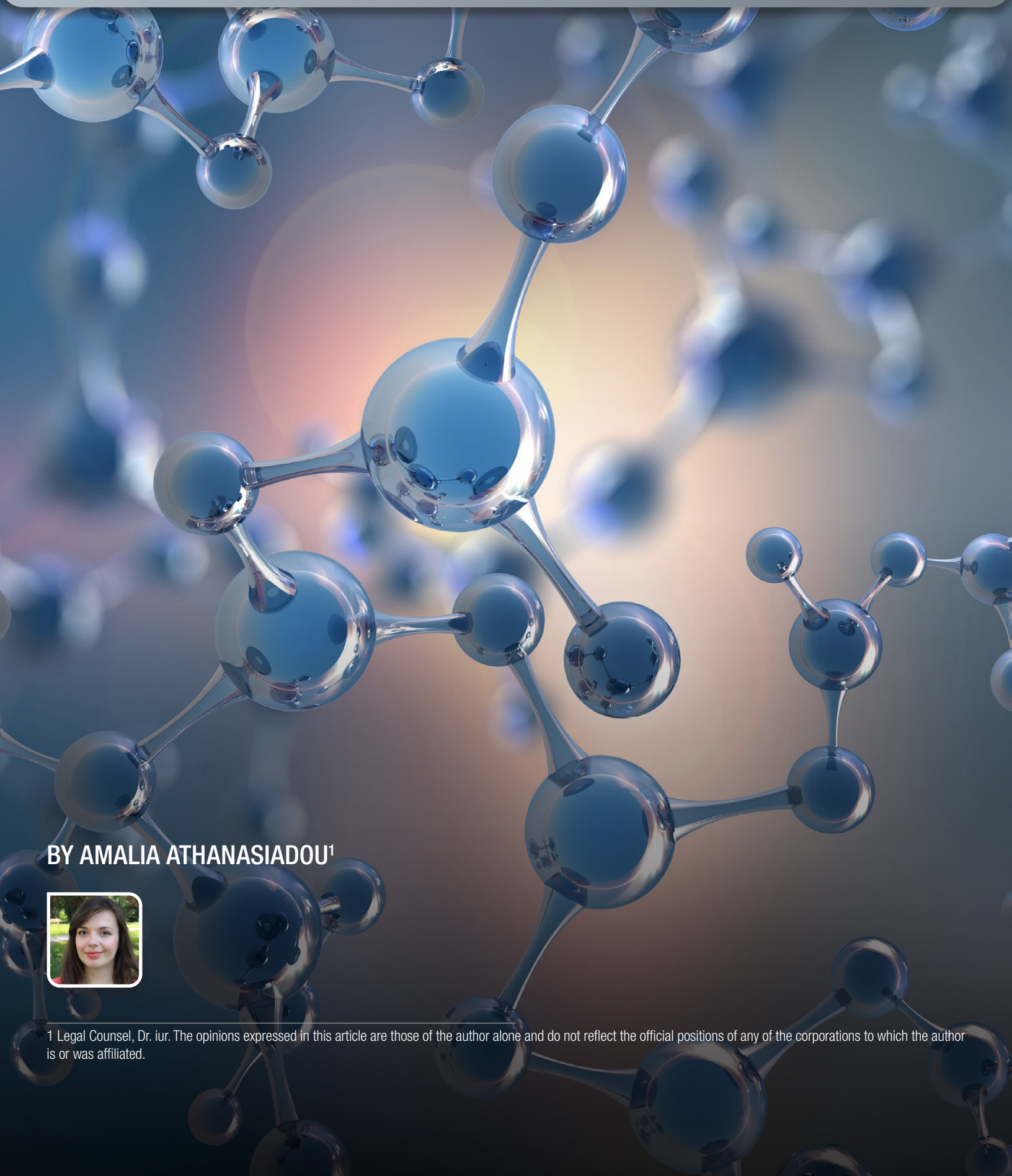
RETHINKING PHARMACEUTICAL PRODUCT REFORMULATIONS



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I. INTRODUCTION

Product reformulations are not *per se* problematic from an antitrust perspective. Introducing a new reformulated version of a pre-existing drug is not in itself anticompetitive. Brand-name manufacturers may legitimately design their product life-cycle management strategies and have serious economic and strategic incentives for focusing on pharmaceutical products which have already been successful in the treatment of patients. Knowing how risky, costly, time-consuming and uncertain an endeavor pharmaceutical R&D is, it is not surprising that brand-name manufacturers invest resources in developing further versions of successful products and in expanding existing technology and know-how.

The main thesis of this piece is that in order to preserve innovation incentives for pharmaceutical companies, such product reformulations should be examined by antitrust enforcers irrespective of whether they are deemed – in their view – to be superior or "genuine" innovations which substantially improve pre-existing products. Rather, enforcers should focus on the company's overall conduct and strategy around such product reformulations. Some product reformulations may be highly problematic, as part of so-called "product-hopping" strategies, aiming to prevent the substitution of the new version of a brand-name drug with generics.[2] Such product-hopping occurs when a brand-name drug manufacturer seeks to switch the demand from a drug product A, whose patent protection is about to expire, to a drug product B, which is usually a modified version of drug product A, but enjoys a longer term of remaining patent protection, thus "killing" the demand for generic versions of product A.[3]

The main goal of anticompetitive product-hopping strategies is to block generic substitution and to prevent demand shifting from the brand-name pharmaceutical product – which is no longer patent protected – to its generic equivalents. The combination of product-hopping strategies with patent settlements or other types of agreements between originators and generic manufacturers have the potential to lead to the elimination of any meaningful competition even *post* generic entry.[4] Generic substitution is the substitution of brand-name pharmaceutical products by therapeutically equivalent and cheaper generic drug versions, which is designed to correct a type of agency problem: the market failure arising from the prescription drug system, namely the disconnect between the physician who chooses to prescribe a specific drug and patients and/or insurers who pay for it.[5]

2 See Shadowen Steve D., Leffler Keith B., Lukens Joseph T., "Bringing Market Discipline to Pharmaceutical Product Reformulations," 42:6 IIC 698, (2011), pp. 698-704.

3 Ginsburg Douglas H., Wong-Ervin Koren W. & Wright Joshua D., "Product Hopping and the Limits of Antitrust: The Danger of Micromanaging Innovation," 12 CPI Antitrust Chronicle 1, (December 2015), p. 2; Cheng Jessie, "An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry," 108 Col. Law Rev. 1471, (October 2008), p. 1488.

4 See for instance Carrier Michael A., "A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product-Hopping," 62 Florida Law Review 1009, (2010), pp. 1033-1036.

5 FTC, *Amicus Brief, Mylan Pharms. v. Warner Chilcott*, 2015, pp. 25-26.

II. HARD vs. SOFT PRODUCT SWITCHES AND GENERIC SUBSTITUTION

Product switching strategies are roughly divided in antitrust literature in two broader categories: "hard" product switches, where the brand-name manufacturer introduces pharmaceutical product B and in parallel withdraws product A from the market, and "soft" product switches where the brand-name manufacturer does not withdraw the product A but continues to market it, shifting however all of its promotion and marketing efforts to drug product B.[6] Courts have rightly followed a more lenient approach when analyzing soft product switches, finding that they do not necessarily amount to consumers' coercion but merely offer them a new product choice.[7] A soft switch comprised of launching a new product without withdrawing in parallel the product's previous version from the market - and absent a gaming of the regulatory system by the brand-manufacturer - represents substantially lower antitrust risks.[8] Nevertheless, the distinction between hard and soft product switches is not always clear-cut. For instance, a brand-name drug manufacturer may not withdraw product A from the market but may instead increase its price to prohibitive levels, practically removing it from the market by making it unaffordable;[9] such strategy would likely have the effect of a "hard" switch, even if formally categorized as a "soft" one. Reducing the price of the new drug product is another option which may lead to a successful product switch.[10] However, both of these strategies presuppose that the regulatory framework on prices would accord such broad freedoms to the brand-name drug manufacturers, without imposing limits or caps that could effectively prevent such abuses. The following sections briefly present three product reformulation strategies which nicely illustrate the complexities of their antitrust analysis.

A. Hard Product Switches and Coercion of Patients

In *New York v. Actavis PLC, Forest Labs LLC* (hereinafter the "*Namenda*" case), the brand-name drug manufacturers allegedly attempted to switch Alzheimer patients from Namenda IR – a drug which was reaching the end of its patent exclusivity in July 2015 – to the newer version of the drug Namenda XR before generic versions of the former entered the market.[11] This could have been a legitimate life-cycle management strategic decision; however, it was combined with the planned withdrawal of Namenda IR from the market,[12] in a hard product switch. The envisioned removal of the older version of the drug from the market prior to the release of generics, and the "forced switch" of patients were criticized for going far beyond mere attempts to minimize the impact of new competition and for having severe effects on consumer welfare in the form of fewer drug choices and diminished price competition.[13] The New York State filed a complaint alleging that the drug's withdrawal from the market would violate antitrust laws; the complaint led to a preliminary injunction barring the brand-name manufacturers from restricting patients' access to Namenda IR prior to the entry of generic IR versions.[14] As affirmed by the 2nd Circuit, the envisioned hard product switch would likely impede generic competition by precluding the generic substitution through State drug substitution laws.[15] Generic manufacturers were deprived of the

6 Shepherd Joanna, "Deterring Innovation: NY v. Actavis and the Duty to Subsidize Competitors' Market Entry," 17:2 Minnesota Journal of Law, Science and Technology 663, (2016), pp. 668-672.

7 *Walgreen Comp. et al. v. AstraZeneca Pharms. et al.*, 534 F. Supp. 2d.146, 148-152 (D.D.C. 2008).

8 Hovenkamp Herbert J., Janis Mark D., Lemley Mark A. & Leslie Christopher R., *IP And Antitrust: an Analysis of Antitrust Principles Applied to Intellectual Property Law*, Wolters Kluwer, 2nd ed. 2015, 15-78.3 – 15.80, arguing that in such cases if the generic has lost any market share this was most probably due to the desirability of the patent owner's new product.

9 Shepherd Joanna, "Deterring Innovation: NY v. Actavis and the Duty to Subsidize Competitors' Market Entry," 17:2 Minnesota Journal of Law, Science and Technology 663, (2016), pp. 668-672, noting that this tactic would be generally considered as a soft switch, but have the same effect as a hard switch.

10 Ho Cynthia M., "Should All Drugs Be Patentable? A Comparative Perspective," 17 Vand. J. Ent. & Tech. L. 295, Winter 2015, pp. 317-321.

11 *New York v. Actavis PLC, Forest Labs LLC*, 787 F.3d 638, 642-643, 647-648 (2nd Cir. 2015). Namenda IR and Namenda XR have the same therapeutic effect and the same active ingredient; the medical difference between the drugs is that Namenda IR is administered twice a day since it is released immediately in the bloodstream and Namenda XR is administered only once, since it is released gradually.

12 *New York v. Actavis PLC, Forest Labs LLC*, 787 F.3d 638, 654 (2nd Cir. 2015).

13 ASPE Issue Brief, Department of Health and Human Services, "Some Observations Related to the Generic Drug Market," (May 16, 2015), pp. 5-7. Available at https://aspe.hhs.gov/sites/default/files/pdf/139331/ib_GenericMarket.pdf. (last accessed on April 23, 2020).

14 See also *The People of New York v. Actavis PLC, Forest Labs LLC*, No. 14 Civ. 7473, (S.D.N.Y. 2014), at 104-109, discussing the anticompetitive conduct of the defendants; at 117-123, granting the preliminary injunction.

15 *New York v. Actavis PLC, Forest Labs LLC*, 787 F.3d 638, 654 (2nd Cir. 2015).

most cost-efficient means of generic distribution: generic substitution.[16] This was not the first time a court found that preventing generic substitution through allegedly manipulative and unjustifiable formulation changes is a restriction on competition.[17]

B. Product-Hopping Combined with No-AG Commitments

Another interesting case is *FTC v. Endo*, in which no-authorized generic ("no-AG") commitments[18] and side-deals on development and co-promotion were combined with alleged product-hopping. On March 2016, the FTC sued Endo Pharmaceuticals Inc. and generic pharmaceutical companies for allegedly violating antitrust laws by concluding a set of reverse payment settlements concerning two of Endo's most important drugs: Opana ER and Lidoderm.[19] Facing the threat of generic entry when the end of the patent term was approaching, Endo had been working on a reformulated version of Opana ER (a crush resistant formula of the drug marketed as Opana ER CRF), allegedly aiming to prevent automatic generic substitution. The generic manufacturer Impax was the first generic challenger to file a paragraph IV Abbreviated New Drug Application ("ANDA")[20] for Opana ER on December 2007; as a result, Endo would not have sufficient time to obtain FDA approval for the reformulated Opana ER before Impax's generic entry. The brand-name manufacturer and the generic challenger subsequently concluded a settlement and license agreement and a co-development and co-promotion agreement. One month after this settlement with Impax, Endo filed a New Drug Application for the reformulated Opana ER CRF, with which generic drug versions of Opana ER were not automatically substitutable.[21] Within two years, and pursuant to Endo's marketing efforts, 90 percent of sales had moved to this new Opana ER CRF version.[22]

The FTC alleged that as part of this settlement, Endo committed not to launch an authorized generic version, granting Impax an absolute generic monopoly during the 180-day exclusivity period that the first generic challenger is accorded in the U.S. In order to ensure the generic manufacturer's supra-competitive profits promised by the settlement, Endo undertook to pay Impax if its reformulation strategy succeeded, and resulted in the devaluation of the no-AG commitment. The FTC alleged that this was indeed the case, leading Endo to make an additional payment of more than $102 million to Impax.[23] Second, Endo had agreed to pay Impax $40 million purportedly for an independent co-promotion and development deal concerning another drug, which the FTC claimed was a side-deal constituting a concealed reverse payment.[24] Endo agreed to settle the FTC charges,[25] but Impax is litigating with the FTC before the 5th Circuit at the moment of this writing.[26]

C. Servier's Hard Product Switch to Second Generation Perindopril

Controversial drug product reformulation strategies are not of course exclusive to the U.S.; however, there have not been many enforcement decisions of the European Commission examining them. An exception is the product reformulation strategy employed by Servier, scrutinised

16 *New York v. Actavis PLC, Forest Labs LLC*, 787 F.3d 638, 655-656 (2nd Cir. 2015); *United States v. Microsoft Corp.* 253 F.3d 34, 63 (D.C. Circuit 2001), finding that barring competitors from the cost efficient means of distribution constitutes an antitrust violation; *United States v. Dentsply International, Inc.*, 399 F.3d 181, 191 (3rd Cir. 2005), ruling that the test for a Section 2 violation of the Sherman Act is not total foreclosure but whether a substantial amount of rivals is barred or the market's ambit is severely restricted. See however *In re Suboxone (Buprenorphine Hydrochloride & Naloxone) Antitrust Litig.*, 13-MD-2445, (ED. Pa. 2016), at *20, arguing that the *Namenda* decision did not hold as a matter of law that automatic generic substitution is the only cost-efficient means of generic competition in every pharmaceutical antitrust case.

17 *Abbott Labs. v. Teva Pharms. USA Inc.*, 432 F. Supp. 2d. 408, 423 (D. Del. 2006).

18 A "No-AG commitment" is a promise not to launch an authorized generic drug, made by the brand-name manufacturer as part of a settlement with a generic competitor. For a detailed analysis of no-AG commitments and their antitrust implications see further Athanasiadou Amalia, "Patent Settlements in The Pharmaceutical Industry under US Antitrust and EU Competition Law," International Competition Law Series, Wolters Kluwer (2018). pp. 176-194.

19 FTC, Complaint, *FTC v. Endo Pharmaceuticals et al.*, 2016. See also FTC Press Release, *FTC Sues Endo Pharmaceuticals Inc. and Others*, 2016.

20 The paragraph IV ANDA is a mechanism introduced by the Hatch-Waxman Act and now found in 21 U.S.C. § 355(j)(5)(B)(iv). Paragraph IV ANDAs aim to challenge and eliminate weak or invalid patents blocking the entry of lower cost generic drugs. Generic manufacturers wishing to enter the market before the expiration of the brand-name manufacturer's patents in the U.S may file a paragraph IV certification, arguing either patent invalidity or non-infringement of the brand-name drug by their generic drug.

21 *In re Opana ER Antitrust Litigation*, 162 F. Supp. 3d 704, 714 (N.D. Ill. Feb. 10, 2016).

22 *In re Opana ER Antitrust Litigation*, 162 F. Supp. 3d 704, 714 (N.D. Ill. Feb. 10, 2016).

23 FTC, Complaint, *FTC v. Endo Pharmaceuticals et al.*, 2016, pp. 17-20.

24 FTC, Complaint, *FTC v. Endo Pharmaceuticals et al.*, 2016, p. 3.

25 *FTC v. Allergan et al.*, Case No. 17-cv-00312 (N.D. Cal.), FTC File No. 1410004, Joint Motion for Entry of Stipulated Order for Permanent Injunction, January 23, 2017.

26 See further, *Impax Laboratories Inc. v. FTC,* (5th Cir.) FTC Brief, 19-60394, (date filed: 12.10.2019).

as part of the *Commission v. Servier* decision in 2014.[27] In an effort to extend the lifecycle of its blockbuster drug perindopril, Servier arguably developed and introduced a second generation product which had – according to the Commission's assessment – no superior medical effect, but served as its "principal weapon" against generic entry.[28] This reformulated version of perindopril was based on a replacement of salts in the second generation product, which generated new patent protection for Servier until 2023, and also involved a shift in the drugs' dosages.[29]

The Commission found that Servier's launch of this second generation product was linked to the regulatory framework on generic substitution: pharmacists could not substitute a drug with one salt for a drug with another salt in certain European Member States, nor could they substitute medicines with different dosages.[30] It was argued that Servier carefully planned the timing of the product switch from the first to the second generation of perindopril, with the parallel withdrawal of the first generation drug from the market. The main objective of Servier's product switch was allegedly to block generic substitution due to the different salt and the different dosages of its new drug product.[31] According to the Commission, it proved to be almost impossible for generics to enter markets where Servier had already successfully switched to the second generation drug before generic entry occurred, such as Belgium, Ireland, and Denmark.[32] In its *Servier* judgment, the General Court of the European Union did not address in detail the Commission's arguments regarding Servier's hard product switch;[33] it will be interesting to see whether the Court of Justice of the European Union proceeds in such an analysis when ruling on the pending appeals.[34]

III. ANALYSING PRODUCT SWITCHES FROM AN ANTITRUST PERSPECTIVE

A. The Timing of Drug Product Reformulation

The cases above make it evident that the *timing* of a product reformulation is a key element which raises controversy, since it may serve as one of the main criteria in determining whether such a reformulation is abusive from an antitrust perspective. A certain number of arguably problematic product reformulations may occur near the end of the drug's patent life and concern changes which may be seen as anticompetitive and principally designed to impair generic competition.[35]

In order to provide for legal certainty regarding the timing of product reformulations that could be unproblematic, two U.S. antitrust experts have proposed time-based safe harbors and antitrust immunity for reformulations occurring within a four-year window, starting eighteen months before the first generic ANDA is filed.[36] The rationale behind this proposal was that within eighteen months, a generic applicant should have sufficient time to reformulate its generic drug version and submit a new ANDA for the reformulated brand-name drug.[37] However, this position does not seem to take into consideration that reformulated brand-name drug versions are often protected by a number of new patents, covering

27 CASE AT.39612 – Perindopril (Servier), Commission Decision of 9 July 2014, relating to a proceeding under Article 101 and Article 102 of the Treaty on the Functioning of the European Union, C(2014) 4955 final, Brussels, 9.7.2014, [cited as: EU Commission Decision, Servier, 2014].

28 EU Commission Decision, *Servier*, 2014, paras 217-228. See especially *idem* paras 225-226, citing internal document of Servier and Teva, mentioning the replacement of the erbumine with the arginine salt lacked added therapeutic benefits but was likely to impede or block generic entry.

29 EU Commission Decision, *Servier*, 2014, para. 8. Due to the different molecular weight of the new salt, this second-generation drug was sold in different dosages. See also *idem*, paras 223-228, arguing that the second version of perindropil did not have superior medical effects when compared to the first version of the drug.

30 EU Commission Decision, *Servier*, 2014, paras 233-234, citing Servier's internal documents.

31 EU Commission Decision, *Servier*, 2014, para. 242.

32 EU Commission Decision, *Servier*, 2014, para. 240-241, mentioning the UK as an exception where generics entered the market after Servier's product switch.

33 Judgment of the General Court of December 12, 2018, *Servier SAS and Others v. European Commission*, Case T-691/14, EU:T:2018:922.

34 See further Appeal brought on 22 February 2019 by the European Commission against the judgment of the General Court (Ninth Chamber, Extended Composition) delivered on December 12, 2018 in Case T-691/14, *Servier and Others v. Commission*, (C-176/19 P); Appeal brought on February 28, 2019 by Servier SAS, Servier Laboratories Ltd, Les Laboratoires Servier SA against the judgment of the General Court (Ninth Chamber, Extended Composition) delivered on December 12, 2018 in Case T-691/14, *Servier and Others v. Commission*, (Case C-201/19 P).

35 See indicatively, Ho Cynthia M., "Should All Drugs Be Patentable? A Comparative Perspective," 17 Vand. J. Ent. & Tech. L. 295, Winter 2015, pp. 317-321; Hughes D., & Ferner R., "New Drugs for Old: Disinvestment and NICE," 340 BMJ (formerly the British Medical Journal) 690, (March 27, 2010), p. 691; Shadowen Steve D., Leffler Keith B. & Lukens Joseph T., "Bringing Market Discipline to Pharmaceutical Product Reformulations," 42:6 IIC 698, (2011), pp. 701-704.

36 Carrier Michael A. & Shadowen Steve D., "Product Hopping: A New Framework," 92:1 Notre Dame Law Review 167 (2016), pp. 206-208.

37 *Ibid.* pp. 206-208.

for instance new ways of producing or administering a drug's active ingredients. Even though often mentioned in antitrust literature as "secondary," these patents may have strong exclusionary potential. Letting aside the scientific and regulatory difficulties of reformulating a generic pharmaceutical product in such a short time-frame, it is also unlikely that generic applicants would be successful in their attempts to reformulate their generic versions without infringing these secondary patents and facing patent infringement litigation. The second safe harbor proposed concerns product reformulations that occur after generic versions enter the market.[38] Even though this makes good sense regarding soft product switches, hard product switches *post* generic entry can also have a devastating impact on generic substitution rates if the reformulated version of the brand-name drug and the generic drug are not deemed therapeutically equivalent, so that granting them automatic antitrust immunity may not be ideal.

Even though it is of paramount importance, the timing of a product reformulation alone should not be the sole criterion of antitrust analysis. Providing for strict safe harbors regarding the timing of product reformulations could lead to abuses and further gaming of generic substitution schemes. The overall context in which the product switch occurs and its combination with parallel strategies or other side-deals is much more important, especially since the legal standard under which such strategies are to be evaluated is the rule of reason in the U.S.[39] and a case-by-case analysis of their object or effect in potentially preventing, restricting or distorting competition in the European Union.[40]

B. Overall Conduct and Combination with Other Strategies

Stating that the overall context of a product reformulation is the one that should be decisive in determining whether it constitutes an abuse or not, is of course easy to claim but very hard to implement. However, there are a number of indications that may make this assessment easier for antitrust authorities. For example, the combination of a product reformulation with the parallel revocation from the market of the older – yet commercially successful version – that happens to be near the end of its patent life is a clear red flag, especially if combined with a settlement with the potential generic entrant that has elements of a pay-for-delay deal. The dichotomization of product reformulations to "hard" and "soft" product switches where the former are almost *ipso facto* deemed to be anticompetitive and the latter tolerable, could however prove to be problematic. Therefore, antitrust analysis should look beyond these two labels, which should not be used without further consideration of the product reformulation at issue and the impact any such reformulation has on the competitive landscape – and most importantly on patient and physician choice, public health schemes and ultimately on consumer welfare.

IV. LIBERAL ECONOMIES AND INNOVATION INCENTIVES

A. Antitrust Liability for Product Portfolio Changes?

Even though this may often be ignored by antitrust enforcers, it remains true that monopolists and successful pharmaceutical companies have no general duty to facilitate their competitors' entry into the market,[41] or to continue selling a particular product.[42] As stated above, merely introducing a new product to the market – irrespective of whether this product is superior or not therapeutically – does not itself amount to exclusionary conduct. Additionally, withdrawing a drug product from the market should not be deemed anticompetitive *ipso facto*. Such a withdrawal could make economic or commercial sense (e.g. if a drug no longer has profitable sales or no longer fits into the portfolio of the brand-name manufacturer) and could be unproblematic from an antitrust perspective, if it is not combined with other types of anticompetitive strategies.

In free market and liberalized economies, there is merit to brand-name manufacturers' arguments that they should not be held liable for taking a commercial decision to stop the marketing or promotion of a drug product.[43] At the end of the day, pharmaceutical companies are

38 *Ibid*. pp. 209-210.

39 *FTC v. Actavis, Inc*., 133 S. Ct. 2223, 2236-2237 (2013).

40 Article 101, TFEU.

41 See for instance Cheng Jessie, "An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry," 108 Col. Law Rev. 1471, (October 2008), pp. 1500-1503, arguing that brand-name manufacturers are not under the duty to "serve as the sales force of generic manufacturers" and that antitrust law should not condemn product-hopping merely on this ground.

42 Hovenkamp Herbert J., Janis Mark D., Lemley Mark A. & Leslie Christopher R., *IP And Antitrust: an Analysis of Antitrust Principles Applied to Intellectual Property Law*, Wolters Kluwer, 2nd ed. 2015, p. 15-78.

43 *Ibid*. p. 15-78.

private corporations that are operating for profit and their behavior in the market – as well as the life cycle management strategies they adopt – are mainly driven by the goal of maximizing their profit margins. Antitrust enforcement does of course play a central role in shaping these strategies, by creating sticks to deter anticompetitive behavior and the adoption of abusive monopolization strategies. It seems that the case law has successfully managed to create such a "stick" regarding hard product switches, which are rightly deemed anticompetitive if combined with wrongful conduct such as disparaging the previous version of the drug product, raising false safety concerns, coercing consumers, or reducing the market's ambit.[44]

B. Who Should Determine What Constitutes Genuine Innovation?

The FTC has argued that even though innovation concerns are important, they should not bar *ipso facto* antitrust liability, especially in the pharma industry where the potential for anticompetitive product redesign is high.[45] While there is merit to this view, it is important that courts, regulators and antitrust enforcers bear in mind that the preservation of incentives to innovate is crucial. Nonetheless, such a preservation of innovation incentives cannot be achieved by lawyers and economists that arbitrarily deem certain product reformulations as "superficial," "marginal" or "fake innovation." First, evidently, lawyers and economists do not have the necessary scientific expertise to evaluate the merits of such innovations from a medical and therapeutic perspective. Second, it has to be borne in mind that even innovations that may be deemed "incremental" have the potential to save human lives and be beneficial for patients – if not for all, at least for some.

The relationship between innovation incentives and antitrust enforcement is already quite a thorny one, where the right balance is difficult to strike. The differentiation of positions in the matter of product hopping has been quite stark. Some commentators argued that product-hopping should be *per se* lawful and be scrutinized under antitrust law in hard switches only when there is objective evidence of sham innovation leading to zero or negative consumer welfare effects.[46] This approach seems rather radical and would require antitrust enforcers to provide an assessment on the merits of a product reformulation and to determine with confidence the lack of any positive effects for patients – a burden that would likely be nearly impossible to carry. On the other extreme, economic models under which product reformulations overall should be prohibited were examined, albeit recognizing the detrimental effects such a ban could have had on *ex ante* innovation incentives.[47] Even though they are extreme opposites, both these approaches have a common – and highly problematic – element: they entail an often arbitrary determination of what constitutes a genuine innovation, which is rarely backed up by scientific, medical and therapeutic data. The burden of proof should be higher for enforcers and antitrust authorities to prove that the innovations at issue in a product reformulation are shams or unimportant. This assessment should be done by medical researchers, biologists, doctors and other healthcare professionals who are in a much better position to judge the importance (or lack thereof) of any scientific improvements.

V. CONCLUSION

Laws governing generic substitution generally prohibit the substitution of brand-name drugs by generic drugs which are not "therapeutically equivalent." Nevertheless, there is no single definition of "therapeutic equivalence."[48] It seems there is a great margin to improve the regulatory frameworks for generic substitution, which could have a much greater and holistic impact on generic penetration, than time-consuming, expensive and fragmented antitrust enforcement in a handful of cases. For instance, broadening or at least clarifying in a uniform way the concept of therapeutic equivalence, could potentially have a much more extensive and effective impact in facilitating generic substitution, without arguably having an adverse effect on the innovation incentives of pharmaceutical companies. Antitrust enforcement is of course a useful tool to remedy market failures, but it is no panacea; a robust regulatory framework that has the reflexes to quickly adapt to the ever-changing life-cycle strate-

44 *In re Suboxone Antitrust Litigation*, 64 F. Supp. 3d. 665, 682 (E.D. Pa. 2014); *United States v. Grinnell Corp. et al.*, 86 S. Ct. 1698, 1704, (Jan. 13, 1966), condemning a behavior under Section 2 of the Sherman Act which was "plainly and explicitly" for the single purpose of willfully acquiring and maintaining monopoly power; *United States v. Microsoft Corp.* 253 F.3d 34, 65 (D.C. Circuit 2001), finding that "[j]udicial deference to product innovation, however, does not mean that a monopolist's product design decisions are per se lawful."

45 FTC, *Amicus Brief, Mylan Pharms. v. Warner Chilcott*, 2015, pp. 27-28.

46 Ginsburg Douglas H., Wong-Ervin Koren W. & Wright Joshua D., "Product Hopping and the Limits of Antitrust: The Danger of Micromanaging Innovation," 12 CPI Antitrust Chronicle 1, (December 2015), pp. 693-707, criticizing the decision and arguing that product-hopping is "the predictable legal response to the incentives created by patent law and state substitution laws," while product shifting frustrates generic manufacturers because they can no longer rely on the marketing efforts of the brand-name drug manufacturers.

47 Lemus Jorge, Okzul Olgu, "Product Hopping and Innovation Incentives," paper presented in the 14th International Conference on Competition and Regulation of CRESSE (2019).

48 *New York v. Actavis PLC, Forest Labs LLC*, 787 F.3d 638, 644-646, (2nd Cir. 2015). See also Jesse Vivian C., "Generic Substitution Laws," U.S. Pharmacist (2008). Available at: http://www.uspharmacist.com/content/s/44/c/9787 (last accessed on April 23, 2020).

gies of the pharma industry is much more likely to prove successful against abusive product reformulations and effectively protect patients and healthcare schemes.

Attaining a balance between antitrust scrutiny of product reformulations while preserving essential innovation incentives is not an easy endeavor. Given the complexity and sophistication of drug product reformulation strategies and the difficulty of making a distinction between hard and soft product switches, a rule of reason analysis should take into consideration the factual specificities of each case. First, it is crucial to examine the *timing* of a product reformulation and its connection to an imminent threat of generic entry. Second, a parallel withdrawal of an older version of the relevant drug from the market could be a potential red flag, especially if this specific version of the relevant drug is expected to face imminent generic entry and there is evidence that the main reason behind such withdrawal is to prevent generic entry and substitution. A third important criterion would be the examination of the overall conduct of the brand-name drug manufacturer and the broad context of its strategies. This is of paramount importance because any parallel strategies aiming to abuse the regulatory framework or to illegitimately delay generic entry would shed a different light on an accompanying product reformulation.

On the flipside, courts and antitrust authorities should be cautious when examining and determining whether specific drug product reformulations are scientifically important, as part of their antitrust inquiry. Since neither courts nor enforcement authorities have the necessary scientific background to objectively determine whether a new drug product is innovative or not, they should generally refrain from setting the bar for what constitutes a "genuine innovation" or a "marginal improvement." Even incremental changes in a drug product have the potential to benefit patients and innovation incentives should not focus exclusively on quantitative criteria: a manifest example of this are the incentives that are provided for R&D targeting orphan diseases that only affect small parts of the population. When scrutinizing product reformulation strategies, extra caution should be exercised so as to ensure that the innovation incentives of originators are preserved also with regard to product reformulations, which should not be automatically considered to amount to lower quality innovation that does not benefit patients or scientific progress.

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