A Dynamic Perspective on Biosimilar Competition

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ABSTRACT

The upcoming biopharmaceutical patent cliff will set the stage for a large-scale market entry with biosimilars over the next decade. Unlike generic producers, their developers may be incentivized to compete beyond the realm of price. The technological and commercial peculiarities of biosimilars suggest that they can be a source of innovation stemming from advances in drug delivery and manufacturing processes. These improvements fit the definition of incremental innovation, although they may produce isolated disruptive effects. Competitive pressure from biosimilars further induces bio-originator producers to respond by subsequent cycles of innovation. From a firm-centric perspective, the freedom to operate in biosimilar R&D is a key condition enabling their manufacturers to potentially expand business models into the originator segment of the industry. All these innovation-related benefits may be foregone if competition agencies are not well-equipped to dismantle anticompetitive strategies eliminating the prospect of a successful biosimilar entry. Considering the lack of strong antitrust precedents, this article proposes the concept of 'potential competition in existing markets' as the appropriate analytical framework for assessing the impact of business conduct on biosimilar innovation. It is capable of effectively protecting dynamic competition, while seamlessly meeting both ex-post and ex-ante enforcement standards in EU competition law.

KEYWORDS: biosimilars, competition policy, entry barriers, innovation

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I. INTRODUCTION

The innovative pharmaceutical industry delivers two main types of medicines – small molecule drugs and biologicals. Small molecules have been for decades the cornerstone of pharmaceutical innovation. Synthesized through chemical processes, these compounds currently represent the vast majority of approved medicines on the market. Trivial examples include aspirin, penicillin, and paracetamol among others. In 1973, biochemists Herbert Boyer and Stanley Cohen managed to create the first genetically engineered organism. The technique used was recombinant DNA – later commercialized by the pioneer biotechnology company Genentech. Recombinant DNA technology, along with the monoclonal antibodies discovery, is considered to largely underpin the emergence of what we know today as the biologics industry.[1]

Biological drugs are large and complex molecules – usually therapeutic proteins – produced or extracted from living organisms such as genetically modified cells.[2] They are "highly sensitive" to the manufacturing process in which even minor changes may impact their structural and functional characteristics.[3] This innovative type of drug has delivered important advances in complex therapeutic fields such as oncology and immunology and is expected to deliver more in the future. AbbVie's Humira, for instance, is an anti-inflammatory biologic used for the treatment of a range of autoimmune conditions, including rheumatoid arthritis, ulcerative colitis, and plaque psoriasis. Biologicals, however, are particularly expensive –

[1] Gary P. Pisano, SCIENCE BUSINESS: THE PROMISE, THE REALITY AND THE FUTURE OF BIOTECH 26-29 (Harvard Business School Press, 2006) and Janet Hope, BIOBAZAAR: THE OPEN SOURCE REVOLUTION AND BIOTECHNOLOGY 32 (Harvard University Press, 2008).

[2] For a comprehensive definition of biologicals, see Italian Medicines Agency, Biologics, available at https://www.aifa.gov.it/en/farmaci-biologici; See also Karin M. Torres-Obreque, Giovanna P. Meneguetti, Jorge J. Muso-Cachumba, Valker A. Feitosa, João H.P.M. Santos, Sónia P.M. Ventura, Carlota O. Rangel-Yagui, *Building better biobetters: From fundamentals to industrial application*, Drug Discov Today 27, 66 (2022) and Michael A. Carrier and Carl Minitti III, *Biologics: The New Antitrust Frontier*, 1 University of Illinois Law Review 1, 5-8 (2018).

[3] See Artem Zharkov, Bettina Barton, Dominik Heinzmannb, Georgios Bakalos and Thomas Schreitmüller, Development Pathways for Subcutaneous Formulations of Biologics versus Biosimilar Development, 7 Expert Review of Precision Medicine and Drug Development, 62 (2022) and the literature cited.

Humira is in fact one of the best-selling drugs of all time. The global biologicals market was estimated at around 335.43 billion USD at the end of 2021 and is expected to grow to 817.48 billion USD by 2032.[4] As of 2022, biologicals were accountable for 35% of medicine spending in Europe.[5]

Both small-molecule drugs and biologicals exit the pipeline and enter the market under patent protection. After patent term expiry, generic entry is expected to exert strong competitive pressure on small molecules, and entry of *biosimilars* on biologics accordingly. That competitive pressure is a key driver of price reduction in both cases. But are generics and biosimilars conceptually identical? From a scientific perspective, the answer is negative. Generics have the same qualitative and quantitative composition in active substances and pharmaceutical form as their reference brand-name medicine.[6] Put differently, they are bioequivalent.[7] By contrast, biosimilars cannot be precise copies of reference biologics – they are highly similar, yet not structurally identical.[8] Since the manufacturing process of the reference biologic is proprietary information protected by trade secret, competitors willing to create a biosimilar need to establish an alternative process, including a new cell line.[9] This renders biosimilar development significantly more complicated, uncertain, and costly in terms of resources and time.[10] This type of R&D also involves the utilization of specific biotech know-how and facilities and requires clinical trials to secure marketing approval.[11] The

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[4] Future Market Insights, *Biologics Market 2022-2032*, available at https://www.futuremarketinsights.com/reports/biologics-market#:~:text=Biologics%20Market%20(2022%20to%202032,US%24%20817.48%20Billion%20by%202032.

[5] IQVIA, *The Impact of Biosimilar Competition in Europe*, White Paper, available at https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2022.pdf

[6] Article 10(2)(b) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[7] *Id*.

[8] See Carrier and Minitti III, supra note 2, 7-8.

[9] Zharkov et al., supra note 3, 65.

[10] Case M.5865 – Teva/Ratiopharm, paras 28-29.

[11] *Id*, para 29, Case M.7559 – Pfizer/Hospira, para 54. See also Zharkov et al, supra note 3, 63, 65-66 (noting that "the EMA and FDA only approve a product as biosimilar once its similarity to the reference product has been

European Commission has in fact observed that biosimilar development resembles more the R&D process of originator than that of generic drugs.[12]

The scientific peculiarity of biosimilars has an important implication on market dynamics. While the business model of generic manufacturers is focused exclusively on cost-effective copying of off-patent medicines, biosimilar companies are incentivized to compete beyond the realm of price. Doctor's inertia, powerful trademark effects, and imperfect information can inhibit the uptake of biosimilars to a higher extent compared to generics – especially if combined with disparaging conduct on behalf of manufacturers of brand-name biologicals. The need for a degree of differentiation, accordingly, induces biosimilar developers to think and act more like innovators, compared to their counterparts in the small-molecule business. Moreover, considering that by 2030 numerous high-selling biological drugs will lose patent exclusivity, a strong increase in global competition with biosimilars can be anticipated. In the US, for example, patents protecting around 190 drugs are expected to expire during that period.[13] This significant patent cliff will affect 69 drugs that have the status of blockbusters, including a number of top-selling biologicals.[14]

This article explores the role of competition policy in ensuring that patients in Europe will enjoy the full set of benefits from the forthcoming wave of biosimilar competition. These benefits are not limited to increased affordability of essential therapies but also relate to potentially improved treatments. The article is accordingly structured into five sections. Section II deconstructs the concept of *pharmaceutical innovation* into three categories – breakthrough, disruptive, and incremental – and explores the effect of biosimilar competition on each of them.

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demonstrated by means of thorough biosimilarity assessment including comparative analytical-, non-clinical and clinical studies").

[12] Teva/Ratiopharm, supra note 10, para 29.

[13] Meagan Parrish, *How steep is pharma's patent cliff?* (2023), available at https://www.pharmavoice.com/news/pharma-patent-cliff-Merck-Keytruda-Pfizer-Seagen-Humira/652914/. (some particularly high-selling biologicals approaching patent expiry include Merck's Keytruda, Regeneron's Eylea, Johnson and Johnson's Stelara, and Bristol Meyers Squibb's Opdivo among others.)

[14] *Id*.

Section III discusses the current state of antitrust enforcement in the biosimilar segment of the industry. European, US, and UK precedents are analyzed as these markets currently generate the highest sales of biopharmaceuticals globally. Section IV suggests that integrating innovation considerations into biosimilar competition policies is facilitated by the commercial and technological specificities of these medicines. It is proposed that such integration can be effectively achieved under the analytical framework of *potential competition in existing antitrust markets*. As a matter of principle, the article concludes that competition authorities are better equipped to promote innovation in that segment of the industry, compared to the field of inter-originator innovation races for future markets.

II. THE INNOVATIVE POTENTIAL OF BIOSIMILARS

When coming across the term innovation, one intuitively imagines novel products or processes that deliver utility. Indeed, any invention that has these characteristics and is commercialized, can be considered an innovation.[15] In the pharmaceutical industry, product innovations are essential because of their promise to improve the outcome of diseases. Based on their therapeutic added value, they can be divided into three main categories: (i) breakthrough, (ii) disruptive, and (iii) incremental. But innovations in the industry need not necessarily be strictly therapeutic – medicines, foremost, need to be successfully administered to patients in order to produce any therapeutic effect. This sets the stage for an important layer of innovation competition – via improvements in drug delivery mechanisms.

Breakthrough innovations in principle push the boundaries of science. They open novel markets by offering utility that is unconceivable under the prior state of the art. Most importantly, these novel markets do not emerge at the expense of rendering existing products

[15] For a definition of "innovation", see OECD/Eurostat (2018), Oslo Manual 2018, *Guidelines for Collecting, Reporting and Using Data on Innovation. The Measurement of Scientific, Technological and Innovation Activities*, (4th ed., OECD Publishing, Paris/Eurostat, Luxembourg), 20.

and technologies obsolete. For example, Alexander Fleming's discovery of penicillin in 1928 and the subsequent Oxford University research that transformed it into a life-saving innovation, gave the world the very first antibiotic. This changed patients' treatment forever without disrupting demand for any specialized prior-generation product.[16] Despite the scientific progress that has occurred throughout the last century, however, there is a significant number of diseases for which no available treatments are currently present. One can think of genetic disorders or tropical diseases. Breakthrough innovations in these therapeutic fields are accordingly strongly anticipated.

By contrast to breakthrough innovations, disruptive products and technologies inevitably emerge at the expense of existing markets. The theory of "disruptive innovation" was introduced by Clayton Christensen in the early 1990s,[17] but its origin can be traced back at least to Joseph Schumpeter's broader concept of creative destruction.[18] The essence is that by focusing on improving the service of the high-profitable end of markets, incumbent companies neglect certain segments of customers – the less demanding and those entirely unserved.[19] This creates opportunities for rivals to create products that better suit their needs in terms of functionality and price or start serving them for the very first time.[20] Benefiting from the lack of "vigorous response" on behalf of incumbents due to neglect, these entrants gradually expand their business models and ultimately overtake incumbents.[21]

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[16] On the broader concept of "nondisruptive creating", which may incorporate also breakthrough innovations, see W. Chan Kim and Renée Mauborgne, BEYOND DISRUPTION: INNOVATE AND ACHIEVE GROWTH WITHOUT DISPLACING INDUSTRIES, COMPANIES OR JOBS (Harvard Business Review Press, 2023)

[17] Joseph L. Bower and Clayton M. Christensen, *Disruptive Technologies: Catching the Wave*, 73 Harvard Business Review 43, 45 (1995).

[18] Joseph A. Schumpeter, CAPITALISM, SOCIALISM AND DEMOCRACY, 1942 (Routledge, 2015).

[19] Clayton M. Christensen, Michael E. Raynor and Rory McDonald, *What is Disruptive Innovation?*, 93 Harvard Business Review 12, 44-53 (2015).

[20] *Id.*

[21] *Id.*

Let us apply this disruption theory to the pharmaceutical industry.[22] First, European pharmaceutical markets are generally not price-sensitive due to the role of national insurers as ultimate payers. Hence, disrupting these markets solely through cheaper products may not be as effective as it would be in other industries. Second, demand for medicines is conceptually different from consumer demand in other sectors – it is inelastic and not driven by willingness or ability to pay. Access to essential medicines is in fact a precondition for the exercise of the fundamental rights to life and highest attainable standard of health.[23] Therefore, a distinction between *more* demanding and *less* demanding customers cannot be made when these customers have the characteristic of patients – all patients are supposed to benefit from an equal quality of treatment. As far as the second category of customers outlined by Christensen is concerned – those entirely unserved – it must be noted that a web of sectoral regulation strives to ensure that such a category does not exist in the first place. In other words, the service of these patients' needs is not conditioned solely upon a market-based system of incentives. Orphan regulation, for example, aims to directly incentivize research and development (R&D) into drugs treating rare diseases with limited markets through an additional exclusivity right.[24] National pricing and reimbursement systems, accordingly, strive to balance the price effect of exclusivities and ensure a certain degree of drug affordability. While it can be debated whether these regulations function seamlessly, the dense regulatory framework suggests that the term "disruptive innovation" in a pharmaceutical context has a distinctive and industry-specific meaning.

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[22] See, e.g., Bernard H. Munos and John J. Orloff, *Disruptive Innovation and Transformation of the Drug Discovery and Development Enterprise,* National Academy of Medicine, Discussion Paper, footnote 2 (2016) (defining "disruptive innovation" as a "transformation of the pharmaceutical industry driven by new technology, new business models, or policy decisions that improve therapy and create value for patients and society in a way that could not be achieved through other means")

[23] See Article 2 Convention for the Protection of Human Rights and Fundamental Freedoms, ECHR, Council of Europe (1950) and Article 12 International Covenant on Economic, Social and Cultural Rights, General Assembly resolution 2200A (XXI) (1966).

[24] See Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

It can be accordingly argued that the disruptive nature of a medicine is primarily determined by its therapeutic advantage in relation to the existing state of the art. Disruptive medicines are expected to offer such a value to patients, that renders the use of existing alternatives irrational and the markets for them obsolete. Recently, a Japanese pharmaceutical start-up announced plans to conduct clinical testing on a world-first medicine enabling natural regrowth of lost teeth in humans.[25] Depending on the success of the project and the potential commercialization conditions – which of course cannot be predicted at this point – it may produce a strong disruptive effect on the dental care industry by offering an alternative to dentures and implants.[26]

Lastly, incremental innovations are improvements of existing products and technologies that produce effects solely within the boundaries of existing markets. These improvements might lead to a redistribution of market shares among competitors or protect incumbents from that threat. Contrary to breakthrough and disruptive innovations, the delivery of incremental improvements ensures the evolution of markets and sustains their lifespan. A follow-on version of a medicine that offers a more convenient mode of administration illustrates well a pharmaceutical innovation that can be labeled as incremental. The field of neovascular age-related macular degeneration (nAMD) treatments provides a useful case study in this regard. In 2022, Roche introduced Vabysmo – an innovative biological administered three times a year as a maintenance therapy in patients without disease activity.[27] This outperformed the mode of administration of Regeneron's 2011 blockbuster Eylea which required injections into the eye six times a year. In response to the strong competitive threat,

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[25] *World's 1st 'tooth regrwoth' medicine moves toward clinical trials in Japan*, availbale at https://mainichi.jp/english/articles/20230609/p2a/00m/0sc/026000c

[26] *Id*.

[27] Kevin Dunleavy, *Regeneron's Eylea HD vs. Roche's Vabysmo: Will the real standard of care please stand up?* (2024), available at https://www.fiercepharma.com/pharma/regenerons-eylea-hd-vs-roches-vabysmo-will-real-soc-please-stand

Regeneron introduced in 2023 a follow-on version of Eylea, reducing the injection frequency while retaining the therapeutic effect.[28]

What innovation along the above-outlined spectrum can one expect a biosimilar to deliver? Biosimilar manufacturers first and foremost compete for a market share by offering lower-priced substitutes to biological treatments.[29] Put differently, their products strive for therapeutic *interchangeability* with reference biologicals. The European regulatory framework governing the approval of biosimilars indeed requires *no clinically meaningful differences* between the biosimilar and the reference biological in terms of safety and efficacy.[30] Hence, it is unlikely that a medicine developed to receive authorization as a biosimilar would ultimately deliver breakthrough or disruptive advances in treatment.[31] In such a hypothetical, interchangeability with the reference biological would be impossible to establish. Besides, therapeutic advances of such a degree would likely merit patent protection and result in supra-competitive pricing of the drug, which would be inconsistent with the price-reducing objective of biosimilar entry. Such a competitive relationship between the first and second-generation drugs would instead resemble a model of an innovation race between originators.[32]

Incremental innovation with biosimilars, however, is both technologically conceivable and commercially desirable. Two types of advances with biosimilars fit the definition of incremental innovation. First, a biosimilar may offer an alternative drug-delivery technology

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[28] Skylar Jeremias, *FDA Approves Higher-Dose Version of Aflibercept* (2023), available at https://www.ajmc.com/view/fda-approves-higher-dose-version-of-aflibercept

[29] See *Pfizer/Hospira*, supra note 11, para 42.

[30] EMA/EC, Biosimilars in the EU. Information Guide for Healthcare Professionals, 8 (2019), available at https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf

[31] Note that some differences between the reference biological and the biosimilar will not affect the latter's approval procedure as long as they have no implications for safety and efficacy. They may include "differences in the formulation of the medicine (e.g. excipients), presentation (e.g. powder to be reconstituted versus solution ready for injection) and administration device (e.g. type of delivery pen)", supra note 30.

[32] See Andrea Pezzoli, *Originators versus Originators: Competition before the Market and Market Power beyond Dominance* in Giovanni Pitruzzella and Gabriella Muscolo, COMPETITION AND PATENT LAW IN THE PHARMACEUTICAL SECTOR. AN INTERNATIONAL PERSPECTIVE (Wolters Kluwer, 2016).

that differentiates it from the reference biologic. Second, biosimilar manufacturers may develop improved production processes in the context of their R&D. These processes may, accordingly, affect positively the quality of the biosimilar and even satisfy patentability criteria. Let us discuss these two scenarios in turn.

One possibility for drug delivery innovation with a biosimilar is the development of a subcutaneous (SC) route of administration where the reference biological is administered only as an intravenous (IV) infusion.[33] This hypothetical is illustrated by the introduction of Remsima SC – a biosimilar version of Remicade, which is a medicine used for the treatment of a range of autoimmune disorders. Remicade is administered as an IV infusion in a clinic which requires the assistance of a healthcare professional. Remsima, however, offers also an alternative mode of drug delivery in the form of an SC injection – i.e., it can be injected under the skin, which allows self-administration at home. The SC route of administration can be thought of as one means to decrease patient discomfort by replacing lengthy and burdensome infusion procedures. Further benefits may include cost-savings for healthcare budgets, reduced drug wastage, and less probability of "medication errors" because of the initially fixed dosages.[34]

Within the field of SC administration, there may be further scope for incremental improvements. The case of Benepali, outlined by Ian Simpson and George Spooner, illustrates this hypothetical.[35] Benepali is a biosimilar of Enbrel – an originator biological prescribed for the treatment of autoimmune diseases. It is administered subcutaneously via an autoinjector

[33] Zharkov et al., supra note 3, 66 (explaining that this development can happen independently of the reference product, and "while the comparability between the IV and SC biosimilar will have to be demonstrated, an analytical or clinical comparison of the SC biosimilar with an SC version of the reference product will not be required.)

[34] See Michael J. Harvey, Yi Zhong, Eric Morris, Jacob N. Beverage, Robert S. Epstein, Anita J. Chawla, Assessing the Transition from Intravenous to Subcutaneous Delivery of Rituximab: Benefits for Payers, Health Care Professionals, and Patients with Lymphoma, 17 PLoS ONE 1, 2 and the literature cited.

[35] Ian Simpson and George Spooner, *Opportunities for Innovations with Biosimilars*, 142 ONdrudDelivery 8 (2023), available at https://ondrugdelivery.com/opportunities-for-innovation-with-biosimilars/.

that requires "the user to press the device against the skin and then press a button to initiate the injection".[36] By contrast, the device through which Benepali is administered initiates an injection automatically when pushed against the skin.[37] Simpson and Spooner contend that "a drive to more self-administration of medication potentially benefits patients and payers and can be facilitated by better drug delivery technology".[38] They expect such technologies to become increasingly important in the field of biosimilars, considering the prospect of increased competition among their manufacturers in Europe and the US in the following years.[39] It is important to note, however, that the scope for innovation competition at the level of drug delivery is constrained by the current state of science. In particular, the introduction of biopharmaceuticals in oral formulation – the least burdensome to administer – seems to be a major hurdle for the industry. It is rendered unfeasible due to "low intestinal absorption and degradation" of the substances.[40] If these obstacles are eventually overcome due to technical advances, orally delivered biopharmaceuticals may reach beyond incremental innovation and ultimately disrupt therapeutic markets.

A second type of innovation biosimilars can deliver stems from advances in production processes. The story of Alteogen's pipeline biosimilar ALT-L9 is illustrative of this possibility. The product is currently under development to enter the market as a substitute competitor to Regeneron's Eylea whose key patents are anticipated to expire throughout the next few years.[41] ALT-L9 is intended to have the same route of administration, therapeutic indication, and

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[36] *Id*.

[37] *Id*.

[38] *Id*.

[39] *Id*.

[40] Zharkov et al., supra note 3, 63; See also Roger New, *Oral Delivery of Biologics via the Intestine*, 13(1) Pharmaceuticals 18 (2021).

[41] Noah Higgins-Dunn, *The top 15 blockbuster patent expirations coming this decade (2021), available at https://www.fiercepharma.com/special-report/top-15-blockbuster-patent-expirations-coming-decade*

dosage as Eylea.[42] Alteogen announced in 2019, however, that it had developed an improved method of producing the biosimilar and a new formulation technology. The latter allegedly made the product more resilient to high temperatures and ensured a "longer shelf life".[43] For these inventions, the company obtained manufacturing method and formulation patents accordingly.

To understand the wider implications of biosimilar innovation, it would be useful to approach this concept from three perspectives – a firm-centric, a patient-centric and a geo-centric. The firm-centric perspective reveals the importance of the freedom to operate in the field of biosimilar R&D as a key driver for developing innovation capabilities *within* firms. The successful introduction of a biosimilar – even one with zero therapeutic advances – requires building substantial scientific and managerial capacity and securing access to valuable tangible and intangible resources.[44] It is in this regard not surprising that pharmaceutical giants, traditionally established in the innovative segment of the industry, began operating biosimilar divisions.[45] While a generic producer of small molecules will unlikely transform into an originator – at least in the medium term – a biosimilar manufacturer may effectively expand their business model with next-generation R&D in purely innovative products. Such a leap in added value is conceivable in the biopharmaceutical segment due to the process of learning by doing and the inherently science-intensive nature of biosimilar development. These prospective innovators may also be better equipped to raise venture capital and enter strategic R&D

[42] Martin David Harp, *Altos Biologics completes patient enrollment in global Phase 3 clinical trial of Eylea biosimilar in neovascular age-related macular degeneration* (2023), available at https://www.ophthalmologytimes.com/view/altos-biologics-completes-patient-enrollment-in-global-phase-3-clinical-trial-of-eylea-biosimilar-in-neovascular-age-related-macular-degeneration

[43] *Alteogen Secures Process Patent for Its Aflibercept Biosimilar* (2019), available at https://www.centerforbiosimilars.com/view/alteogen-secures-process-patent-for-its-aflibercept-biosimilar

[44] *Pfizer/Hospira*, supra note 11, para 54: "Clinical trials required to provide the necessary evidence for regulatory approval… require also certain R&D capabilities.".

[45] Pfizer and Novartis are two examples of established innovators that also compete through the manufacture of biosimilars.

alliances compared to their counterparts in the generics industry.[46] If, however, the prospect of a successful biosimilar market entry is eliminated, an important driver for within-firm capacity building and development may be lost.

The patient-centric perspective on biosimilar innovation, in turn, reveals certain nuances to the incrementality label we attributed to this notion. It suggests that the innovative value of a new pharmaceutical technology may be perceived differently across stakeholder groups. Indeed, mainstream patients may perceive a novel form of drug delivery or better product durability as incremental improvements with a limited inventive step over established alternatives. These very features, however, may be seen as *disruptive* to the market status quo by consumers with specific needs such as infant, elderly or disabled patients. The same holds for patients living in rural areas without swift access to medical facilities or in cities with strained infusion centers. Put differently, such improvements may effectively capture the *entire* therapeutic demand of these groups. Antitrust regulators, to the contrary, may perceive these improvements as product life-cycle strategies bordering with anticompetitive evergreening, especially when adopted by established innovators.

Lastly, a geo-centric approach to biosimilar innovation draws attention to the circumstance that a single product innovation may be released on different geographic markets at different times. It is widely accepted that European pharmaceutical markets are national in scope, due to divergences in pricing and reimbursement of medicines. In such a context, patent litigation or anticompetitive conduct may effectively obstruct the expansion of competitors from one geographic market to another and require a certain degree of scrutiny.

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[46] See, e.g., Ian M. Cockburn, *The Changing Structure of the Pharmaceutical Industry,* 23 Health Affairs 10 (2004) (observing that "drug companies began to look and behave more like universities, with increasing emphasis on collaboration, publication, and exchange of (precompetitive) information"). Indeed, strategic collaborations that divide R&D labour between public research institutions, biotech start-ups, and established firms are increasingly common in the biopharmaceutical industry. Especially for emerging companies, it is crucial to identify such partnerships, due to the high costs associated with the testing of pipeline drugs in clinical trials. Beyond the financial factor, the widespread upstream patenting in the pharmaceutical industry necessitates entering into strategic licensing agreements. For an outlook on this trend, consult annual reports of publicly traded biopharmaceutical companies.

In essence, a distinctive characteristic of biosimilar innovation is that, although it is generally incremental, it may produce isolated disruptive effects. As pressure from biosimilars is essential to stimulate originator manufacturers to engage in further cycles of innovation, impediments to their entry into key markets can produce an additional negative effect on the overall level of biopharmaceutical innovation. This suggests the importance of developing a workable dynamic framework for analyzing biosimilar competition. The rest of our discussion will be devoted to this objective.

III. IMPEDIMENTS TO BIOSIMILAR COMPETITION AND THE RESPONSE OF ANTITRUST

The first biosimilar was launched in Europe in 2006. Since large-scale competition with biosimilars is a relatively recent phenomenon, the antitrust precedents across jurisdictions are accordingly limited. Nevertheless, they require attention as they allow us to develop an understanding of antitrust enforcers' perception of this peculiar form of competitive pressure. This section is devoted to discussing the landmark antitrust precedents in the field of biosimilar competition and whether innovation considerations played any role in the decision-making process.

A. United States

The uptake of biosimilars in the United States has been lower compared to Europe. As of 2023, the European Medicines Agency has granted marketing authorization for 86 biosimilars.[47] By contrast, as of March 2023, the approved biosimilars by the US Food and Drug Administration

[47] EMA, *Biosimilar medicines can be interchanged* (2022), available at: https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged

were 40, of which 25 were launched.[48] Some authors have raised concerns that anticompetitive practices may be among the reasons behind the slow entry of biosimilars into the US market.[49] The *Remicade* and *Humira* cases constitute in this regard the two US precedents that shed light on the competitive dynamics in that segment of the industry.

In the *Remicade* antitrust action, the plaintiff Pfizer alleged that its biosimilar Inflectra was blocked from competing against Johnson and Johnson's ('J&J') originator Remicade, due to the presence of exclusionary contracts and bundled rebates.[50] Pfizer accused J&J of deploying a strategy of securing contractual commitments from insurers to exclude biosimilars from coverage under their plans, or to condition their reimbursement upon a prior failure with a Remicade therapy.[51] To that end, according to Pfizer, a rebate program was introduced. Pursuant to it, a discount on Remicade for all existing patients (who are by default unlikely to switch to biosimilars) was offered, thereby incurring significant savings for payers and obstructing competition for new patients. J&J was also accused of bundling rebates across multiple products – if an insurer refused to grant exclusivity to Remicade, they would be forced to pay a higher price on other products by the company.[52]

Pfizer claimed that despite its biosimilar's lower unit-for-unit price, bundling the substantial base of existing Remicade patients with new patients, effectively excluded it from competing for the new demand.[53] J&J accordingly contended that the reasons behind the low sales of Inflectra are attributable to the design of Pfizer's own sales practices and to "providers'

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[48] Cyrus Fan, *Comparison of Humira Biosimilars in the US and Europe* (2023), available at: https://www.pharmaceutical-technology.com/pricing-and-market-access/comparison-humira-biosimilars/?cf-view

[49] See Giulio Federico, Fiona Scott Morton and Carl Shapiro, *Antitrust and Innovation: Welcoming and Protecting Disruption*, 20 Innovation Policy and the Economy 125, 177-178 (2020).

[50] 345 F. Supp. 3d 566 (E.D. Pa. 2018).

[51] *Id*.

[52] *Id*.

[53] *Id*.

lack of comfort and awareness of biosimilars".[54] The company also contested Pfizer's argument that it indeed offered a competitive price with Inflectra.[55] In 2021, the parties settled the dispute under undisclosed terms.

The *Humira* case concerned allegations on behalf of indirect purchasers that AbbVie anticompetitively built a so-called patent thicket[56] around its biological, and asserted it for the purpose of obstructing potential biosimilar competition.[57] The plaintiffs also argued that the web of patents was exploited "as a leverage" during negotiations with potential competitors, "forcing them to agree to delay their market entry in return for licensing agreements that cut through AbbVie's patent thicket".[58] These agreements entitled biosimilar manufacturers to a "near-immediate" entry into the European market in exchange for commitments to delay entry into the US market.[59] The claimants invoked accordingly sham behavior, pay-for-delay and market allocation theories of antitrust harm. AbbVie, in turn, argued that the accumulation of a broad patent portfolio constitutes a legitimate and lawful business strategy. It did not consider the settlements to be anticompetitive either, because they ultimately entitled competitors to enter markets before patents expire, did not involve reverse cash payments, and "only [divided] the market in ways consistent with AbbVie's patent rights".[60] Likewise, the District Court did not view AbbVie's overall strategy as a violation of antitrust but rather as an ordinary utilization of intellectual property rights benefitting from a presumption of validity. The

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[54] *Id*.

[55] *Id*.

[56] See Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, 1 Innovation Policy and the Economy 119 (2000).

[57] AbbVie applied for 247 patents, of which it obtained 132. More than 90% of the patents were issued in 2014 or later, even though Humira was released on the market in 2002, see 465 F. Supp. 3d 811, 9 (N.D. Ill. 2020).

[58] *Id*. For an analysis of this case, see Michael A. Carrier, *Back to 2012: The Seventh Circuit's Reliance on Pre-Actavis Law in Dismissing Patent-Thicket Claims*, Competition Policy International (2022), available at SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4267354 and Michael A. Carrier and S. Sean Tu, *Why Pharmaceutical Patent Thickets are Unique*, Texas Intellectual Property Law Journal, Forthcoming, Rutgers Law School Research Paper, available at SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4571486.

[59] Supra note 57, 36.

[60] *Id*, 17.

complaint was accordingly dismissed in 2020. Upon appeal, the Seventh Circuit upheld the judgment in 2022.

Neither *Remicade* nor *Humira*, however, involved an innovation theory of harm. Pfizer's Inflectra was in no way superior in terms of therapeutic performance compared to J&J's Remicade. Likewise, the indirect purchasers of Humira alleged a monopoly pricing antitrust injury from AbbVie's strategy, without raising innovation-related arguments.

B. United Kingdom

At the end of 2015, the Competition and Markets Commission ('CMA') opened an investigation into whether Merck Sharp & Dohme ('MSD') abused its dominant position on the market for the supply of Remicade and its biosimilars in violation of the Competition Act 1988 and TFEU. The investigated conduct concerned a discount scheme for the sale of Remicade in the UK introduced by MSD. It was essentially designed to inhibit the uptake of biosimilars by setting such a low effective price on Remicade, that would force biosimilars to compete at commercially unviable terms.[61] An increase of Remicade's price, however, would occur, if the volume purchased fell to the benefit of biosimilars.[62] This was expected to create a situation where it is more costly to satisfy a unit of demand with both Remicade and biosimilars than exclusively with Remicade. Evidence gathered during the investigation suggested that the "cost pressure would persist until sufficient demand was switched to biosimilars to offset the higher price of Remicade".[63]

In 2019, the CMA closed the investigation. It considered that although the scheme was designed to produce an exclusionary effect, the factual circumstances present at the time it was

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[61] CMA, *No Ground For Action Decision*, Competition Act 1988, Remicade, 50236, available at https://assets.publishing.service.gov.uk/media/5c8a353bed915d5c071e1588/Remicade_No_Grounds_For_Action_decision_PDF_A.pdf.

[62] *Id*, 51.

[63] *Id*, 54.

implemented, made it unlikely to have such.[64] First, according to the CMA, there was a higher general willingness to prescribe biosimilars than predicted by MSD. This had accordingly enabled their manufacturers to compete not only for new demand but also for existing patients.[65] In addition, the risk of short-term price increases was considered to have had a limited impact on the decisions of those buyers who favored longer-term views on the costs and benefits of biosimilars.[66] The quicker patients are switched to biosimilars, accordingly, the shorter any cost pressure from MSD would remain in effect.[67] Second, the CMA considered that the lack of retroactivity of the investigated scheme further reduced its strength.[68]

The UK Remicade decision is not only notable for the endorsement of a full effect-based assessment. It also reflects CMA's understanding of the nature of biosimilar competition as one centered inherently on price, at least in the light of that case. As noted by the Commission, "by their nature…biosimilars could not offer better quality than Remicade. Accordingly, price was the key competitive factor on which biosimilars could seek to compete with Remicade".[69]

C. European Union

Following the Pharmaceutical sector inquiry from 2009, the European Commission has demonstrated increased scrutiny of business practices that may inhibit the entry of cheaper small-molecule generics into the market. A static theory of antitrust harm was developed both under Articles 101 and 102 TFEU through pay-for-delay, regulatory abuse, and denigration

[64] *Id*, 69.
[65] *Id*, 59-60.
[66] *Id*, 59.
[67] *Id*, 60.
[68] *Id*, 60-61.
[69] *Id*, 54, footnote 181.

precedents.[70] Considering that biosimilars are viewed as an important source of price competition to particularly expensive medicines,[71] the spillover effect of this theory in the biopharmaceutical segment of the industry was easily foreseeable. Indeed, for the 2009-2017 period, the Commission reported investigation work on competition concerns in more than 100 cases that did not ultimately result in an intervention decision. 13 percent of the cases related to alleged barriers to the entry of not only generics but also biosimilars.[72] In its 2020 proposal for a European pharmaceutical strategy, the Commission announced that it "will consider targeted policies that support greater generic and biosimilar competition…accompanied by enforcement of EU competition rules".[73]

The *Pfizer/Hospira* merger suggests, however, that the future European approach toward the antitrust regulation of biosimilar competition need not necessarily be solely price-centric, akin to the field of generics. The case concerned Pfizer's proposed acquisition of Hospira. Pfizer was developing a pipeline biosimilar to Remicade.[74] Hospira was marketing its own Remicade biosimilar – Inflectra – together with Celltrion.[75] Lastly, Celltrion had developed and marketed Remsima – a biosimilar that competed solely in price with Inflectra because of the full interchangeability between the two products.[76]

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[70] For an illustration of a pay-for-delay theory of harm, see Case C-307/18 – Generics (UK) and Others, ECLI:EU:C:2020:28. In relation to the concept of regulatory abuse, see Case T-321/05 – AstraZeneca v Commission, ECLI:EU:T:2010:266. The French Competition Authority has been particularly active in pursuing disparagement conduct. For a detailed discussion, see Adrien Giraud, Juliette Raffaitin, Constance Dobelmann, *Disparagement in the European Union and France* in EU COMPETITION LAW AND PHARMACEUTICALS 173 (Wolf Sauter, Marcel Canoy, Jotte Mulder eds, Edward Elgar, 2022). Moreover, in Case C-179/16 – F. Hoffmann-La Roche and Others, ECLI:EU:C:2018:25, the Court of Justice stated that colluding for the purpose of disparaging medicines, may, under certain circumstances, constitute a restriction of competition by object within the meaning of Article 101(1) TFEU.

[71] European Commission, Competition Enforcement in the Pharmaceutical Sector (2009-2017), Brussels, 28.1.2019 COM(2019) 17 final, 22.

[72] *Id*, 12.

[73] European Commission, *Pharmaceutical Strategy for Europe*, Brussels, 25.11.2020, COM(2020) 761 final, 7.

[74] Pfizer/Hospira, supra note 11, para 39.

[75] *Id*.

[76] *Id*, para 44: "This is a unique feature of the market, specific to infliximab, where two commercially distinct biosimilar products are in fact identical in their molecular structure and clinical evidence."

The Commission considered that the concentration of ownership over Pfizer's pipeline biosimilar and Hospira's Inflectra will result in two alternative scenarios, both of which problematic. Under the first scenario, Pfizer will be incentivized to delay or discontinue its own R&D into a Remicade biosimilar to the benefit of the acquired drug.[77] Under the second scenario, it would instead focus on its pipeline medicine, rendering Celltrion the sole supplier of Hospira's Inflectra.[78] This would accordingly eliminate the existing price competition between Inflectra and Celltrion's Remsima. In 2015, the merging companies proposed a divestiture of Pfizer's pipeline development which was accepted by the Commission.[79] In 2016, Novartis announced that it had acquired the divestment.[80]

This merger decision is particularly important because the Commission's concerns in relation to the biosimilar market were not solely based on a static theory of harm. Although it was primarily concerned about reduced price competition due to the elimination of a future substitute, or of competition between two interchangeable products, innovation concerns can also be identified.

First, the Commission upheld its previous position in *Teva/Ratiopharm* and *Lonza/Teva/JV* that markets for biosimilars require a different treatment than those for generics.[81] It recognized that patients already stable on a bio-originator are unlikely to switch to a biosimilar, so biosimilars essentially competed for new demand both via price reduction and product differentiation.[82] As not the entire market is contestable, however, price reduction does not guarantee significant shifts in market shares.[83] Moreover, the Commission considered

[77] *Id*.
[78] *Id*.
[79] European Commission, supra note 71, 38.
[80] *Id*.
[81] Pfizer/Hospira, supra note 11, paras 18, 32-38.
[82] *Id*, para 36.
[83] *Id*, para 37.

that once biosimilars build "their own stock of locked-in patients, they face the trade-off between continuing to price low to attract additional patients and increasing prices to exploit their stock of locked-in patients".[84] Overall, this trade-off suggested that biosimilar manufacturers' incentives to price low at entry diminish as they establish their market position, so they begin to compete less aggressively in price for new patients.[85] At the same time, they are incentivized to differentiate their products, for example "through investment on the development of a superior clinical evidence".[86] Consequently, non-price competition was considered to play a role in biosimilar markets.

Second, and most importantly for our discussion, the Commission went further and suggested that the reduced incentives to continue the development of Pfizer's pipeline biosimilar post-concentration, would "translate into lessening of innovation competition".[87] It reasoned that patients would be deprived of a potential "differentiated" product, which market participants assessed positively on the basis of the available clinical data.[88] It must be noted that the term *innovation competition* is typically used in a pharmaceutical context to illustrate the process of rivalry between originator companies that focus on satisfying unmet or insufficiently met therapeutic needs. Its use in relation to a pipeline biosimilar should not be overlooked, as it hints at the Commission's understanding of the peculiar nature of biosimilar competition and its potential to deliver benefits beyond the realm of price. In the report on its competition enforcement activity in the pharmaceutical sector, the Commission in fact referred to the divestiture of Pfizer's pipeline biosimilar as a successful remedy ensuring that there will be "future innovation in biosimilars".[89]

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[84] *Id*, para 38.
[85] *Id*.
[86] *Id*, para 36.
[87] *Id*, para 58.
[88] *Id*.
[89] European Commission, supra note 71, 44.

IV. PROTECTING INNOVATION BY FACILITATING THE MARKET ENTRY OF BIOSIMILARS

The central question of this section, as well as of this article, is how the innovation aspect of biosimilar competition can be integrated into competition law analysis. This is an important question for three reasons. First, as already noted, biosimilar competition from potential entrants is expected to increase substantially due to the expiry of numerous patents over biological drugs. Second, the lack of strong precedents provides us with little guidance as to how potential cases involving effects on biosimilar innovation will be approached – especially under Articles 101 and 102 TFEU. And third, the introduction of innovation through biosimilars may be more vulnerable to potentially anticompetitive obstructions compared to inter-originator drug development races.

In essence, two innovation-related theories of antitrust harm can be identified. Under the first theory, competition authorities sanction conduct on the grounds that it has or is likely to reduce competition, and thereby negatively impact the level or pace of innovation.[90] This theory is based on the assumption that innovation is one of the benefits that competitive market structures deliver. Enforcers, accordingly, infer harm to innovation by establishing a distortion of the competitive process to the necessary standard.[91] The effect of the investigated conduct on competition is assessed within the framework of existing or future relevant markets.[92]

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[90] For a detailed discussion of this theory of harm, see OECD (2023), The Role of Innovation in Competition Enforcement, OECD Competition Policy Roundtable Background Note, 12-21, avalable at www.oecd.org/daf/competition/the-role-of-innovation-in-competition-enforcement-2023.pdf

[91] See Pablo Ibáñez Colomo, *Restrictions on Innovation in EU Competition Law,* 41(2) European Law Review 201, 206-209 (2016) and the case-law cited.

[92] Supra note 90; With regard to the role of market definition in competition law analysis, the European Commission states that: "Market definition is a tool to identify and define the boundaries of competition between firms… The objective of defining a market in both its product and geographic dimension is to identify those actual competitors of the undertakings involved that are capable of constraining those undertakings' behaviour and of preventing them from behaving independently of effective competitive pressure", European Commission, *Commission Notice on the definition of relevant market for the purposes of Community competition law*, OJ C 372, 9.12.1997, para 2.

Existing markets are defined where anticompetitive conduct or a merger is capable of preventing the commercialization of incremental innovations by potential or existing competitors. In other words, these new products are substitutes for products that are already marketed by the company committing a violation of Articles 101/102 TFEU or acquiring the new product's manufacturer. Essentially, the introduction of the intended product is expected to expand the existing market by taking a market share from rivals. Where the inventive step of a pipeline product is expected to be higher, however, substitutability with existing products cannot be established. Therefore, its introduction is expected to create a new market. If companies attempt to prevent the commercialization of such products, the effects of their strategies need to be assessed within the analytical framework of future product markets.[93] In any case, the focus of assessment remains on the way in which the reduced levels of competition *in* or *for* the market impact the innovation *incentives* of the firm and its competitors.[94] The Commission's approach in the *Pfizer/Hospira* merger, discussed above, is one manifestation of this theory of harm.

Under the second innovation theory of harm, the relationship between competition and innovation is in a sense reversed. Competition agencies have viewed innovation itself as an object of protection as it has been considered a driver of competition.[95] This approach can be suitable for assessing the competitive effects of conduct in high-technology industries, where companies primarily compete in the context of R&D races. The theory revolves around the idea that, by eliminating a rival pipeline project, a company eases competitive pressure to innovate. It also risks depriving consumers of alternative products in the future that potentially

[93] Future markets have been traditionally defined for the purpose of merger control, see, e.g., Case No IV/M.737 – Ciba-Geigy/Sandoz, para 42. The Italian *Google v Enel X* case is a rare example of integrating future market considerations into abuse of dominance analysis. One of the concerns in that case was that by refusing to render Enel's JuicePass application interoperable with Android Auto platform, Google was capable of impeding competition for user data which could in turn be used for new product innovations. For an outline of the case, see OEDC (2023), supra note 90, 15.

[94] OECD (2023), supra note 90, 43.

[95] *Id*.

compete with each other. The definition of relevant product markets, on which the levels of pre- and post-transaction competition are assessed, is replaced by concepts such as innovation markets, innovation spaces or competition in innovation.[96] The anticompetitive effect of conduct is assessed in relation to the innovative potential of the affected rival. This may include *inter alia* her innovation capabilities, access to tangible and intangible resources, past record of innovation, and patent activity.[97] Under this approach, innovation is perceived as a dynamic process whose optimal functioning is ensured by targeted antitrust interventions.[98] Let us illustrate the rationale for this analysis by referring to a hypothetical.

Suppose an innovation race between two manufacturers of *originator* medicines. They are not competing within the framework of existing markets but through parallel pipeline projects that aim to satisfy a single unmet therapeutic need. In other words, they race to establish a novel market. This is a very common scenario in the pharmaceutical industry.[99] Now imagine that one of the two competitors patents strategically or refuses to license an upstream technology to its R&D rival, thereby allegedly blocking her pipeline project. Protecting innovation through the toolbox of competition law in such factual circumstances is indeed challenging. Pharmaceutical R&D is characterized by a high degree of scientific and

[96] The concept of innovation markets originated in the US, see Richard J. Gilbert & Steven C. Sunshine, *Incorporating Dynamic Efficiency Concerns in Merger Analysis: The Use of Innovation Markets*, 63 Antitrust L.J. 569 (1994). In Europe, the innovation market framework has not played a substantial role in antitrust enforcement. The impact of conduct on innovation has been rather assessed through the lens of innovation spaces (e.g., Case M.7932 – *Dow/DuPont,* paras 342-352) or competition in innovation (e.g., Case M.8955 – Takeda/Shire, para 94). For a broader discussion on these concepts, see OECD (2023), supra note 90, 23-28 and Victoria H.S.E Robertson, COMPETITION LAW'S INNOVATION FACTOR: THE RELEVANT MARKET IN DYNAMIC CONTEXTS IN THE EU 145-151 (Hart Publishing, 2020).

[97] In relation to the role of capabilities assessment in competition law enforcement, see Nicolas Petit and David Teece, *Capabilities Checklist for Mergers with Nascent Competitors*, 14(3) Journal of European Competition Law and Practice 135 (2023) and Federico, Morton and Shapiro, supra note 40, 146-150.

[98] For a criticism of this theory, see Colomo, supra note 80, 214-218 (arguing against the direct introduction of innovation considerations into antitrust analysis. This approach is criticized on the grounds that it is speculative, modifies competition law into a parallel regime for promoting innovation and fine-tuning markets, and creates conditions for arbitrariness in administrative action.)

[99] For instance, the intense PCSK9 inhibitors development race between Amgen on the one side, and Sanofi and Regeneron on the other, ended in a lengthy patent battle that was only recently resolved by the US Supreme Court. See 598 U.S. (2023).

commercial complexity, serendipity and notoriously high failure rates.[100] This renders administrative interventions aimed at promoting innovation inherently prone to errors. Even patent offices, for instance, have been criticized for issuing weak or overly broad patents that impede rather than promote innovative activity.[101] Antitrust agencies are unlikely to be better equipped to regulate drug development races through administrative actions. In certain circumstances, they may succeed in dismantling the foreclosing effect of conduct as long as they engage in particularly sophisticated technological and economic analyses of the specific cases.[102] This, however, is a resource-intensive activity that also requires strong industry-specific expertise and data. Demonstrating an antitrust violation to the substantive standards under Articles 101 and 102 TFEU will accordingly be difficult. Unsurprisingly, the European antitrust precedents dealing with restraints on the development of pipeline medicines are concentrated in the field of merger control, which is by default probabilistic and forward-looking.

Let us turn back to the field of biosimilars. Their market entry represents a mixture of price and innovation competition. Biosimilar manufacturers are incentivized to differentiate their products from the bio-originator and from other biosimilars *only* in ways compatible with

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[100] Different estimates converge on the conclusion that the overall success rate of pharmaceutical R&D revolves around 10%. Hay *et al.* report a success rate of 10.4%, Thomas *et al.* – at 7.9%, and Wong and Siah – at 13.8%. See Michael Hay, David W. Thomas, John L. Craighead, Celia Economides and Jesse Rosenthal, *Clinical development success rates for investigational drugs*, 32 Nature Biotechnology 40 (2014); David Thomas, Daniel Chancellor, Amanda Micklus, Sara LaFever, Michael Hay, Shomesh Chaudhuri, Robert Bowden, Andrew W. Lo, *Clinical Development Success Rates and Contirbuting Factors 2011–2020,* Biotechnology Innovation Organization, Informa Pharma Intelligence and QLS Advisors (2021), and Chi Heem Wong and Kien Wei Siah, *Estimation of clinical trial success rates and related parameters*, 20(2) Biostatistics 273, 277 (2019).

[101] Recently, in support of the respondents in the PCSK9 patent litigation, Pfizer stated that "[it] does not object to an innovator obtaining broad claims for genuine "breakthrough" inventions that satisfy the statutory requirements and are based on a disclosure that is commensurate in scope with the claims. However, the claims at issue are not commensurate with the inventors' contribution. They are a naked attempt to preempt future innovation and an unwarranted extension of the patent monopoly", Brief of Amicus Curiae Pfizer Inc. in Support of Respondents, 598 U.S. (2023).

[102] See, e.g., Velizar K. Kirilov, *Sector-Specific Essential Facilities Doctrine: A Tool for Remedying Distortions of Innovation Competition for Future Markets*, 45(1) European Competition Law Review 16 (2024) (proposing a sector-specific antitrust test for assessing the legality of input foreclosures that bar a competitor from introducing a market-creating innovation).

price competition. As suggested in previous sections, this may include drug delivery innovations or the development of superior clinical data. The results of these differentiation efforts may be particularly important for niche patients, such as children, the elderly, or patients with accompanying diseases. The prospect of effective commercialization of their own biosimilar also induces companies to invest in R&D capabilities similar to the ones needed for the development of purely innovative medicines. But biosimilar R&D will only occur if there is sufficient freedom to operate. As long as anti-competitive conduct limits that freedom by eliminating the prospect of effective market entry, competition policy has a regulatory role to play. To that end, competition authorities need to carefully consider the technological and commercial peculiarities of biosimilars. This can be done at two stages: (i) at the stage of priority setting and (ii) at the stage of substantive analysis of business conduct.

First, a degree of scrutiny is desirable in relation to unilateral and multilateral strategies that may inhibit the market entry of biosimilars. This is not only because of their own innovative potential which was subject to discussion in Section II. It is the credible threat of biosimilar competition that pressures originator manufacturers to innovate preemptively and further improve brand-name biologicals. These procompetitive responses may take two forms – a novel drug delivery technology or a biobetter.

The case of Merck's cancer immunotherapy Keytruda is one example of a preemptive drug delivery innovation. The drug is currently administered intravenously in a clinic. As US patent protection for the IV formulation is anticipated to expire in 2028, the company is currently carrying out clinical tests to introduce a subcutaneous formulation of the medicine.[103] Such will likely offer a competitive advantage over future IV biosimilars. This probability is suggested by the story of another blockbuster – Roche's oncology biological Tecentriq SC. A

[103] See Nick Paul Taylor, *Chasing Roche, Merck talks up subcutaneous Keytruda ahead of phase 3 data drop* (2023), available at https://www.fiercepharma.com/pharma/chasing-roche-merck-talks-subcutaneous-keytruda-ahead-phase-3-data-drop .

subcutaneous formulation of this IV-administered treatment was recently authorized for marketing by the European Commission. It significantly reduces treatment time for patients – from a 30-60-minute infusion with the IV formulation to approximately 7 minutes with the subcutaneous technology.[104]

Another procompetitive response to the threat of biosimilar entry may be the development of a biobetter. As a matter of definition, biobetters are "structurally and/or functionally altered" biologicals aimed to achieve "an improved or different clinical performance".[105] They preserve the therapeutic objective of the reference biological molecule but demonstrate a degree of superiority.[106] The latter can stem from "a difference in amino acid sequence or protein folding, from a chemical modification, from a difference in the humanization process, or from differences in the production process, such as a more efficient purification protocol".[107] A biobetter is by default more innovative than a biosimilar. At the same time, its development costs and risks are lower than those of developing a drug with a novel mechanism of action. Thus, its introduction may be an efficient strategy for preempting biosimilar competition.[108] If the therapeutic advantage of a biobetter over the state of the art is significant enough, it may effectively disrupt demand for biosimilars or considerably reduce their market share.[109]

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[104] Phalguni Deswal, *Subcutaneous drugs grant a new lease on life to checkpoint inhibitors* (2023), available at https://www.pharmaceutical-technology.com/features/subcutaneous-drugs-grant-a-new-lease-on-life-to-checkpoint-inhibitors/?cf-view

[105] Martina Weise, Marie-Christine Bielsky, Karen De Smet, Falk Ehmann, Niklas Ekman, Gopalan Narayanan, Hans-Karl Heim, Esa Heinonen, Kowid Ho, Robin Thorpe, Camille Vleminckx, Meenu Wadhwa, Christian K Schneider, *Biosimilars-why terminology matters*, 29(8) Nature Biotechnology 690, 691 (2011).

[106] Ashish Sharma, Nilesh Kumar, Baruch D. Kuppermann, *Bandello Francesco and Anat Loewenstein, Biologics, biosilimars, and biobetters: different terms or different drugs?*, 33(7) Eye (Lond) 1032 (2019).

[107] Torres-Obreque, supra note 2, 66.

[108] See René Anour, *Biosimilars versus 'biobetters' – a regulator's perspective*, 3(4) Generics and Biosimilars Initiative Journal 166 (2014) (illustrating this hypothetical with the development of Roche's biobetter Gazyvara – "an anti-CD20 monoclonal antibody, which has shown superior efficacy in the treatment of chronic lymphocytic leukaemia (CLL) compared to its 'originator'…MabThera. Gazyvara gained EU marketing authorization for previously untreated CLL in 2014 – before biosimilar candidates of [MabThera] managed to finish their development programmes".)

[109] Malgorzata Kesik-Brodacka, *Progress in Biopharmaceutical Development*, 65(3) Biotechnology and Applies Biochemistry 306, 308 (2018) (noting that "the development of biobetters requires more extensive research

As pipeline biosimilars may themselves be a source of innovation, they arguably exert a stronger pressing effect on originator manufacturers compared to generics. Apart from inducing follow-on improvements in established medicines, biosimilar entry reduces the overall health expenditure and curbs the supra-competitive profits of biological manufacturers. This frees resources for public funding of R&D in areas of unmet therapeutic needs and incentivizes originator manufacturers to seek novel marketing opportunities in the long run. Incentives for developing breakthrough and disruptive products are accordingly generated. This incentive mechanism seems to be well understood in the field of small molecules.[110] It is even to a greater extent relevant to biopharmaceutical markets.

Second, from a substantive perspective, promoting biosimilar innovation through the means of competition policy is facilitated by the specificities of the biosimilar innovation process. Although similar to the process of originator innovation, it is differentiated precisely in those aspects that dispel technological and commercial uncertainty. The inventive steps delivered by a patented originator and a biosimilar with a novel form of administration or improved thermal durability are indeed incomparable. The former innovations are in principle breakthrough or disruptive, while the latter are in principle incremental with potentially limited disruptive effects. These disruptive effects, however, do not necessitate resorting to concepts such as innovation markets, innovation spaces, or competition in innovation, to delineate the area affected by the restriction on the entry of innovative biosimilars. It will suffice to assess such biosimilars as a source of *potential competition to existing product markets*, encompassing the reference biologic and its already marketed biosimilars. As it is unlikely that the very first biosimilar of a reference biological will be innovative, there will certainly be an existing

than biosimilars, greatly increasing the costs of drug development. For this reason, it is crucial for a drug's success for that drug to have therapeutic benefits that are significant enough to justify its broad application, despite its potentially higher price").

[110] AstraZeneca, supra note 70, paras 338, 367, 664.

market, even where the reference biological is not part of it due to physicians' reluctance to switch existing patients.

Traditional theories of harm that translate harm to competition into innovation harm will suffice to effectively tackle potential conduct that restricts the market entry of innovative biosimilars, be it under Article 101, 102 TFEU or merger control. The higher observability of biosimilar innovation is a factor that potentially enables market incumbents who feel threatened to respond vigorously. They can respond either by a competing product improvement or by defensive strategies focused on rent-seeking and driven by a replacement effect.[111] The first type of response illustrates well-functioning markets. As long as competition law enforcers have to deal with the second scenario, they are enabled to substantiate their enforcement action by reference to the conduct's effect on potential competition in an existing market. Let us illustrate this with an example.

Suppose that a biological manufacturer disparages a newly marketed biosimilar with a novel delivery mechanism in its communication with physicians. Competition authorities certainly do not need to resort to innovation-centric theories of antitrust harm, akin to the ones necessary for regulating originator drug development races. As soon as it is established that the disparaging conduct is capable of eliminating a potential competitor from the market, that conduct falls within the ambit of Article 102 TFEU and the marketing of the innovative biosimilar can be protected. This assessment is applicable also to potential Article 101 TFEU cases and – even to a higher extent – to merger control. In essence, the peculiar nature of biosimilar innovation facilitates the integration of dynamic considerations into antitrust analysis.

[111] Kenneth J. Arrow, Economic Welfare and the Allocation of Resources to Invention in NATIONAL BUREAU OF ECONOMIC RESEARCH, THE RATE AND DIRECTION OF INVENTIVE ACTIVITY 609 (Princeton University Press, 1962).

V. CONCLUSION

Pharmaceutical innovation policies should certainly focus on the promotion of disruptive and breakthrough innovations in treatments. Yet, the innovation process in some segments of the industry is inevitably more static and focused on sequential improvements in existing products. While pharmaceutical companies have been criticized for investing resources in incremental innovations rather than focusing on breakthrough discoveries, this represents a legitimate business model in the field of biosimilars. Their manufacturers are constrained by a mixture of regulatory, technological, and commercial factors in their ability to compete with products of a higher inventive step – at least in the short term. At the same time, they are incentivized to differentiate their products for the purpose of capturing a market share, which, in some cases, can have a substantial added value to certain groups of patients. In cases where disruptive and breakthrough innovations are unfeasible, competition policy can effectively ensure that at least incremental developments reach patients in a timely manner.

Competition law enforcers should stay vigilant for anticompetitive strategies that may block or delay the market entry of potentially differentiated biosimilars. To that end, a dynamic framework for assessing the impact of conduct on the commercialization of innovative biosimilars needs to be developed. As long as it is focused on assessing potential competition in existing markets, it can seamlessly meet both ex-post and ex-ante enforcement standards and ensure optimal levels of biosimilar innovation in the EU internal market.