The Economics of Biosimilar Drugs and New Considerations in Intellectual Property and Antitrust Litigation

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Introduction

Intellectual property and antitrust litigation involving pharmaceuticals has long been widespread in the U.S. The vast majority of brand drugs experiencing initial generic entry over the past decade had one or more patent challenges associated with generic drug applications.[2] IP litigation involving these patent challenges has frequently led to subsequent antitrust lawsuits alleging that competition from generic drugs was delayed by the filing and litigating of fraudulent patents or reverse-payment settlements of the IP litigation.[3] Recently, the emergence of biosimilar drugs has raised a number of questions around how this litigation will evolve and how it will differ from the experience of traditional brand and generic drugs. To date, there is little evidence on biosimilar competition in the U.S.; as of May 2018, the U.S. Food and Drug Administration (FDA) had approved ten biosimilar drugs referencing seven different brand biologics,[4] only three of which have so far launched in the U.S. Although biosimilar approval is still in its infancy, key differences between large-molecule (biologic) and traditional small-molecule (chemical) drugs distinguish their economics, which are likely to result in differences in the nature of competition and litigation surrounding biosimilar drugs.

Biologics dominate the list of top selling drugs in the U.S., creating potentially substantial economic incentives for manufacturers to develop biosimilars. The growing importance of biologic drugs, both in terms of therapeutic benefits and financial costs to payers and patients, also has triggered substantial interest from regulators and insurers in the potential for biosimilars to reduce costs. However, the complexity and costs of developing biosimilar drugs, along with substantially different regulatory and market conditions will shape biosimilar competition. Understanding what factors will impact biosimilar competition and how those factors will evolve over time will play a key role in the economic considerations of future IP and antitrust litigation.

Regulatory and Institutional Factors

The nature of competition between branded and generic drugs was defined by the Drug Price Competition and Patent Term Restoration Act of 1984 (generally referred to as the Hatch-Waxman Act),[5] which established a pathway for generic drug entry for small-molecule drugs. For such drugs, it is typically possible to fully characterize the structure of the drug molecule and consistently reproduce that structure through chemical synthesis. As such, the FDA does not usually require clinical trials for generic drug approval, thereby reducing costs associated with drug development, and often rates generics as therapeutically equivalent to the reference brand drug.[6]

The determination of therapeutic equivalence has important implications on the economics of pharmaceutical competition. A series of regulatory and institutional factors go into effect that are designed to promote switching from brand drugs to their less-expensive generic equivalents, such as mandatory or encouraged pharmacy substitution of generics to fill prescriptions written for the brand and preferred placement on insurance formularies. These mechanisms treat generics as interchangeable with the reference brand drug, and facilitate rapid generic penetration without the generic manufacturer needing to engage in any marketing or promotional efforts. On average, the generic captures 70 percent of sales from the brand in the first full month of generic entry, and 88 percent within one year following initial generic entry.[7] The substantial loss in sales that often immediately follows generic entry is characterized as the "patent cliff." Typically, multiple generic versions of a drug enter the market (particularly for drugs with large brand sales prior to generic entry),[8] and on average, competition drives the generic price down to a 78 percent discount from the brand price within one year following entry.[9] While the actual generic penetration and generic price discounts vary substantially from drug to drug and across therapeutic areas and customers, the typical pattern of substantial generic penetration and price discounts underlies many economic arguments associated with pharmaceutical IP and antitrust litigation.

However, biologics are very different from small-molecule drugs. Biologics are produced as cultures of living cells resulting in large and highly complex molecules. As such, the structure of the drug and the related safety and efficacy can depend on a relatively

narrowly defined manufacturing process. For brand biologics, this manufacturing process is typically protected by an array of patents and trade secrets.

The Biologics Price Competition and Innovation Act of 2009 (BPCIA) paved the way for biosimilar entry. The BPCIA was enacted as part of the Patient Protection and Affordable Care Act of 2010 (ACA), and amends the Public Health Service Act (PHS Act) and other statutes to create an abbreviated pathway for FDA to approve biosimilars.[10] This legislation is similar in spirit to the Hatch-Waxman Act in that both aim to balance IP and other protections that encourage the innovation of new drugs with facilitating entry of generic and biosimilar competitors to potentially reduce drug costs. However, there are important differences in the implementation of the BPCIA compared to the Hatch-Waxman Act, reflecting the greater complexity of biologic drugs and having implications for the nature of competition and litigation between biologics and their biosimilars.

Unlike small-molecule drugs, the large and highly-complex molecules that make up biologic drugs cannot be completely characterized, which can result in many potential differences between a biosimilar and the reference brand biologic. Even small differences may impact the safety and efficacy characteristics of the drug. Consequently, the FDA requires far more evidence to support a biosimilar approval, including costly clinical trials in humans.[11] To date, the FDA has not approved any biosimilars as therapeutically equivalent to the reference brand biologic. As such, currently approved biosimilars are not treated as interchangeable with their reference brand biologics and do not benefit from the same institutional mechanisms, such as pharmacy substitution, that drive conversion from brand to generic sales in small-molecule drugs.

Further, whereas prescriptions for most small-molecule drugs are filled in pharmacies, where mechanisms such as pharmacy substitution drive generic uptake, biologic drugs are frequently administered by nurses and physicians. Pharmacy substitution does not apply for drugs administered by healthcare providers, and uptake of biosimilars in this setting is dependent on an active decision by the prescribing physician to use the biosimilar over the brand biologic. Variability between innovator brand and biosimilar drugs, the lack of a therapeutic-equivalence rating for the biosimilars, and the physician's role in administering many biologic drugs all suggest that biosimilar manufacturers will need to take a more active role in promoting their product than is required for generic drug manufacturers. The different economic factors characterizing biosimilars may therefore result in biosimilar competition more closely reflecting traditional brand-brand drug competition than brand-generic competition.

Economic Implications for Biosimilar Competition

The characteristics of and regulatory framework for biologic drugs have important implications on the economics of competition from biosimilars.

More limited biosimilar entry:

The costs and complexity of developing, obtaining FDA approval, and producing biosimilar drugs is likely to limit the number of competing biosimilar entrants. Pfizer states that the cost of developing a biosimilar drug is over $100 million (over 5 to 9 years), compared to $1 to $2 million (over 2 years) to develop a generic drug.[12] Many fewer companies will have the financial ability and technological know-how to develop biosimilars. For example, to date there are only two biosimilars approved for Humira, a drug that had over $18 billion in sales in 2017.[13]

Effort required for market acceptance:

The FDA has yet to rate a biosimilar as therapeutically equivalent to the brand biologic, and requires additional clinical trials (at additional costs) to obtain such a rating.[14] Furthermore, biologic drugs are typically injected or infused, and many are administered by healthcare providers during out-patient visits or in-patient hospital stays. Generic substitution laws do not apply in cases where a healthcare provider administers the drug, and biosimilars may not benefit from a therapeutic-equivalence rating in such cases. Rather, biosimilar adoption may require more marketing and promotional effort by the manufacturer, and exhibit a far slower rate of biosimilar uptake than for generics. Many of the manufacturers developing biosimilars are traditionally brand drug manufacturers, including Pfizer, Amgen, Merck, and Allergan. These companies have a long history of marketing drugs, and such activities may be critical to encouraging payers to implement formulary/managed care mechanisms that encourage switching between the innovator brand and biosimilar, and to increase physician and patient comfort with biosimilars.

Price discounts may be constrained:

The higher costs of biosimilar development and production, the costs of marketing and promoting the biosimilar, and the potential for fewer biosimilar entrants may all limit the extent of price discounts offered by biosimilar entry. In addition, as the administration of biologics often require infusion or injection, they are typically administered by healthcare providers and therefore reimbursed as medical, rather than pharmacy benefits. The different reimbursement structure associated with medical benefit reimbursement of drugs, and the evolving Medicare Part B structure for biologic and biosimilar reimbursement can all impact price competition.[15]

Evidence from Biosimilar Entry

The anticipated growth in available biosimilars in the U.S. represents a massive change and one of the most impactful events to hit the drug industry in decades. Although the FDA has only approved 10 biosimilar drugs as of May 2018, many more are anticipated over the next few years. As of December 2017, 59 biosimilars were in the FDA Biosimilar Product Development Program,[16] and other biosimilars have applications currently under review at the FDA.

Table 1: FDA Approved Biosimilars

Brand Biologic (Manf.)	Biosimilar (Manf.)	Biosimilar Approval	Biosimilar Launch
Neupogen (Amgen)	Zarxio (Sandoz)	Mar 2015	Sep 2015
Remicade (Janssen)	Inflectra (Hospira)	Mar 2016	Nov 2016
	Renflexis (Samsung/Merck)	Apr 2017	Jul 2017
	Ixifi (Pfizer)	Dec 2017	—
Enbrel (Amgen)	Erelzi (Sandoz)	Aug 2016	—
Humira (AbbVie)	Amjevita (Amgen)	Sep 2016	—
	Cyltezo (Boehringer)	Aug 2017	—
Avastin (Roche)	Mvasi (Amgen/Allergan)	Sep 2017	—
Herceptin (Roche)	Ogivri (Mylan)	Dec 2017	—
Procrit (Janssen) / Epogen (Amgen)	Retacrit (Hospira)	May 2018	—

Note: Procrit and Epogen both have the same active ingredient, epoetin alfa.

The global market for biologic drugs has been forecasted to exceed $390 billion by 2020, with some analysts predicting substantial cost savings from biosimilars.[17] For example, a recent study by Rand Corporation estimates that biosimilars will generate cost savings of $54 billion in the U.S. from 2017 through 2026.[18] However, the speculative nature of such estimates given the limited experience of biosimilars in the U.S. to date is reflected in the study placing a wide range around that estimate of anywhere from $24 to $150 billion.

Table 2: U.S. Biosimilar and Average Generic Drug Prices and Shares

	Share of Sales	Price Discount from Brand
Generic Drug Average (1 year post launch)	88%	78%
Zarxio: biosimilar to Neupogen (2 years post launch)	34%	15%
Granix: quasi-biosimilar to Neupogen (4 years post launch)	25%	21%
Inflectra: biosimilar to Remicade (1 year post launch)	4%	15%

Source: Biosimilar drug outcomes, Symphony Health Solutions. Generic Drug Average, Grabowski et al. (2016).

The limited available evidence on biosimilar competition in the U.S. suggests a much more modest impact than that of generics. As summarized in Table 2, two years after its launch, the first approved biosimilar, Zarxio, had captured approximately 34 percent of the branded biologic, Neupogen, sales and was priced at a 15 percent discount to Neupogen. Granix a quasi-biosimilar form of Neupogen that launched in the U.S. in November 2013 has a similar experience as Zarxio. Even less traction was gained by the biosimilar Inflectra against its reference brand biologic Remicade. Inflectra gained less

than 10 percent share from Remicade in its first year on the market, at a similar 15 percent discount from the brand price.[19] It would be inappropriate to rely on the experience of just two biosimilars, Zarxio and Inflectra, to infer what all biosimilar competition may look like in the future. On the one hand, physicians and payers are still becoming familiar with biosimilars, and the lack of real-world experience may result in more cautious adoption for these early biosimilar drugs. On the other hand, the first biosimilars have targeted older and less complex biologic drugs, and even greater caution may apply as biosimilars enter for more complex biologics that may be more difficult to produce.

Biosimilar Litigation and Economic Considerations

As the structure of the biologic molecule (and associated safety and efficacy of the drug) is highly dependent on the manufacturing process,[20] brand biologics may be protected by an array of process patents and trade secrets. Therefore, IP litigation involving biosimilars may be associated with a far more complex array of patents, and far different considerations with respect to economic valuation of the patents both individually and as a whole, than has historically been the case for generic drugs.

Each of the ten FDA-approved biosimilars has triggered IP litigation with the brand biologic manufacturer. These lawsuits have sparked debate not only on the validity of the associated patents, but also on the process for patent litigation as set out in the BPCIA. The BPCIA lays out a process for a series of potentially complex private information exchanges among the biosimilar manufacturer and the reference product sponsor (i.e., innovator brand manufacturer) to determine which patents may be at-issue in the first phase of litigation – the so-called "Patent Dance." The Supreme Court has recently issued a ruling interpreting the Patent Dance as not being a mandatory requirement of the IP litigation process under the BPCIA.[21] The BPCIA also requires the biosimilar manufacturer to provide a 180-day "pre-market notification" before selling the biosimilar product, and allows for a second phase of litigation involving any patents not litigated in the first phase. The Supreme Court further ruled that the biosimilar manufacturer can issue the 180-day "pre-market notification" before receiving final FDA approval of the biosimilar product.[22]

Biosimilar manufacturers have made substantially different decisions regarding whether or not to pursue the Patent Dance, and when to launch their biosimilar. In the case of Zarxio, Sandoz chose to forego the Patent Dance, and to launch Zarxio on an "at-risk" basis while the patent litigation was ongoing, leaving open the potential for follow-on litigation should Amgen's patents on Neupogen be upheld and Sandoz be found to infringe on those patents. On the other hand, with Erelzi, Sandoz chose to engage in the Patent Dance, and also agreed to a consent preliminary injunction that enjoins it from launching Erelzi while the patent litigation is ongoing.[23]

In the case of Humira, AbbVie and Amgen chose to settle the patent litigation with an agreement allowing Amgen to launch its biosimilar Amjevita in the U.S. in January of 2023.[24] Although there is no current allegation of anticompetitive conduct, settlements

of patent disputes for generic drugs have long been associated with follow-on litigation with claims of antitrust violations and allegations of "delayed entry."

Finally, Pfizer/Hospira has brought an antitrust suit against Johnson & Johnson/Janssen alleging that Johnson & Johnson entered into exclusionary contracts with health insurers for its biologic Remicade that blocked sales of Pfizer's biosimilar Inflectra.[25]

While many of the initial biosimilar-related IP litigation cases have focused on a few key patents, future cases may become far broader in scope. For example, in two of its IP litigation cases for the biologic Humira, AbbVie has asserted a handful of patents; 10 patents in the first-phase litigation with Amgen, and 8 patents in first-phase litigation with Boehringer Ingelheim. However, in both cases AbbVie identified a much broader array of patents that it could potentially assert in second-phase litigation (51 patents in the case of Amgen's biosimilar, and 66 patents in the case of Boehringer Ingelheim's biosimilar).[26] The valuation of patents within this structure is likely to be far more complex than in the case of a typical small-molecule drug, and raise unique challenges in IP litigation involving biosimilars.

Remaining uncertainty and dispute regarding the provisions of the BPCIA, the complexity of patent litigation for biosimilars, and the uncertain economic framework for evaluating the impact of biosimilar entry may result in a wide range of outcomes and potential follow-on litigation.

Because of the many key differences between biologic and generic drugs, it is not exactly clear what the litigation landscape will look like for biosimilars in the future. However, given the complex manufacturing process and the array of associated patents, as well as the challenging nature of establishing "similarity" to the referenced brand, the potential for lawsuits is broad, and raises many questions for future litigation: As the patents asserted in infringement litigation can be a moving target, is "at-risk" entry more or less likely than for traditional generic drugs? How will the high costs associated with drug development and promotion for biosimilars affect the timing and strategies associated with an early launch? How will the different economics of competition between biologics and biosimilars inform the likelihood and methods by which patent litigation may be settled?

Developing an appropriate economic consideration of at-risk biosimilar entry, preliminary injunctions, patent litigation settlements, and alleged anticompetitive conduct (among other issues) requires an understanding of the unique characteristics of biosimilar competition and how it differs from the typical "patent cliff" story for generic drugs.

Endnotes

1 Richard Mortimer is a Managing Principal and Brian Ellman is a Vice President at the economic consulting firm Analysis Group, Inc.

2 For example, over 90 percent of the new molecular entity brand drugs experiencing initial generic entry between 2011 and 2014 had one or more patent challenges associated with a generic application. Henry Grabowski, Genia Long, Richard Mortimer, and Ani Boyo, *Updated Trends in US Brand-Name and Generic Drug Competition*, J. OF MEDICAL ECON., Apr. 2016 [hereinafter Grabowski et al. 2016].

3 Antitrust cases alleging delayed or diminished generic entry have also been associated with allegations of so-called "product hopping" activities by the brand, as well as the filing of allegedly "sham" citizen petitions.

4 The first U.S. biosimilar, Zarxio, was approved by the FDA in March 2015, three more followed in 2016, five in 2017, and one so far in 2018.

5 *See* Pub. L. No. 98-417, 98 Stat. 1585. The Hatch-Waxman Act is applicable to drugs approved under the Food, Drug, and Cosmetic Act (FD&C Act)--typically small-molecule drugs.

6 A finding of therapeutic equivalence indicates to the healthcare community that the generic drug is "expected to have the same clinical effect and safety profile [as the branded drug] when administered to patients under the conditions specified in the labeling." U.S. Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 38th Edition, 2018, p. vii, https://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf.

7 Grabowski et al. 2016, *supra* note 2.

8 Grabowski et al. 2016, *supra* note 2.

9 IMS Institute for Healthcare Informatics, *Price Declines after Branded Medicines Lose Exclusivity in the U.S.*, Jan. 2016.

10 *See* Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, § 7001-7003, 124 Stat. 119, 804-21 (2010) [hereinafter BPCIA]. Applications under this pathway are to demonstrate that "the biological product is biosimilar to the reference product [brand biologic]," utilizing the same mechanism(s) of action as the reference product (if known), and is to be used for the same condition(s) with the same route of administration, dose and strength as the reference product. Id. § 7002.

11 *See*, e.g., U.S. Food and Drug Administration, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*, Apr. 2015.

12 *See* https://www.pfizerbiosimilars.com/biosimilars-development. Pfizer's estimates for biosimilar development cost and timing are consistent with earlier estimates of 8 years and $100 to $150 million. *See* Ludwig Burger, *Battle over Biosimilar Drugs is only for the Brave*, REUTERS (July 2, 2010), https://uk.reuters.com/article/biosimilar-drugs/battle-over-biosimilar-drugs-is-only-for-the-brave-idUKLNE66102R20100702.

13 *See* Tamara Mathias, *AbbVie, Samsung Bioepis in Deal; Humira Biosimilar U.S. Release in 2023*, REUTERS (Apr. 5, 2018), https://www.reuters.com/article/us-abbvie-biogen/abbvie-in-deal-with-biogen-to-delay-humira-biosimilar-u-s-launch-to-2023-idUSKCN1HC1SP.

14 U.S. Food and Drug Administration, *Considerations in Demonstrating Interchangeability With a Reference Product*, Jan. 2017.

15 *See* Jackie Syrop, *CMS Reverses Its Policy on Biosimilar Reimbursement, Will Issue Unique J-Codes*, THE CENTER FOR BIOSIMILARS, Nov. 3, 2017, http://www.centerforbiosimilars.com/news/cms-reverses-its-policy-on-biosimilars-reimbursement-will-issue-unique-jcodes.

16 *See* U.S. Food and Drug Administration, "Cumulative number of biosimilar development programs in the BPD Program in the month," https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&status=public&id=CDER-RRDS-Number-of-biosimilar-dev-programs-in-BPD-Program&fy=2018.

17 *See* IMS Institute for Healthcare Informatics, *Delivering on the Potential of Biosimilar Medicines, The Role of Functioning Competitive Markets* at 1, Mar. 2016 (figures reported in Euros have been converted to U.S. dollars).

18 Andrew Mulcahy, Jakub Hlavka, and Spencer Case, *Biosimilar Cost Savings in the United States*, Rand Corporation Perspective, 2017.

19 Results reflect analyses of data from Symphony Health Solutions.

20 *See*, e.g., U.S. Food and Drug Administration, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry* at 5, Apr. 2015.

21 *See* Sandoz Inc. v. Amgen Inc., No. 15-1039 (U.S. June 12, 2017).

22 *See* id.

23 Limin Zheng, *The Biosimilar Patent Dance: What Can We Learn from Recent BPCIA Litigation?* Biosimilar Development, Guest Column, Mar. 6, 2018.

24 *See Amgen and AbbVie Agree to Settlement Allowing Commercialization of Amjevita,* https://www.amgen.com/media/news-releases/2017/09/amgen-and-abbvie-agree-to-settlement-allowing-commercialization-of-amgevita/.

25 Caroline Humer, *Pfizer Files Suit Against J&J Over Remicade Contracts*, REUTERS, Sept. 20, 2017, https://www.reuters.com/article/us-pfizer-trial-johnson-johnson/pfizer-files-suit-against-jj-over-remicade-contracts-idUSKCN1BV1S8.

26 *See* Complaint, *AbbVie Inc. v. Amgen Inc.*, No. 1:16-cv-00666 (D. Del. Aug. 4, 2016); Complaint, *AbbVie Inc. v. Boehringer Ingelheim International GMBH*, No. 1:17-cv-01065 (D. Del. Aug. 2, 2017).