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After Lull In Biosimilar IP Litigation, 2021 Could Bring Influx

By **Joshua Whitehill and Jay Deshmukh** (January 7, 2021, 5:35 PM EST)

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A biosimilar is biological product that is highly similar to and has no clinically meaningful differences from an existing approved reference biological product.

Much like the Hatch-Waxman Act did for generic drugs decades ago, the Biologics Price Competition and Innovation Act, enacted in 2010 as part of the Affordable Care Act, established an abbreviated regulatory pathway and unique patent litigation framework for biosimilars in the U.S.

Through this pathway, the U.S. Food and Drug Administration approved the first biosimilar in 2015 and progressively approved more biosimilars each year. To date, the FDA has approved a total of 29 biosimilars, of which at least 18 have entered the U.S. market.

In terms of market penetration and consumer cost savings,[1] 2020 was hailed by many analysts as a breakthrough year[2] and golden age [3] for U.S. biosimilars. According to a recent IQVIA report, biosimilars are poised to save the U.S. health care system $100 billion over the next five years[4] — a resounding success compared to where the U.S. was just a couple years ago.[5]

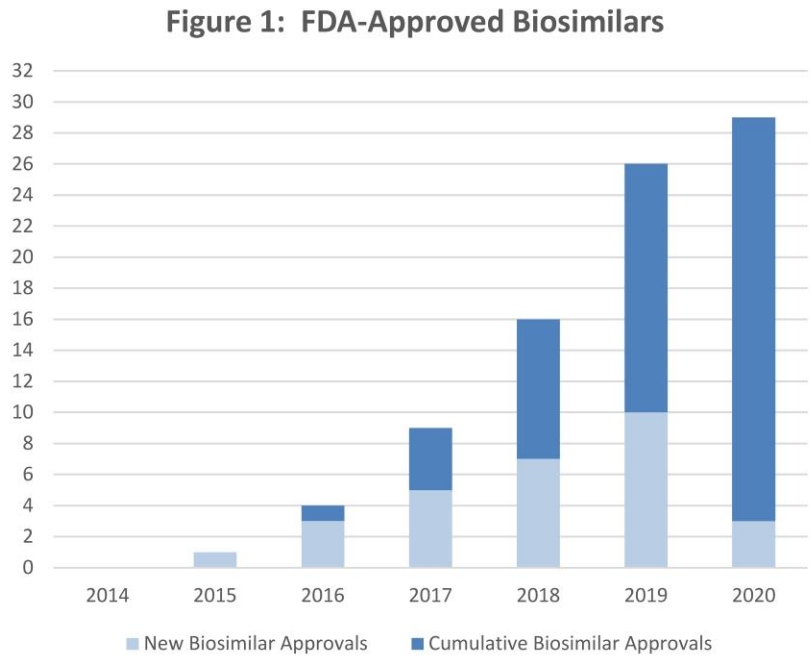
Notwithstanding this newfound market success, 2020 was an off year for U.S. biosimilars in terms of new regulatory approvals and patent litigation activity. This article examines the state of U.S. biosimilars and what this relative dearth of new approvals and litigation actually means.

At first blush, some might view this ostensible biosimilar cliff as a possible sign of withering interest in biosimilars in the U.S., but a deeper dive suggests that 2020 more likely represents the ebbing tide before the next big wave of biosimilars.

The State of Biosimilar Approvals and Launches

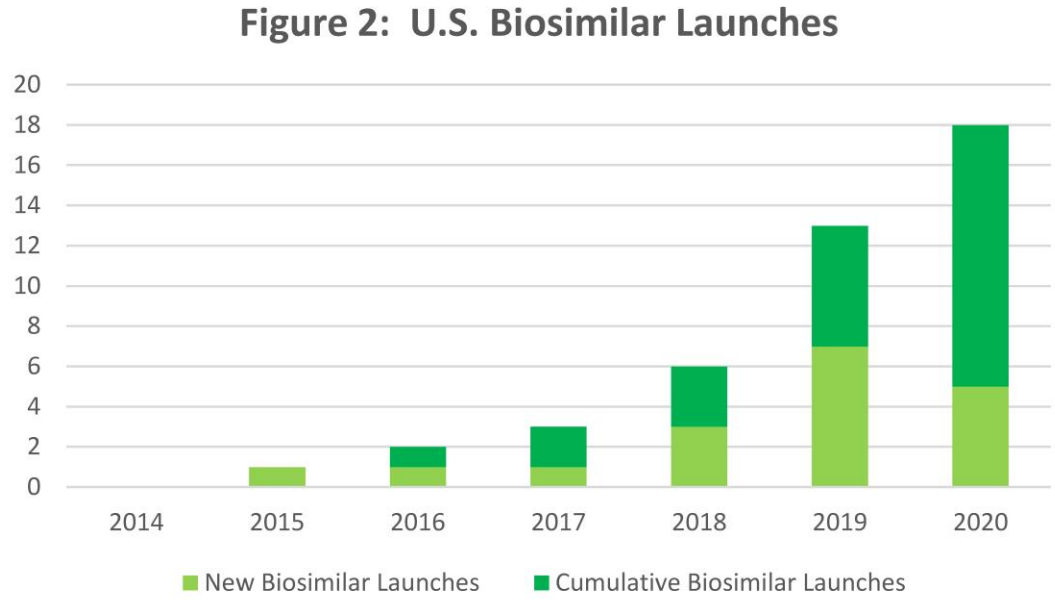
Biosimilar approvals increased steadily from 2015-2019, but last year saw a precipitous drop from a record 10 in 2019 to just three in 2020, a five-year low. In 2020, the following biosimilars received approval: Pfizer Inc.'s pegfilgrastim-apgf drug, Nyvepria, the fourth biosimilar of Neulasta; Mylan NV's adalimumab-fkjp drug, Hulio, the sixth biosimilar of Humira; and Amgen Inc.'s rituximab-arrx drug,

Riabni, the third biosimilar of Rituxan.



Although new approvals declined, new launches remained relatively high in 2020. Launching in 2020 were Pfizer's rituximab-pvvr drug, Ruxience, referencing Rituxan; Amgen's infliximab-axxq drug, Avsola, referencing Remicade; as well as three biosimilars of Herceptin: Pfizer's trastuzumab-qyyp drug, Trazimera; Celltrion Inc. and Teva Pharmaceutical Industries Ltd.'s trastuzumab-pkrb drug, Herzuma; and Samsung Bioepis Co. Ltd. and Merck & Co.'s trastuzumab-dttb drug, Ontruzant.

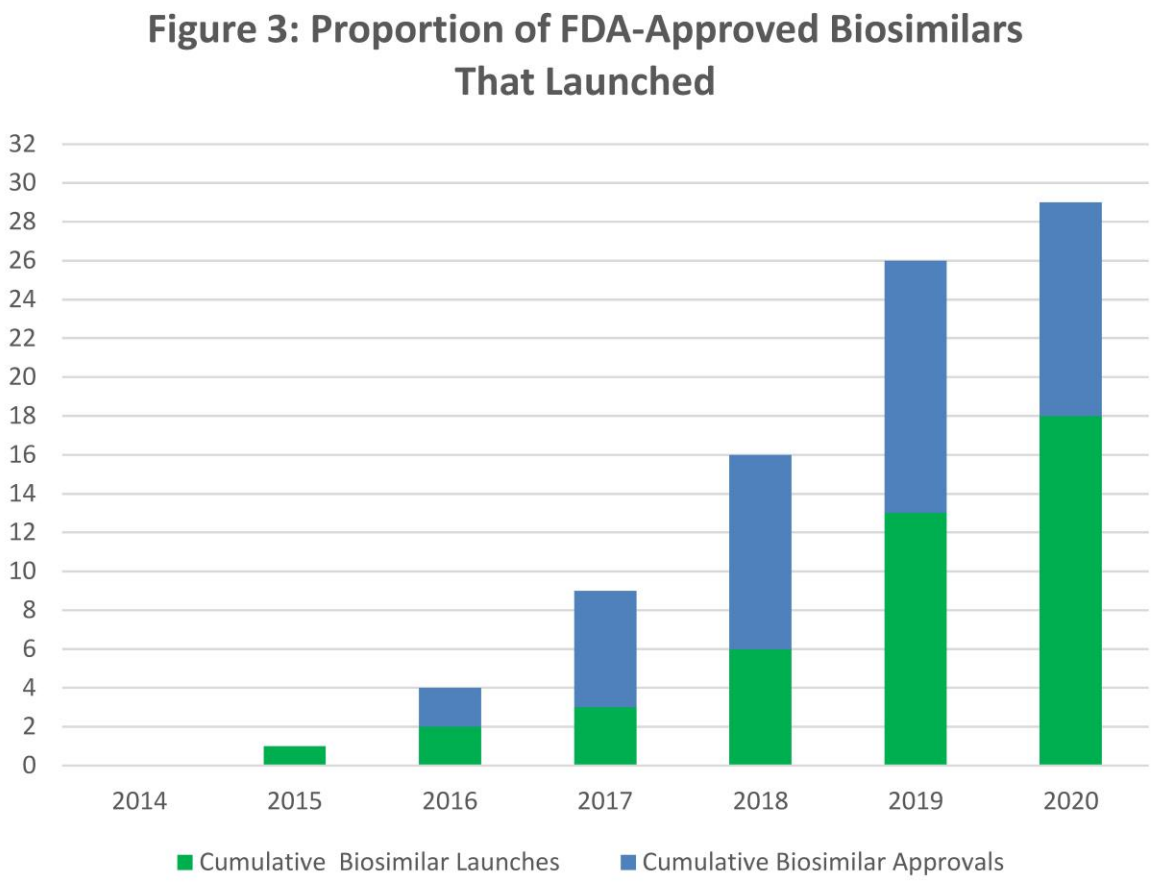
The five launches in 2020 reflected a slight drop from the record-setting seven in 2019 but were still the second most since the BPCIA's enactment.



Despite the generally upward trend in new launches, few biosimilar launches are anticipated for 2021,

mainly because most approved biosimilars have already launched.

Of the 29 approved biosimilars, 18 have launched; six are adalimumab biosimilars that cannot launch until 2023 pursuant to settlements; two are etanercept biosimilars that are held up by patent litigation; and one is a long-approved infliximab biosimilar, Ixifi, that Pfizer appears to have no intention to launch. With regard to the two remaining approved biosimilars, Amgen's rituximab-arrx drug, Riabni, is slated to launch this month, but Pfizer's launch plans for its pegfilgrastim-apgf drug, Nyvepria, currently in litigation, are unclear.



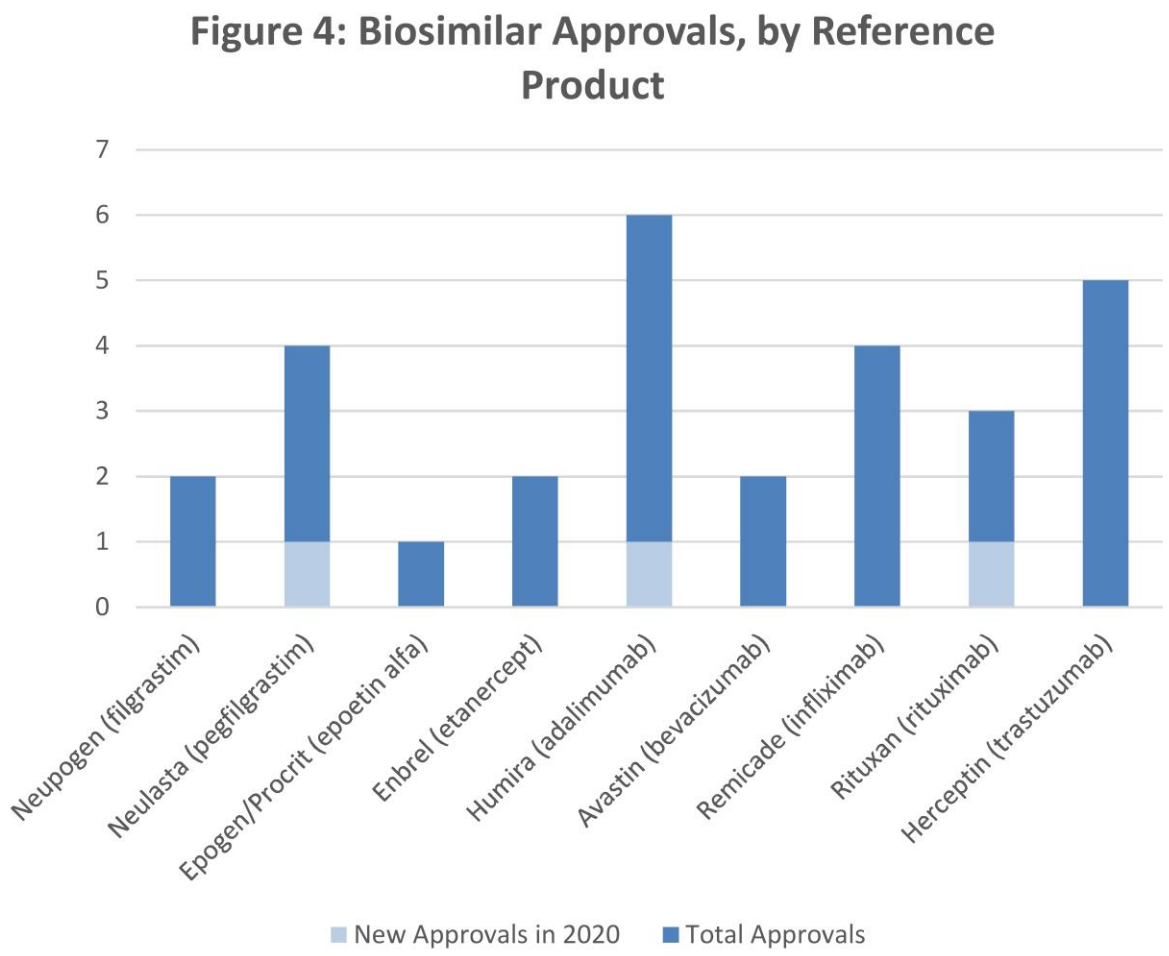
Still, it is possible that the FDA will approve one or more newly submitted biosimilar applications, i.e., abbreviated biologics license applications, or aBLAs, in 2021.

Some biosimilar developers announced that they submitted new aBLAs in 2020, including, for example, Bio-Thera Solutions Ltd. for bevacizumab; collaborators Mylan and Biocon Ltd. for bevacizumab; Centus Biotherapeutics Ltd. and Fujifilm Kyowa Kirin Biologics Co. Ltd. for bevacizumab; Teva Pharmaceuticals' and Alvotech ehf. for adalimumab; and Samsung Bioepis and Biogen Inc. for ranibizumab.

The ranibizumab application is noteworthy because it is the first of its kind[6] and may mark the beginning of the next big wave of biosimilars. The 29 biosimilars that the FDA has already approved concern just nine reference biologics, all of which are current or former blockbusters.

Indeed, although the FDA approved 13 biosimilars over the past two years, not a single one concerned a new reference molecule. Because these nine reference products are all older biologics, biosimilars were

not blocked under the BPCIA's four-year data exclusivity[7] or 12-year market exclusivity[8] provisions and many of the reference biologics' original patents had already expired or were close to expiring when the aBLAs were filed.



In contrast, ranibizumab and a slew of other biologics facing the looming prospect of biosimilars are generally newer products with later expiring regulatory exclusivities and patent estates. Accordingly, a plethora of new biosimilar molecules are expected over the next few years, as reference biologics near exclusivity and patent expiries. In addition to Samsung Bioepis and Biogen, at least two other groups are reportedly preparing to submit ranibizumab aBLAs in 2021.

This year could also see the first aBLAs for biosimilars of the insulin aspart drug, Novolog, and the aflibercept drug, Eylea.

The near future, though not necessarily 2021, may further bring aBLAs referencing Amgen's denosumab drug, Prolia/Xgeva, Janssen Biotech Inc.'s ustekinumab drug, Stelara, Alexion Pharmaceuticals Inc.'s eculizumab drug, Soliris, Biogen's natalizumab drug, Tysabri, Genentech Inc. and Novartis Pharmaceuticals Corp.'s omalizumab drug, Xolair, and AbbVie Inc.'s onabotulinumtoxinA drug, Botox, among others.

The State of Biosimilar Litigation

The BPCIA's patent litigation procedures are triggered when the FDA accepts an aBLA for review. Naturally, the explosion of aBLA submissions beginning in 2014 was followed closely by a litany of patent litigations under the BPCIA, as originators of biological products sought to protect their market positions against biosimilar competition.

But the corresponding wave of new litigation peaked in 2018 and has since dissipated. There are a number of reasons for this phenomenon. First, after a huge influx of BPCIA cases in 2017-2018 — 15 total — fewer new cases under the BPCIA were filed in 2019-2020 — just three each year.

Second, of the 29 BPCIA cases ever filed, 14 settled, and six concluded with a final judgment or dismissal over the course of 2018-2020 alone. Over the past two years, 15 case conclusions have far outpaced six new filings, and, as a result, only five BPCIA litigations remained pending as of Dec. 31, 2020.

Figure 5: BPCIA Litigation Commencements and Conclusions

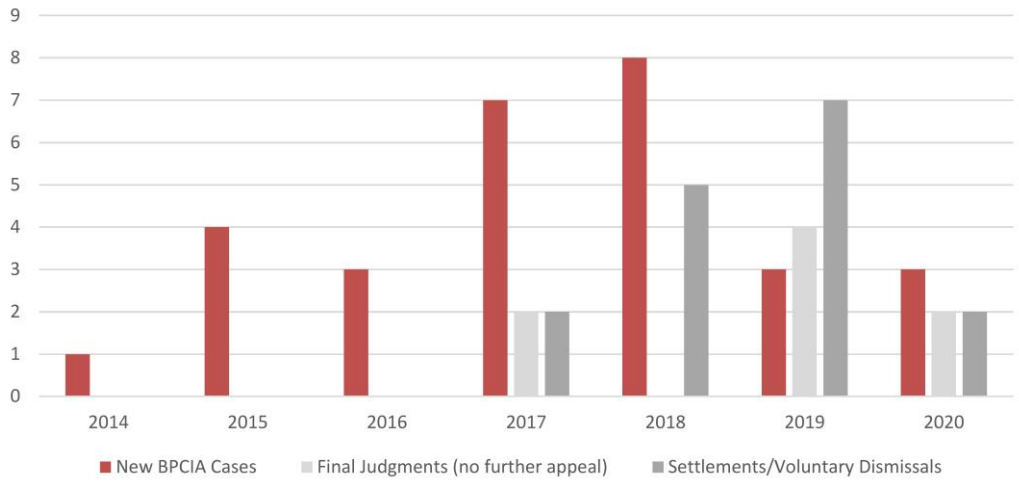
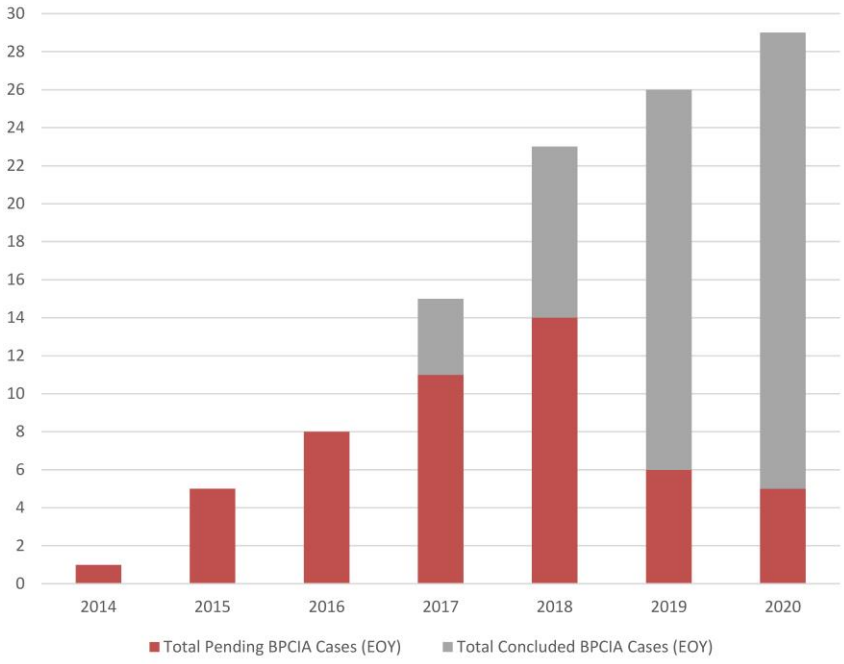


Figure 6: Remaining BPCIA Cases



New and Pending Litigation

Last year brought three new BPCIA litigations. First, in Amgen v. Hospira Inc., filed on Feb. 11, 2020, in the U.S. District Court for the District of Delaware,[9] Amgen sought to block Pfizer and its Hospira subsidiary from marketing a biosimilar of its pegfilgrastim drug, Neulasta.

Second, in Genentech v. Samsung Bioepis, filed on June 28, 2020,[10] Genentech sought to block Samsung Bioepis from marketing its biosimilar of its bevacizuma drug, Avastin. Both of these cases are in discovery and scheduled for trial before U.S. District Judge Colm Connolly of the District of Delaware in July 2022 and July 2023, respectively.

The third new BPCIA litigation is Genentech v. Centus, which was filed on Nov. 12, 2020 in the U.S. District Court for the Eastern District of Texas, and is still in the pleadings phase.[11] Genentech is seeking to block collaborators Centus and Fujifilm Kyowa Kirin Biologics from marketing an Avastin biosimilar. This is the first BPCIA litigation in Texas, as well as the first for these biosimilar developers.

Additionally, two other BPCIA litigations remain pending from previous years. The first, another Amgen v. Hospira case in the District of Delaware,[12] concerns Hospira's already marketed filgrastim-aafi biosimilar, Nivestym, and is scheduled for a jury trial before Judge Connolly on May 17.

Lastly, Immunex Corp. v. Samsung Bioepis,[13] which concerns an etanercept biosimilar of Enbrel, was filed in 2019 in the U.S. District Court for the District of New Jersey but has been administratively stayed, subject to a confidential stipulation, since January 2020.

Concluded Litigation

Two BPCIA litigations ended in settlement last year. In each case, Genentech sued Amgen for seeking FDA approval to market a biosimilar of either the trastuzumab drug, Herceptin, or the bevacizumab drug, Avastin .

In both cases, Amgen signaled that it intended to launch, and Genentech sought temporary restraining orders and preliminary injunctions, though on different grounds in each case. Judge Connolly denied Genentech's motions, enabling Amgen to launch both biosimilars. Genentech filed interlocutory appeals, but ultimately was unsuccessful.

First, on March 6, 2020, the U.S. Court of Appeals for the Federal Circuit affirmed, without opinion, the District of Delaware's denial of Genentech's motion to enjoin sales of Amgen's trastuzumab-anns drug, Kanjinti.[14] Judge Connolly had denied the motion primarily because Genentech unduly delayed in seeking supposedly emergency injunctive relief.[15]

Then, on July 6, 2020, a Federal Circuit panel affirmed the District of Delaware's decision not to block sales of Amgen's bevacizumab-awwb drug, Mvasi. The panel upheld the lower court's ruling[16] that Amgen had complied with the BPCIA's notice of commercial marketing provision[17] when it provided its notice years earlier, and that subsequent aBLA supplements neither negated the prior notice nor necessitated a new notice.[18] Both cases settled by the next day.

Two other BPCIA cases reached final judicial resolutions in 2020. First, on March 5, in Janssen v. Celltrion, a case concerning Celltrion and Hospira's infliximab-dyyb biosimilar, Inflectra, the Federal

Circuit affirmed, without opinion, the U.S. District Court for the District of Massachusetts' grant of summary judgment that the defendants' product did not infringe Janssen's patent under the doctrine of equivalents, Janssen's sole infringement theory.[19]

In granting summary judgment, the lower court applied the ensnarement doctrine to bar Janssen's equivalence theory, finding that the range of equivalents necessary to cover the biosimilar would improperly ensnare prior art embodiments.[20]

In the second case, Immunex v. Sandoz, on July 1, a Federal Circuit panel affirmed the New Jersey district court's judgment in a case concerning Sandoz's etanercept-szzs biosimilar, Erelzi. In a split 2-1 decision, the panel upheld the validity of Immunex's patents in spite of Sandoz's obviousness-type double patenting and obviousness challenges.

In rejecting Sandoz's double patenting defense, the majority held that Immunex did not hold all substantial rights to the reference patent, notwithstanding Immunex's "paid-up, irrevocable, exclusive license" with the first right to rectify any alleged infringement and option to purchase, and, therefore, the asserted and reference patents were not commonly owned, as required for double patenting to apply.

The full Federal Circuit denied rehearing en banc shortly thereafter. Consequently, Sandoz is enjoined from marketing its FDA-approved biosimilar until patent expiry in 2029, potentially securing Immunex 31 years of exclusivity for Enbrel following its FDA approval in 1998. This case is significant in that it is the first in which a biologics maker has fully succeeded in blocking a biosimilar through the BPCIA procedures, absent a settlement.

In 2020, the Federal Circuit also resolved several appeals of inter partes review decisions relating to biosimilar products, though in most cases the petitioner biosimilar developer had already settled before the Federal Circuit issued its decision.[21]

Coinciding with 2020's BPCIA litigation drop-off, it appears that no clearly biosimilar-related IPR petitions were filed in 2020. Since the early days of BPCIA litigation, biosimilar developers have flooded the U.S. Patent and Trademark Office with IPR petitions — typically more than a dozen each year.

The apparent disappearance of IPRs in 2020 is not necessarily surprising, however, and likely is only temporary. The nine reference biologics for which biosimilars are approved have already been heavily litigated in both the courts and USPTO, and a considerable proportion of those cases settled. Moreover, many of the early biosimilar-related IPRs concerned now-expired patents to technologies fundamental to the biologics industry, e.g., the Cabilly patents.[22]

In short, there were essentially no patents that biosimilar developers needed to challenge via IPR in 2020, but the impending wave of new biosimilars is likely to bring with it a new IPR wave.

Anticipated New Litigation

Coming off the surge in biosimilar litigation activity just a few years ago, the current lull does not appear to be a reflection of things to come. Given the flourishing U.S. market and the bursting biosimilar pipelines and clinical trial activity, the future looks bright for biosimilars in the U.S.

If anything, 2020 reflects the waning days of the first major wave of biosimilars, during which biosimilar

developers inundated the FDA, the courts and the USPTO with submissions, culminating in 29 approvals and 29 BPCIA litigations concerning just nine reference biologics over about six years. But new biosimilars — and, consequently, new BPCIA litigations — are likely around the corner.

As 2021 begins, many biosimilar developers have already filed or are poised to file new aBLAs for previously unlitigated biologics, such as the ranibizumab drug, Lucentis, the aflibercept drug, Eylea, the insulin aspart drug, Novolog, and potentially others — any of which could spur new litigation. Additionally, new BPCIA litigations concerning the pegfilgrastim drug, Neulasta, the bevacizumab drug, Avastin, the adalimumab drug, Humira, and the etanercept drug, Enbrel, can reasonably be expected in 2021.

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[1] See, e.g., The Center for Biosimilars, Amgen Sees Biosimilar "Give and Take" (May 2, 2020), available at https://www.centerforbiosimilars.com/view/amgen-sees-biosimilar-give-and-take-.

[2] See, e.g., Joshua Cohen, Will 2021 Be Another Break-Through Year For Biosimilars?, Forbes (Dec. 3, 2020), available at https://www.forbes.com/sites/joshuacohen/2020/12/03/will-2021-be-another-break-through-year-for-biosimilars/.

[3] See, e.g., Anna Rose Welch, From "Musty Towel" To "Golden Age:" Biosimilars In 2021 And Beyond, Life Science Leader (Dec. 1, 2020), available at https://www.lifescienceleader.com/doc/from-musty-towel-to-golden-age-biosimilars-in-and-beyond-0001; Arlene Weintraub, Pfizer, Amgen will rake in billions during 'golden age' for biosimilars: analyst, Fierce Pharma (Aug. 5, 2020), available at https://www.fiercepharma.com/pharma/pfizer-amgen-will-rake-billions-during-golden-age-for-biosimilars-analyst.

[4] The IQVIA Institute, Biosimilars in the United States 2020–2024 Competition, Savings, and Sustainability (Sept. 29, 2020), available at https://www.iqvia.com/insights/the-iqvia-institute/reports/biosimilars-in-the-united-states-2020-2024; see also Amgen, 2020 Biosimilars Trends Report (Oct. 21, 2020), available at https://www.amgen.com/stories/2020/10/where-biosimilars-are-headed-in-the-us.

[5] See, e.g., Peter B. Bach & Mark Trusheim, Time to Throw In the Towel on Biosimilars, Wall Street Journal (Aug. 21, 2019), available at https://www.wsj.com/articles/time-to-throw-in-the-towel-on-biosimilars-11566428299; Joshua Cohen, In U.S. Biosimilars Run Into More Roadblocks, Forbes (Sept. 12, 2019). Cf. Kelly Davio, Throwing in the Towel on Biosimilars Wouldn't Be Easy, Expert Says, The Center for Biosimilars (Sept. 5, 2019), available at https://www.centerforbiosimilars.com/view/throwing-in-the-towel-on-biosimilars-wouldnt-be-easy-expert-says; Richard Saynor, Biosimilars in the US: Time to stop the towels blocking the deckchairs, LinkedIn (Aug. 28, 2009), available at https://www.sandoz.com/news/biosimilars-us-time-stop-towels-blocking-deckchairs.

[6] Collaborators Coherus Biosciences, Inc., Bioeq AG, and Formycon AG were actually first to submit a ranibizumab aBLA, but they withdrew the application in early 2020 to address FDA data requests. See

Formycon AG Press Release, Formycon Informs about the Current Status of the BLA Review Process of the Lucentis® Biosimilar Candidate FYB201 (Feb. 4, 2020), available at https://www.formycon.com/en/press-release/formycon-informs-about-the-current-status-of-the-bla-review-process-of-the-lucentis-biosimilar-candidate-fyb201/.

[7] 42 U.S.C. § 262(k)(7)(B).

[8] 42 U.S.C. § 262(k)(7)(A).

[9] Amgen Inc. v. Hospira, Inc., Civil Action No. 20-cv-201 (D. Del.).

[10] Genentech, Inc. v. Samsung Bioepis Co. Ltd., Civil Action No. 20-cv-859 (D. Del.).

[11] Genentech, Inc. v. Centus Biotherapeutics Limited, Civil Action No. 2:20-cv-361 (E.D. Tex.).

[12] Amgen Inc. v. Hospira, Inc., Civil Action No. 18-cv-1064 (D. Del.).

[13] Immunex Corp. v. Samsung Bioepis Co., Ltd., Civil Action No. 2:19-cv-11755 (D.N.J.).

[14] Genentech, Inc. v. Amgen Inc., 796 F. App'x 726 (Fed. Cir. 2020).

[15] Genentech, Inc. v. Amgen Inc., No. 18-924-CFC, 2019 WL 3290167 (D. Del. July 18, 2019).

[16] Genentech, Inc. v. Immunex Rhode Island Corp., 395 F. Supp. 3d 357 (D. Del. 2019).

[17] 42 U.S.C. § 282(l)(8)(A) states: "The subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)."

[18] Genentech, Inc. v. Immunex Rhode Island Corp., 964 F.3d 1109, 1112 (Fed. Cir. 2020) ("A biosimilar applicant that has already provided Section 262(l)(8)(A) notice regarding its biological product need not provide another notice for each supplemental application concerning the same biological product.").

[19] Janssen Biotech, Inc. v. Celltrion Healthcare Co, Ltd., 796 F. App'x 741 (Fed. Cir. 2020).

[20] Janssen Biotech, Inc. v. Celltrion Healthcare Co, Ltd., No. 17-11008-MLW, 2018 WL 10910845 (D. Mass. July 30, 2018).

[21] See AbbVie Biotechnology, Ltd. v. United States, 789 F. App'x 879 (Fed. Cir. 2020); Genentech, Inc. v. Hospira, Inc., 946 F.3d 1333 (Fed. Cir. 2020); Genentech, Inc. v. Iancu, 809 F. App'x 781 (Fed. Cir. 2020); Biogen, Inc. v. Iancu, No. 19-1364, 2020 WL 7381816 (Fed. Cir. Dec. 16, 2020).

[22] See, e.g., Eric Palmer, With Roche's loss of 'Cabilly patents' more than $600M in royalties dissipate as well, Fierce Pharma (Oct. 13, 2017), available at https://www.fiercepharma.com/pharma/roche-s-loss-cabilly-patents-about-800m-royalties-dissipate-as-well.