WILLKIE FARR & GALLAGHER LLP

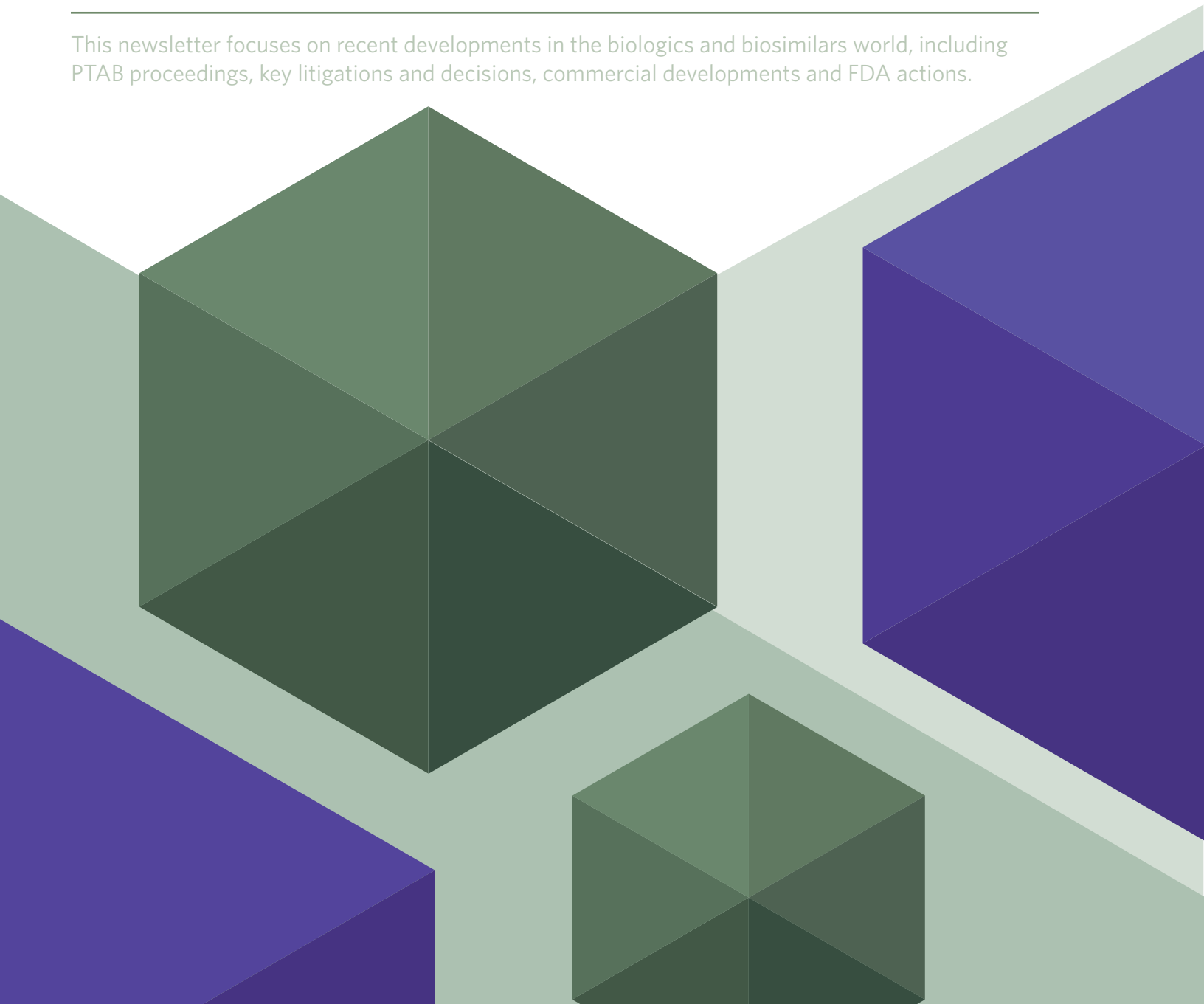
NEW YORK WASHINGTON HOUSTON PALO ALTO SAN FRANCISCO PARIS LONDON FRANKFURT BRUSSELS MILAN ROME

INTELLECTUAL PROPERTY NEWSLETTER

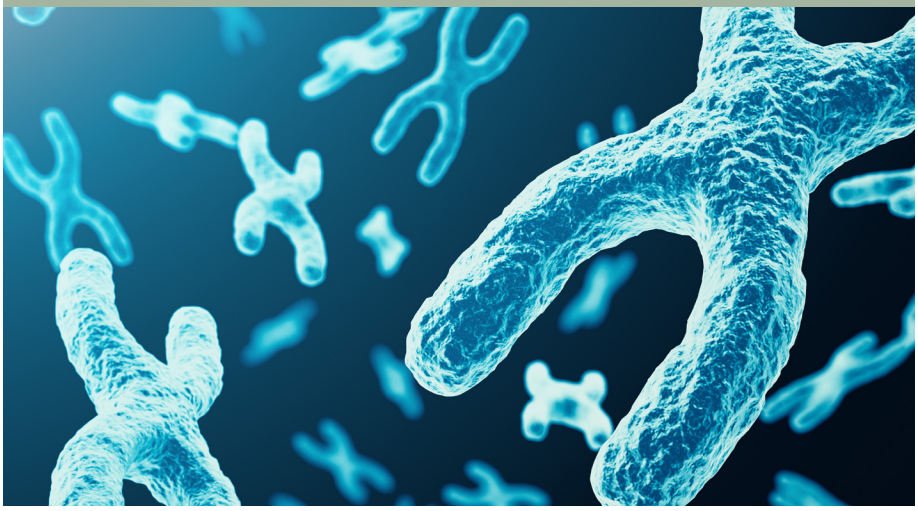
October 2019

THE BIO-QUARTERLY:
WILLKIE'S BIOLOGICS AND BIOSIMILARS NEWSLETTER

This newsletter focuses on recent developments in the biologics and biosimilars world, including PTAB proceedings, key litigations and decisions, commercial developments and FDA actions.



Contents



Key developments at the Patent Trial and Appeal Board ("PTAB") regarding biologics

PTAB Quarterly Update

Adalimumab (Humira®):

On September 17, 2019, Fresenius Kabi filed a petition for post-grant review of Coherus's patent, U.S. Patent No. 10,155,039 (PGR1029-00064). The '039 patent is directed towards a stable aqueous adalimumab formulation comprising a buffer, polysorbate 80, a sugar, wherein the composition is free of mannitol, citrate and phosphate buffers and sodium chloride, and wherein the composition has a pH of about 5 to 6. Fresenius Kabi brought the petition asserting the following three grounds: (1) the specification of the '039 patent does not provide adequate written description support for all claims; (2) the specification does not enable the full scope of all claims of the '039 patent; and (3) all claims of the '039 patent are indefinite because the term "free of … citrate and phosphate buffers" is subject to two reasonable constructions. Notably, both Fresenius Kabi and Coherus are pursuing adalimumab biosimilars. Coherus may file a preliminary response by December 17, 2019.

Eculizumab (Soliris®):

On August 30, 2019, the PTAB instituted review of three of Alexion's patents, U.S. Patent Nos. 9,725,504 (IPR2019-00739), 9,718,880 (IPR2019-00740), and 9,732,149 (IPR2019-00741) based on Amgen's IPR petitions. All of the patents are directed to eculizumab and/or methods of treatment with eculizumab.

The petitions each assert anticipation and/or obviousness grounds based on overlapping references. Hillmen, one of the primary references relied upon by Amgen, discloses the results of a clinical trial studying the effects of administering pharmaceutical compositions of eculizumab. In a representative ground, Amgen argued that Hillmen disclosed each and every limitation of certain claims, except for eculizumab's amino acid sequence, thereby anticipating the claims. The PTAB disagreed, finding that although Hillmen discloses a clinical trial of eculizumab, it does not explicitly identify the structure of the antibody tested, other than calling it by that name and referencing another disclosure that disclosed a version of eculizumab different from that claimed. Therefore, Amgen failed to show there is a reasonable likelihood that the claims would have been invalid over Hillmen.

In another representative ground, Amgen asserted that the claims were invalid as anticipated over Bowdish, a reference that allegedly disclosed the entirety of the claimed anti-C5 antibody except for the heavy chain sequence. Alexion argued that Bowdish does not anticipate because it would not have enabled the specific anti-C5 antibody of claim 1, and that Bowdish

never uses the term eculizumab. The PTAB agreed with Amgen and found that Bowdish disclosed a starting antibody identical to the claimed anti-C5 antibody, and credited Amgen's expert to find that only standard, well-known, and cellular biology methods would have been required to identify the starting antibody structure of Bowdish and make the claimed antibody. Therefore, the PTAB found that Amgen showed there is a reasonable likelihood that the claims are anticipated by Bowdish. The PTAB also found that Amgen showed there is a reasonable likelihood that the claims are obvious over Bowdish and two other references.

Filgrastim (Neupogen ®):

On September 11, 2019, the PTAB instituted review of two of Amgen's patents, U.S. Patent Nos. 8,940,878 (IPR2019-00791) and 9,643,997 (IPR2019-00797) based on Kashiv's IPR petitions. Both the '878 and '997 patents are directed towards a method of purifying a non-native limited solubility form in a non-mammalian expression system comprising a series of steps including lysing, solubilizing, forming a refold solution, applying the refold solution to a separation matrix, washing, and eluting.

Kashiv challenged certain claims as anticipated and/or obvious over Ferré and Komath, in view of other references. In a representative ground, Kashiv contends that Ferré discloses a method of purifying protein expressed in a non-native limited solubility form in a non-mammalian expression system, and that it discloses solubilizing, forming a refold solution, applying the refold solution to a separation matrix, washing, and eluting. The PTAB found that the petitioner showed a reasonable likelihood of success that Ferré anticipated the asserted claims. The PTAB was not persuaded by Amgen's argument that there is a concentration requirement inherent in the claims.

Amgen also argued that the PTAB should deny the petition under 35 U.S.C. § 314(a) because the parties were engaged in a district-court litigation in which validity contentions had been exchanged. According to Amgen, Kashiv unfairly used the contentions to draft its petition. Although the PTAB recognized that events in other proceedings related to the same patents may constitute a reason to deny a petition, the PTAB was ultimately not persuaded that Kashiv had used the validity contentions as a "roadmap" in an unfair way. The PTAB noted that both parties exchanged contentions, and thus, they both had access to the other's litigation positions. Therefore, the PTAB declined to deny the petition on this basis.

For questions, or if you would like copies of any of the decisions, please contact us here.

Key appellate and district court decisions, new suits, settlements, and other notable events

Litigation Quarterly Update

Key Appellate Developments

Genentech v. Amgen. On July 19, 2019, Genentech filed a pair of appeals in the Court of Appeals for the Federal Circuit challenging the District Court for the District of Delaware's denial of Genentech's requests for a temporary restraining order and/or preliminary injunction to prevent Amgen's launch of KANJINTI™ (trastuzumab-anns) and MVASI™ (bevacizumab-awwb), its biosimilars of Genentech's HERCEPTIN® (trastuzumab) and AVASTIN® (bevacizumab), respectively. In both appeals, Genentech simultaneously filed emergency motions in both the Federal Circuit and the district court seeking injunctions against Amgen pending these appeals. The district court denied Genentech's motions the same day they were filed, and the Federal Circuit followed suit after giving the parties an opportunity to brief the issue, denying Genentech's motion in the trastuzumab appeal on August 7, 2019, and in the bevacizumab appeal on August 16, 2019. For a more detailed analysis of both the district court's decisions and the arguments raised in the Federal Circuit appeals, please see this edition's featured article.

Amgen v. Iancu. Amgen filed an appeal to the Federal Circuit on July 22, 2019, challenging Apotex's successful IPR petition against U.S. Patent No. 8,952,138, which claims a protein refolding method related to the manufacture of Amgen's NEULASTA® (pegfilgrastim) and NEUPOGEN® (filgrastim) products. In its notice of appeal, Amgen challenged the PTAB's claim construction, the PTAB's original Final Written Decision finding that all but one of the challenged claims of the '138 patent were invalid as obvious, "whether the PTAB's *sua sponte* amendment of its Final Written Decision (in its Decision Denying Petitioner's Request for Rehearing and Amending Prior Decision …) violated the Administrative Procedure Act or was otherwise unlawful," and the PTAB's determination in that same decision that the sole remaining challenged claim was also invalid as obvious. On August 5, 2019, Apotex notified the Federal Circuit that it did not intend to participate in the appeal, and the Federal Circuit, on August 16, 2019, ordered the Director of the United States Patent and Trademark Office ("USPTO"), Andrei Iancu, "to inform the court whether he intends to intervene." The USPTO filed its Notice of Intervention on September 13, 2019.

Amgen v. Coherus. On July 29, 2019, the Federal Circuit affirmed the District Court for the District of Delaware's grant of Coherus's motion to dismiss for failure to state a claim under Rule 12(b)(6), in the parties' litigation concerning Coherus's UDENCYA™ (pegfilgrastim-cbqv). In a precedential opinion, the Federal Circuit held that the district court was correct in finding that infringement under the doctrine of equivalents was foreclosed by

Amgen's repeated, clear, and unmistakable statements during prosecution disclaiming combinations of salts different from the particular combinations of salts recited in the claims.

Amgen v. Sandoz. On September 3, 2019, the Federal Circuit denied Amgen's request for panel and *en banc* rehearing of its earlier decision, which affirmed the District Court for the Northern District of California's grant of summary judgment of non-infringement of U.S. Patent No. 8,940,878, in litigation concerning Sandoz's ZARXIO® (filgrastim-sndz) and its proposed biosimilar of Amgen's NEULASTA® (pegfilgrastim). Although Amgen's request for rehearing was denied, the panel modified its earlier opinion to remove language, which Amgen had objected to as the basis of its petition, indicating that the doctrine of equivalents only applied in "exceptional cases." The *en banc* petition was subsequently dismissed as moot.

Key District Court Developments

Immunex v. Sandoz. On August 9, 2019, the District Court for the District of New Jersey entered an opinion finding valid all asserted claims of U.S. Patent No. 8,063,182, a composition patent claiming etanercept, and U.S. Patent No. 8,163,522, a process patent claiming methods of manufacturing etanercept. The parties had stipulated that ERELZI™ (etanercept-szzs), Sandoz's biosimilar of ENBREL® (etanercept), would infringe any valid claims of the patents-in-suit, and a bench trial on validity was held in September 2018, with closing arguments on November 19, 2018. The parties entered a stipulation on October 7, 2019, agreeing to entry of judgment against Sandoz, a permanent injunction enjoining Sandoz "from making, using, offering to sell, or selling within the United States . . . any product containing etanercept" until the later of the expiration of any infringed and valid claim of the '182 patent on November 22, 2028, or of the '522 patent on April 24, 2029. The parties further stipulated to the dissolution of the prior stipulated preliminary injunction, and dismissal with prejudice of any claim of infringement of two related Immunex patents. Pursuant to this stipulation, final judgment was entered by U.S. District Court Judge Claire C. Cecchi on October 8, 2019. Sandoz filed its notice of appeal to the Federal Circuit the same day.

Amgen v. Sanofi. On August 28, 2019, the District Court for the District of Delaware granted Sanofi's motion for judgment as a matter of law ("JMOL"), finding all asserted claims of the patents-in-suit invalid for lack of enablement in the parties' dispute regarding patents related to REPATHA® (evolocumab), which Amgen asserted also covered Sanofi's PRALUENT® (alirocumab). In March 2019, a jury found that two of the five asserted claims of U.S. Patent Nos. 8,829,165 and 8,859,741 lacked enablement, but that the remaining claims were valid and infringed. However, the Court credited Sanofi's post-trial argument that "undue experimentation would be needed to practice the full scope of the claimed invention" and granted JMOL in favor of Sanofi on that issue as to all asserted claims. The Court rejected Sanofi's written description arguments, however, and also dismissed Amgen's motion for a permanent injunction based on the jury's verdict as moot in light of the Court's ruling of invalidity.

Genentech v. Amgen. While the dispute referenced above regarding the denial of Genentech's motion for a temporary restraining order or preliminary injunction is reviewed by the Federal Circuit, discovery and trial preparation have continued in Genentech's suit against Amgen regarding KANJINTI™ (trastuzumab-anns). On August 28, 2019, the District Court for the District of Delaware entered a memorandum order denying Amgen's motion for re-argument of the Court's June 20, 2019 order granting Genentech's motions to compel production of privileged communications, other than those with outside trial counsel, which related to Amgen's advice-of-counsel defense. Following Amgen's launch of KANJINTI™, the parties stipulated to the filing of a Third Amended Complaint, which was filed on September 4, 2019. This complaint reduced the number of patents-in-suit from an initial count of 37 down to

nine, and added a demand for a jury trial. The original scheduling order contemplated a bench trial starting on December 9, 2019, but this has now been rescheduled as a jury trial beginning on the same date. Finally, on September 23, 2019, the Court granted a stipulation in which the parties dismissed all claims and counterclaims relating to U.S. Patent Nos. 7,993,834; 8,076,066; and 8,440,402 in order "to streamline the issues in this case for trial," bringing the total number of patents remaining in the suit down to six.

New Litigation

FTC v. Johnson & Johnson. As reported in previous editions of the Litigation Quarterly Update, several entities, including Pfizer, Walgreens, Kroger, and direct and indirect purchasers, have filed suits alleging that Johnson & Johnson violated U.S. antitrust laws in its attempts to protect its sales of REMICADE® (infliximab). In its third-quarter filings with the U.S. Securities and Exchange Commission, Johnson & Johnson reported that "[i]n June 2019, the United States Federal Trade Commission ('FTC') issued a Civil Investigative Demand to Johnson & Johnson in connection with its investigation of whether Janssen's REMICADE contracting practices violate federal antitrust laws."

Amgen v. Tanvex. Amgen sued Tanvex BioPharma USA in the District Court for the Southern District of California on July 23, 2019. The BPCIA complaint accuses Tanvex's proposed biosimilar of Amgen's NEUPOGEN® (filgrastim) of infringing U.S. Patent No. 9,856,287, which claims a method of protein refolding in non-mammalian expression systems. In its complaint, Amgen notes that Tanvex provided its notice of commercial marketing on April 1, 2019, and Amgen is seeking a judgment of infringement and injunctive relief. Tanvex filed its answer to the complaint on September 23, 2019, and counterclaimed seeking declaratory judgments of non-infringement and invalidity of the '287 patent.

Cabaret v. Kite. On September 16, 2019, Cabaret Biotech, Ltd. and Kite Pharma, Inc. (a subsidiary of Gilead Sciences, Inc.) each filed suits seeking declaratory judgments regarding the validity and infringement of Cabaret's U.S. Patent No. 7,741,465, which claims methods of reprogramming a patient's immune cells to attack cancer cells within the patient's body, a process commonly called CAR-T. Cabaret's complaint, brought in the District of Delaware under the BPCIA, seeks a declaratory judgment that the '465 patent is valid, and alleges that Kite, which was granted an exclusive license to commercialize the '465 patent in the oncology field, is trying to invalidate the '465 patent in order to avoid paying Cabaret royalties based on sales of YESCARTA® (axicabtagene ciloleucel), which Cabaret alleges is a commercial embodiment of the '465 patent, and thus would infringe that patent but for the license. Kite's complaint, filed in the District Court for the Eastern District of Virginia, alleges that all claims of the '465 patent are invalid, specifically arguing that they lack written description, are not enabled, are indefinite, and would have been obvious, and that it cannot infringe an invalid patent.

Settlements and Stipulations

Amgen v. Mylan. On September 17, 2019, Judge Mark R. Hornak of the District Court for the Western District of Pennsylvania approved the joint stipulation by Amgen and Mylan terminating their litigation concerning FULPHILA™ (pegfilgrastim-jmdb), Mylan's biosimilar pegfilgrastim product, which launched in July 2018. According to the stipulation, Amgen's position regarding infringement of the sole patent remaining in the litigation, U.S. Patent No. 9,643,997, was effectively foreclosed by the Federal Circuit's construction of similar claim language in a related patent, U.S. Patent No. 8,940,878, in the *Amgen v. Sandoz* pegfilgrastim appeal decision, reported in the previous edition of the Litigation Quarterly Update. In that decision, the Federal Circuit held that the claim language at issue in both cases required separate "washing" and "eluting" steps.

It is uncontested that Mylan, like Sandoz, employs only a single step.

Genentech v. Pfizer. On September 19, 2019, Genentech and Pfizer filed a joint stipulation dismissing the BPCIA suit in the District of Delaware regarding TRAZIMERA™ (trastuzumab-qyyp), Pfizer's FDA-approved biosimilar of Genentech's HERCEPTIN® (trastuzumab). In the stipulation, approved by United States District Judge Colm F. Connolly on September 20, 2019, the parties stated that they "have entered into a settlement agreement, and mutually agree to voluntarily dismiss all claims and counterclaims asserted in the above-captioned case without prejudice." Willkie Farr & Gallagher represents Pfizer in this matter.

For questions, or copies of any of the decisions or documents discussed herein, please click here.

New biologic and biosimilar launches, and other marketplace developments

Market Quarterly Update

Pricing and Reimbursement Updates

Drug pricing initiatives continue to proliferate at both the legislative and regulatory levels, with many proposals potentially affecting reimbursement for biologic and biosimilar drugs.

On September 4, more than 20 groups representing patients, employers, and other stakeholders signed onto a letter to HHS Secretary Alex Azar seeking to end cost-sharing for Medicare Part B patients when providers administer a biosimilar rather than a biologic drug. The letter contends that such efforts to reduce or eliminate out-of-pocket costs would help develop a more robust market for biosimilars in the United States.

On September 19, House Speaker Nancy Pelosi unveiled a proposed drug pricing plan that would allow Medicare to directly negotiate prices on as many as 250 name-brand drugs each year that lack generic or biosimilar competition. Drug companies unwilling to comply would face excise taxes ranging from 65 to 95 percent of the previous year's gross sales of the drug at issue.

Also on September 19, the Advancing Education on Biosimilars Act of 2019 was introduced in the House of Representatives as a companion bill to one introduced earlier this year in the Senate. According to a statement from sponsors Rep. Larry Bucshon (R-Ind.) and Eliot Engel (D-N.Y.), the bill would require FDA to create a public website to educate patients and providers about biosimilar products. The bill also calls for the development of continuing education programs for health care providers to increase uptake of biologics and biosimilars.

On September 20, Rep. Kurt Schrader (D-Ore.) and Greg Gianforte (R-Mont.) introduced the Bolstering Innovative Options to Save Immediately on Medicines (BIOSIM) Act. The Act would principally increase Medicare Part B reimbursement for biosimilar drugs and reduce patient copayments. Currently, Medicare reimburses providers at the average sales price (ASP) plus six percent; the bill would lift that rate to the ASP plus eight percent. In a statement, Rep. Schrader asserted that the Act will help biosimilars "gain market share by providing an incentive for biosimilars that are lower cost than the biologic."

Biologic and Biosimilar Launches

On July 18, Amgen and Allergan announced that they had launched MVASI™ (bevacizumab-awwb) and KANJINTI™ (trastuzumab-anns), biosimilar to Genentech's AVASTIN® and HERCEPTIN®, respectively. The list price of each biosimilar is set at 15% below its reference biologic drug. MVASI™ will cost $677.40 per 100 mg and $2,709.60 per 400 single-dose vial. KANJINTI™, which is supplied in a 420 mg multi-dose vial, will cost $3,697.26. The two products are the first biosimilars to cancer drugs available in the United States. On September 30, Pfizer announced that it planned to launch its own bevacizumab biosimilar, ZIRABEV™, on December 31, 2019.

Other Market Developments

On July 1, Boehringer Ingelheim announced that it had licensed a biologic candidate developed by South Korea-based Yuhan Co., in a deal worth up to $870 million. The molecule is a dual GLP1R/FGF21R agonist, for the treatment of non-alcoholic steatohepatitis and related liver diseases.

On August 2, Momenta announced that it was abandoning a proposed adalimumab biosimilar in its pipeline after failing to secure a commercial partner for the program.

On August 23, 2019, Amgen and Allergan announced positive topline results of a study of a proposed rituximab biosimilar, ABP 798, in patients with non-Hodgkin's lymphoma (NHL). The study's PK endpoints evaluated were (1) the area under the serum concentration-time curve and (2) maximum serum concentration, and both fell within the pre-specified equivalence margin. Safety and immunogenicity were also found to be comparable among all treatment groups.

On September 3, Sandoz announced that it had reached an agreement with Poland-based Polpharma Biologics to commercialize the latter's proposed natalizumab biosimilar, referencing Biogen's TYSABRI®. The biosimilar is currently in Phase III clinical development for the treatment of relapsing-remitting multiple sclerosis. Terms of the agreement were not made publicly available.

Key developments at the FDA regarding biologics and biosimilars

FDA/Regulatory Quarterly Update

FDA Releases Revised Guidance on the Use of Citizen Petitions

On September 18, 2019, the FDA issued a revised and final guidance interpreting Section 505(q) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act") that is intended to stop branded drug manufacturers from improperly using citizen petitions to delay the market entry of generic or biosimilar products. This guidance revises the guidance for the industry entitled "Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act" issued in November 2014 to account for recent regulatory changes and to describe a change in the FDA's current thinking on what constitutes a Section 505(q) petition.

By way of background, prior to the enactment of Section 505(q), where a citizen petition related to the approvability of a pending ANDA, 505(b)(2) application, or 351(k) biosimilar application, and where the matter would likely involve litigation, a citizen petition could delay final approval of an application until the FDA completed the petition process and finalized an administrative record that resolved the challenge.

Section 505(q) was enacted as part of the Federal Food, Drug and Cosmetic Act ("FD&C Act") to prevent the FDA citizen petition process from being improperly used to delay approval of generic or biosimilar applications. Under Section 505(q), the FDA is required to take final action within 150 days on any petition that requests any form of action that, if taken, may delay the approval of a currently pending ANDA, 505(b)(2), or 351(k) biosimilar application. Further, the FDA is prohibited from delaying the approval of such application because of a petition unless the FDA finds that delay is necessary to protect the public health. If the delay is deemed necessary to protect public health, the FDA is required to notify the applicant that such determination was made, provide a brief summary of the specific issues raised in the petition that led to such decision, and describe any data that the applicant should submit to allow prompt review of the petition by the FDA. Under section 505(q), the FDA may also deny a petition submitted with the primary purpose of delaying an ANDA, 505(b)(2) application, or 351(k) biosimilar application approval. However, in a 2019 report to Congress, the FDA opined that Section 505(q) did not "discourage the submission of petitions that are intended primarily to delay the approval of competing drug products and do not raise valid scientific issues."

The final guidance provides details on how the FDA will interpret provisions of section 505(q) regarding the FDA's treatment of citizen petitions, namely (1) if Section 505(q) applies to a particular petition; and (2) if

a petition would delay the approval of a pending ANDA, 505(b)(2) application or a 351(k) biosimilar application. The guidance sets forth five requirements that a petition must meet in order for Section 505(a) to apply:

(1) The petition is submitted on or after September 27, 2007 (if relating to an ANDA or 505(b)(2) application) or July 9, 2012 (if relating to a biosimilar application);

(2) The petition is submitted in writing, pursuant to 21 C.F.R. 10.30 (citizen petition) or 10.35 (request for administrative stay);

(3) An ANDA, 505(b)(2) application or biosimilar application relating to the petition is pending at the time the petition is submitted, and the application's user fee goal date is on or before the 150-day deadline for FDA action on the petition;

(4) The petition requests an action that could delay approval of the related ANDA, 505(b)(2) application or biosimilar application; and

(5) The petition does not fall within any of the statutory exceptions.

With respect to the fourth factor, the guidance also detailes a number of factors that the FDA will consider in determining if a petition would delay the approval of an application, including:

(1) Petitioner has taken an unreasonable length of time from when it learned of pertinent information to submit the petition;

(2) Submission of multiple or serial petitions or supplements that describe information petitioner knew or should have known at the time of the earlier submission;

(3) Submission that is close to the time an application is likely to be approved;

(4) Submission deficient in information supporting raised scientific issues;

(5) Submission containing information that had already been reviewed by the FDA;

(6) Submission with information concerning standards for approval for which the FDA has provided an opportunity for public input;

(7) Submission requesting the applicants to meet testing standards that are more rigorous than FDA standards; and

(8) History of the petitioner with the FDA.

If the FDA finds that the petition would delay approval of an application, the FDA will determine if the petition should be denied because its main purpose is to delay the approval and does not raise valid scientific or regulatory issues. If the FDA determines that the petition's main purpose is to delay the approval of the application, the FDA will deny the petition and could refer the matter to the FTC and include it in its annual report to Congress. However, if the FDA determines that the petition should not be denied because it raises valid issues, the FDA will determine whether the application would be ready for approval *but for* the issues raised in the petition. If the application would be ready for approval within the 150-day period for the FDA's action on the petition, then the FDA would have to determine whether the delay in the approval is necessary to protect the public health. Issues that are considered at this step are, for example, whether a proposed generic meets bioequivalence standards or whether the proposed labeling omitted a patented indication. Once a determination has been made, the FDA must notify the applicant within 30 days and include a brief summary of the specific issues that led to the specific determination. However, regardless of whether the delay is necessary to protect the public health, the FDA will continue to consider the 150-day period for final action to apply to the petition.

The guidance next provides requirements for certifications and verifications to be included with petitions in order to receive FDA consideration. A certification is required with a petition subject to Section 505(q), while a verification is required when supplemental information on a petition is submitted. In both instances, the guidance provides the specific language to be used, which must be in writing, and must include the date on which the information in the petition became available to petitioner. If such a certification or verification is found to be deficient, the FDA will not review the petition. In the case of a deficient certification, the petitioner may submit a letter withdrawing the deficient petition and resubmit the petition with the correct certification. In the case of a deficient verification, the petitioner may resubmit the supplemental information with the required verification to the FDA.

Lastly, the guidance addresses the relationship between the review of petitions under section 505(q) and review of ANDA, 505(b)(2) and 351(k) biosimilar applications which have not yet been approved by the FDA. Section 505 of the FD&C Act and 21 C.F.R. part 314 regulate the procedures by which the FDA determines whether a drug application should be approved or denied. The statute and the regulations describe a process by which an applicant may challenge the FDA's determination. Thus, such a determination is not considered a final action. However, petitions subject to Section 505(q) are final FDA decisions which are subject to immediate review by the court. The guidance provides clarification that when the final decision on the approvability of an application has not been made, Section 505(q) does not require the FDA to make a substantive final decision on a petition, and may deny the petition without comment on the substantive approval issue.

Recent FDA Biologics and Biosimilar Approvals

FDA Approves JYNNEOS

On September 24, 2019, the FDA approved Bavarian Nordic's JYNNEOS (vaccine) for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. The vaccine is made with attenuated vaccinia virus (Modified Vaccinia Ankara, MVA-BN) for subcutaneous administration. It is the only non-replicating vaccine to receive FDA approval for smallpox. The FDA granted the application Priority Review and with this approval, the FDA issued a material threat medical countermeasure (MCM) priority review voucher to Bavarian Nordic A/S.

FDA Approves SCENESSE® (afamelanotide)

On October 8, 2019, the FDA approved Clinuvel Pharmaceuticals LTD's SCENESSE® (afamelanotide) for treatment of patients who suffer from erythropoietic protoporphyria, a rare disorder (exposure to light causes extreme pain). The FDA granted this application Priority Review designation. SCENESSE® also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

FDA Approves BEOVU® (brolucizumab-dbll)

On October 8, 2019, the FDA approved Novartis's BEOVU® (brolucizumab-dbll) for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD). Brolucizumab-dbll is a VEGF inhibitor and is designed to suppress the growth of abnormal blood vessels and the potential for fluid leakage into the retina and to maintain eligible wet AMD patients on a three-month dosing interval immediately after a three-month loading phase without a decrease in efficacy.

For questions, or copies of the documents discussed herein, please click here.

This article provides a summary of Amgen's launch at risk of its trastuzumab and bevacizumab biosimilars and the status of the appeals and district court litigations

FEATURED ARTICLE | By Guest Author Zachary Travis

Two At-Risk Launches Under the BPCIA: Amgen Launches Its Bevacizumab and Trastuzumab Biosimilars

On July 18, 2019, Amgen announced its launch of Kanjinti™ and Mvasi™ – biosimilar versions of Genentech's Herceptin® (trastuzumab) and Avastin® (bevacizumab), respectively. These are the first trastuzumab and bevacizumab biosimilars on the market. Prior to these launches, however, Genentech moved for injunctive relief on July 10, 2019 in ongoing Delaware District Court litigations before Judge Colm Connolly. As discussed below, Judge Connolly denied both of Genentech's requests for injunctive relief on July 18, 2019 and Amgen announced its launch later that day.

Genentech v. Amgen - Trastuzumab Litigation

Background

In July 2017, Amgen announced it had submitted a BLA seeking approval for its trastuzumab biosimilar, ABP 980, or Kanjinti™. According to pleadings, Genentech and Amgen engaged in the BPCIA exchange process, and in May 2018, Amgen provided its notice of commercial marketing pursuant to 42 U.S.C. § 262(*l*)(8). Shortly thereafter, Genentech filed suit against Amgen in the District of Delaware, alleging that Amgen's trastuzumab biosimilar would infringe 37 Genentech patents. *Genentech, Inc. v. Amgen Inc.*, Case No. 18-cv-00924-CFC (D. Del. June 21, 2018). Genentech subsequently dismissed many of these patents, such that six patents remain in suit currently.

Kanjinti™ was approved by the FDA on June 13, 2019. During the week of July 8, Genentech learned through market intelligence that Amgen's launch was forthcoming, and brought a motion for a preliminary injunction on July 10. Genentech sought injunctive relief based on Amgen's alleged infringement of three related patents on the dosing of trastuzumab – U.S. Patent Nos. 6,627,196 ("the '196 patent"), 7,371,379 ("the '379 patent") and 10,160,811 ("the '811 patent") (collectively "the 3-Weekly Dosing Patents"). These patents all claim methods of treating cancer with trastuzumab using a specific dosing regimen separated by three weeks. Two of the asserted patents, the '196 and '379 patents, were previous upheld as patentable in IPR challenges by Pfizer, joined by Samsung, and Celltrion, where each Final Written Decision found that the petitioner had failed to establish that a skilled artisan would have a

reasonable expectation of success in using the claimed dosing regimen.

The District Court Decision Denying Injunctive Relief

After expedited briefing by the parties, the court denied Genentech's motion for a preliminary injunction on July 18, mainly focusing on Genentech's failure to establish irreparable harm. First, the court opined that Genentech had unduly delayed in seeking injunctive relief. The court noted that Genentech had ample evidence to expect a launch in July 2019. In April 2019, Amgen had produced documents with its launch plan redactions removed and five Amgen witnesses testified that Amgen was preparing to launch in July 2019. The court also noted that Genentech should have been aware that the FDA could potentially approve Kanjinti™ in June 2019. But even after the FDA approved Kanjinti™ on June 13, 2019, Genentech did not move for a preliminary injunction. The court emphasized that Genentech's delay was contrary to the spirit and purpose of the BPCIA, which provides the 180-day period following the notice of commercial marketing to allow orderly adjudication of such matters. Because of this finding of undue delay, the court concluded that there was no irreparable harm. Although not mentioned in the decision, Amgen also pointed in its briefing to statements from Genentech that they were "not presently seeking injunctive relief" at a May 16, 2019 discovery hearing on the production of Genentech's trastuzumab settlement agreements.

The court also found that Genentech's pattern and practice of licensing the patents underlying the preliminary injunction motion undercut Genentech's irreparable harm arguments. Based on this apparent practice of granting licenses to the 3-Weekly Dosing Patents, the court found it reasonable to expect that Genentech is capable of placing a value on its patent rights. The court therefore found that "any potential damages for sales in the next four months should be quantifiable."

Given the rushed nature of the inquiry and the necessity of irreparable harm to the granting of an injunction, the court declined to address Genentech's likelihood of success on the merits or the balancing of harms. In a footnote, however, the court found that the public interest weighed against granting an injunction because Genentech was only asserting its patents against two out of four methods of using Kanjinti™ found on the label. The court did not evaluate what percentage of patients would be treated with infringing methods of using Kanjinti™ as opposed to noninfringing methods.

Genentech has since amended the complaint to reduce the number of asserted patents, add claims related to Amgen's launch and add a jury demand. The parties have stipulated to further narrow the issues by removing certain patents. After a teleconference with the court, the trial has been changed to a five-day jury trial starting on December 9, 2019. Damages will be addressed separately, if necessary.

The Federal Circuit Appeal

Genentech appealed to the Federal Circuit on July 19 and requested an injunction pending the appeal, which was denied by both the district court and the Federal Circuit. The Federal Circuit also denied Genentech's request for expedited briefing, stating that "while Genentech has and can continue to self-expedite its own filings, it has not shown that Amgen's time should be shortened. This appeal will be placed on the next available oral argument calendar after briefing is completed."

Genentech's briefing argues that the district court's denial of the preliminary injunction rests on several legal errors.

First, Genentech reasons that there cannot be undue delay as a matter of law when a party moves for an injunction before the launch of the allegedly infringing product. It further argues that Amgen did not make the decision to launch until just before the preliminary injunction motion, so Genentech did not, as a matter of

fact, delay in seeking injunctive relief. Amgen responds that the district court correctly found that Genentech's failure to bring a preliminary injunction within a reasonable time frame was undue delay.

Second, Genentech argues that licenses for future market entry do not show a lack of irreparable harm in the present and that the district court's lack of analysis of the substance of the license agreements suggests that it applied an inappropriate categorical rule. Genentech further notes that the district court's decision will have a chilling effect on settlement in the future. Amgen argues that the district court's reasoning was correct and notes that any failure to evaluate the licenses in more detail was the result of Genentech's production of the settlement agreements that withheld virtually all material terms of the licenses from the district court. Amgen further argues that Genentech waived its argument that licenses for future market entry cannot show a lack of present irreparable harm by failing to raise it in the original briefing before the district court.

Third, Genentech argues that the district court erred in its brief public interest analysis by failing to consider how much of the use of Kanjinti™ would be noninfringing. In response, Amgen emphasizes that two of the indications on the Kanjinti™ label are noninfringing.

Fourth, Genentech argues that it is likely to succeed based on the merits based on favorable IPR decisions upholding the patentability of two of the 3-Weekly Dosing Patents. Genentech notes that Amgen failed to submit any expert testimony and that Amgen's invalidity grounds are substantially similar to the grounds in the IPR. Genentech disputes Amgen's additional evidence of likelihood of success as based on the testimony of extraordinarily skilled individuals with additional information not publicly available at the time of the invention. Amgen responds that the decision in the IPR found only that there would not have been a reasonable expectation of success, and testimony from the Genentech's witnesses, including the named inventors on the patents, now shows a likelihood of success.

Both parties briefly address the balancing of harms on appeal, arguing that it tips in their favor. The parties completed briefing, with Genentech expediting the filing of both its opening and reply briefs, and submitted the joint appendix on September 27, 2019. Oral argument is not scheduled yet.

Genentech v. Amgen – Bevacizumab Litigation

Background

Amgen filed its aBLA for its bevacizumab biosimilar Mvasi™ on November 14, 2016, and received approval from the FDA in September 2017. On October 6, 2017, Amgen sent its notice of commercial marketing, and Genentech filed suit against Amgen that same day. *Genentech, Inc. et al. v. Amgen Inc.*, Case No. 17-cv-01407-CFC (D. Del. Oct. 6, 2017). While this litigation was ongoing, Amgen filed a third supplemental BLA ("sBLA") with the FDA on August 16, 2018. In this supplement, Amgen requested approval to use Immunex's Rhode Island facility for bevacizumab drug substance manufacturing. On August 27, 2018, Amgen filed a fourth sBLA, which sought to change the labelling for Mvasi™. Genentech then took the position that the sBLA filings triggered new BPCIA patent exchanges. In an October 2018 hearing, Genentech told the court that they were reviewing the application to determine which patents to assert. Genentech then allegedly sent Amgen another 3(A) list based on the sBLAs filed by Amgen. Notably, the list included two patents that had not previously been included in any 3(A) or supplemental list. Amgen disagreed with Genentech's interpretation of the BPCIA and chose not to provide contentions under § 262(*l*)(3)(B) or a new notice of commercial marketing.

The District Court Decision Denying Injunctive Relief

After the court resolved certain issues related to the protective order, Genentech filed a new suit against Amgen on March 29, 2019, based on Amgen's sBLA filings and Genentech's new 3(A) list. *Genentech, Inc. et al. v. Immunex Rhode Island Corp. et al.*, Case No. 19-cv-00602-CFC (D. Del. Mar. 29, 2019). Amgen moved to dismiss the complaint, arguing that its production of the sBLAs in the prior case was not a disclosure under 262(*l*)(2)(A), but rather discovery responses provided in the ordinary course of litigation. As such, Amgen argued that Genentech's new complaint impermissibly split a single cause of action into successive lawsuits.

While that motion was pending, Amgen's sBLA was approved on June 24, 2019. The pleadings indicate that Amgen made the final decision to launch Mvasi™ on July 8. Genentech received market intelligence that Amgen was planning to launch its bevacizumab biosimilar, and on July 10 filed a motion for a temporary restraining order and a motion to enforce the statutory prohibition on commercial marketing. In seeking injunctive relief, Genentech did not assert any patents. Instead, Genentech argued that Amgen failed to provide a notice of commercial marketing for any Mvasi™ produced at Amgen's Rhode Island facility or used under Amgen's amended label.

Genentech's request for injunctive relief raised a novel issue of statutory construction: Does a product made under an sBLA require a new notice of commercial marketing?

Under Genentech's view of the BPCIA, Mvasi™ produced at Amgen's Rhode Island facility or used under Amgen's amended label is a new "biological product licensed under subsection (k)" and therefore the BPCIA required a new notice of commercial marketing under § 262(*l*)(8)(A). Genentech emphasized that Amgen's new location and new label could not have been "licensed under subsection (k)" because they were not submitted to the FDA at the time of Amgen's original notice of commercial marketing (or even after the 180 days had run). In support, Genentech focused on the requirements for an application under § 262(*k*)(2), which include manufacturing facilities and labelling, and the BPCIA's definition of a "subsection (k) applicant" as "a party that submits an application under subsection (k)." Genentech further pointed to the limitation in § 262(*k*)(7) to the "first licensed" reference product as evidence that Congress was aware that these products would be subject to supplemental changes and exempted such supplements from the BPCIA when Congress wished. Genentech also argued that Amgen's interpretation is inconsistent with the statutory scheme, noting that Amgen's interpretation of the BPCIA would deny the reference product sponsor from seeking orderly injunctive relief on potentially infringing supplemental applications and encourage gamesmanship. Notably, although Genentech argued that the traditional four-factor balancing test did not apply to the enforcement of the notice of commercial marketing requirement, Genentech nevertheless submitted a second motion for a temporary restraining order addressing the balancing test.

Under Amgen's view of the BPCIA, Mvasi™ is the same biological product regardless of any sBLAs, so no new notice of commercial marketing is required for supplements under the BPCIA. In its briefing, Amgen noted that the Supreme Court in *Sandoz v. Amgen* found that the phrase "of the biological product licensed under subsection (k)" modifies commercial marketing instead of notice and therefore the product must be licensed on the date of the first commercial marketing. Amgen also pointed out that *Sandoz v. Amgen* found that § 262(*l*)(8)(A) contains a single timing requirement and "nothing in § 262(*l*)(8)(A) turns on the precise status or characteristics of the biosimilar application." Finally, Amgen pointed to the express definition of "biological product" under § 262 and argued that the statute distinguishes biological product from the facility in which it is made and the conditions of its use.

Amgen also noted that Genentech had not asserted any injunctive relief on its patent rights.

The court denied both of Genentech's requests for injunctive relief, declaring that the parties' dispute could be reduced to a slightly different question – "whether subsection (k) allows the FDA to approve a supplement to an application for a biosimilar after the FDA has approved the application." According to the court, if the FDA has the authority to approve changes to the Mvasi™ product's manufacturing and labelling after approval the original application, then the Mvasi™ product under the sBLA is the same as the Mvasi™ product under the original application. If Mvasi™ produced under the sBLA is the same product as the Mvasi™ produced under the original BLA, then the BPCIA does not require Amgen to provide a new notice of commercial marketing.

In answering its question, the court found that the language of § 262(*k*) suggested that the same biosimilar can be the subject of an application and a supplement to an application. *See*, *e.g.*, § 262(*k*)(3) ("Upon review of an *application* (or *a supplement to an application*)…") (emphasis added). The court found further support in FDA regulations, which predated the passage of the BPCIA, defining supplement as "a request to approve a change in an approved license application." Based on these findings, the court reasoned that subsection (k) allows the FDA to approve a supplement and therefore a supplement under subsection (k) would concern the same biological product. Therefore, Amgen did not have to provide a new notice of commercial marketing.

In rejecting Genentech's arguments, the court noted the express definition of biological products in the BPCIA and agreed with Amgen that the BPCIA distinguishes a biological product from both the facility in which it is made and the conditions of its use. Finally, the court disagreed that the language in § 262(*k*)(7) supported Genentech's interpretation, instead finding that it supports the proposition that a single biologic product can be licensed on multiple occasions. Because the court found that Genentech was unlikely to succeed on the merits of its arguments, the court also denied Genentech's motion for injunctive relief based on the balancing test.

There have been no developments in *Genentech, Inc. et al. v. Immunex Rhode Island Corp. et al.*, Case No. 19-cv-00602-CFC (D. Del. Mar. 29, 2019) since Amgen launched. In the main litigation concerning Mvasi™, *Genentech, Inc. et al. v. Amgen Inc.*, Case No. 17-cv-01407-CFC (D. Del. Oct. 6, 2017), the parties provided the court with updated proposed schedules. Genentech sought a lengthy extension of fact discovery that moved the trial date back a few months to Fall 2020, while Amgen proposed a new schedule that kept the July 2020 trial date. There was no mention of Genentech moving for a preliminary injunction on their patent rights in either proposed schedule. Ultimately, the court adopted a schedule that kept the July 2020 trial date and briefly extended fact discovery until September 30, 2019.

The Federal Circuit Appeal

Genentech appealed on July 19. Both the district court and the Federal Circuit denied Genentech's motion for an injunction pending appeal. Genentech filed its opening brief on September 17, 2019 (the day it was due), arguing that the district court erred by relying on the definition of "biological product" instead of determining if a product made under an sBLA is a new "biological product licensed under subsection (k)" and that the district court's interpretation undermines the BPCIA by preventing reference product sponsors from seeking orderly injunctive relief for supplemental BLAs. Amgen's response is due October 28, 2019.

To receive ongoing updates for this litigation, or for any questions, please contact Mike or Tara.

Contacts

Thomas J. Meloro

Chair, Intellectual Property

+1 212 728 8248

tmeloro@willkie.com

Michael W. Johnson

Partner, Intellectual Property

+1 212 728 8137

mjohnson1@willkie.com

Tara L. Thieme

Associate, Intellectual Property

+1 212 728 8489

tthieme@willkie.com

M. Diana Danca

Associate, Intellectual Property

+1 212 728 8692

ddanca@willkie.com

Ronald A. Lee

Associate, Intellectual Property

+1 212 728 8943

rlee@willkie.com

Devon W. Edwards

Associate, Intellectual Property

+1 212 728 8650

dedwards@willkie.com

Eric L. Saunders

Associate, Intellectual Property

+1 212 728 8806

esaunders@willkie.com

If you have any questions regarding this newsletter, please contact Michael or Tara.

WILLKIE FARR & GALLAGHER LLP