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INTELLECTUAL PROPERTY NEWSLETTER

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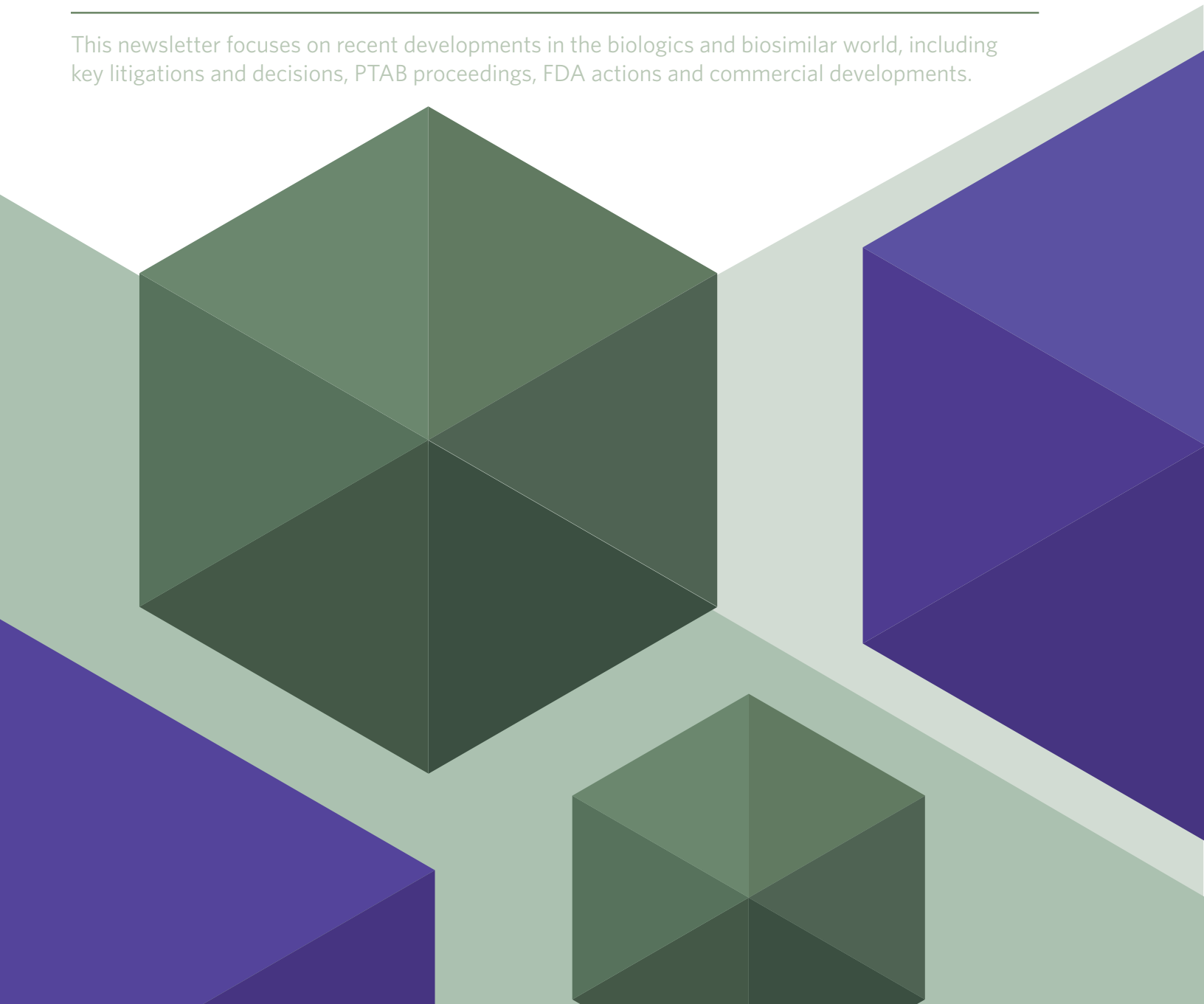
THE BIO-QUARTERLY:
WILLKIE'S BIOLOGICS AND BIOSIMILARS NEWSLETTER

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



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The Supreme Court recently confirmed that biosimilar applicants may opt out of the BPCIA exchanges. Another pending Court case may derail IPR challenges, an increasingly popular method of challenging biologic patents.

FEATURED ARTICLE

Supreme Court Decisions May Impact Biologics Practice and BPCIA Litigation

In June, the United States Supreme Court issued its first interpretation of the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA"), which provides an abbreviated approval pathway for biological products shown to be biosimilar with a referenced, FDA-licensed biological drug. Specifically, the Supreme Court provided guidance to parties and courts as they navigate patent disputes and the statutory requirements arising from the submission of an abbreviated Biologics Licensing Application ("aBLA").

The case, *Sandoz Inc. v. Amgen Inc.*, __ U.S. __, 137 S. Ct. 1664 (2017), involved Sandoz's attempt to gain FDA approval for a biosimilar filgrastim product, ZARXIO®, using Amgen's NEUPOGEN® as the reference product. In accordance with the notice provisions of 42 U.S.C. § 262, Sandoz informed Amgen that its application had been accepted for review by FDA. Much like the Hatch-Waxman Act, the BPCIA creates an "artificial" act of infringement from the submission of an aBLA allowing patentees to bring litigation prior to market entry. Although the statute requires an applicant to provide its application to the manufacturer of a reference product (the "sponsor"), Sandoz refused to do so.

Under the statutory framework of the BPCIA, infringement litigation may be brought according to various timetables, owing to the lengthy development and approval process for biologic products. If the parties comply with its framework, they will engage in the so-called "patent dance." First, the applicant provides its application and manufacturing information. Second, the sponsor provides a list of patents it believes might be infringed by the manufacture, sale, or use of the aBLA product as well as patents it would be willing to license. Third, the applicant shall provide arguments as to why the identified patents are not infringed and/or are invalid, and may identify additional relevant patents, as well as responding to the sponsor's offers to license. And, finally, the sponsor provides its own arguments regarding infringement, enforceability, and validity as to each relevant patent. This exchange then provides the basis for two phases of patent litigation: first, the parties work to identify patents for immediate litigation; later, when the applicant provides notice of commercial marketing, a second phase of litigation involving any identified relevant patents that were not litigated in the first phase may be commenced.

This process was preempted, however, when Sandoz declined to provide its application and manufacturing information to Amgen. As a result, Amgen filed suit, not only for patent infringement, but also seeking an injunction under state and federal law precluding

Sandoz from marketing ZARXIO®. The Supreme Court, in a unanimous decision, held that the BPCIA did not provide for an injunction under federal law to enforce the requirement of providing such information under 42 U.S.C. § 262(*l*)(2)(A), but declined to reach the question of whether state law may allow for such a remedy.

The Court rested its first determination on two key prongs. First, it reasoned, unlike the submission of an aBLA, an applicant's failure to provide application and manufacturing information is not an independent act of infringement. 137 S. Ct. at 1674. Rather, the BPCIA itself provides a specific remedy in the event that an applicant fails to make such a production: the sponsor may immediately bring an action for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or its use. *Id.* That remedy, the Court held, precludes any additional ones—including injunctive relief. *Id*. at 1675.

However, in holding that an injunction could potentially be available under state law, it overturned the portion of the decision below, by the Court of Appeals for the Federal Circuit, which had reasoned that no injunctive relief could issue under state law. *Id.* at 1676. The Supreme Court asked the lower court, on remand, to analyze first whether California law would treat the failure to produce as "unlawful" and second whether the BPCIA preempts any other relief, including injunctive relief. *Id.*

The Court next analyzed when an applicant must provide notice of commercial marketing to the sponsor, which kicks off the second phase of patent litigation. Sandoz had provided such notice before receiving FDA approval; Amgen argued that this constituted a violation of the BPCIA notice provisions. In concluding that the applicant need not receive FDA approval prior to providing such notice, the Court reversed the Federal Circuit. The determination rested solely on statutory interpretation: under the BPCIA, the applicant "must give 'notice' at least 180 days 'before the date of the first commercial marketing.'" *Id.* at 1677. The Court held that this timing requirement does not provide any further limitations, and that Amgen's policy arguments were better directed to Congress, not the courts. *Id.* at 1677-78.

Notably, Justice Breyer filed a concurring opinion, seeking to defer some autonomy to the FDA. Although the "Court's interpretation of the statutory terms before us is a reasonable interpretation," Justice Breyer noted that "if [the FDA], after greater experience administering this statute, determines that a different interpretation would better serve the statute's objectives, it may well have authority to depart from, or to modify, today's interpretation." *Id.* at 1678.

In sum, the Supreme Court's *Amgen* decision provides guidance both for aBLA applicants and sponsors of FDA-licensed biologics. Should an applicant decline to provide application and manufacturing information, rather than engage in the "patent dance," sponsors may immediately bring infringement litigation, though the BPCIA provides no injunctive relief for failure to produce such information. And, moreover, applicants need not wait until receiving FDA approval to provide notice of commercial manufacturing, allowing the second phase of patent litigation to begin as soon as such notice is provided. On remand, the Federal Circuit will consider whether a failure to provide application and manufacturing information constitutes a violation of state unfair competition law, and whether an injunction is available under those statutes. Notably, the federal government submitted an amicus brief to the court arguing that, in the BPCIA, Congress had drafted a "carefully calibrated scheme" which preempted any remedy under state law.

In addition to its decision in *Amgen*, the Supreme Court is set to issue a second opinion that could seriously alter how manufacturers of biosimilar drugs approach the decision to pursue new products. In *Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC,* Docket No. 16-712, the Court will weigh in on the constitutionality of proceedings before the Patent Trial and Appeal

Board (PTAB): *inter partes* review (IPR), post-grant review (PGR) and covered business method (CBM) patentability challenges.

Created by the Leahy-Smith America Invents Act in 2012, these adversarial, post-issuance proceedings allow interested parties—including those accused of infringement—to challenge the validity or patentability of any issued patent, though only under certain grounds and in accordance with certain procedures laid out by statute. (See ***USPTO, Major Differences between IPR, PGR, and CBM.***) This pathway has become a valuable tool for the biosimilar applicant, which may seek to invalidate patents covering a reference product before filing an aBLA, or concurrent adjudication of validity and enforceability under the faster, more streamlined PTAB review process even after litigation has commenced.

Unlike small molecule drugs, which often have just a handful of patents covering their manufacture, product, or use, companies marketing biologic drugs often have secured dozens of patents or more covering their products. For instance, in its complaint against aBLA applicant Boehringer Ingelheim, AbbVie explained that development of its biologic drug HUMIRA® "has resulted in more than 100 issued United States patents concerning the HUMIRA® product, 74 of which AbbVie has identified as infringed." D.I. 1, Complaint, *AbbVie Inc. v. Boehringer Ingelheim Int'l GMBH,* No. 1:17-cv-01065 (Aug. 2, 2017). Because of the difficulty of litigating so many patents at once, many companies in the biologics space have turned to IPR proceedings for expedited resolution.

In June, however, the Supreme Court agreed to hear *Oil States*, and its decision may close off the PTAB pathway for those seeking to invalidate patents. The Court granted certiorari with respect to the first question raised in the petition, and will analyze "[w]hether inter partes review . . . violates the Constitution by extinguishing private property rights through a non-Article III forum without a jury." In essence, the case comes down to a somewhat esoteric question of Constitutional law—whether patents are public rights, which can be revoked by an administrative agency, or private rights, which carry the right to a jury trial before the federal district courts.

Oral argument in *Oil States* is set for November 27, 2017, and a decision from the Supreme Court can be expected in mid-to-late 2018.

In this section, we will provide a quarterly summary of litigation involving biologics and biosimilars.

Litigation Quarterly Update

The information below will keep you up to date on key appellate decisions, district court decisions, new suits, and settlements, in addition to any other notable events that have taken place in the courts during the last quarter.

Key Appellate Decisions

On June 12, 2017, the Supreme Court issued its decision in *Sandoz Inc. v. Amgen Inc.,* reversing the Federal Circuit and holding that the notice of commercial marketing may be provided either before or after receiving FDA approval. The Court found that "[b]ecause the phrase 'of the biological product licensed under subsection (k)' modifies 'commercial marketing' rather than 'notice,' 'commercial marketing' is the point in time by which the biosimilar must be 'licensed.'" The Court further noted that the context of the statute as a whole confirmed this reading, because section 262(*l*)(8)(A) "contains a single timing requirement (180 days before marketing), rather than the two requirements posited by the Federal Circuit (after licensing, and 180 days before marketing)."

The Supreme Court further ruled that section 262(*l*)(2)(A) is not enforceable by injunction. The Court found that section 262(*l*)(9)(C) provides the remedy for an applicant's failure to turn over its application, authorizing the sponsor, but not the applicant, to bring an immediate declaratory-judgment action, "thus vesting in the sponsor the control that the applicant would otherwise have exercised over the scope and timing of the patent litigation and depriving the applicant of the certainty it could have obtained by bringing a declaratory-judgment action prior to marketing its product." The Court found that the presence of this remedy, combined with the lack of other "textually specified remedies, indicates that Congress did not intend sponsors to have access to injunctive relief, at least as a matter of federal law, to enforce the disclosure requirement." The Supreme Court did, however, leave open the possibility that injunctions may be available under state law.

On August 10, 2017, the Federal Circuit issued its decision in *Amgen Inc. v. Hospira Inc.*, finding that Amgen lacked appellate jurisdiction. In the district court proceedings, Amgen sought to compel production of information regarding the components of Hospira's cell culture medium. When Hospira opposed this discovery, the district court denied Amgen's motion to compel as unrelated to any of the patents-in-suit. Amgen appealed that discovery decision to the Federal Circuit under the collateral order doctrine, and alternatively sought mandamus under the All Writs Act. The Federal Circuit first held that the lack of immediate appeal over orders

denying discovery of BPCIA information does not render such orders "effectively unreviewable," a requirement to qualify for the collateral order doctrine. As such, the Federal Circuit found that it lacked jurisdiction over Amgen's appeal under the collateral order doctrine.

The Federal Circuit then turned to Amgen's contention that it was entitled to mandamus under the All Writs Act, focusing on whether Amgen established a "clear and indisputable" right to the discovery it sought. The court noted that although Amgen could have listed its cell culture media patents on its 3(A) List, it failed to do so. Amgen argued that it was unable to list the culture media patents because Hospira failed to provide the requested information, but the panel confirmed that no Rule 11 basis was required to include a patent on Amgen's 3(A) List; rather, only a good faith basis was needed. Ultimately, the panel held that Amgen was not entitled to discovery on its unlisted cell culture media patents, and thus that Amgen had not established a clear and indisputable right to the discovery it sought. As such, the court found that Amgen failed to establish the prerequisites to issue a writ of mandamus.

Key District Court Decisions

In a recent discovery dispute in the *Amgen v. Sandoz* litigation involving Sandoz's biosimilar versions of NEUPOGEN® and NEULASTA®, Amgen sought discovery regarding Sandoz's expected approval, marketing and sales. Sandoz fought this discovery, arguing that the information was competitively sensitive and irrelevant because Sandoz agreed not to launch its product until after the March 2018 trial. The court disagreed, however, noting that the issue of injunctive relief was still before the jury, and thus the information sought by Amgen was relevant. Sandoz then moved to separate the issue of Amgen's entitlement to future injunctive relief, specifically for the accused product (pegfilgrastim) that will not have been approved for sale by the time of trial, until after trial on the validity of Amgen's patent and infringement of the patent. Under Sandoz's proposal, the jury trial would consider the factual issues of infringement regarding the two accused Sandoz products – filgrastim (an FDA-approved product on sale in the United States), and pegfilgrastim (a yet-to-be approved product) which has never been sold or otherwise marketed, and of the validity of the asserted patent. Sandoz also moved to stay discovery relating to the expected approval, marketing and sales of Sandoz's proposed pegfilgrastim product. In its August 24, 2017 decision, the court found that a stay is not warranted at this point. Sandoz's arguments are premised on two assumptions: that the court will bifurcate the injunctive relief from the March 2018 trial and that Amgen will not prevail on its validity and infringement claims. Because neither outcome was certain, the court found that Amgen was entitled to discovery on the approval, marketing, and sales of Sandoz's proposed pegfilgrastim product so that it may seek its injunctive relief. Subsequently, in its September 8, 2017 decision, the court denied Sandoz's motion to separate equitable relief, noting that it was not clear that judicial resources would be conserved under Sandoz's approach and that the prejudice Sandoz claimed was overstated.

On September 22, 2017, following a five-day jury trial, the jury returned a verdict in the *Amgen Inc. v. Hospira Inc.* litigation involving Hospira's biosimilar version of Amgen's erythropoietin product, EPOGEN®. Amgen asserted two expired patents: U.S. Patent No. 5,756,349, related to cells capable of producing erythropoietin at certain rates, and U.S. Patent No. 5,856,298, related to erythropoietin isoforms. The jury found that Hospira did not infringe the '349 patent, but that Hospira had infringed the '298 patent. The jury also found the '298 patent valid. The jury also found that seven out of 21 batches of Hospira's product were protected by the regulatory safe harbor of 35 U.S.C. § 271(e)(1). The jury awarded $70 million in damages to Amgen. Post-trial briefing is currently ongoing.

New Litigation

In the past quarter, several new biosimilars-related suits have been filed. On August 2, 2017, AbbVie filed suit against Boehringer Ingelheim in the District of Delaware asserting infringement of eight patents related to Boehringer's biosimilar version of AbbVie's adalimumab product, HUMIRA®. Notably, AbbVie identified 74 patents during the BPCIA exchange process, but only eight of those patents are a part of this first-wave litigation.

On September 22, 2017, Amgen filed suit against Mylan in the Western District of Pennsylvania, alleging infringement related to Mylan's biosimilar version of Amgen's pegfilgrastim product, NEULASTA®.

Settlements

On September 28, 2017, AbbVie and Amgen settled their dispute relating to the drug adalimumab (HUMIRA®). Although the financial terms of the settlement were not disclosed, the parties' respective press releases reported that Amgen will pay a royalty and will be granted "a non-exclusive license to AbbVie's intellectual property relating to HUMIRA® beginning on certain dates in certain countries[.]" The license period will begin on January 31, 2023 in the United States, and on October 16, 2018 in most European countries.

In this section, we will provide a quarterly summary on key developments that occurred at the Patent Trial and Appeal Board ("PTAB") regarding patents related to biologics.

PTAB Quarterly Update

The information below will keep you up to date on filings, institutions, and final decisions of PTAB reviews, in addition to any other notable events, that took place at the PTAB in the last quarter.

Adalimumab (HUMIRA®)

During the past few months, there has been a fair amount of activity at the PTAB regarding AbbVie's anti-TNFα antibody HUMIRA® (adalimumab). Early in the quarter (June and July), the PTAB issued Final Written Decisions in favor of Petitioners Coherus and Boehringer-Ingelheim, invalidating three of AbbVie's patents directed towards a method of treating rheumatoid arthritis (U.S. Patent Nos. 8,889,135, 9,017,680 and 9,073,987). The PTAB also denied institution in September of four IPRs filed by Coherus regarding one of AbbVie's patents directed to an aqueous formulation comprising adalimumab (U.S. Patent No. 9,085,619). In addition, during this quarter, Sandoz filed seven petitions for IPR against AbbVie's patents directed to a formulation comprising adalimumab (U.S. Patent No. 8,802,100), a method of treating psoriasis (U.S. Patent No. 9,512,216 (two petitions filed) and 9,090,689), a method of treating Crohn's disease (U.S. Patent No. 8,911,737), a method of treating ulcerative colitis (U.S. Patent No. 8,974,790), and a method of treating psoriatic arthritis (U.S. Patent No. 9,067,992). Currently, we anticipate that the PTAB will begin to act on Sandoz's petitions early next year, and continue into the second quarter of 2018.

Rituximab (RITUXAN®)

In the last quarter, the PTAB has also been active regarding Genentech's anti-CD20 antibody RITUXAN® (rituximab). Specifically, in July, the PTAB instituted Pfizer's petition for IPR of Genentech's patent directed towards a method of treating rheumatoid arthritis with a combination of rituximab and methotrexate (U.S. Patent No. 7,820,161). The PTAB also joined Pfizer's petition with a petition by Celltrion on the same patent filed earlier in the year. Moreover, in late August, Pfizer and Sandoz separately filed petitions for IPR of Genentech's patent directed towards a method of treating rheumatoid arthritis (U.S. Patent No. 7,976,838). We currently expect that the PTAB will act on Pfizer's and Sandoz's petitions around the second quarter of 2018. Furthermore, in early October, the PTAB denied institution of Celltrion's IPRs regarding patents directed towards a method of treating a patient with diffuse large cell lymphoma with a combination therapy comprising rituximab (U.S. Patent No. 8,557,244), and a method of treating low grade B-cell non-Hodgkin's lymphoma comprising a rituximab maintenance therapy (U.S. Patent No. 8,329,172).

Trastuzumab (HERCEPTIN®)

Several developments at the PTAB regarding patents related to Genentech's anti-HER2 antibody HERCEPTIN® (trastuzumab) have occurred during this quarter as well. In July, the PTAB instituted three petitions for IPR filed by Hospira on patents directed to a method of treating a patient with breast cancer that overexpresses the HER2 receptor with trastuzumab (U.S. Patent Nos. 6,627,196 and 7,371,379) and a combination treatment that includes trastuzumab as one of the components (U.S. Patent No. 7,892,549). The PTAB also denied institution on two petitions filed by Hospira: another petition on the '549 patent and a petition on a combination treatment patent comprising an antibody that could include trastuzumab (U.S. Patent No. 7,846,441). Moreover, in early October, the PTAB instituted review of Celltrion IPRs filed with Teva on the '196, '379, '549, and '441 patents.

A few petitions were also filed during this quarter. In July, Pfizer filed two separate petitions for IPR on one of Genentech's patents related to a method of treating patients with nonmetastatic HER2 positive breast cancer by administering anthracycline/cyclophosphamide based chemotherapy treatment, followed by sequential administration of a taxoid and trastuzumab (U.S. Patent No. 8,591,897). Pfizer also filed two petitions in late August for IPR of Genentech's patents directed towards a composition comprising a mixture of anti-HER2 antibody such as trastuzumab and one or more acidic variants (U.S. Patent Nos. 6,339,142 and 9,249,218). In addition, Pfizer filed a petition for IPR in September of the '441 patent. In late August, Samsung Bioepsis filed three petitions for IPR on the '196, '379, and '549 patents, and concurrently filed a motion to join with the respective Hospira IPRs. Samsung Bioepsis and Boehringer-Ingelheim also separately filed two petitions for IPR on U.S. Patent No. 6,407,213. We currently anticipate that the PTAB will act on Boehringer-Ingelheim's and Samsung Bioepsis's petitions on the '213 patent around the second quarter of 2018.

Other Biologics

There were a few developments at the PTAB related to LANTUS® (insulin glargine), ERBITUX® (cetuximab), DUPIXENT® (dupilumab), and ENBREL® (etanercept). On June 5, Mylan filed two petitions for IPR of Sanofi's patents directed to a formulation of insulin glargine (U.S. Patent Nos. 7,476,652 and 7,713,930). On July 13, the PTAB issued a Final Written Decision in favor of Petitioner Eli Lilly for an IPR regarding a patent directed to a method of treating an individual with a tumor characterized by tumor cells that comprise EGFR by administering an antibody, such as cetuximab, that disrupts kinase activity mediated by EGFR (U.S. Patent No. 7,625,558). On July 28 and 31, Sanofi filed a petition on each day for IPR of Immunex's patent directed towards an isolated human antibody that competes for binding to human IL-4 receptor, such as dupilumab (U.S. Patent No. 8,679,487). These are Sanofi's second and third petitions for IPR on the '487 patent. On October 4, Sanofi's first petition on the '487 patent was denied institution. On August 4, Coherus filed a petition for IPR of Hoffman-La Roche's patent directed towards a method of making etanercept (U.S. Patent No. 8,163,522). On September 7, Coherus filed another petition for IPR of Hoffman-La Roche's compound patent related to etanercept (U.S. Patent No. 8,063,182). In addition, on August 31, Boehringer-Ingelheim filed two petitions for IPR on Genentech's patent titled "Protein Purification" (U.S. Patent No. 6,870,034).

In this section, we will provide a quarterly summary on key developments that occurred at FDA regarding biologics and biosimilars.

FDA/Regulatory Quarterly Update

The information below will keep you up to date on recent FDA developments, such as new biologics and biosimilars approvals and new guidance, compliance and regulatory information issued related to biologics and biosimilars.

FDA Draft Guidance: "Statistical Approaches To Evaluate Analytical Similarity" (September 2017)

On September 22, 2017, FDA issued a draft guidance for industry entitled "Statistical Approaches to Evaluate Analytical Similarity." The guidance is intended to inform the sponsor of an application for a proposed biosimilar product of the type of structural and functional characterization data necessary to demonstrate that a biosimilar product is "highly similar" to the reference product. The guidance also describes how that data should be used to develop an analytical similarity assessment plan and the statistical approaches to be applied in evaluating analytical similarity.

An integral part of the plan is the number of biosimilar product lots to be tested to allow for meaningful comparisons. To establish "meaningful similarity acceptance criteria," FDA recommended "a minimum of 10 reference product lots be sampled" and the lots "should represent the variability of the reference product." Furthermore, according to FDA, a minimum of 10 biosimilar lots should be included in the analytical similarity assessment to allow for meaningful comparisons.

FDA recommended that the sponsor should provide a list of "every manufactured drug substance and drug product lot of the proposed biosimilar product" that was evaluated in any manner, even if the lot was not used in the final similarity assessment. According to the guidance, the list should include a justification as to why the particular lot was included or excluded from the similarity assessment. FDA also stated that the analytical similarity assessment plan may include data from lots manufactured using different processes or scales only if additional data is submitted to show comparability between the different manufacturing processes and scales.

The final analytical similarity report should include the analytical similarity assessment plan, which should describe: (1) differences in age of the lots produced at testing; (2) multiple testing results; (3) assay performance; and (4) differences in attributes that will be considered acceptable.

FDA also described three tiers with appropriate similarity acceptance criteria that should be used to demonstrate similarity. Tier 1 is equivalence testing and "is typically recommended for quality attributes with the highest

risk ranking and should generally include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought." Tier 2 is the use of quality ranges, which "is recommended for quality attributes with a lower risk ranking." Finally, Tier 3 uses visual comparisons and "is recommended for quality attributes with the lowest risk ranking."

In conclusion, FDA noted that its "final assessment as to whether a proposed biosimilar is highly similar to the reference product is made upon the totality of the evidence, rather than the passing or failing of the analytical similarity criteria of any one tier or any one attribute." A full copy of the draft guidance can be found here.

Novartis' Kymriah™ - First-Ever CAR T-cell Therapy Approved in U.S.

On August 31, 2017, Novartis' Kymriah™ (tisagenlecleucel; CTL019) was approved by FDA for the treatment of B-cell acute lymphoblastic leukemia in pediatric and young adult patients. A novel treatment approach, Kymriah™ is the first-ever CAR-T cell therapy to win approval in the United States. CAR-T offers a new treatment approach; it is specifically manufactured for each individual patient. T cells are drawn from a patient's blood and then genetically coded to target and attack the patient's cancer cells. Specifically, the harvested T cells are genetically engineered to produce new surface proteins (the CARs, or chimeric antigen receptors) that allow them to recognize and attack cancer cells more effectively. After expanding the number of these enhanced T cells, doctors infuse them back into patients to begin attacking the cancer cells.

According to Novartis, this first-in-class therapy showed an 83 percent overall remission rate in patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

The National Cancer Institute reports that only about 3,100 Americans aged 20 and younger are diagnosed with acute lymphoblastic leukemia each year. Of those, about 600 patients whose disease relapses or doesn't respond will be eligible for the Novartis treatment. Additionally, in order to evaluate long-term safety, Novartis must conduct post-approval observational studies on patients undergoing treatment with Kymriah™.

FDA approves bevacizumab biosimilar MVASI™

On September 14, 2017, the FDA approved the first biosimilar of Amgen's bevacizumab, MVASI(R), an antibody used to treat cancer. The product is a proposed biosimilar to Avastin that was approved by FDA in 2004 and is manufactured by Genentech. Bevacizumab is a humanized monoclonal antibody that prevents angiogenesis (the formation of new blood vessels) by inhibiting the action of vascular endothelial growth factor A (VEGF-A). Bevacizumab slows and/or prevents the growth of new blood vessels in tumors and is used to treat various cancers, including colorectal, lung, breast, glioblastoma, kidney and ovarian.

FDA said that the approval was based on "structural characterizations, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other safety and effectiveness data." Mvasi™ has been approved for the treatment of several types of cancer, including in combination with chemotherapy for non-squamous non-small cell lung cancer, in combination with chemotherapy for metastatic colorectal cancer, glioblastoma, metastatic renal cell carcinoma in combination with interferon alfa and in combination with chemotherapy for persistent, recurrent or metastatic carcinoma of the cervix. FDA granted approval of Mvasi™ to Amgen, Inc.

This section will provide quarterly highlights on new biologic and biosimilar drug approvals, launches, and FDA reviews, as well as corporate developments that may impact the marketplace for biologic and biosimilar drugs.

Commercial Activities and Market Quarterly Update

New Biologic Approvals this Quarter

RITUXAN HYCELA™ (rituximab and hyaluronidase human), manufactured by Genentech, Inc., was approved June 22, 2017, and is indicated for the treatment of adult patients with follicular lymphoma, diffuse large b-cell lymphoma, and chronic lymphocytic leukemia. TREMFYA™ (guselkumab), manufactured by Janssen Biotech, Inc., was approved July 13, 2017, and is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. BENLYSTA® (belimumab), manufactured by Human Genome Sciences, Inc. (a subsidiary of GlaxoSmithKline), was approved July 20, 2017, and is indicated for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus who are receiving standard therapy. BESPONSA™ (inotuzumab ozogamicin), manufactured by Wyeth Pharmaceuticals Inc., was approved August 17, 2017, and is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. MYLOTARG®, manufactured by Wyeth Pharmaceuticals Inc., was approved September 1, 2017, and is indicated for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia and treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients two years and older.

Biosimilars Update

On July 13, 2017, the FDA Oncologic Drugs Advisory Committee unanimously voted in favor of approving two aBLA candidates: Amgen's ABP 215 (biosimilar to Genentech's AVASTIN®) and Mylan's MYL-1401O (biosimilar to Genentech's HERCEPTIN®); Amgen and Allergan received approval for their biosimilar, MVASI™ on September 14, 2017, the first biosimilar approval indicated for the treatment of cancer. Additional information about MVASI™ is available in the Regulatory Quarterly Update section of this newsletter. Merck and Samsung Bioepis launched RENFLEXIS™ (infliximab-abda; biosimilar to Johnson & Johnson's REMICADE®) on July 24, 2017. RENFLEXIS™ is indicated for Crohn's disease, pediatric Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. CYLTEZO™ (adalimumab-adbm; biosimilar to Amgen's HUMIRA®), manufactured by Boehringer Ingelheim Pharmaceuticals, Inc., was approved August 25, 2017, indicated for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis. On September 1, Fresenius Kabi announced that it had completed acquisition

of Merck KGaA's biosimilars business, a transaction announced in April 2017. Per the terms of its settlement with Amgen, AbbVie's AMJEVITA™ (adalimumab-atto) is set to launch January 1, 2023.

Biosimilars Accepted for Review

On June 30, 2017, Celltrion and Teva announced that FDA had accepted for review its application to manufacture a biosimilar to Genentech's RITUXAN® (rituximab). On July 31, 2017, Celltrion and Teva announced that FDA had accepted for review its application to manufacture a biosimilar to Genentech's HERCEPTIN® (trastuzumab). On July 31, 2017, Amgen and Allergan announced the submission of ABP 980, a biosimilar to Genentech's HERCEPTIN®. On September 11, 2017 Adello Biologics announced that FDA had accepted for review its application to manufacture a biosimilar to Amgen's NEUPOGEN® (filgrastim). On September 12, 2017, Sandoz announced that FDA had accepted for review its application to manufacture a biosimilar to Genentech's RITUXAN® (rituximab). On September 14, 2017, Adello Biologics announced that FDA had accepted for review its application to manufacture a biosimilar to Amgen's NEUPOGEN®.

Biologics Accepted for Review

On June 30, 2017, Theratechnologies announced that FDA had accepted for accelerated review its BLA for ibalizumab as a treatment for multidrug-resistant HIV-1; in October, Theratechnologies presented 48-week efficacy and safety results. On July 19, Evolus announced that FDA had accepted for review its BLA for DWP-450 (botulinum toxin Type A) for treatment of adult patients with glabellar lines. On July 20, 2017, Amgen announced that FDA had accepted for review its BLA for AIMOVIG™ (erenumab) for the prevention of migraines. On August 15, 2017, Portola Pharmaceuticals announced that FDA had accepted for review its BLA for ANDEXXA® (andexanet alfa) for reversal of anticoagulation in patients treated with a direct or indirect Factor Xa inhibitor. On August 16, 2017, Seattle Genetics, Inc. announced that FDA had accepted for review its supplemental BLA for ADCETRIS® (brentuximab vedotin) in cutaneous T-cell lymphoma. On September 22, 2017, Janssen Biotech received a Complete Response Letter for its sirukumab BLA, seeking approval for the treatment of moderately to severely active rheumatoid arthritis; in August, the FDA's Arthritis Advisory Committee did not recommend approval.

New Biologic Highlight

On August 30, FDA approved Novartis's KYMRIAH™ (tisagenlecleucel). KYMRIAH™ is the first gene therapy approved in the United States; each dose is a customized treatment using a patient's own T-cells, which are genetically modified and infused back into the patient (CAR-T). The BLA product is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. Additional information about KYMRIAH™ is available in the Regulatory Quarterly Update section of this newsletter.

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

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