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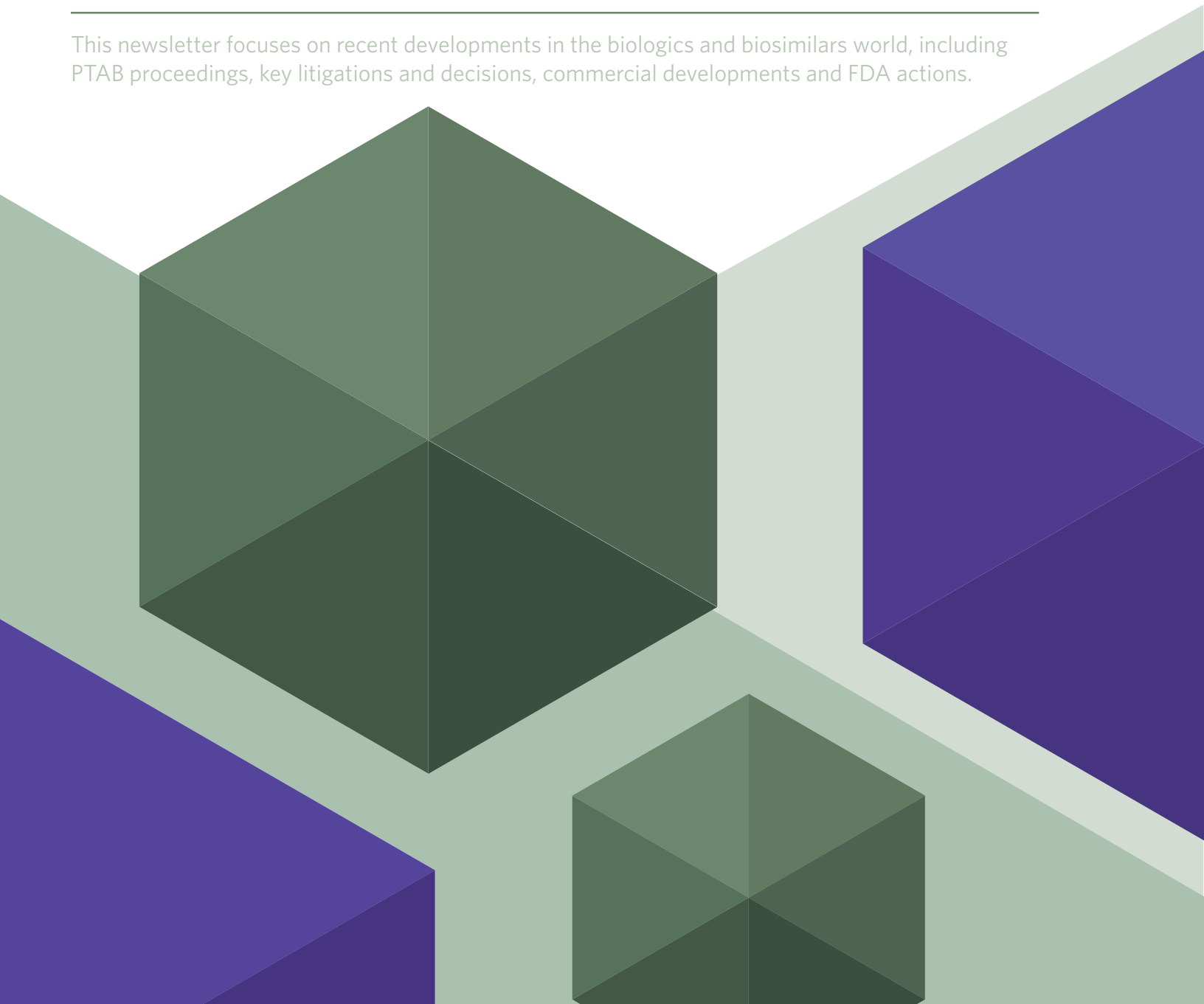
INTELLECTUAL PROPERTY NEWSLETTER

October 2018

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.



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Willkie recently presented a three-part webinar series, focusing on regulatory and market issues affecting biologics and biosimilars in the United States and Europe, with Taylor Wessing LLP. For more information, see the feature article of this newsletter, or contact us here.

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

PTAB Quarterly Update

USPTO Issues Final Rule Changing Claim Construction Standard in PTAB Proceedings

On October 11, 2018, the USPTO issued a final rule revising the claim construction standard for interpreting claims in IPR, PGR, and CBM proceedings. The PTAB will no longer construe terms under the broadest reasonable interpretation standard, but will now construe terms using the "same claim construction standard used by Article III federal courts and the ITC, both of which follow *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), and its progeny." The final rule also includes a provision stating that the USPTO will consider any prior claim construction determination in a civil action, or proceeding before the ITC, regarding a term of the claim in an IPR, PGR, or CBM proceeding, if that determination is timely filed in the record of the IPR, PRR, or CBM proceeding. According to the USPTO, having the same claim construction standard for both the original patent claims and proposed substitute claims will "reduce the potential for inconsistency in the interpretation of the same or similar claim terms."

The new rule takes effect on November 13, 2018 and applies to all IPR, PGR, and CBM petitions filed on or after the effective date.

Questions about the final rule change? Click here.

Trastuzumab (HERCEPTIN®):

On July 31, 2018, the PTAB granted Boehringer Ingelheim's unopposed request for adverse judgment in its IPRs against Genentech's patent, U.S. Patent No. 6,407,213, directed towards a humanized antibody variable domain comprising non-human CDR amino acid residues. (Case Nos. IPR2017-02031 and -02032). The PTAB had previously instituted both petitions on all grounds.

On October 3, 2018, the PTAB issued Final Written Decisions in favor of Petitioners Hospira, Samsung Bioepis, and Celltrion, finding that all 17 claims of Genentech's patent, U.S. Patent No. 7,892,549, are unpatentable as obvious over the prior art. (Case Nos. IPR2017-00737, -01960, -01122). Claim 1 of the '549 patent recites a method for treating breast cancer with a combination of trastuzumab, a taxoid, and a further growth inhibitory agent. Claims 16 and 17 further require that the treatment is administered in the absence of an anthracycline derivative. The PTAB found that a person of ordinary skill in the art ("POSA") would have understood that taxoids were used in combination therapy for the treatment of breast cancer, were suggested to be particularly useful for treating HER2 breast cancer, and demonstrated synergy in combination with anti-HER2 antibodies in animal models. Further, the PTAB agreed with the Petitioners that a POSA would have expected

many patients had previous anthracycline treatment, and for those patients, it would have been obvious not to include the drug in the combination of trastuzumab and a taxoid.

The PTAB also issued a Final Written Decision regarding Genentech's patent, U.S. Patent No. 7,846,441, directed towards a method of treating a patient with a combination of trastuzumab and a taxoid in the absence of an anthracycline derivative, without increase in overall severe adverse events. (Case Nos. IPR2017-00731, -01121). For confidentiality reasons, the decision was not published when it was decided. On October 17, 2018, Genentech submitted an unopposed statement that the Final Written Decision does not contain confidential information.

Also on October 3, the PTAB issued Final Written Decisions in favor of Genentech, finding that Petitioners Hospira, Samsung Bioepis, and Celltrion did not show that the asserted claims of U.S. Patent Nos. 6,627,196 (Case Nos. IPR2017-00804/1958, -01139) and 7,371,379 (Case Nos. IPR2017-00805/1959, -01140) were unpatentable over the prior art. Both the '196 and '379 patents recite a method of treating cancer by administering an initial dose of 5 mg/kg of trastuzumab, and subsequent doses separated by at least two weeks. The '379 patent further recites administering a chemotherapeutic agent to the patient.

The PTAB for IPR2017-00804/805 found that the prior art teaches weekly dosing, and that a POSA would have been motivated to extend the dosing interval from weekly to once every three weeks. However, according to the PTAB, the Petitioners did not meet their burden of establishing a reasonable expectation of success. The Petitioners failed to point to any prior art reference discussing the feasibility or viability of a tri-weekly antibody dosing regimen. In addition, the prior art did not contain sufficient data for a POSA to reliably predict the plasma concentration for trastuzumab over a three-week dosing interval. In IPR2017-01139/1140, the PTAB found that a POSA would have been motivated to extend the dosing interval of trastuzumab to every three weeks to match that of paclitaxel, another cancer drug that was known to be co-administered with trastuzumab. The PTAB, however, determined that the Petitioner failed to meet its burden in addressing the motivation for a POSA to modify the dosage amounts for the recited loading and maintenance dose from the dosage amounts taught in the prior art. Thus, the PTAB concluded that the Petitioners failed to show that the asserted claims of the '196 and '379 patents were unpatentable.

Rituximab (RITUXAN®):

On August 21, 2018, the PTAB heard oral arguments on Celltrion's IPR against Biogen's and Genentech's patent, U.S. Patent No. 9,296,821, directed towards a method of treating low-grade or follicular non-Hodgkin's lymphoma (Case No. IPR2017-01095), and on October 4, 2018, the PTAB issued a Final Written Decision in favor of Celltrion. The '821 patent has six independent claims. Claim 1 recites a method for treating low grade or follicular non-Hodgkin's lymphoma ("NHL") comprising administering to a patient 375 mg/m2 of rituximab during a chemotherapeutic regimen, wherein the method provides a beneficial synergistic effect in the patient. Celltrion asserted five grounds, arguing that the claims of the '821 patent are anticipated and/or obvious based on different combinations of 10 references.

The PTAB determined that one of the parent applications to the '821 patent did not provide adequate written description support for claims 4–6, and thus, such claims were not entitled to receive the benefit of the parent application's priority date. This decision affected Celltrion's reliance on a reference published after the parent application's priority date, and would therefore be prior art only to claims 4–6. The PTAB found that claims 4–6 were unpatentable as anticipated. Celltrion also asserted that claims 1–3 were obvious over four references, including an annual report filed with the U.S. Securities and Exchange Committee ("SEC"). The Patent Owner argued that the SEC report was not a printed

publication, and the PTAB agreed. Although Celltrion demonstrated that the SEC report was published and made available to the public in a searchable database, Celltrion did not explain that a person of ordinary skill in treating NHL would have known to locate the SEC report. This decision did not impact the PTAB's final decision, however, which found that claims 1–3 were unpatentable as obvious over the three remaining references.

Bevacizumab (AVASTIN®):

On August 2, 2018, the PTAB denied institution of Pfizer's IPR against Genentech's patent, U.S. Patent No. 9,795,672, directed towards treating a cancer patient with a grade III hypertensive event with bevacizumab and an antihypertensive agent (Case No. IPR2018-00373). Pfizer's petition challenged all claims of the '672 patent as anticipated and/or obvious over the prior art. Pfizer had pointed to statements made by the applicant during prosecution, and argued that the '672 patent was not entitled to the provisional application filing date for priority because the challenged claims are not supported by the written description of the provisional application. The PTAB agreed with Genentech, however, finding that the provisional application provided adequate written description support. This determination of priority impacted Pfizer's grounds that were based on prior art published after the priority date, and denied institution on those grounds. The PTAB also exercised its discretion under § 325(d) and declined to consider grounds based on prior art previously considered by the office. For the remaining grounds, the PTAB denied institution because the Petitioner did not show a reasonable likelihood of prevailing in showing the unpatentability of the challenged claims.

Galcanezumab:

On August 8, 2018, Eli Lilly filed six IPR petitions challenging Teva's patents directed towards (1) a human or humanized monoclonal anti-CGRP (Calcitonin Gene-Related Peptide) antagonist antibody that preferentially binds to human α-CGRP as compared to amylin (U.S. Patent No. 9,340,614; Case No. IPR2018-01422); (2) a human anti-CGRP antagonist antibody that binds human α-CGRP and inhibits cyclic adenosine monophosphate (cAMP) activation in cells (U.S. Patent No. 9,266,951; Case No. IPR2018-01423); (3) a human anti-CGRP antagonist antibody that binds human α-CGRP and inhibits human α-CGRP from binding to its receptor as measured by a radioligand binding assay in SK-N-MC cells (U.S. Patent No. 9,346,881; Case No. IPR2018-01424); (4, 5) a humanized monoclonal anti-CGRP antagonist antibody (U.S. Patent Nos. 9,890,210 and 9,890,211; Case Nos. IPR2018-01425, -01426); and (6) an isolated human anti-CGRP antagonist antibody with a binding affinity (KD) to human α-CGRP of 50 nM or less as measured by surface plasmon resonance at 37° C (U.S. Patent No. 8,597,649; Case No. IPR2018-01427). Teva will need to file a response by November 2018, and we anticipate the PTAB will act on these petitions around February 2019.

Other Biologics:

On August 2, 2018, the PTAB heard oral arguments for Pfizer's IPRs against Chugai Pharmaceutical's patents entitled "Method of purifying protein" and "Protein purification method" (U.S. Patent Nos. 7,332,289 and 7,927,815; Case Nos. IPR2017-01357, -01358, respectively). We anticipate that the PTAB will likely issue a final written decision around December 2018.

On September 6, 2018, the PTAB heard oral arguments for Mylan's IPR of Sanofi's patents drawn toward a formulation of insulin glargine (U.S. Patent Nos. 7,476,652 and 7,713,930; Case Nos. IPR2017-01526, -01528, respectively). Currently, we anticipate that the PTAB will likely issue a final written decision around December 2018.

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

I. Key District Court Decisions

Janssen v. Celltrion. On July 30, 2018, the District Court for the District of Massachusetts granted Celltrion's motion for summary judgment of non-infringement in its litigation surrounding Celltrion and Hospira's INFLECTRA® - a biosimilar of Janssen's REMICADE® (infliximab). Janssen alleged infringement only under the doctrine of equivalents of U.S. Patent No. 7,598,083 ("the '083 patent"), which relates to the use of "chemically defined media useful in the culture of eukaryotic cells." The District Court agreed with Celltrion that the scope of equivalents sought by Janssen would improperly ensnare the prior art.

After an extensive analysis of the four obviousness factors, and acknowledging the burden-shifting framework of the ensnarement analysis, the court concluded that the asserted equivalents would have been obvious and that "Janssen has not produced sufficient evidence to prove that the scope of equivalents would not ensnare the prior art." As the '083 patent was the only patent-in-suit, final judgment of non-infringement was entered on July 31, 2018. Janssen filed its notice of appeal from the judgment to the Court of Appeals for the Federal Circuit on August 24, 2018, and Celltrion filed a notice of cross appeal on August 31, 2018, from both this judgment and from an October 2017 order denying its motion to dismiss for lack of standing.

Amgen v. Hospira. On August 27, 2018, the District Court for the District of Delaware ruled on the parties' post-trial motions in this litigation, which concerns Hospira's RETACRIT®, an FDA-approved biosimilar to Amgen's EPOGEN® (epoetin alfa). After a jury trial in September 2017, Hospira was found to have infringed U.S. Patent No. 5,856,298 ("the '298 patent"), which claims a method of protein purification, but was found not to infringe U.S. Patent No. 5,756,349 ("the '349 patent"). Hospira had argued that all of these batches were manufactured for use in seeking FDA approval and were thus sheltered by the safe harbor provisions of 35 U.S.C. § 271(e)(1). After trial, both parties filed motions for judgment as a matter of law, or in the alternative for a new trial, challenging portions of the jury verdict and contesting the proper calculation of damages.

The court denied Hospira's motions, finding substantial evidence in the trial record to support the jury's verdict on the issues of the safe harbor defense under § 271(e)(1), noninfringement and invalidity of the '298 patent, and the amount of the damages award. The court also denied Amgen's motions for judgment as a matter of law or, in the alternative, for a new trial on the issue of infringement of the '349 patent, again citing substantial evidence that the jury could credit in the trial record,

and granted-in-part Amgen's motion for prejudgment and post-judgment interest. Final judgment was entered on September 11, 2018. Hospira filed its notice of appeal from the judgment and other orders to the Court of Appeals for the Federal Circuit on October 3, 2018. Amgen cross-appealed on October 15, 2018.

Teva v. Eli Lilly. On September 27, 2018, the District Court for the District of Massachusetts granted Lilly's motion to dismiss Teva's amended complaints for lack of subject-matter jurisdiction under Rule 12(b)(1). The suits were filed under the Declaratory Judgment Act, with Teva seeking an injunction barring Lilly from marketing EMGALITY™ (galcanezumab) because it would infringe nine patents related to Teva's AJOVY™ (fremanezumab). The cases were not brought under the BPCIA framework because the two products contain distinct antibodies, and because Lilly's galcanezumab application was a BLA under 42 U.S.C. § 262(a), rather than a § 262(k) aBLA. However, both galcanezumab and fremanezumab are humanized monoclonal antibodies that treat migraine headaches by targeting calcitonin gene-related peptide.

The court held that, at the time that Teva filed its Complaints, Lilly had not yet received FDA approval for EMGALITY™, and the prospect of approval was too uncertain or speculative to establish an actual case or controversy sufficient for the court to exercise jurisdiction under the DJA. Moreover, the only actions Lilly had undertaken to commercialize its product were those related to seeking regulatory approval from FDA, and the court held that to find declaratory judgment jurisdiction would be to "eviscerate" the protection provided by Congress to such activities under the § 271(e)(1) safe harbor. Following the dismissal, Teva filed a new complaint asserting direct and induced infringement of the same nine patents based on FDA approval of EMGALITY™, which Lilly received the same day these suits were dismissed. Although EMGALITY™ has now launched (see the Marketing Update section for more information), this new suit also repeats the claims for a declaratory judgment of future infringement from the earlier suits.

Want to learn more about these cases? Please contact us here.

II. New Litigation

On July 18, 2018, Amgen filed a patent infringement suit in the District of Delaware against Hospira relating to Hospira's aBLA filing for its biosimilar candidate to Amgen's NEUPOGEN® (filgrastim). Amgen asserts that the manufacturing process of Hospira's aBLA product infringes U.S. Patent No. 9,643,997, which claims a method of purifying "proteins expressed in a non-mammalian system."

On August 7, 2018, Amgen filed a third Complaint in the Southern District of Florida relating to Apotex's proposed biosimilars to Amgen's NEUPOGEN® (filgrastim) and NEULASTA® (pegfilgrastim). In this action, Amgen asserts U.S. Patent No. 9,856,287, granted January 2, 2018, which claims a process for refolding proteins. Last November, the Court of Appeals for the Federal Circuit affirmed the District Court's findings in two related cases that Apotex's aBLA products did not infringe an earlier protein refolding patent asserted by Amgen.

On August 10, 2018, AbbVie filed a complaint in the District of New Jersey relating to Sandoz's aBLA filing for a proposed biosimilar to AbbVie's HUMIRA® (adalimumab). AbbVie asserts that Sandoz's biosimilar will infringe two patents, which claim a method of treating inflammatory bowel disease and a human antibody formulation for treating TNFα associated disorders. On October 12, 2018, the parties filed a stipulation dismissing this action as part of a global settlement agreement between the parties resolving all ongoing litigation relating to Sandoz's biosimilar adalimumab product. According to a press release announcing the settlement, AbbVie has granted a license that will allow Sandoz to begin commercial marketing of its adalimumab biosimilar in most European countries on

October 16, 2018 and in the United States on September 30, 2023.

On September 4, 2018, Genentech filed suit in the District of Delaware against Samsung Bioepis, alleging that Samsung's aBLA filing for its biosimilar candidate to Genentech's HERCEPTIN® (trastuzumab) infringes 21 patents drawn generally to manufacturing processes and methods of treatment related to trastuzumab.

III. Settlements and Stipulations

Genentech v. Amgen. On July 19, 2018, the parties in this action, relating to Amgen's biosimilar candidate to Genentech's HERCEPTIN® (trastuzumab), filed a Joint Stipulation and Order to Dismiss Patents, which was approved by the District Court for the District of Delaware on July 23, 2018. As discussed here last quarter, Genentech originally asserted 37 patents. Through the BPCIA's negotiation and exchange process, the parties agreed to dismiss 19 of the asserted patents. Genentech filed an amended complaint asserting only the remaining 18 patents-in-suit on the same day that the stipulation was filed.

Immunex v. Sandoz. On September 10, 2018, Sandoz stipulated to infringement of claims of two of the patents-in-suit on the eve of trial in its litigation relating to Sandoz's aBLA filing for a biosimilar candidate to Immunex's ENBREL® (etanercept). A bench trial was held as to infringement of the remaining patents-in-suit, as well as on Sandoz's invalidity defenses on the two patents covered by the stipulation. The trial was held before Judge Cecchi of the District Court for the District of New Jersey from September 11, 2018 to September 25, 2018.

Genentech v. Celltrion. On October 15, 2018, the parties in this pair of actions, both relating to Celltrion and Teva's biosimilar candidate to Genentech's HERCEPTIN® (trastuzumab), filed a Joint Stipulation and Order, which was approved by the District Court for the District of Delaware on October 18, 2018, agreeing to dismiss all claims and counterclaims related to 22 previously asserted patents. Through the BPCIA's negotiation and exchange process, the parties narrowed the patents-in-suit from the 40 patents that Genentech had initially asserted in each suit, which were drawn generally to manufacturing processes and methods of treatment related to trastuzumab.

New biologic and biosimilar launches, and other marketplace developments

Market Quarterly Update

Pricing and Reimbursement Updates

USMCA, the renegotiated trilateral trade deal between the United States, Mexico, and Canada, included a provision extending exclusivity for biologic innovators throughout North America. As part of the agreement, which replaced NAFTA, biologic drugs will be free from competition for at least 10 years, up from the current eight years in Canada and five years in Mexico. In the United States, new biologics enjoy a 12-year period without biosimilar competition, a time frame that was not affected by the agreement.

For a summary of other IP provisions of the Agreement, please contact us here.

On October 15, 2018, the Centers for Medicare & Medicaid Services announced a proposed rule that would require prescription drug manufacturers include in direct-to-consumer television advertisements the wholesale acquisition cost for drugs covered by those programs. Under the proposed rule, the listed price would be that of a typical course of treatment for an acute medication, or the cost for a 30-day supply for chronic conditions. Prescription drugs costing less than $35 per month would be exempt from the requirement.

New Biologic and Biosimilar Launches

On July 26, 2018, Mylan confirmed that it had launched FULPHILA™ (pegfilgrastim-jmdb), biosimilar to Amgen's NEULASTA®, which was approved in June to decrease the incidence of infection as manifested by febrile neutropenia in patients receiving myelosuppressive chemotherapy. The wholesale cost for FULPHILA™ is $4175 per syringe, which represents a 33% discount from the reference product, according to the Center for Biosimilars. Upon launch, FULPHILA™ became the fourth biosimilar available in the United States.

On September 27, 2018, Eli Lilly announced that its EMGALITY™ (galcanezumab-gnln) had received final approval from FDA and would launch "shortly after approval." The third of three anti-CGRP approved for the treatment of migraines this year, Eli Lilly announced a list price of $6,900 per year, the same as Amgen's AIMOVIG® (erenumab) and Teva's AJOVY™ (fremanezumab), which also launched in late September. According to a press release, EMGALITY™ will be offered at no cost to patients with commercial insurance for up to 12 months. According to a Bloomberg report, EMGALITY® is forecast to reach $700 million in sales by 2022, with anti-CGRP medications totaling a $2.2 billion market.

For more information regarding the dispute between Teva and Lilly, please see the Litigation section of this newsletter (p.7).

On October 1, 2018, Pfizer launched NIVESTYM™ (filgrastim-aafi), biosimilar to Amgen's NEUPOGEN®, joining Sandoz's ZARXIO® (filgrastim-sndz) and Teva's GRANIX® (tbo-filgrastim, a follow-on product approved prior to the BPCIA) as filgrastim biosimilars on the market. Like the reference product, NIVESTYM™ is approved to treat neutropenia and to mobilize autologous progenitor cells into peripheral blood for leukapheresis. According to the Center for Biosimilars, the wholesale acquisition cost for the biosimilar is $350.40 per prefilled syringe, approximately 30% lower than the pricing for NEUPOGEN®, 20% below Zarxio®, and 14.1% below Granix®. Upon launch, NIVESTYM™ became the fifth biosimilar available in the United States.

Other Market Developments

On July 23, 2018, Eli Lilly announced an agreement worth up to $1.05 billion with New Jersey-based Anima Biotech, with $30 million upfront and the remainder based on development and commercial milestones, according to a press release. Anima, which is focused on a new class of translation inhibitors, will use its platform to discover lead candidates for Lilly, who will be responsible for development and marketing of any products to come out of the collaboration.

On August 17, 2018, Novo Nordisk announced its acquisition of Ziylo, which was spun out from the University of Bristol, in a deal worth upwards of $800 million. According to Novo Nordisk's press release, Ziylo's platform is based on synthetic glucose binding molecules for therapeutic and diagnostic applications. Although Ziylo is yet to move candidates into human testing, Novo seeks to develop glucose responsive insulins for the treatment of diabetes.

On September 10, 2018, Amicus announced its purchase of Celenex, in a deal that includes $100 million in upfront payments and that could reach $452 million. Celenex, a gene therapy developer with a portfolio of 10 programs in lysosomal storage disorders (LSD), has candidates aimed at Baten disease, Niemann Pick C, Wolman disease, Tay Sachs disease, and other unspecified CNS disorders, according to Amicus's press release.

On September 26, 2018, Alexion announced its acquisition of Boston-based Syntimmune in a deal worth $400 million up front, with an additional $800 million in milestone payments. Syntimmune's lead candidate, SYNT001, is currently in phase 1b/2a trials for a variety of conditions characterized by high levels of IgG antibodies, and may be a candidate for the treatment of additional other rare diseases, Alexion stated.

On October 1, 2018, Merck announced that it signed a research and development collaboration agreement with Cambridge, Massachusetts-based Dragonfly Therapeutics, which is developing a platform (TriNKET) aimed at stimulating natural killer (NK) cells to attack solid tumors. Although terms of the agreement were not announced, the deal could be worth up to $695 million, Dragonfly announced.

On October 18, Novartis announced that it had entered into an agreement to purchase West Lafayette, Indiana-based Endocyte for $2.1 billion. According to the release, Endocyte uses drug conjugation technology to develop targeted therapies with companion imaging agents; its lead candidate, Lu-PSMA-617, is an investigational radioligant therapy for the treatment of metastatic castration-resistant prostate cancer, and is currently in Phase III trials.

Key developments at FDA regarding biologics and biosimilars

FDA/Regulatory Quarterly Update

FDA Issues Revised Guidance on the Use of Citizen Petitions

On October 2, 2018, FDA issued a revised draft guidance which will allow it to reject 505(q) petitions if the agency determines the primary purpose of the petition is to delay the approval of an abbreviated new drug application (ANDA) or abbreviated Biologics License Application (aBLA). The guidance also states that FDA intends to inform the Federal Trade Commission if it determines that a petition has been filed in order to delay a generic drug's approval. FDA will also seek to respond within 150 days to Citizen Petitions filed during the review of a generic application (ANDA or aBLA), given the agency's new goal to issue determinations within 10 months of a generic application.

FDA also provided for a means to determine whether a petition would delay approval of a generic drug, such as matters related to public health. The guidance states that issues that would involve public health are, for example, whether a patent-protected indication can be safely omitted from the label, or whether the proposed generic has shown that it is bioequivalent to the reference drug. The new guidance also states that FDA will require a petition to include a certification and that supplemental information or comments to a petition must also include a verification.

For questions, or for a copy of the draft guidance, please click here.

New Biosimilars

FDA Approves NIVESTYM™ (filgrastim-aafi)

On July 20, 2018, FDA approved Pfizer Inc.'s NIVESTYM™ (filgrastim-aafi), the second approved filgrastim biosimilar to Amgen's NEUPOGEN®. The drug is approved for the same indications as the reference product, such as severe chronic neutropenia and neutropenia-related side effects from cancer treatment. NIVESTYM™ is the third biosimilar approved in 2018.

Biosimilars Under Development

On September 27, 2018, Samsung Bioepis announced that FDA has accepted a Biologics License application (BLA) for its adalimumab biosimilar, SB5, referencing HUMIRA®. SB5, under the name Imraldi, is expected to launch in the European Union next month, along with several other adalimumab biosimilars, and health systems are beginning to prepare for the arrival of these cost-saving biosimilars.

On September 12, 2018, Boehringer Ingelheim announced results from a Phase III study, confirming

that CYLTEZO® (adalimumab-adbm) is a biosimilar to HUMIRA®, with no clinically meaningful differences in efficacy, safety and immunogenicity in people with moderate-to-severe chronic plaque psoriasis. The 16-week data was presented at the European Association of Dermatology and Venereology Annual Meeting (EADV 2018) in Paris. Boehringer Ingelheim is currently conducting a clinical trial looking to demonstrate interchangeability between adalimumab-adbm and the reference product.

On August 29, 2018, Celltrion announced that the company has completed a Phase III clinical trial for biosimilar infliximab (CT-P13). CT-P13 is already sold in the United States as INFLECTRA® and in other territories as REMSIMA™. Celltrion announced that it will now prepare a marketing authorization application for submission to the European Medicines Agency (EMA).

On July 26, 2018, Glenmark Pharmaceuticals announced that its Phase I study of GBR 310 revealed similar pharmacokinetic, pharmacodynamic, safety, and immunogenicity profiles between its proposed omalizumab biosimilar and the reference product XOLAIR®.

This article analyzes FDA's new Biosimilars Action Plan, and describes certain efforts by biologics manufacturers to delay biosimilar market entry.

FEATURED ARTICLE

FDA's Biosimilars Action Plan: No More "Regulatory Whack-a-Mole"

On July 18, 2018, FDA Commissioner Scott Gottlieb announced that the agency was undertaking a plan to advance policies and streamline the development of biosimilars. According to the commissioner, the key to reducing costs and increased innovation is to enable a more efficient path to competition for biologics. Dr. Gottlieb stated that the biosimilars action plan (BAP) would contribute to a reduction in costs for biosimilar applicants while giving innovators an added incentive to invest in further research, which could lead to the discovery of even better drugs with additional benefits for patients.

The commissioner noted that biologics currently represent 40% of the total spending on prescription drugs even though less than 2% of Americans use biologics. In fact, biologic drug costs represented 70% of the growth in drug spending from 2010 to 2015, and are predicted to be the fastest-growing segment of drug spending over the next several years. According to Dr. Gottlieb, cost savings from marketed biosimilars have been disappointing and the lack of competition in the biosimilar space cost U.S. patients more than $4.5 billion in 2017. To date, FDA has approved only 12 biosimilar products, and just five are available on the market; pointing to these numbers, Dr. Gottlieb called the U.S. market for biosimilars "anemic."

Thus, Dr. Gottlieb stated, the BAP "is aimed at promoting competition and affordability across the market for biologics and biosimilar products." To support the biosimilar manufacturers in their process to bring a biosimilar to market, FDA's BAP calls for four key categories of regulatory action:

- Improving the efficiency of the biosimilar and interchangeable product development and approval process:
- Maximizing scientific and regulatory clarity for the biosimilar product development community
- Developing effective communications to improve understanding of biosimilars among patients, providers, and payers
- Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay market competition to follow-on products

To improve the efficiency of the biosimilars' approval process, FDA will develop and implement new FDA review tools, like standardized review templates tailored to marketing applications for biosimilar and interchangeable products. It will also create information resources and development tools, such as *in silico* models and pharmacometrics to improve clinical study design. Lastly, FDA proposed setting up potential data

–sharing agreements with foreign regulators to facilitate increased use of non-U.S.-approved biosimilars.

To maximize scientific and regulatory clarity for biosimilar developers, FDA proposes to establish an Office of Therapeutic Biologics and Biosimilars to handle communications between the agency and applicants and support policy development and implementations. In addition, FDA committed to publish final or revised guidance on biosimilar product labeling and on the use of data–analysis methods. Furthermore, it also committed to providing additional clarity as to how biosimilar manufacturers can demonstrate interchangeability, including clarity and flexibility on analytical approaches to support such a showing. Lastly, FDA committed to providing additional support to product developers regarding product quality and manufacturing processes by identifying the critical physical product quality attributes and ways to reduce the number of reference product lots necessary for testing.

To support market competition and improve the understanding of biosimilars among patients and providers, and to reduce attempts to unfairly delay market competition to follow-on products, FDA announced it will continue to educate health care professionals about biosimilar and interchangeable products. Furthermore, it will continue to engage in public dialogue about the biosimilar program and potential policy steps FDA should consider in order to enhance the biosimilar program. Lastly, FDA proposed taking new steps to challenge gaming tactics by partnering with the Federal Trade Commission to address anticompetitive behavior.

Indeed, Dr. Gottlieb expressed his frustration with some of the tactics employed by the brand biologics makers: "Sometimes it feels as if we're seeing the biosimilars version of 'Groundhog Day,' with brand drug makers replaying many of the same tactics, and all of us being too susceptible to many of the same misconceptions about biosimilars' safety and efficacy relative to originator biologics." Continuing his criticism, the commissioner stated that reference product sponsors engaged in similar tactics as previously used to deter generic competition following the passage of the Hatch-Waxman Act. He warned that FDA would not "play regulatory whack-a-mole with companies trying to unfairly delay or derail the entry of biosimilar competitors." These comments suggest that FDA may take active measures to ensure that the market will embrace competition from biosimilars.

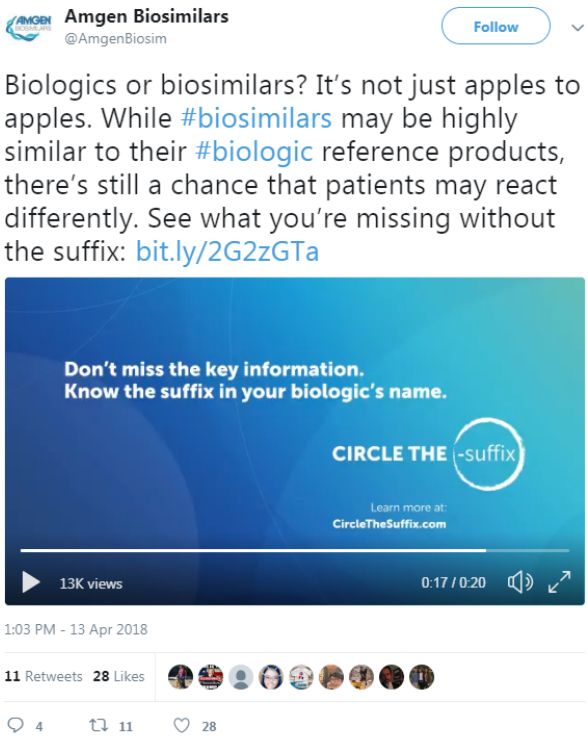
The commissioner's frustration with reference product sponsors' tactics to delay market entry of biosimilars was also echoed in a recent citizen's petition. Encouraged by FDA's recent show of support for biosimilars market penetration, on August 22, 2018, Pfizer submitted a Citizen Petition in which it asked FDA to issue a draft guidance clarifying the type of communications reference product sponsors may release with regard to biosimilars. According to Lisa M. Skeens, Ph.D., vice president of global regulatory affairs for Pfizer Essential Health, "the efforts of certain reference product sponsors to disseminate false and misleading information that casts doubt about the safety and efficacy of biosimilars in the minds of patients and prescribers." Similarly to Dr. Gottlieb, Dr. Skeens noted that the development of reimbursement policies that would encourage biosimilar use is thwarted by misinformation streaming from the reference product sponsors.

Pfizer's Citizen Petition cited several examples of such misinformation:

- Genentech's "Examine Biosimilars" website, which states that "the FDA requires a biosimilar to be highly similar, but not identical to the existing biologic medicine." According to Pfizer, Genentech failed to properly communicate the definition of a biosimilar by not stating that an approved biosimilar must have no clinically meaningful differences from its reference product.
- Janssen Biotech's patient brochure for REMICADE® states that a biosimilar works "in a similar way" but does not inform the patient that the biosimilar has (and must have) the same mechanism of action as the reference product. Furthermore, the brochure states that an "infliximab biosimilar is not approved as an

interchangeable with REMICADE" and "no infliximab biosimilar has yet proven" that switching from REMICADE® to a biologic would be safe or effective. Pfizer argued that this language is misleading.

- An April 13, 2018 tweet by Amgen suggested that patients may react differently to biosimilars than to reference products. Pfizer argued that an Amgen YouTube video is also misleading by implying that switching to a biosimilar is unsafe for patients who are well controlled on a current therapy:



In its petition, Pfizer proposed that FDA issue new draft guidance addressing these and similar tactics to deter biosimilar usage. Pfizer recommended that the guidance should clarify that a reference product sponsor's statement that a biosimilar is not "identical" should also state that there are no clinically meaningful differences between the biosimilar and the reference product. Otherwise, Pfizer argued, reference product sponsors may give the false impression that the biosimilar is not as safe or effective as the reference product. Furthermore, Pfizer requested that the guidance deem statements that represent or suggest that a biosimilar product is inferior to an interchangeable biologic in terms of quality or similarity as misleading and in violation of the FD&C Act. Lastly, Pfizer suggested that the guidance describe and provide examples of the types of false and misleading claims about biosimilars and interchangeability that could cause confusion and mistrust among patients and physicians.

Notably, several biosimilar product sponsors, including Mylan and Boehringer, indicated their agreement with Pfizer in their responses to FDA's Part 15 public hearing held on September 4, 2018 and accompanying request for comments on its "approach to enhancing competition and innovation in the biological products marketplace."

The biologics and biosimilars industry can expect further analysis from FDA as Dr. Gottlieb said the agency will soon release the details of its analysis that correlated timely marketing of biosimilars in the U.S. with more than $4.5 billion in 2017 in consumer savings. With only five of the 12 FDA-approved biosimilars currently on the market, FDA intends to make clear that promoting the approval of additional biosimilars is a top priority for the agency. However, it remains to be seen how FDA will ensure fair competition in the market and whether FDA will implement any of the comments made by biosimilar sponsors, such as those made by Pfizer in its Citizen Petition.

For a complete copy of the draft guidance, please contact us here.

Willkie recently conducted a three-part webinar series on biosimilars in the United States and Europe, in conjunction with Taylor Wessing. Part one of the webinar focused on the regulatory framework for biosimilars and the patent dance in the United States under the BPCIA. Part two discussed interchangeability, naming, and advertising issues facing biosimilars. Part three looked at biosimilar pricing, market structure, and competition issues. *For a copy of the slides, please click* here.

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

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