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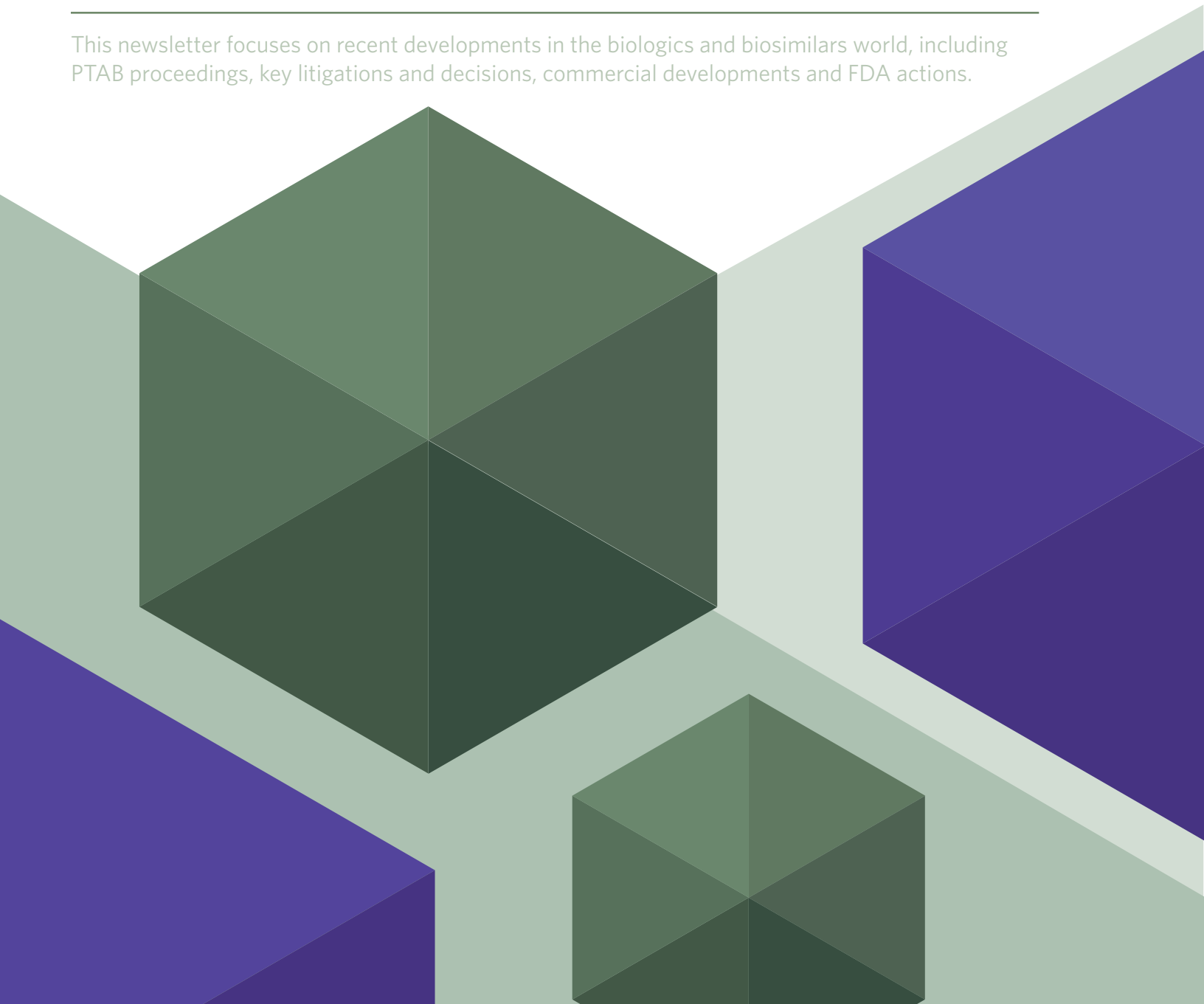
INTELLECTUAL PROPERTY NEWSLETTER

July 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.



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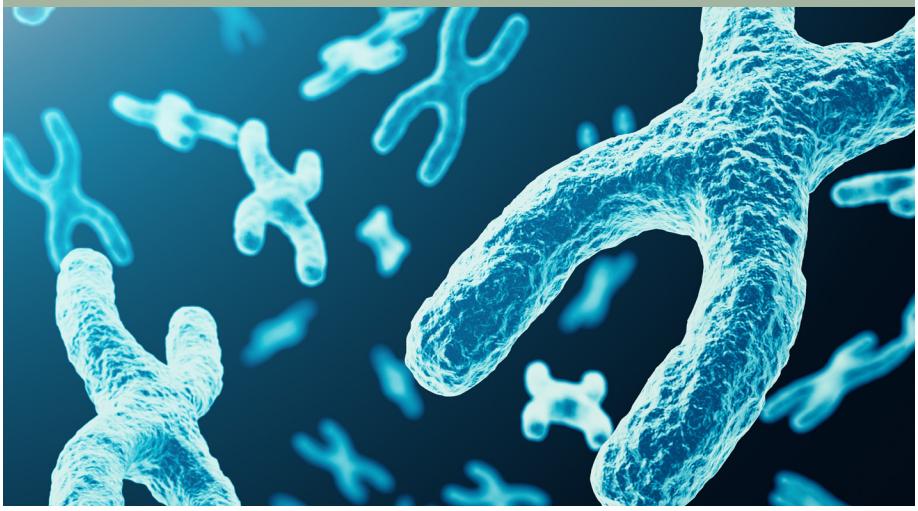

Key developments at the Patent Trial and Appeal Board ("PTAB") regarding biologics

PTAB Quarterly Update

Institution Decisions

The PTAB issued the following institution decisions relating to biologics during the past quarter.

Filgrastim (Neupogen®)

On April 19, 2019, in PGR 2019-00001, the panel instituted post-grant review of Amgen's U.S. Patent No. 9,856,287. As a preliminary matter, the panel found that on the current record, Petitioner Adello Biologics LLC established that the '287 patent was not entitled to claim priority to the parent applications filed before March 16, 2013 due to lack of written description support in those parent applications. As such, the panel concluded that the '287 patent was eligible for post-grant review. The panel concluded that it was more likely than not that the challenged claims lacked written description support because the specification did not adequately disclose a representative number of examples to support the claim limitation where "at least about 25% of the proteins are properly refolded." With respect to enablement, the panel found that because the claims broadly encompass a large number of redox conditions and provide no limitation on the protein, the specification of the '287 patent provides insufficient guidance to enable the full scope of the claims.

Petitions for Review

Filgrastim (Neupogen®)

On April 14, 2019, in IPR2019-00971, Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH petitioned for *Inter Partes* Review of Amgen's U.S. Patent No. 9,856,287 (discussed above). Fresenius Kabi argued that the basic "redox" refolding method recited in the'287 patent claims was in common use as of the patent's earliest priority date. In particular, Fresenius Kabi argued that it was understood that for a given protein, the yield could be optimized in part by varying the ratio and strength of the oxidant and reductant (i.e., thiol pair) to determine which combinations produced the highest yield at a given protein concentration. On this basis, Fresenius Kabi argued that the challenged claims of the '287 patent are anticipated or would have been obvious.

In addition, on June 8, 2019, in IPR2019-01183, Fresenius Kabi petitioned for *Inter Partes* Review of Amgen's U.S. Patent No. 9,643,997. The '997 patent is directed to a method for the purification of any limited solubility proteins expressed in non-mammalian cells. Fresenius Kabi argued that Amgen has asserted that the claimed process improved upon the prior art by eliminating the perceived need for removing components of a refold

solution before applying the protein to the matrix, but that the prior art demonstrated that skilled artisans understood that such intervening steps were not necessary for the purification of all proteins using all separation matrices (as encompassed by the challenged claims), and had already identified ways to avoid these intervening steps. On this basis, Fresenius Kabi argues that the challenged claims are anticipated by three separate references and that the challenged claims would have also been obvious.

Ixekizumab (Taltz®)

On April 2, 2019, in PGR2019-00043, Eli Lilly petitioned for post-grant review of Genentech's Patent No. 10, 011,654. The '654 patent is directed to a genus of antibodies that are functionally defined by the ability to bind protein IL-17A/F. Relying on *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017), *cert. denied*, 139 S. Ct. 787 (2019), Eli Lilly argued that the '654 patent fails to satisfy the written description requirement because it provides nothing more than a mere characterization of the protein to which the claimed genus of antibodies bind. According to Eli Lilly, the '654 patent—and its asserted priority applications—fail to disclose a representative number of antibodies falling within the scope of the claimed genus or any structural features common to the members of the genus such that one of skill in the art could visualize or recognize the members of that genus. As such, Eli Lilly argues that the patent and its priority applications do not provide written description support for any of the granted claims.

Other Biologic-Related Patents

On May 6, 2019, in IPR2019-01027 and IPR2019-01028, Pfenex Inc. sought *Inter Partes* review of GlaxoSmithKline's U.S. Patent No. 9,422,345. The '345 patent relates to the expression of diphtheria toxins, including the diphtheria toxin mutant, CRM197, and broadly claims polynucleotides comprising a 5′ signal sequence portion and a specified 3′ toxin sequence. The 5′ signal sequence portion is limited by requiring that (1) it encodes a polypeptide capable of directing transport of the 3′ toxin to the bacterial periplasm when expressed in a bacterial host, and (2) the signal sequence is not from *C. diphtheria*. In IPR2019-01027, Pfenex argued that the challenged claims were anticipated by an Indian patent application, Mekada, teaching the use of diphtheria toxin mutants, including CRM197, as a therapeutic agent in the treatment of cancer. Mekada further disclosed CRM197 in *E. coli* using a plasmid vector that encoded the non-*C. diphteria* derived PelB signal peptide. Pfenex also argued that the challenged claims would have been obvious over Mekada in view of known plasmid vector series from Novagen. In IPR2019-01028, Pfenex argued that the challenged claims would have been obvious over two separate prior art combinations.

On May 2, 2019, Pfizer filed a number of petitions for review on patents related to insulin, insulin analogs, and injectors for insulin, and it has sought to join these IPRs with Mylan's instituted IPRs. Specifically, Pfizer has filed motions to join IPR2019-00977 with IPR2018-01675, IPR2019-00978 with IPR2018-01676, IPR2019-00979 with IPR2018-01670, IPR2019-00980 with IPR2018-01678, IPR2019-00981 with IPR2018-01679, IPR2019-0982 with IPR2019-00122, IPR2019-01023 with IPR2018-01682, and IPR2019-00987 with IPR2018-01684.

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

Amgen v. Sandoz. On May 8, 2019, the Court of Appeals for the Federal Circuit affirmed the Northern District of California's decision granting summary judgment of non-infringement of U.S. Patent No. 8,940,878. According to the Federal Circuit, the claimed protein purification method required separate washing and eluting steps, whereas the purification process used by Sandoz in the manufacture of its filgrastim and pegfilgrastim biosimilars involved a single, simultaneous washing and eluting step. Therefore, the Federal Circuit affirmed the district court's finding of no literal infringement. Addressing the doctrine of equivalents, the Federal Circuit agreed with Sandoz and the district court that Sandoz's one-step, one-solution process does not function in the same way as the claimed process. The Federal Circuit further stated that "[t]he doctrine of equivalents applies only in exceptional cases and is not 'simply the second prong of every infringement charge, regularly available to extend protection beyond the scope of the claims.'" On June 7, 2019, Amgen petitioned for rehearing *en banc*, arguing that the panel's holding that the doctrine of equivalents only applies in exceptional cases is contrary to Supreme Court and Federal Circuit precedent. Sandoz has been invited to respond.

Apotex v. Amgen. On July 22, 2019, Amgen filed a notice of appeal from the PTAB's February 15, 2018 Final Written Decision in Apotex's IPR2016-01542, as well as from the denial of Amgen's Request for Rehearing and Amending Prior Decision of the PTAB on May 20, 2019. In its original Final Written Decision, the PTAB found one challenged claim of U.S. Patent No. 8,952,138 ("the '138 patent") to be not unpatentable, but found the remaining challenged claims to be unpatentable as obvious under 35 U.S.C. § 103(a). In its decision denying Amgen's request for rehearing, the PTAB amended its earlier Final Written Decision and found that all claims of the '138 patent were invalid for obviousness. On appeal, Amgen challenges the PTAB's claim construction, the original obviousness finding, the PTAB's *sua sponte* amendment of its Final Written Decision in its denial of Amgen's rehearing request, and the PTAB's determination in that decision that the previously upheld claim was also invalid for obviousness.

Key District Court Developments

Genentech v. Amgen. On July 22, 2019, the District Court for the District of Delaware denied Genentech's motion for a preliminary injunction against Amgen's trastuzumab biosimilar, Kanjinti™ (trastuzumab-anns). Judge Connolly found that Genentech had delayed in

filing its July 10, 2019 motion, noting that Genentech's motion came 14 months after receiving a notice of commercial marketing, three months after receiving discovery that detailed a fairly specific launch date, and almost one month after Amgen received FDA approval of Kanjinti™. The court also found that the timing of Genentech's motion was contrary to the 180-day period triggered by the notice of commercial marketing under the BPCIA. Thus, the court concluded that Genentech had not established any irreparable harm sufficient to support a preliminary injunction. The court also noted, however, that a finding of no irreparable harm was supported by the fact that Genentech could place a value on Amgen's market entry, as a number of the patents at issue had previously been licensed to competitors. The court did not provide an analysis of the other preliminary injunction factors, but noted in a footnote that there was a public interest in affordable access to these drugs. Genentech has filed a notice of appeal and has also moved for an emergency stay pending appeal.

New Litigation

Immunex v. Samsung Bioepis. On April 29, 2019, Immunex and its parent company, Amgen, filed a new BPCIA action in the District of New Jersey. In its complaint, Immunex alleged that Samsung's etanercept biosimilar infringed five patents related to Enbrel® (etanercept). The complaint also alleged that Samsung failed to provide plaintiffs with a copy of its aBLA under 42 U.S.C. § 262(*l*)(2) and notice of commercial marketing pursuant to 42 U.S.C. § 262(*l*)(8)(A). On April 29, 2019, Samsung received FDA approval for its proposed biosimilar, Eticovo™ (etanercept-ykro). The complaint seeks a jury trial, an injunction against Samsung and recovery for any damages resulting from the alleged infringement.

Amgen v. Tanvex. On July 23, 2019, Amgen filed a BPCIA action against Tanvex BioPharma in the Southern District of California. In its complaint, Amgen alleged that the manufacture of Tanvex's proposed biosimilar to Amgen's Neupogen® (filgrastim), as described in Tanvex's aBLA, infringes U.S. Patent No. 9,856,287 ("the '287 patent"), which claims methods of refolding recombinant proteins used in the manufacture of a biological product. The complaint seeks a jury trial; a declaratory judgment that the manufacture, use, offer to sell, or sale within the United States of Tanvex's filgrastim biosimilar will infringe claims of the '287 patent; an injunction against Tanvex; damages; and attorneys' fees.

Settlements and Stipulations

Amgen v. Coherus. On May 2, 2019, Coherus announced that it has settled the trade secret action brought by Amgen against Coherus that was pending in the Superior Court of California County of Ventura, California related to Amgen's Neulasta® and Coherus' Udenyca® products. As we previously reported, Amgen filed a complaint in 2017 alleging that Coherus targeted former Amgen employees and encouraged former Amgen employees to retain, disclose, and use Amgen trade secrets and know-how in their work for Coherus. The details of the settlement are confidential, but Coherus will continue to market Udenyca® and will pay a mid-single digit royalty to Amgen for five years.

Boehringer Ingelheim v. AbbVie. On May 14, 2019, AbbVie announced that it has resolved the U.S. Humira® litigation with Boehringer Ingelheim. Under the terms of the agreement, AbbVie will grant Boehringer a non-exclusive license to its Humira®-related intellectual property in the United States beginning on July 1, 2023. Boehringer will pay royalties to AbbVie for licensing its Humira® patents and acknowledged the validity and enforceability of the licensed patents. According to a press release by AbbVie, AbbVie will make no payments of any kind to Boehringer.

Genentech v. Samsung. On June 28, 2019, Genentech and Samsung filed a joint stipulation of dismissal in their BPCIA patent litigation concerning Ontruzant® (trastuzumab-dttb), Samsung's biosimilar of

Genentech's Hercpetin®, informing the court that the parties had entered into a settlement agreement and agreed to dismiss all claims and counterclaims asserted in the case. The parties also jointly moved to dismiss Samsung's appeal of the PTAB's final written decisions upholding the patentability of the challenged claims of U.S. Patent Nos. 6,627,196 and 7,371,379. On July 1, 2019, the Federal Circuit granted the motion and dismissed the appeal. Samsung also moved to withdraw from a pending Federal Circuit appeal in which Genentech is seeking to overturn a final written decision of unpatentability in an IPR of U.S. Patent No. 7,892,549. The court has granted this motion and invited the USPTO to intervene in the appeal.

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

Marketplace developments affecting biologics and biosimilars

Market Quarterly Update

Pricing and Reimbursement Updates

As discussed in last issue's feature article, a variety of proposed bills regarding drug pricing are currently before Congress. On June 27, 2019, the Senate Judiciary Committee voted to advance four bills:

- **S. 440, the Preserving Access to Cost Effective Drugs (PACED) Act.** This bill provides that a patent owner may not assert sovereign immunity as a defense to a derivation proceeding, reexamination, *inter partes* review, or post-grant review, or a review by a U.S. court of any such proceeding. However, these provisions apply only to the extent permitted under the 11th Amendment, and do not apply to any U.S. state or "institution of higher education" that is a public institution.
- **S. 1416, the Affordable Prescriptions for Patients Act.** According to a statement on sponsor Senator Cornyn's website, this bill "aims to curb the pharmaceutical drug industry's anti-competitive behaviors of 'product hopping' and 'patent thicketing' that restrict access to generic and biosimilar drugs." This bill defines product hopping and patent thicketing, and allows the FTC and/or courts to challenge drugmakers who engage in such tactics.
- **S. 1224, the Stop Significant and Time-wasting Abuse Limiting Legitimate Innovation of New Generics (Stop STALLING) Act.** Pursuant to this bill, a person submitting a citizen's petition to the FDA that is a "sham" will be liable for engaging in an unfair method of competition under the Federal Trade Commission Act. The bill empowers the FTC to pursue violators in district courts to recover a civil penalty and any other appropriate relief. The civil penalty for each violation is capped at the greater of any revenue earned from the sale of any drug product referenced in a covered petition, or $50,000 for each calendar day that a covered petition was under review by the Secretary of Health and Human Services.
- **S. 1227, the Prescription Pricing for the People Act.** This bill would require the FTC to study the role of intermediaries, such as pharmacy benefit managers, in the pharmaceutical supply chain, and to provide Congress with appropriate policy recommendations.

Additionally, on July 25, 2019, the Senate Finance Committee advanced the Prescription Drug Pricing Reduction Act (PDPRA). According to a statement from co-sponsor Senator Grassley, among other efforts to modernize and improve Medicare Part B, Part D, and Medicaid, the bill would set an out-of-pocket spending cap for Medicare Part D beneficiaries, and limit price

increases by setting inflation-based rebates on Medicare Part D and Part B drugs.

Other Market Developments

On April 30, 2019, Sandoz announced a deal with Taiwan's EirGenix Inc. to commercialize a trastuzumab biosimilar currently in Phase III development. According to the press release, EirGenix will be responsible for development and manufacturing, while Sandoz has the right to commercialize the product in all markets outside of Taiwan and China.

On May 8, 2019, Pfizer announced its acquisition of Therachon Holding AG, a privately-held clinical-stage biotechnology company focused on rare diseases. Under the terms of the agreement, Pfizer will acquire Therachon for $340 million upfront with an additional $470 million in additional payments contingent on the achievement of certain milestones.

On May 21, 2019, Merck announced that it will acquire Peloton Therapeutics, a privately held clinical-stage biopharmaceutical company for $1.05 billion in cash plus up to $1.15 billion in additional payments based on the achievement of certain milestones. The companies anticipate the acquisition will close in the third quarter of 2019.

On June 25, 2019, AbbVie Inc. and Allergan announced that the companies have entered into a definitive transaction agreement under which AbbVie will acquire Allergan in a cash and stock transaction for a transaction equity value of approximately $63 billion, based on the closing price of AbbVie's common stock. A press release published by AbbVie characterized the move as "transformative," and noted that the deal would provide the combined company with new growth platforms, immediate scale and enhanced profitability.

Key developments at the FDA regarding biologics and biosimilars

FDA/Regulatory Quarterly Update

New and Updated Guidance from the FDA

FDA Releases a Proposed Rule on Biologics License Applications and Master Files

On June 28, 2019, the FDA issued a proposed rule to amend its regulations concerning the use of master files for biological products. As we previously reported, the FDA has been working to implement Congress's direction to transition biological products approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) as drug products (such as insulin) to be "deemed licensed" as biologics under the Public Health Service Act. The FDA has identified approximately 89 approved new drug applications that will transition on March 23, 2020; however, approximately 17 of these applications incorporate certain information related to the drug in drug master files (DMF). This presents a complication for the transition because under current FDA practice, licensed biologics are not permitted to reference master files for this type of information.

If finalized, the proposed rule would allow certain applications for biological products that were originally approved under the FD&C Act to continue incorporating by reference information on drug substances, drug substance intermediates, or drug products contained in drug master files (DMF) after the approved applications for those products are deemed to be licenses under the Public Health Service Act (PHS Act) on March 23, 2020. The proposed rule would also codify the FDA's existing practice that an application for a biological product under the PHS Act may rely on a master file, except for information on drug substances (active pharmaceutical ingredient, or API), drug substance intermediates (a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API), or drug products (finished dosage forms, such as tablets or capsules). In addition, the proposed rule would codify the FDA's existing practice that information from a master file, including drug substance, drug substance intermediate or drug product information, may be relied on at the investigational phase of development for a product subject to licensure under the PHS Act.

Comments must be submitted on or before August 27, 2019, at https://www.regulations.gov. If finalized on or before February 22, 2020, this rule would take effect on March 23, 2020.

FDA Releases Guidance on Demonstrating Interchangeability with the Reference Product

On May 9, 2019, the FDA issued a final Guidance intended to give applicants more clarity in demonstrating interchangeability with a reference biological product. Under the BPCIA, to demonstrate interchangeability, the applicant must show that the biological product is (1) "biosimilar to the reference product" and (2) "expected to produce the same clinical result as the reference product in any given patient." If interchangeability is demonstrated, the approved biologic product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

As in the 2017 draft Guidance, the final Guidance discussed the amount and type of data necessary to prove interchangeability. This generally includes information such as switching studies, characterization based on structural complexity, and the use of a non-U.S. licensed comparator.

The final Guidance differs from the draft in several key aspects, however. One key difference relates to the types of data necessary to demonstrate interchangeability. In the draft Guidance, the FDA focused on a "fingerprint-like" characterization to reduce residual uncertainty regarding interchangeability, and that this detailed characterization could lead to a more selective and targeted approach to the clinical studies necessary to demonstrate interchangeability. In the final Guidance, however, the FDA focused on the context provided by the molecule when determining the level of characterization required to demonstrate biosimilarity using two examples. Hypothetical Product A has a relatively low structural complexity and a low incidence of serious adverse events related to immunogenicity, and the reference product has no history of inducing severe immune responses. In this case, the FDA noted that sufficiently expansive comparative analytical data supporting a finding that Product A is highly similar to the reference product, along with a switching or integrated study "may be sufficient to support a demonstration of interchangeability." Hypothetical Product B and its reference product are structurally complex and have a history of life-threatening adverse events related to immunogenicity. In this case, postmarketing data for the product as a licensed biosimilar, in addition to a switching study, may provide the additional data and information necessary to support interchangeability.

In contrast to the draft Guidance, the final Guidance also allows a sponsor to use a non-U.S.-licensed comparator product in a switching study, so long as it can provide "adequate data and information to establish a bridge between the non-U.S.-licensed comparator and the U.S.-licensed reference product."

In addition, the final Guidance includes a more detailed discussion of switching studies, including an example design, and omits a previous discussion relating to the presentation of interchangeable products.

FDA Releases Draft Guidance on the Development of Therapeutic Protein Biosimilars

On May 21, 2019, the FDA issued a draft Guidance intended to assist applicants in demonstrating that a proposed product is biosimilar to a reference product under section 351(k) of the PHS Act. This Guidance revises a 2015 final Guidance on quality considerations for demonstrating biosimilarity and replaces the withdrawn 2017 draft Guidance on statistical approaches to evaluating biosimilarity.

A potentially major difference between the current and previously withdrawn Guidance is the use of the term "analytical assessment" instead of "analytical similarity." The FDA has emphasized that when a biosimilar product does not fully match biosimilarity attributes, the sponsor may demonstrate why these differences are not critical to the safety and efficacy of the biosimilar product.

The draft Guidance describes the FDA's recommendations for the design and evaluation of comparative analytical studies, including considerations for the development of a comparative analytical assessment plan using a stepwise approach, to support a demonstration of biosimilarity. It also provides applicants with recommendations on certain other aspects of the chemistry, manufacturing, and controls (CMC) portion of a marketing application for a proposed biosimilar product. The Guidance recommends that applicants provide adequate characterization of the lot-to-lot variability between the reference and the proposed biosimilar products. The Guidance states that "[c]onsidering the inherent heterogeneity present in protein products and the expected lot-to-lot variability stemming from manufacturing processes, the Agency recommends that a sponsor include at least 10 reference product lots (acquired over a time frame that spans expiration dates of several years), in the analytical assessment to ensure that the variability of the reference product is captured adequately." The Guidance further states that according to the FDA at least 6 to 10 lots of the proposed product in the comparative analytical assessment should be included, such as "lots manufactured with the investigational- and commercial-scale processes" as well as validation lots, and "product lots manufactured at different scales, including engineering lots."

Lastly, an applicant intending to use a non-U.S.-licensed comparator in certain studies "should provide comparative analytical data and analysis for all pairwise comparisons (i.e., U.S.-licensed product versus proposed biosimilar product, non-U.S.-licensed comparator product versus proposed biosimilar product, and U.S.-licensed product versus non-U.S.-licensed comparator product)." The current Guidance also removes the tier system of the statistical testing allowing for only physical comparison of data and the use of an equivalence range based on the attribute variability in the reference product.

Recent FDA Biologics and Biosimilar Approvals

FDA Approves HADLIMA™ (adalimumab-bwwd)

On July 23, 2019, the FDA approved Samsung Bioepis's HADLIMA™ (adalimumab-bwwd), a biosimilar approved for the following indications of the reference product HUMIRA® (adalimumab): rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's Disease, ulcerative colitis and plaque psoriasis.

FDA Approves RUXIENCE™ (rituximab-pvvr)

On July 23, 2019, the FDA approved Pfizer's RUXIENCE™ (rituximab-pvvr), a biosimilar approved for the following indications of the reference product RITUXAN® (rituximab): non-hodgkin's lymphoma, chronic lymphocytic leukemia and granulomatosis with polyangiitis and microscopic polyangiitis.

FDA Approves ZIRABEV™ (bevacizumab-bvzr)

On June 28, 2019, the FDA approved Pfizer's ZIRABEV™ (bevacizumab-bvzr), a biosimilar approved for the following indications of the reference product AVASTIN® (bevacizumab): metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC); recurrent glioblastoma; metastatic renal cell carcinoma (RCC); and persistent, recurrent or metastatic cervical cancer.

FDA Approves DUPIXENT® (dupilumab)

On June 26, 2019, the FDA approved Regeneron Pharmaceuticals's DUPIXENT® (dupilumab), a monoclonal antibody, for the treatment of adults with nasal polyps (growths on the inner lining of the sinuses) accompanied by chronic rhinosinusitis (prolonged inflammation of the sinuses and nasal cavity). The FDA granted this application Priority Review.

FDA Approves KANJINTI™ (trastuzumab-anns)

On June 13, 2019, the FDA approved Amgen's KANJINTI™ (trastuzumab-anns), a biosimilar approved for the following indications of the reference product HERCEPTIN® (trastuzumab): treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

FDA Approves EMGALITY® (galcanezumab-gnlm)

On June 4, 2019, the FDA approved Eli Lilly's EMGALITY® (galcanezumab-gnlm) solution for injection for the treatment of episodic cluster headache in adults. Galcanezumab-gnlm is a humanized monoclonal antibody that binds to calcitonin gene-related peptide ligand and blocks its binding to the receptor.

FDA Approves ZOLGENSMA® (onasemnogene abeparvovec-xioi)

On May 24, 2019, the FDA approved AveXis's (a Novartis company) ZOLGENSMA® (onasemnogene abeparvovec-xioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy, a leading genetic cause of infant mortality.

FDA Approves CYRAMZA® (ramucirumab)

On May 10, 2019, the FDA approved Eli Lilly's CYRAMZA® (ramucirumab) as a single agent for hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been previously treated with sorafenib. Ramucirumab is a fully human monoclonal antibody (IgG1) developed for the treatment of solid tumors.

FDA Approves DENGVAXIA® (Dengue Tetravalent Vaccine, Live)

On May 1, 2019, the FDA approved Sanofi's DENGVAXIA® (Dengue Tetravalent Vaccine, Live) for the prevention of dengue disease caused by serotypes 1-4 of the virus in individuals 9 through 16 years of age living in endemic areas of the U.S. with a laboratory-documented prior infection. DENGVAXIA® is a sterile suspension for subcutaneous injection containing 4.5-6.0 log10 CCID50 of each of the chimeric yellow fever dengue virus serotypes 1, 2, 3, and 4.

FDA Approves ETICOVO™ (etanercept-ykro)

On April 26, 2019, the FDA approved Samsung Bioepis's ETICOVO™ (etanercept-ykro), a biosimilar to U.S.-licensed ENBREL® (etanercept) for the treatment of all eligible indications such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.

FDA Approves EVENITY™ (romosozumab-aqqg)

On April 9, 2019, the FDA approved Amgen's EVENITY™ (romosozumab-aqqg) for the treatment of osteoporosis in postmenopausal women at high risk for bone fracture. EVENITY™ is a bone-building humanized monoclonal antibody designed to inhibit the activity of sclerostin,

which results in increased bone formation and to a lesser extent decreased bone resorption.

Biologics and Biosimilars Under Development

On June 22, 2019, Alexion announced that the FDA has accepted for priority review its long-acting C5 complement inhibitor, ravulizumab (ULTOMIRIS™), which offers less frequent administration than eculizumab (SOLIRIS®). The FDA will review ravulizumab for the treatment of atypical hemolytic uremic syndrome, a progressive disease that can lead to irreversible organ damage and premature death.

At the 24th Congress of the European Hematology Association, held on June 13-16 in Amsterdam, the Netherlands, Amgen researchers reported data from a phase 1 trial of ABP 959, a proposed biosimilar of eculizumab, which showed PK and PD equivalence, and demonstrated similar safety and immunogenicity profiles to the reference product.

At the American Diabetes Association 79th Scientific Sessions, held on June 7-11, 2019, in San Francisco, California, Sanofi researchers presented data on SAR341402, a proposed biosimilar of insulin aspart (NOVOLOG®), made by Novo Nordisk. The reported results showed that adverse events, hypoglycemia reports, immunogenicity and safety profiles were similar and that the biosimilar was noninferior to the reference product.

At the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting held between May 31 and June 4, three research teams from Sandoz, Fresenius Kabi, and Gema Biotech shared their findings on biosimilar pegfilgrastim development programs. Studies on Fresenius Kabi's proposed pegfilgrastim biosimilar, MSB11455, and Sandoz's pegfilgrastim biosimilar LA-EP2006 showed PK and PD similarity of the biosimilars with both the U.S. and E.U. references. A clinical study using Peg-Neutropine, Gema Biotech's pegfilgrastim product, in patients with breast cancer who were scheduled to receive 4 to 6 cycles of chemotherapy showed that the product is biosimilar to the reference.

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

This article provides a summary of factors influencing biosimilars markets

FEATURED ARTICLE

Despite FDA Approvals and the Potential for Savings, Biosimilar Markets Continue to Lag

Biosimilars provide the potential for significant savings for the United States healthcare industry. For example, Mvasi, a bevacizumab biosimilar, was recently made available at a list price of $677.40 per 100 mg, and $2709.60 per 400-mg single-dose vial. Kanjinti, a trastuzumab biosimilar, was recently made available at a list price of $3697.26 per 420-mg multi-dose vial. These list prices put Mvasi 12% below Avastin's average selling price (ASP), and Kanjinti 13% below Herceptin's ASP.[1]

In addition, the number of approved biosimilars continues to grow. As can be seen from the table below, the United States currently has 21 approved biosimilars. However, of these biosimilars, only nine currently appear to be available commercially. Moreover, these nine biosimilars correspond to only six reference products: filgrastim, infliximab, bevacizumab, epoetin alfa, trastuzumab and pegfilgrastim.

Table 1. Summary of Biosimilars Approved in the United States

Date of Licensure	Biosimilar	Market Access
March 6, 2015	**filgrastim-sndz/ Zarxio**	**Currently Marketed**
April 5, 2016	**infliximab-dyyb/ Inflectra**	**Currently Marketed**
August 30, 2016	etanercept-szzs/ Erelzi	Subject to Patent Litigation
September 23, 2016	adalimumab-atto/ Amjevita	Settlement Delayed Launch until 2023
April 21, 2017	**infliximab-abda/ Renflexis**	**Currently Marketed**
August 25, 2017	adalimumab-adbm/ Cyltezo	Settlement Delayed Launch until 2023
September 14, 2017	**bevacizumab-awwb/ Mvasi**	**Currently Marketed**
December 1, 2017	trastuzumab-dkst/ Ogivri	License Agreement Delayed Launch – Launch Speculated Late 2019
December 13, 2017	infliximab-qbtx/Ixifi	No Launch Planned
May 15, 2018	**epoetin alfa-epbx/ Retacrit**	**Currently Marketed**
June 5, 2018	**pegfilgrastim-jmbd/ Fulphila**	**Currently Marketed**
July 2018	**filgrastim-aafi/ Nivestym**	**Currently Marketed**
October 2018	adalimumab-adaz/ Hyrimoz	Settlement Delayed Launch until 2023

[1] For a discussion of this data, click here: https://www.centerforbiosimilars.com/news/amgen-and-allergan-launch-mvasi-and-kanjinti-the-first-anticancer-biosimilars-in-the-united-states.

Date of Licensure	Biosimilar	Market Access
November 2018	**pegfilgrastim-cbqv/ Udenyca**	**Currently Marketed**
November 2018	rituximab-abbs/ Truxima	License Agreement Delayed Launch – No Launch Date Announced
December 2018	trastuzumab-pkrb/ Herzuma	License Agreement Delayed Launch – Launch Speculated Late 2019
January 2019	trastuzumab-dttb/ Ontruzant	License Agreement Delayed Launch – Launch Speculated Late 2019
March 2019	trastuzumab-qyyp/ Trazimera	License Agreement Delayed Launch – Launch Speculated Late 2019
April 2019	etanercept-ykro/ Eticovo	Subject to Patent Litigation
June 2019	bevacizumab-bvzr/ Zirabev	Subject to Patent Litigation
June 2019	**trastuzumab-anns/ Kanjinti**	**Currently Marketed**
July 2019	adalimumab-bwwd/ Hadlima	Settlement Delayed Launch until 2023
July 2019	rituximab-pvvr/ Ruxience	License Agreement Delayed Launch – No Launch Date Announced

Thus, despite multiple approved products in the United States and the significant discounts these products provide, market uptake of biosimilars continues to lag. Indeed, as reported by the *Journal of Clinical Pathways*, IQVIA market share data by product per molecule as of January 2019 indicates that biosimilars continue to struggle to gain market share:[2]

Table 2. IQVIA Market Share Data

Filgrastim	Neupogen (48%)	Zarxio (31.7%)	Granix (20.3%)	Nivestym (0%)
Infliximab	Remicade (96.4%)	Inflectra (3.2%)	Renflexis (0.4%)	
Pegfilgrastim	Neulasta Onpro (61.0%)	Neulasta (38.2%)	Fulphila (0.8%)	

Analysts and commentators have attributed this lagging market uptake to a number of factors, including settlement delays, patent litigation, and reimbursement policies. This article provides an overview of these key factors affecting market access for biosimilars.

Several Factors Present Barriers to Market Access

As can be seen from Table 1 above, the most common barrier to market access appears to be settlement agreements that allow for a future launch only. For example, as we reported in our March 2019 webinar, nine different biosimilars manufacturers have reported settlements with AbbVie to market a biosimilar of AbbVie's adalimumab product, Humira®. However, under the terms of each of these settlements, launch will be delayed until at least 2023. In contrast, at least five adalimumab biosimilars are currently commercially available in Europe. These settlements have faced criticism from U.S. lawmakers, including Senators Amy Klobuchar (D-Minnesota) and Chuck Grassley (R-Iowa), who have urged the FTC to examine these settlements. Recently proposed legislation, such as S. 64, The Preserve Access to Affordable Generics and Biosimilars Act, and H.R. 1499, The Protecting Consumer Access to Generic Drugs Act, may heighten the antitrust scrutiny these types of agreements receive.

BPCIA patent litigation also continues to be a substantial barrier for both approved and pending biosimilars. The table below provides a summary of BPCIA patent litigation to date:

Table 3. BPCIA Litigation by Product

Reference Product	Litigation
Neupogen/Neulasta (filgrastim/pegfilgrastim)	Nine BPCIA patent litigations. Of those, seven remain pending, either in district court (four) or on appeal (three).
Remicade (infliximab)	Two BPCIA patent litigations. Of those, one remains pending. Additional antitrust litigation is ongoing.
Enbrel (etanercept)	Two BPCIA patent litigations, both of which are pending.

[2] For the full article, click here: https://www.journalofclinicalpathways.com/news/iqvia-data-show-biosimilars-struggling-market-share-us.

Reference Product	Litigation
Humira (adalimumab)	Three BPCIA patent litigations, all of which have settled. Additional litigation between Coherus and Amgen ongoing.
Avastin (bevacizumab)	Three BPCIA patent litigations, two of which remain pending.
Rituxan (rituximab)	Two BPCIA patent litigations, both of which have settled.
Herceptin (trastuzumab)	Five BPCIA patent litigations, one of which remains pending.
Epogen (epoetin alfa)	One BPCIA patent litigation, which is pending.

Others have noted that U.S. drug pricing and reimbursement policy creates the conditions to block biosimilars from market access. Former FDA Commissioner Scott Gottlieb has stated that competition for biosimilars was "anemic because consolidation across the supply chain has made it more attractive for manufacturers, Pharmacy Benefit Managers, Group Purchasing Organizations and distributors to split monopoly profits through lucrative volume-based rebates on reference biologics—or on bundles of biologics and other products—rather than embrace biosimilar competition and lower prices." Congress, however, has taken aim at drug pricing policy, and has proposed a number of bills intended to curb excessive drug costs and increase Medicare bargaining power. For example, as discussed in further detail in the Market Update in this newsletter, the Senate Finance Committee recently advanced The Prescription Drug Pricing Reduction Act, which would set an out-of-pocket spending cap for Medicare Part D beneficiaries, and limited price increases by setting inflation-based rebates.

Conclusions

Market access for biosimilars continues to evolve, and remains a critical issue for the success of biosimilars in the United States. Both Congress and the FDA have made biosimilars a priority, but it remains to be seen whether their actions will actually help the biosimilars market develop and grow. Ultimately, this remains a multifaceted problem with no clear solution.

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