WILLKIE FARR & GALLAGHER LLP

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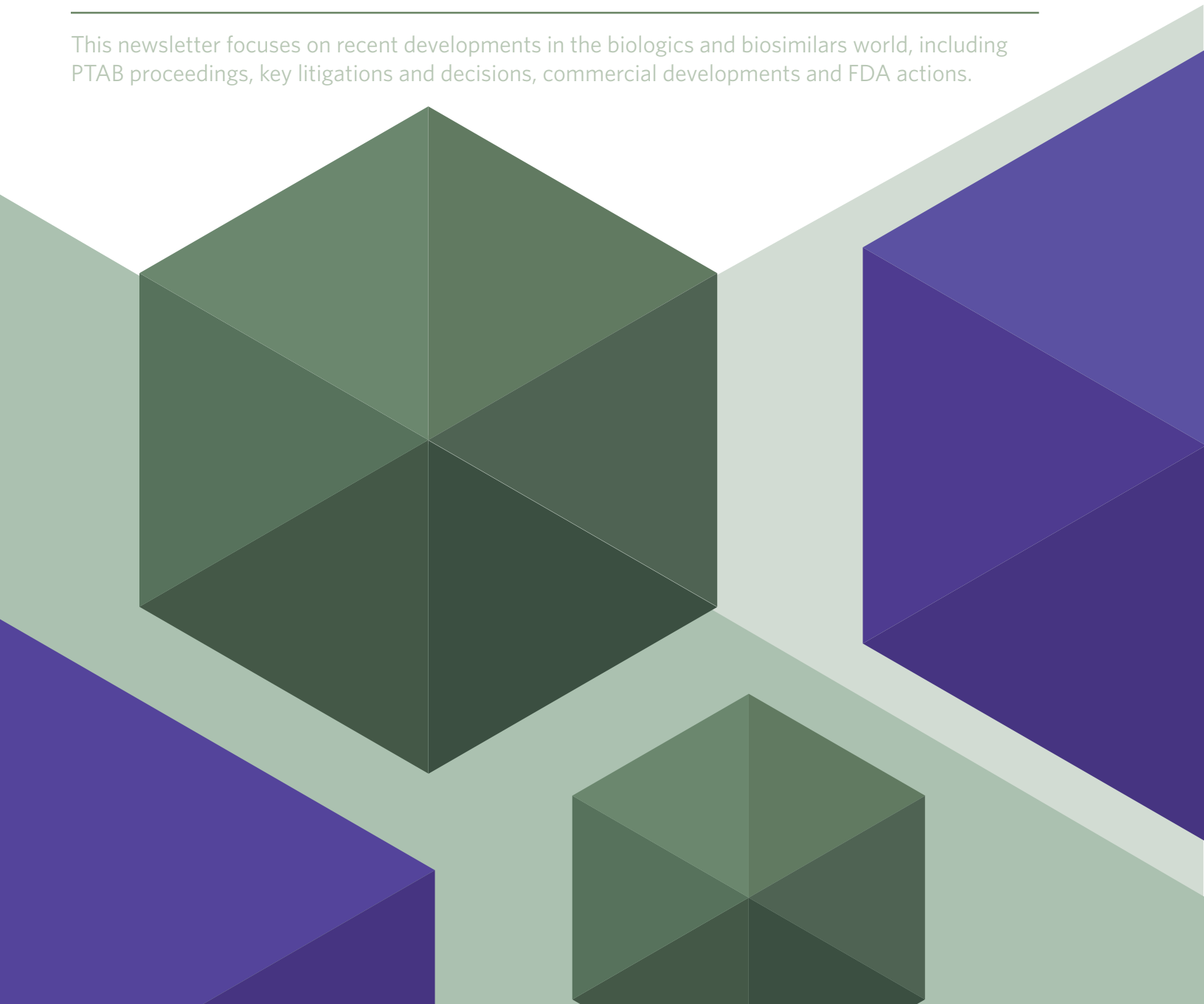
INTELLECTUAL PROPERTY NEWSLETTER

February 2021

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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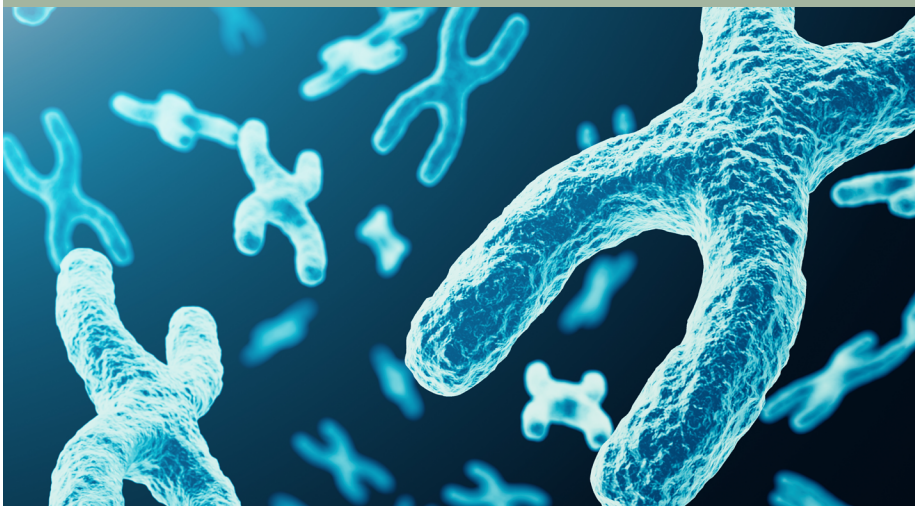

Key developments at the Patent Trial and Appeal Board ("PTAB") regarding biologics

PTAB Quarterly Update

Lupin Files Petition for *Inter Partes Review* on Method Patent Previously Asserted in Litigations Involving Filgrastim and Pegfilgrastim

Pegfilgrastim (NEULASTA®):

On December 15, 2020, Lupin Ltd. filed a petition against an Amgen patent directed to a method of refolding proteins, U.S. Patent No. 9,856,287. The '287 patent has previously been challenged in proceedings before the Board filed by Adello Biologics and Fresenius. The Adello Biologics petition for review was settled after institution. The PTAB exercised its discretion to not institute the first Fresenius petition, and the parties settled before institution of the second Fresenius Petition.

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

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

Litigation Quarterly Update

Key Appellate Developments

Sanofi-Aventis v. Mylan. On November 19, 2020, the Federal Circuit docketed Sanofi-Aventis's appeal from the final judgment entered on November 2, 2020 by the District Court for the District of New Jersey pursuant to its findings of fact and conclusions of law dated March 9, 2020. After a bench trial, the district court found that Mylan and partner Biocon's biosimilar insulin glargine product SEMGLEE™ (insulin glargine) would not infringe U.S. Patent No. 9,526,844, related to the pen injector device used to deliver Sanofi-Aventis's LANTUS® (insulin glargine), and that multiple claims of that patent are invalid for lack of written description. In its appeal, Sanofi-Aventis challenged both of those findings, the final judgment, and all subsidiary rulings in favor of Mylan, including the district court's claim construction order. Mylan originally filed for FDA approval of SEMGLEE™ via an NDA, which was approved on June 11, 2020. It was subsequently deemed a BLA pursuant to § 7002(e)(4)(B) of the BPCIA.

New Litigation

Seagen v. Daiichi Sankyo. On October 19, 2020, Seagen Inc. filed a new suit in the District Court for the Eastern District of Texas accusing Daiichi Sankyo's ENHERTU® (fam-trastuzumab deruxtecan-nxki), part of a class of biologic products known as antibody-drug conjugates ("ADCs"), of infringing Seagen's U.S. Patent No. 10,808,039 (the "'039 Patent"), which claims ADCs having a particular chemical structure. Daiichi Sankyo and its U.S. commercialization partner AstraZeneca responded by filing suit in the District Court for the District of Delaware on November 13, 2020, seeking a declaratory judgment that ENHERTU® does not have the specific structure claimed in the '039 Patent, and therefore does not infringe. Daiichi Sankyo previously filed a third suit against Seagen (under its former name, Seattle Genetics, Inc.) on November 4, 2019, in the District of Delaware, seeking a declaratory judgment that Seagen had no ownership rights in multiple issued patents and patent applications related to ADCs filed by Daiichi Sankyo. This third action is also ongoing.

Genentech v. Centus. On November 12, 2020, Genentech filed a new complaint under the BPCIA in the District Court for the Eastern District of Texas against Centus Biotherapeutics Ltd. and its partners Fujifilm Kyowa Kirin Biologics Co., Ltd., as well as the parent companies of that joint venture, Fujifilm Corp. and Kyowa Kirin Co., Ltd. (collectively, "Centus"). The suit accuses Centus's FKB238, a biosimilar to Genentech's AVASTIN® (bevacizumab), of infringing ten patents related to methods of manufacture and methods of treatment

involving bevacizumab. Notably, although Genentech asserted in its complaint that Centus's production of its aBLA for FKB238 was insufficient to satisfy its disclosure obligations under 42 U.S.C. § 262(*l*)(2)(A), unlike in its prior BPCIA suits, Genentech did not include a count for declaratory judgment that Centus has not complied with its patent-dance obligations under the BPCIA. The complaint seeks an injunction barring importation or sale of FKB238 in the United States, declaratory judgment of future infringement based on Centus's provision of a notice of commercial marketing, and damages.

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New biologic and biosimilar launches, and other marketplace developments

Market Quarterly Update

Omnibus Spending Bill Includes Biosimilars Provisions

On December 27, the President signed the Consolidated Appropriations Act. The $2.3 trillion omnibus spending bill included two provisions relating to biosimilars. The first permits, but does not require, aBLA applicants to show that the biosimilar has the same conditions of use as those approved in the reference biologic. The second requires the FDA to create a searchable, electronic list of licensed biologics, to be updated monthly, with patent information and exclusivities included on (3)(A) lists. In addition, under this provision, each reference product sponsor that provides a (3)(A) list to a biosimilar applicant must share it with the FDA within 30 days.

Pricing Announced for Amgen's Rituximab Biosimilar

On December 17, the FDA approved Amgen's RIABNI™ (rituximab-arrx), biosimilar to Genentech's RITUXAN®. That same day, Amgen announced its pricing plans for the biosimilar. RIABNI™ will be listed at $716.80 per 100 mg and $3,584 per 500 mg vial, each a 23.7% discount over the reference biologic. That price is the same list price as Pfizer's rituximab biosimilar, RUXIENCE®, and is 15.2% lower than Teva's TRUXIMA®. Amgen announced the launch of RIABNI™ on January 12, 2021. Amgen did not provide a launch date for RIABNI™, but stated in an interview with the Center for Biosimilars that launch was expected in January 2021.

Other Market Developments

In November, Samsung Biologics and Astrazenca dissolved their joint venture, Archigen Biotech, and abandoned development on their rituximab biosimilar, SAIT101, according to a report from the Korea Biomedical Review. The proposed biosimilar had entered phase 3 trials for follicular lymphoma in June 2016.

On November 23, Bristol Myers Squibb announced a deal worth up to $2.7 billion with New York-based Schrodinger Inc., according to a press release. The agreement will allow BMS access to Schrodinger's drug discovery platform, as well as for development and commercialization of two early-stage biological targets currently being studied in kidney cancer as well as SOS1- and KRAS-driven tumors.

Also on November 23, Merck announced its acquisition of Rockville, MD-based OncoImmune, for an upfront payment of $425 million in cash. OncoImmune's lead target is CD24Fc, a fusion protein currently undergoing

phase 3 testing for the treatment of patients with severe or critical COVID-19.

On December 2, Janssen announced that it acquired the rights to a gene therapy candidate from Waltham, Mass.-based Hemera Biosciences. The drug, HMR59, is administered as a one-time injection to help preserve vision in patients with a severe form of age-related macular degeneration (AMD). HMR59 completed a first phase 1 study in December 2019, and a second phase 1 clinical trial is currently being finalized. Terms of the acquisition were not made public.

On December 10, Boehringer Ingelheim announced its acquisition of Swiss firm NBE Therapeutics. The deal, worth $1.5 billion, is centered on NBE's pipeline of antibody-drug conjugates (ADCs), including lead compound NBE-002, an anti-ROR1 ADC currently in phase I clinical studies for breast cancer and other solid tumors.

On December 15, Eli Lilly announced that it had entered an agreement to acquire New York-based Prevail Therapeutics in a deal worth $880 million upfront, with an additional $160 million contingent upon regulatory approval. Prevail's portfolio focuses on AAV9-based gene therapies; its lead therapies in clinical-stage development include PR001, for patients with Parkinson's disease and neuropathic Gaucher disease, and PR006 for patients with frontotemporal dementia.

For more information or copies of any of the documents discussed herein, please click here.

Key developments at the FDA regarding biologics and biosimilars

FDA/Regulatory Quarterly Update

New FDA Draft Guidance on Biosimilarity and Interchangeability

On November 19, 2020, the FDA published a new draft Guidance entitled "Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act" in which the FDA provides insight into the application process, review and labeling of interchangeable biosimilars.

In the first of four Q&As, the FDA explained how it will handle applications for interchangeable biosimilars that include data sufficient to support licensure as a biosimilar but that fail to provide data sufficient to grant approval as an interchangeable product. The Guidance explains that if a BLA submitted under section 351(k) seeks licensure for an interchangeable product, then it must include an affirmative statement to that effect. If there is no affirmative statement seeking licensure for an interchangeable product, then the application will only be evaluated for licensure for a biosimilar product. If a BLA application contains sufficient information to support licensure of the product as a biosimilar product but not as an interchangeable product, the FDA will split the application. The FDA would then license the product as a biosimilar product and separately review and respond, in a complete response letter, regarding deficiencies with licensure as an interchangeable biosimilar.

The second Q&A addressed the procedure by which a 351(a) BLA holder may proceed if it seeks licensure of its product as a biosimilar or interchangeable product (i.e., they wish to license their own product as a biosimilar). In such a case, the 351(a) BLA holder must submit a new BLA application under 351(k) demonstrating that its product is a biosimilar or interchangeable to the reference product.

In the third Q&A, the FDA addressed which provisions of the prior Guidance, "Labeling for Biosimilar Products," would also apply to interchangeable products. The FDA reiterated that the biosimilar product labeling should not include data from clinical studies conducted to demonstrate biosimilarity or interchangeability because such studies are not designed to demonstrate the safety or efficacy of the product.

In the fourth and final Q&A, the FDA addressed an additional labeling requirement for interchangeable biosimilars under which a statement of interchangeability should be placed beneath the "Initial U.S. Approval" portion of the "Highlights of Prescribing Information" portion of the label.

Boehringer Ingelheim Files Citizen Petition

On December 2, 2020, Boehringer Ingelheim submitted a Citizen Petition asking the FDA to revise its interpretation of the word "strength" used in section 351(k) of the Public Health Service Act. Boehringer Ingelheim's request seeks to interpret the word "strength" to mean "total drug content" without taking into account the concentration. According to Boehringer Ingelheim, its proposed interpretation would prevent "evergreening" tactics such as using concentration changes to prevent competition from developing biosimilar and interchangeable products. Under the FDA's current interpretation, no biological product can be considered a biosimilar or interchangeable product if there is a variation in the inactive drug volume.

Boehringer Ingelheim's adalimumab biosimilar was approved in August 2017. However, due to a publicly announced settlement with AbbVie, Boehringer Ingelheim is unable to launch its adalimumab biosimilar until July 1, 2023. Boehringer Ingelheim's application used AbbVie's original-concentration Humira™ as the reference drug. Since Boehringer Ingelheim received approval, AbbVie obtained approval and began marketing a high-concentration form of Humira®. According to Boehringer Ingelheim, its original concentration adalimumab biosimilar cannot be considered biosimilar or interchangeable to Boehringer Ingelheim's high concentration Humira® formulation.

Recent FDA Biologics and Biosimilar Approvals

FDA Approves INMAZEB™ (atoltivimab, maftivimab, and odesivimab-ebgn)

On October 14, 2020, the FDA approved Regeneron Pharmaceuticals' INMAZEB™ (atoltivimab, maftivimab, and odesivimab-ebgn), indicated for treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients. The treatment contains a mixture of three monoclonal antibodies and is the first FDA-approved treatment for Ebola virus. The FDA granted the application Orphan Drug and Breakthrough Therapy designations.

FDA Approves DANYELZA® (naxitamab-gqgk)

On November 25, 2020, the FDA approved Y-mABs Therapeutics' DANYELZA® (naxitamab-gqgk), indicated for treatment of pediatric patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow. The FDA granted the application Priority Review, Orphan Drug, Breakthrough Therapy, and Rare Pediatric Disease designations.

FDA Approves RIABNI™ (rituximab-arrx)

On December 17, 2020, the FDA approved Amgen's RIABNI™ (rituximab-arrx), indicated for treatment of patients with Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, Granulomatosis with Polyangiitis, and Microscopic Polyangiitis. Riabni™ is a biosimilar to Genentech's Rituxan®.

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A discussion of the California Affordable Drug Manufacturing Act of 2020

California's State Generic and Biosimilar Plan: Placebo, or Breakthrough Therapy?

On September 29, 2020, California Governor Gavin Newsom signed S.B. 852, the California Affordable Drug Manufacturing Act of 2020 (the "Act"), which purportedly aims to reduce drug pricing by allowing the state itself to enter the market for generics and biosimilars and compete with established drug makers. If the Act is exercised to sell pharmaceutical products, California would become the first state with its own drug label: Cal Rx. But the Act recognizes that such market entry may not be "viable" due to legal and economic roadblocks. California's efforts may also prompt concerns regarding FDA preemption and questions as to the scope of sovereign immunity.

The Act Enables California to Partner with Drug Manufacturers – and to Act Independently

Under the terms of the new law, the California Health and Human Services Agency (the "Agency") shall "enter into partnerships" with drug manufacturers "to increase competition, lower prices, and address shortages in the market for generic prescription drugs, to reduce the cost of prescription drugs for public and private purchasers, taxpayers, and consumers, and to increase patient access to affordable drugs." Act at § 127692(a). Pursuant to the Act, the Agency must (1) identify by July 2022 "top drugs" that may have the greatest impact on these goals, and (2) "determine if viable pathways exist for partnerships to manufacture or distribute prescription drugs." *Id.* § 127693(a)(2). In particular, the Act specifies that the partnerships "shall include the production of at least one form of insulin," with additional priority for drugs "for chronic and high cost conditions," and potential priority for drugs "that can be delivered through mail order." *Id.* § 127693(c).

In addition, the Act further contemplates that by July 2023, California may move beyond such partnerships and instead enter the market itself. By that date, the Agency is required to submit a report "that assesses the feasibility of directly manufacturing generic prescription drugs and selling generic prescription drugs at a fair price." Act at § 127694(a). The Act sets out various means for accomplishing that goal, "including chartering a private organization, a public-private partnership, or a public board of directors." *Id.*

Do "Viable Pathways Exist" for California to Enter the Market?

Recognizing potential roadblocks to market entry, the Act itself acknowledges that it may not be "viable" for California to enter the generic and biosimilar drug market. In particular, the Agency must consider "the relevant legal, market, policy, and regulatory factors" prior to entering partnerships for pharmaceutical manufacturing and distribution, including analysis of FDA user fees, ANDA acquisition costs, and mandatory rebates, in addition to contracting, administrative, operating, production, and research and development costs. Act at § 127693(b).

Among the "legal" and "regulatory" factors are FDA regulation, as state efforts to regulate drug marketing and approval may be preempted by federal law. In the context of generic drug labeling, for instance, the Supreme Court has repeatedly recognized that the Federal Food, Drug, and Cosmetic Act (the "FDCA") predominates over state efforts to regulate in the space. Most recently, in *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, 475-76 (2013), the Court recognized that the FDCA imposes a host of requirements on generic drugs, including that it have "the same active ingredients, route of administration, dosage form, strength, and labeling as the brand-name drug on which it is based." *Id.* at 483-84. In striking down the state law in *Bartlett*, the Court affirmed its decision just two years prior in *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 621 (2011), which recognized that a state law requiring generic manufacturers to amend their drug labels was preempted by the FDCA and the Hatch-Waxman Amendments.

Thus, it is likely that any generic or biosimilar drug California seeks to market—either in partnership with a drug manufacturer or, eventually, on its own—must still conform to the years-long and costly FDA approval process, including for methods of use and labeling. The state likely would not, for instance, be able to attempt to improve access to its lower-cost options by encouraging off-label use for unapproved indications, or by substituting products of different strengths. And any generic or biosimilar drug it offers must likewise meet the FDCA requirements, including equivalence or biosimilarity with a reference product.

Could California Take Advantage of Sovereign Immunity to Fast-Track Market Entry?

While federal preemption offers some possible constraints on California's ability to enter the generic drug market, the sovereign immunity doctrine hints at a possible upside. If California is able to move forward with a generic or biosimilar application—and in particular if they are able to do so without partnering with a drug manufacturer—questions surrounding their ability to invoke the Eleventh Amendment to circumvent patent assertion and statutory limits on approval and marketing will need to be resolved.

As the Supreme Court has held, state governments cannot be sued for patent infringement. *See Florida Prepaid Postsecondary Educ. Expense Bd. v. College Sav. Bank*, 527 U.S. 627 (1999). The Federal Circuit affirmed recently that the California Department of Health Services—a division of the Agency—enjoys such sovereign immunity unless expressly waived in a given case. *Biomedical Patent Management Corp. v. Cal. Dept. of Health Servs.*, 505 F.3d 1328, 1342 (Fed. Cir. 2007), *cert. denied*, 555 U.S. 1097 (2009). Further, courts have endorsed in some instances the doctrine of *derivative* sovereign immunity, in which private contractors performing government functions may enjoy the same protections as the state itself. *See Campbell-Ewald Co. v. Gomez*, 577 U.S. 153 (2015). These immunities may complicate the balancing act between innovators and generic and biosimilar applicants established by the Hatch-Waxman Amendments and the BPCIA.

Indeed, both statutory regimes expressly contemplate patent assertion in governing approval and marketing

of generic and biosimilar drugs. The Hatch-Waxman Amendments provide for a 30-month stay of approval in cases involving a Paragraph IV certification, while the BPCIA involves the two-phase "patent dance" and notice to the reference biologic prior to any commercial marketing. If a state-affiliated drug applicant could invoke sovereign immunity to ward off a patent challenge from an innovator, it could argue that these regimes are not applicable, hastening generic/biosimilar entry.

These issues, among others, illustrate the thorny issues that may need to be resolved – especially if other states seek to follow in California's footsteps and compete directly in an effort to lower drug prices.

For more information or copies of any of the documents discussed herein, please click here.

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