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INTELLECTUAL PROPERTY NEWSLETTER

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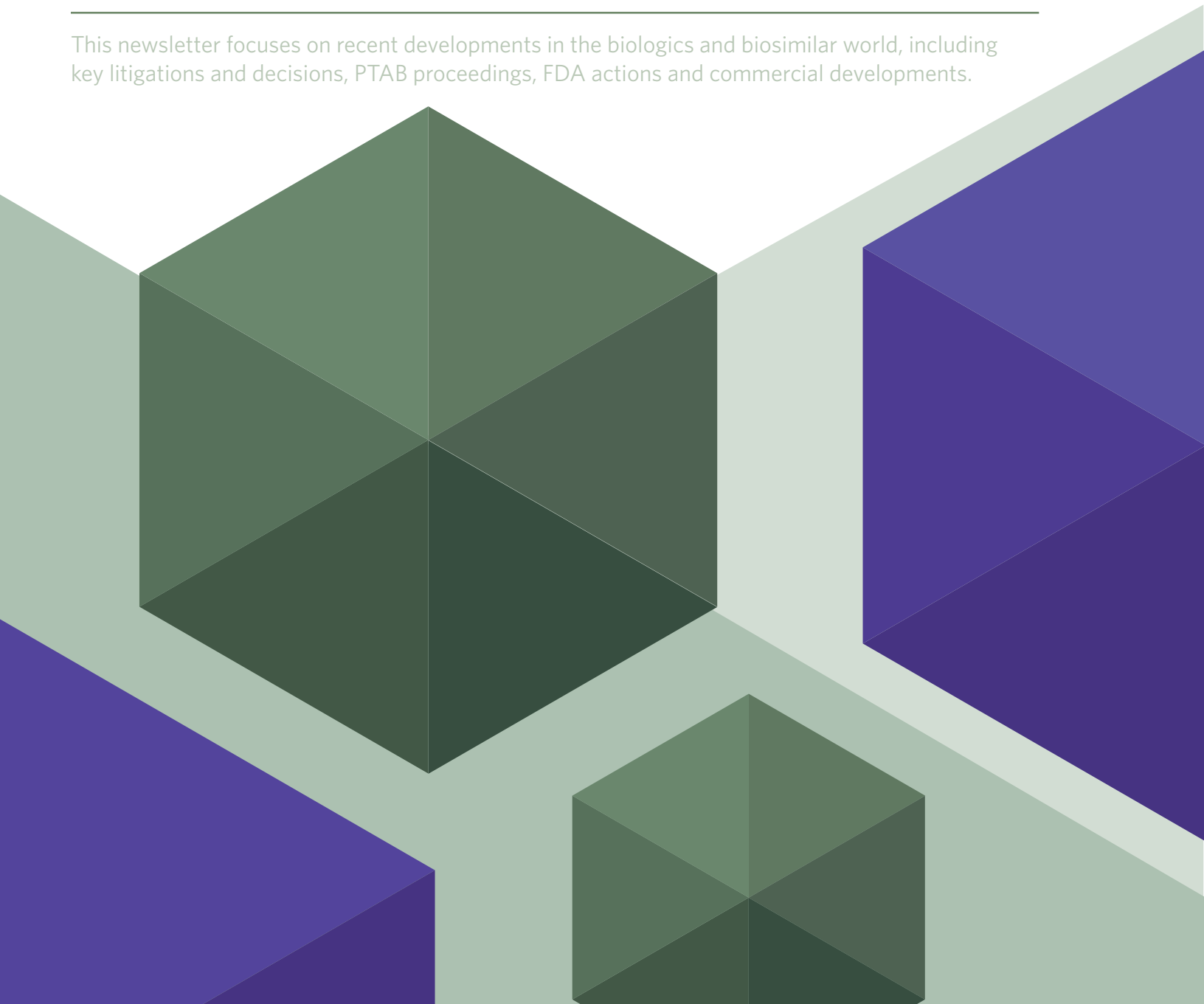
THE BIO-QUARTERLY:
WILLKIE'S BIOLOGICS AND BIOSIMILARS NEWSLETTER

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



Contents

The ongoing litigation between Genentech and Amgen over Amgen's bevacizumab biosimilar demonstrates that surprises may still be in store for biosimilar litigants.

FEATURED ARTICLE

Genentech v. Amgen - MVASI™ Patent Dance - It Takes Two To Tango

Many of the BPCIA cases to date have followed a relatively similar procedural pattern, with the reference product sponsor filing a complaint against the biosimilar applicant after the completion of the BPCIA exchanges (or after the biosimilar applicant "opts-out"). However, the ongoing dispute between Genentech and Amgen over Amgen's MVASI™, a biosimilar of Genentech's cancer drug AVASTIN®, demonstrates that ambiguities in the BPCIA leave open the possibility of new procedural tactics.

Genentech Sues to Enforce § 262(*l*)(2)(A) Compliance

Amgen filed its aBLA for MVASI™ in November 2016. Shortly thereafter, Genentech filed a complaint for declaratory judgment in the District Court for the District of Delaware against Amgen, alleging that although Amgen had "opted in" to the BPCIA exchange procedures, Amgen declined to provide to Genentech certain specific categories of manufacturing information. Genentech also alleged that Amgen refused to allow Genentech's external experts to review the documents for the purpose of determining whether infringement actually occurred. Based on these allegations, Genentech asserted that it was entitled to a declaratory judgment directing Amgen to comply, resetting the BPCIA deadlines for resolving patent disputes, and prohibiting Amgen from selling MVASI™ until the BPCIA exchange procedures were completed. After a hearing on the complaint in March 2017, the court dismissed the action but provided Genentech with 45 days to file an amended complaint alleging patent infringement pursuant to 42 U.S.C. § 262(*l*)(9)(C) if it, in fact, believed that Amgen had violated the BPCIA. To date, Genentech has not filed an amended complaint.

The California Action – Amgen Sues for Declaratory Judgment

On September 14, 2017, Amgen's biosimilar MVASI™ received FDA approval and on October 6, 2017, Amgen provided its notice of commercial marketing. On the same day it provided its notice, Amgen filed a complaint against Genentech in the Central District of California (the "California Action"), seeking a declaratory judgment that MVASI™ does not infringe any of the 27 patents identified by Genentech during the BPCIA exchanges, that the patents are invalid, and that one of the patents was unenforceable for inequitable conduct.

Genentech moved to dismiss the California Action for lack of subject matter jurisdiction on November 15, 2017, arguing that the BPCIA bars Amgen's preemptive declaratory judgment action, and that the court should decline to exercise jurisdiction over Amgen's action. Specifically, Genentech argued that § 262(*l*)(9)(C) prohibits declaratory judgement actions by subsection (k) applicants who, like Amgen, have not complied with their production obligations under § 262(*l*)(2)(A). Genentech further argued that even if Amgen had complied with § 262(*l*)(2)(A), § 262(*l*)(9)(B) preserves the patent owner's right to sue first by prohibiting preemptive declaratory judgment actions like Amgen's complaint before completion of the "patent dance." In the alternative, Genentech sought to stay the California Action pending resolution of the related cases (discussed below).

Briefing on the motion to dismiss is ongoing, and the court is scheduled to hear arguments on January 8, 2018 at 8:30 am.

The Delaware Action – Genentech's Response to the California Action

Meanwhile, on the same day that the California Action was filed, Genentech filed a complaint in the District of Delaware, alleging that MVASI™ infringes 24 patents and that Amgen violated certain BPCIA obligations (the "Delaware Action"). Regarding the infringement allegations, Genentech alleged that Amgen infringed its patents under 35 U.S.C. § 271(a) and, for certain patents, asserted that Amgen "knew, understood and believed" the patent was infringed. This allegation appears to be based on representations made by Amgen in its 3(B) statement, although specific details are redacted. Notably, Genentech does not assert infringement under 35 U.S.C. § 271(e)(2)(C).

Regarding the BPCIA violations, Genentech repeated the allegations from its earlier complaint, alleging that Amgen did not provide Genentech with any documents other than Amgen's aBLA and as a result, Amgen failed to comply with its statutory obligations under the BPCIA. In addition, Genentech alleged that it served infringement and validity contentions pursuant to 42 U.S.C. § 262(*l*)(3)(C), but upon receiving these contentions, Amgen refused to negotiate regarding the scope of the litigation under 42 U.S.C. § 262(*l*)(4). As a result, Amgen allegedly improperly delayed completion of the BPCIA exchanges. Amgen also allegedly made certain representations (the details of which are redacted) that are in conflict with Amgen's assertion that it may begin marketing its biosimilar no later than 180 days from October 6, 2017. This behavior, Genentech argued, deprived Genentech of its right under the BPCIA to thoroughly evaluate potential infringement before Amgen's biosimilar comes to market, and to select the forum for litigation.

In response, Amgen filed a motion to transfer the Delaware Action to the Central District of California, the same district as the California Action. Amgen first argued that the "first-filed rule" supports transfer, because Amgen's California Action was filed prior to the Delaware Action. Amgen also argued that the Delaware Action could have been brought in California because all of the actions alleged in Genentech's complaint to establish infringement took place or originated from within the Central District of California. Amgen then discussed a number of private interest factors, including Plaintiff's and Defendant's forum preference, whether the claims arose elsewhere, convenience of the parties and witnesses, and location of relevant evidence. Amgen also discussed certain public interest factors, including practical considerations and court congestion. Amgen concluded that the factors weighed in favor of transfer.

In opposition, Genentech argued that Amgen's motion to transfer was disingenuous, as Amgen was a "serial litigant" in the District of Delaware and each of the parties was incorporated in Delaware. In addition, Genentech argued that each of the private and public factors identified by Amgen weighed against transfer. Genentech also addressed Amgen's "first-filed" argument, noting that Amgen's complaint was

"plainly anticipatory in seeking declaratory judgments on its defenses to the claims it knew [Genentech was] about to bring." As such, Genentech asserted that Amgen's California Action was purely a litigation tactic and should be given little to no deference for venue. Genentech also argued that Amgen's California Action is expressly prohibited by the BPCIA because Amgen failed to comply with the provisions of § 262 (*l*)(2)(A), and thus merited no deference.

In reply, Amgen again addressed the public and private factors, arguing that the factors weighed in favor of transfer. Amgen also asserted that it had complied with § 262 (*l*)(2)(A), and thus its suit was not barred. Amgen further argued that its declaratory judgment action was not anticipatory because, once it gave its notice of commercial marketing, "it had a statutory right to sue to 'clear any cloud of suspicion that might hang over it.'" This motion is currently pending.

Amgen has also moved to dismiss Genentech's claim to enforce the "promise" made by Amgen regarding the date it would begin to market its biosimilar. Amgen argued that Genentech's complaint identifies no underlying federal or state law giving rise to its claim for a declaration of rights. Amgen further noted that Amgen's statement of intention did not create a binding, enforceable promise as a matter of law. Genentech allegedly failed to allege any detrimental reliance on Amgen's "promise." In response, Genentech filed a sealed amended complaint.

The Second Delaware Action – Genentech Sues Again After Completion of the BPCIA Patent Dance

While the California and Delaware Actions were pending, Genentech and Amgen continued to conduct negotiations regarding the number of patents to litigate pursuant to § 262(*l*)(5). After these negotiations concluded, Genentech filed another suit on October 18, 2017, in the District Court for the District of Delaware again asserting infringement of 24 patents, but in this instance asserting infringement under both 35 U.S.C. § 271(a) and § 271(e)(2)(C). In addition, Genentech added several new counts related to Amgen's alleged violations of the BPCIA exchange provisions. Genentech also sought damages for the product Amgen had already manufactured, arguing that Amgen's manufacturing was not protected by the safe harbor provisions of 35 U.S.C. § 271(e)(1). Amgen has moved to transfer this action to the Central District of California. Briefing on the motion to transfer is currently ongoing.

Key Issues for Consideration

The ongoing dispute between Genentech and Amgen raises several issues that could have far-reaching consequences for biosimilar applicants and reference product sponsors alike.

One key issue is whether Amgen, a biosimilar applicant, could properly bring suit for declaratory judgment prior to the completion of the BPCIA exchanges. This has potentially far-reaching consequences, as it may allow biosimilar applicants to effectively truncate the BPCIA exchanges. However, this case is factually distinct from many other BPCIA cases, as declaratory judgment was sought after Amgen's biosimilar product had received FDA approval.

Another important issue raised in this case is what exactly a biosimilar applicant needs to do to comply with § 262(*l*)(2)(A). Compliance with § 262(*l*)(2)(A) has been raised in a number of cases, and thus has the potential to affect multiple biosimilar applicants.

In addition, although much of the information is redacted, it appears possible that Amgen's 3(B) list did not contest validity or infringement for certain patents. However, Amgen's declaratory judgment complaint alleged that these patents are invalid and not infringed. Genentech's complaints seem to be setting up an argument that "biosimilar applicants like Amgen must include all bases for its contentions of non-infringement and invalidity" in the 3(B) statements.

Thus, resolution of these cases has the potential to impact many different facets of biosimilar litigation.

Please contact Michael W. Johnson (mjohnson1@willkie.com) or Tara L. Thieme (tthieme@willkie.com) if you would like to receive ongoing updates regarding developments in this litigation.

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

Litigation Quarterly Update

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

Key Appellate Decisions

Amgen v. Sandoz. On December 14, 2017, on remand from the Supreme Court, the Federal Circuit affirmed the dismissal of Amgen's state law claims against Sandoz, ruling that such state law claims were preempted by the BPCIA.

By way of background, Amgen originally appealed a decision of the United States District Court for the Northern District of California (1) granting partial judgment on Sandoz's claims that a notice of commercial marketing may be provided prior to final approval of the biosimilar product; (2) dismissing Amgen's state law unfair competition claims and conversion claims; and (3) denying Amgen's motion for a preliminary injunction based on its state law claims. The Federal Circuit affirmed the dismissal of Amgen's state law claims, but held that the notice of commercial marketing could only be provided after final approval of the biosimilar. After rehearing *en banc* was denied, Sandoz filed a petition for a writ of certiorari, presenting the question of whether the notice of commercial marketing could be given prior to FDA approval of the biosimilar. Amgen filed a conditional cross-petition, presenting the question of whether a biosimilar applicant is required to provide the reference product sponsor with a copy of its aBLA under 42 U.S.C. § 262(*l*)(2)(A), and whether declaratory judgment is the sole remedy for a failure to provide the aBLA. The Court held that an injunction under federal law is not available to enforce 42 U.S.C. § 262(*l*)(2)(A), and a biosimilar applicant may provide the notice of commercial marketing either before or after receiving FDA approval. The Supreme Court remanded, noting that the Federal Circuit should determine whether California law would treat noncompliance with § 262(*l*)(2)(A) as "unlawful," and if so, whether the BPCIA preempts any additional remedy under state law.

On remand, Amgen argued that (1) Sandoz waived its preemption defense to its state law claims; (2) the BPCIA does not preempt state law remedies for failure to comply with § 262(*l*)(2)(A); and (3) failure to comply with § 262(*l*)(2)(A) is both "unlawful" and an act of conversion. Sandoz responded that (1) the Federal Circuit has discretion to address preemption; (2) both field and conflict preemption bar Amgen's state law claims; (3) Amgen's state law claims fail under California law; and

(4) Amgen abandoned its conversion claim. The panel first addressed the parties' waiver arguments, finding that although Sandoz had not raised preemption as an affirmative defense in the proceedings below, the panel nevertheless had discretion to address preemption and that the specific facts of this case weighed in favor of exercising that discretion. In particular, the panel noted that the Supreme Court expressly instructed the panel to consider preemption, and that the issue was "a significant question of general impact or of great public concern." In addition, the panel noted that Sandoz had preserved its right to raise this defense on remand before the district court, so there was no prejudice to Amgen by resolving the issue.

The panel next turned to the parties' preemption arguments. The panel noted that "[u]nder field preemption, 'state law is pre-empted where it regulates conduct in a field that Congress intended the Federal Government to occupy exclusively.'" Amgen argued that field preemption does not apply to its state law claims because "the federal statute does not provide a meaningful remedy for the state-recognized interests that have been injured by Sandoz's failure to comply with 42 U.S.C. § 262(*l*)(2)(A)." Sandoz responded that field preemption bars Amgen's state law claims because the BPCIA's comprehensive framework demonstrates Congressional intent that federal law exclusively occupy the field of patent dispute resolution triggered by the filing of a biosimilar application. The panel agreed with Sandoz, noting that the BPCIA is "comprehensive" and "provide[s] a full set of standards governing" the exchange of information in biosimilar patent litigation, "including the punishment for noncompliance." The panel thus found that the BPCIA's comprehensive, carefully calibrated regulatory framework was "so pervasive as to make reasonable the inference that Congress left no room for the States to supplement it." The panel also found that permitting states to impose their own penalties for violations of federal law would conflict with the careful balance Congress established in the BPCIA. As such, the panel held that Amgen's state law claims were preempted.

Because the panel concluded that Sandoz did not waive its preemption defense and Amgen's state law claims are preempted, the panel did not reach the parties' arguments relating to (1) whether Sandoz preserved its conversion claims; or (2) whether failure to comply with § 262(*l*)(2)(A) is "unlawful" under California law or an act of conversion. The case was decided unanimously by Judges Newman, Lourie, and Chen.

Amgen v. Apotex. On November 13, 2017, the Federal Circuit affirmed a district court judgment that Apotex did not infringe Amgen's U.S. Patent No. 8,952,138. Apotex filed two aBLAs seeking approval to market biosimilar versions of Amgen's pegfilgrastim and filgrastim products, NEULASTA® and NEUPOGEN®. During the BPCIA exchanges, Amgen identified the '138 patent, which was generally related to methods for obtaining properly folded proteins from "inclusion bodies" (misfolded proteins) using a carefully controlled reduction-oxidation reaction at "a high protein concentration[] . . . at or above about 1 g/L." In certain pre-litigation letters to Amgen, Apotex stated that the concentration of its protein was limited to 0.9 through 1.4 g/L, the "inclusion body concentration" listed in Apotex's aBLAs. Amgen then filed suit against Apotex asserting, among other things, that Apotex infringed the '138 patent. The district court held a bench trial in July 2016, and found that Amgen had failed to prove that Apotex's two products would infringe the '138 patent. Specifically, the district court credited the testimony of an Apotex fact witness who testified that because "inclusion bodies" are mostly water, the concentration of "protein" in Apotex's process never exceeded 0.708 g/L, well below the claimed 1.0 g/L minimum concentration.

On appeal, Amgen challenged the district court's finding on three grounds: (1) that the district court erred in finding Apotex's pre-litigation letters to lack probative value; (2) that the district court erred in not treating "protein concentration" as interchangeable

with "inclusion body concentration"; and (3) that the district court erred in not finding the required 1.0 g/L protein concentration based on what Apotex's aBLAs permit. With respect to the pre-litigation letters, the panel noted the general legal principle that the "district court cannot ignore letters sent during the BPCIA's information exchange if properly offered into evidence." However, upon reviewing the district court's decision, the panel concluded that the district court simply found that the letters were not sufficiently probative to outweigh the other evidence, not that the letters lacked any probative value. The panel concluded that the letters did not render the district court's findings on protein concentration clearly erroneous.

With respect to Amgen's arguments on the construction of "protein concentration," the panel found that the specification "pervasively" disproved Amgen's assertion that "protein" was used interchangeably with "inclusion body." Instead, the specification made clear that proteins were dispersed within inclusion bodies. With respect to Amgen's arguments regarding the disclosures in the aBLAs, the panel found that the district court had a sufficient basis for understanding the aBLA's as not authorizing processes that infringed, but rather constraining the processes to non-infringing levels. As such, the panel rejected Amgen's arguments and affirmed the district court's ruling. This case was decided unanimously by Judges Lourie, O'Malley, and Taranto.

Key District Court Decisions

Janssen v. Celltrion. On October 31, 2017, the District Court of Massachusetts denied Celltrion and Hospira's motion to dismiss for lack of jurisdiction and lack of standing, finding that despite the defendants' arguments to the contrary, Janssen is the sole owner of the patent-in-suit. The litigation relates to the monoclonal antibody called infliximab, sold by Janssen as REMICADE®. The patent-in-suit, U.S. Patent No. 7,598,083, relates to the composition of a cell culture media and names six inventors.

In two preceding cases, Celltrion moved to dismiss those actions for lack of standing due to Janssen's alleged failure to join all co-owners of the '083 patent. Celltrion's arguments were based on several inventor agreements with Centocor (Janssen's predecessor company), which allegedly assigned the inventors' rights in the '083 patent to both Centocor and Johnson & Johnson. During the litigation, Janssen and Johnson & Johnson entered into an agreement that states that Johnson & Johnson never owned any interest in the '083 patent. However, prior to a decision, the parties agreed to the dismissal of all claims relating to the '083 patent in both preceding actions. Janssen then filed the current action in May 2017 and defendants again moved to dismiss based on a failure to join all necessary parties.

The District Court for the District of Massachusetts analyzed the employment agreements and found that the patent rights were assigned to "the Company," which was defined in relevant part as Centocor, Johnson & Johnson, and "any" of the Johnson & Johnson family of companies. Defendants argued that this language assigned the patent rights to both Centocor and Johnson & Johnson. Janssen argued, however, that within the context of the provision, "the Company" meant the entity that employed the inventor when the invention was conceived or made. The district court found the provision ambiguous, but ultimately concluded that Janssen's interpretation was most consistent with the intent of the parties as discerned from the understanding of Janssen and Johnson & Johnson, as well as from indications in other provisions of the agreement. The district court thus denied Celltrion and Hospira's motion to dismiss. Celltrion and Hospira are currently seeking to certify this order for immediate appeal and to stay the case pending that appeal.

Settlements/Dismissals

On November 10, 2017, Janssen Biotech and Samsung Bioepis stipulated to dismissal of the litigation between the parties relating to Samsung's biosimilar of the drug infliximab (REMICADE®). A spokesperson for Janssen explained that, after reviewing Samsung's aBLA, Janssen determined that Samsung's manufacturing process did not infringe Janssen's patents and thus withdrew the suit. Samsung Bioepis and Merck & Co. launched their REMICADE® biosimilar, RENFLEXIS®, in July of 2017.

New Litigation

In the past quarter, several new biosimilar-related suits have been filed. As described in the featured article of this issue, several new complaints have been filed by Genentech and Amgen relating to Amgen's biosimilar of Genentech's bevacizumab product, AVASTIN®. In addition, on November 17, 2017, Genentech filed suit against Pfizer, Inc. in the District Court for the District of Delaware, alleging infringement of 40 patents relating to Pfizer's biosimilar of Genentech's trastuzumab product, HERCEPTIN®. Genentech has also filed suit against Sandoz in the District of New Jersey, alleging infringement of 24 patents by Sandoz's RIXATHON, a biosimilar version of Genentech's RITUXAN® (rituximab).

Please contact Michael W. Johnson (mjohnson1@willkie.com) or Tara L. Thieme (tthieme@willkie.com) if you would like to receive copies of any of the pleadings discussed above.

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

PTAB Quarterly Update

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

Adalimumab (HUMIRA®)

During the past few months, there has been little activity in the PTAB regarding the anti-TNFα antibody HUMIRA® (generic name adalimumab). In early November, Sandoz filed its eighth IPR regarding adalimumab against AbbVie's patent directed toward a method of treating idiopathic inflammatory bowel disease (U.S. Patent No. 9,187,559). We anticipate that the PTAB will act on Sandoz's eight petitions early next year, continuing into the second quarter of 2018.

Rituximab (RITUXAN®)

In the last quarter, the PTAB has been fairly active regarding the anti-CD20 antibody RITUXAN® (rituximab). In early October, the PTAB instituted review of Celltrion's petition for IPR of Biogen's patent directed toward a method for treating low grade or follicular non-Hodgkin's lymphoma (U.S. Patent No. 9,296,821). In mid and late October, the PTAB denied institution of two petitions filed by Celltrion against Genentech's patent directed toward a method of treating chronic lymphocytic leukemia (U.S. Patent No. 7,682,612). Further, in early November, the PTAB instituted Pfizer's petition for IPR of Biogen's patents directed toward a method of treating a patient with diffuse large cell lymphoma (U.S. Patent No. 8,821,873), and denied institution of Pfizer's petition for IPR of another Biogen patent directed toward a method of treating a patient with diffuse large cell lymphoma (U.S. Patent No. 8,557,244). Moreover, in late October, the PTAB heard oral arguments on IPRs filed by Celltrion and Pfizer against Genentech's patent directed toward a method of treating rheumatoid arthritis with a combination of rituximab and methotrexate (U.S. Patent No. 7,820,161). A decision on these petitions is expected in the first quarter of 2018.

A few petitions were also filed during this quarter. In early October, Pfizer filed petitions for IPR of the '612 patent and another Genentech's patent directed toward a method of treating chronic lymphocytic leukemia (U.S. Patent No. 8,206,711). In December, Pfizer also filed petitions for IPR against the '821 patent, Biogen's patent directed toward a method of treating a 60-year old or older patient with diffuse large cell lymphoma (U.S. Patent No. 9,504,744), and Biogen's patent directed toward a method of treating low grade B-cell non-Hodgkin's lymphoma (U.S. Patent No. 8,329,172).

We currently anticipate that the PTAB will act on Pfizer's petitions around the second quarter of 2018.

Trastuzumab (HERCEPTIN®):

A few developments at the PTAB regarding patents related to the anti-HER2 antibody HERCEPTIN® (trastuzumab) have occurred during this quarter. In late October, the PTAB granted Hospira's request for rehearing and instituted review of its petition for IPR of Genentech's patent directed toward a method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor (U.S. Patent No. 7,846,441). The PTAB had previously denied Hospira's petition in July. Furthermore, in early December, the PTAB instituted review of Celltrion's and Pfizer's petitions against U.S. Patent No. 6,407,213. The PTAB also instituted review of Samsung Bioepis's petitions on patents directed toward a method of treating a patient with breast cancer that overexpresses the ErbB2 receptor (U.S. Patent Nos. 6,627,196; 7,371,379; and 7,892,549), and joined its petitions with Hospira's respective IPRs that were previously instituted. In early October, Pfizer filed a second petition for IPR of the '441 patent, and in December, Pfizer filed a second petition for IPR of Genentech's patents directed toward compositions comprising a mixture of an anti-HER2 antibody with one or more acidic variants (U.S. Patent Nos. 9,249,218 and 6,339,142). Samsung Bioepis also filed a petition for IPR of the '441 patent in late November.

Other Biologics:

In late November, the PTAB heard oral arguments on Hospira's petition for IPR of Genentech's patent entitled "Reducing Protein A Leaching During Protein A Affinity Chromatography." Also, in early December, the PTAB instituted review of Pfizer's petitions for IPR against Chugai Pharmaceutical's patents entitled "Method of purifying protein" (U.S. Patent No. 7,332,289) and "Protein purification method" (U.S. Patent No. 7,927,815). Also in December, the PTAB instituted review of Mylan's petitions for IPR of Sanofi's patents directed toward a formulation of insulin glargine (U.S. Patent Nos. 7,476,652 and 7,713,930). The PTAB also heard oral arguments in December for Apotex's IPR against Amgen's patent directed toward a method of refolding a protein expressed in a non-mammalian expression system (U.S. Patent No. 8,952,138).

For a more detailed analysis of the PTAB institution decisions discussed above, please contact Michael W. Johnson (mjohnson1@willkie.com) or Tara L. Thieme (tthieme@willkie.com).

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

FDA/Regulatory Quarterly Update

Recent FDA Approvals

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

FDA Approves LUXTURNA™ (voretigene neparvovec)

On December 19, 2017, the FDA approved LUXTURNA™, a new gene therapy for the treatment of an inherited form of vision loss that may result in blindness. LUXTURNA™ is approved for the treatment of patients with confirmed biallelic RPE65 mediated retinal dystrophy. LUXTURNA™ received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases. LUXTURNA™ also received Priority Review and Breakthrough Therapy designations. LUXTURNA™ was developed by Spark Therapeutics Inc., who also received a Rare Pediatric Disease Priority Review Voucher under a program intended to encourage development of new drugs and biologics for the prevention and treatment of rare pediatric diseases.

FDA Approves New Biosimilar, IXIFI™ (infliximab)

On December 13, 2017, the FDA approved Pfizer's infliximab product IXIFI™, a biosimilar to Janssen's REMICADE®. Infliximab is a chimeric human-murine monoclonal antibody that works against tumor necrosis factor. IXIFI™ has been approved in the U.S. for all eligible indications of the reference product, including rheumatoid arthritis, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. This is the third FDA-approved biosimilar to U.S.-licensed REMICADE®.

FDA Approves ADMELOG® (insulin) for the Treatment of Diabetes

On December 11, 2017, FDA approved Sanofi's ADMELOG®, the first short-acting "follow-on" insulin product for the treatment of diabetes. ADMELOG® is intended to improve control in blood sugar levels in adults and pediatric patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus. In the U.S., ADMELOG® was approved as a drug, not a biologic

product. However, in Europe, it was granted marketing authorization as a biosimilar.

FDA Approves First Trastuzumab Biosimilar, OGIVRI™

On December 1, 2017, the FDA approved Mylan's OGIVRI™, the first biosimilar to Genentech's trastuzumab product, HERCEPTIN®. OGIVRI™ is indicated for use in the treatment of human epidermal growth factor receptor –positive (HER+) breast cancer and also HER2+ metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma).

Previously, Mylan reached an agreement with Genentech, Inc. and F. Hoffmann-La Roche Ltd. in relation to patents for HERCEPTIN® (trastuzumab), which provides Mylan with global licenses for its trastuzumab product. The license allows Mylan to commercialize trastuzumab in all countries except Japan, Mexico and Brazil. As part of the settlement, Mylan withdrew its pending IPR challenges against Genentech's U.S. Patent Nos. 6,407,213 and 6,331,415. All other terms and conditions of the settlement are confidential.

FDA Approves HEMLIBRA® (emicizumab)

On November 16, 2017, the FDA approved HEMLIBRA® (emicizumab) as a treatment to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A who have developed antibodies called Factor VIII inhibitors, which can interfere with the effectiveness of currently available treatments for hemophilia. Hemophilia A is an inherited blood-clotting disorder that affects one in every 5,000 males in the U.S., according to the National Institutes of Health. Patients with hemophilia A are missing a gene that produces Factor VIII, a protein that enables blood to clot. HEMLIBRA® works by bridging other factors in the blood to restore blood clotting. HEMLIBRA® is a weekly preventative (prophylactic) treatment administered via subcutaneous injection. The FDA granted approval of HEMLIBRA® to Genentech, Inc.

FDA Approves MEPSEVII™ (vestronidase alfa)

On November 15, 2017, the FDA approved MEPSEVII™ (vestronidase alfa) for the treatment of mucopolysaccharidosis type VII (MPS VII), also known as Sly syndrome, in pediatric and adult patients. MPS VII is an extremely rare, progressive, and inherited metabolic condition that affects most tissues and organs. MEPSEVII™ replaces the enzyme called beta-glucuronidase, which is responsible for the removal of toxic materials from the body's cells.

MEPSEVII™ was approved under the Fast Track designation, which expedites the approval process for drugs that are intended to treat serious conditions. MEPSEVII™ also received the Orphan Drug designation, which incentivizes the development of drugs for rare conditions. MEPSEVII™ was developed by Ultragenyx Pharmaceutical, Inc.

FDA Approves FASENRA™ (benralizumab)

On November 14, 2017, the FDA approved FASENRA™ (benralizumab) for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. FASENRA™ is the only respiratory biologic that provides direct, rapid and near-complete depletion of eosinophils, a type of white blood cell, that are a normal part of the body's immune system. FASENRA™ is a monoclonal antibody that binds to the IL-5α receptor on an eosinophil and uniquely attracts natural killer cells to induce apoptosis.

FASENRA™ was developed by AstraZeneca plc and Medimmune, LLC.

FDA Approves SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

On October 23, 2017, the FDA approved SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted) for the prevention of shingles in adults aged 50 and older. SHINGRIX is a non-live, recombinant subunit vaccine administered via intramuscular injection in two doses. It combines an antigen, glycoprotein E, and an adjuvant system that generates a strong and long-lasting immune response that can help overcome the decline in immunity as people age. SHINGRIX was developed by GlaxoSmithKline plc.

FDA Approves YESCARTA™ (axicabtagene ciloleucel)

On October 18, 2017, the FDA approved YESCARTA™ (axicabtagene ciloleucel) for the treatment of relapsed or refractory large B-cell lymphoma in adult patients who have undergone two or more lines of systemic therapies. Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell immunotherapy that consists of genetically modified autologous T-cells that produce a CAR protein that allows the T-cells to identify and eliminate CD19-expressing normal and malignant cells. YESCARTA™ was developed by Kite Pharma, Inc.

Biologics and Biosimilars Under Development

On December 11, 2017, Eli Lilly and Co. announced that the FDA accepted for review its aBLA for galcanezumab, a monoclonal antibody developed to prevent migraines in adults.

On November 28, 2017, Kyowa Hakko Kirin announced that the FDA accepted for review its aBLA for mogamulizumab to treat cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy; the application was granted Priority Review status with an action date of June 4, 2018.

On November 1, 2017, Momenta and Mylan announced that their M834, a proposed biosimilar of Bristol-Myers Squibb's ORENCIA® (abatacept) did not meet its primary endpoints in a Phase 1 trial.

On October 10, 2017, the FDA issued a complete response letter for Biocon and Mylan's MYL-1401H, a proposed biosimilar for Amgen's NEULASTA® (pegfilgrastim); Sandoz's proposed pegfilgrastim biosimilar, LA-EP2006, received a complete response letter in July 2016.

On September 22, 2017, the FDA issued a complete response letter for Janssen's aBLA for its proposed PLIVENSIA™ sirukumab, an IL-6 inhibitor for the treatment of rheumatoid arthritis.

Biopharma Comment on FDA Draft Guidance for Evaluating Biosimilarity

In September 2017, the FDA published the draft guidance titled "Statistical Approaches to Evaluate Analytical Similarity." The guidance described the type of data and information sponsors of proposed biosimilar products should produce regarding the structural/physicochemical and functional attributes of the reference product. Furthermore, the guidance described how that data should be used in the development of an analytical similarity assessment plan for the proposed biosimilar, as well as statistical approaches for evaluating analytical similarity. Comments from biopharmaceutical companies and some other interested parties were recently published. Among the commenters were Amgen, Boehringer Ingelheim, Genentech, Novartis, Pfizer, Sanofi, Momenta, and Shire.

In its comments, Amgen pointed out that FDA's expectations in establishing guidelines may evolve over time and requested "that the Agency proactively communicate with the sponsor when there are significant changes in Agency expectations from those which were previously agreed upon during early consultation with the sponsor." Amgen also recommended that "the concepts of structural/physicochemical attributes [be] separate from that of functional attributes in the final guidance in locations where risk assessments are discussed."

Genentech stated the importance of having a protocol for both the statistical methods and experimental design to ensure rigorous assessment. The protocol "will describe the data collected prior to experimentation on the reference and biosimilar products, the data to be collected during experimentation, the statistical methods, and acceptance criteria to determine if the data collected during experimentation supports the hypothesis of similarity." Genentech further added that "[o]ne of the guidance's first sections should describe the protocol, the interactions the agency is prepared to have with the sponsor on protocol development, and the milestones in place prior to performing the assessment."

Genentech also urged the FDA to promote testing of multiple attributes because "[i]n clinical trials, multiple testing procedures are designed to control consumer risk; in analytical similarity testing, the procedures need to be designed to control producer risk as well." According to Genentech it is appropriate to use "multiple testing procedures to control both types of risk."

One of Pfizer's suggestions was to use statistical analyses as a supportive tool "when data are amenable to statistics and the statistical analyses results are meaningful to the understanding or interpretation of data, rather than a default expectation." The company also noted that while the draft guidance "acknowledges that there are many challenges and limitations to applying statistical analyses in the evaluation of analytical similarity data," "it is not clear how a risk-based approach in the analytical similarity assessment of quality attributes addresses the challenges outlined." Pfizer also pointed out that the draft guidance does not address the "challenge of determining an appropriate biologically or clinically meaningful margin for equivalence testing," which, according to Pfizer, is a fundamental factor in the approach outlined by the guidance.

In its comments, Boehringer Ingelheim, while supporting the development of an analytical similarity assessment plan, urged the agency to apply scientific and regulatory consistency to all biologics, including biosimilars and interchangeable biologics, "to prevent any disparate treatment of these products." Next, the company recommended that the agency continue to recognize that a critical element for evaluating similarity is prior knowledge of all biologics, which includes understanding quality attributes, the disease a biologic is meant to treat, and understanding the dynamics of vulnerable populations, "and that this is particularly relevant for biosimilars and interchangeable biologics, but not unique to them."

Boehringer Ingelheim also suggested that the FDA accommodate "those instances where equivalence may not be achieved because, for example, modern manufacturing methods allow for better manufacturing control than was historically the case (e.g., control of aggregates and consequential immunogenicity, or where changes may have occurred with the reference product for safety reasons)." The company acknowledged that while this could lead to noticeable differences, it may be "reasonable to conclude that both the biosimilar and its reference product will still achieve the same clinical outcomes." However, it also stated that the FDA should decide on a case-by-case basis.

The Association for Accessible Medicines ("AAM") and the Biosimilars Forum were among the other interested parties to post comments. Both parties commented on the FDA's suggestion that a minimum of 10 drug product lots should be used for analytical similarity assessment. The Biosimilar Forum asked for further

clarification on whether the FDA still recommends the "use of independent drug product lots (drug product lots manufactured from different drug substance lots)" because the concept was not addressed in this guidance but had been in previous guidances. This mirrored AAM's question on whether the biosimilar lots should be independent or can be manufactured from the same drug substance lot.

The comment period for the draft guidance closed on Nov. 21, 2017.

Please contact Michael W. Johnson (mjohnson1@willkie.com) or Tara L. Thieme (tthieme@willkie.com) if you would like copies of the draft guidance or comments discussed above.

Breaking News

- On December 20, 2017, the FDA approved PERJETA® (pertuzumab, Genentech, Inc.) for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2+ early breast cancer at high risk of recurrence. The FDA also expanded approval of OPDIVO® (nivolumab, Bristol-Myers Squibb Company) for certain melanoma patients who have undergone complete resection. On December 21, 2017, the FDA approved GIAPREZA™ (angiotensin II) for the treatment of low blood pressure in adults with septic or other distributive shock. These approvals will be discussed in greater detail in our next issue.

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

Market Quarterly Update

New Biologic Approvals this Quarter

On October 18, 2017 Kite Pharma's YESCARTA™ (axicabtagene ciloleucel) became the second CAR-T gene therapy approved by FDA, following Novartis' KYMRIAH™ in August. Like KYMRIAH™, treatment with YESCARTA™ will involve administration of a single dose of an individually tailored infusion to a patient. Reports indicate that YESCARTA™ will be cheaper than KYMRIAH™, with a cost per patient of $373,000 as compared to $475,000. In contrast to KYMRIAH™, which is indicated for leukemia treatment, YESCARTA™ received approval to treat lymphoma, though both Novartis and Kite Pharma are expected to seek expanded indications for other blood cancers. YESCARTA™ will be introduced gradually, with only 10-15 participating cancer centers offering it at launch, with an estimated 70-90 authorized institutions by the end of 2018.

GlaxoSmithKline's SHINGRIX (zoster vaccine recombinant, adjuvanted), was approved October 20, 2017. The CDC's Advisory Committee on Immunization Practices recommended SHINGRIX in patients over 50, finding that the vaccine was more than 90% effective in preventing shingles. Merck's ZOSTAVAX® was previously the only approved shingles vaccine, and was found to be about 51% effective. The two-dose SHINGRIX vaccine is expected to cost about $280. This price point is higher than that of ZOSTAVAX®, which sells for $213. SHINGRIX is expected to become widely available in the first half of 2018.

AstraZeneca's FASENRA™ (benralizumab) was approved November 14, 2017, and is the third IL-5 inhibitor approved for the treatment of severe asthma. FASENRA™ will compete with three other biologics in the same space: GlaxoSmithKline's NUCALA® and Teva's CINQAIR®, which have been on the market since 2015 and 2016, respectively, and Novartis' XOLAIR®, first approved in 2003. For the first year of treatment, FASENRA™ will cost $38,000 annually – in line with the other biologics – dropping to $28,000 – $33,000 per year after that. As of press time, launch of FASENRA™ is imminent.

On November 15, 2017, Ultragenyx received approval for its MEPSEVII™ (vestronidase alfa-vjbk), for the treatment of a very rare enzyme disorder, mucopolysaccharidosis type VII (MPS VII), thought to affect about 200 patients in the developed world. MEPSEVII™ will cost about $375,000 per year after discounts (about $550,000 annually before discounts), with about $75 million in peak sales projected. Although Ultragenyx will have the only MPS VII treatment approved in the market, perhaps a greater upside to the approval was the receipt of a priority review voucher, which could potentially be sold or transfered to another company. For example,

Gilead and AbbVie have paid $125 million and $350 million, respectively, for the chance to put their biologic applications on the priority track.

Roche and Genentech's HEMLIBRA® (emicizumab-kxwh), was approved November 16, 2017. HEMLIBRA® is the first new treatment for hemophilia A with inhibitors in about 20 years. Treatment will cost $482,000 for the first year and $448,000 for subsequent years. Analysts are projecting annual sales of $2 billion to $5 billion by 2025 for HEMLIBRA®, which will compete primarily with Shire's hemophilia franchise, purchased in its buyout of Baxalta. Shire's ADVATE® and ADYNOVATE® carry a typical cost to patients between $200,000 and $350,000 per year. Genentech has not announced a timeline for launch for HEMLIBRA®.

New Biosimilar Approvals

Mylan and Biocon's OGIVRI™ (trastuzumab-dkst), biosimilar to Genentech's HERCEPTIN®, was approved on December 1, 2017. OGIVRI™ was previously approved in 19 other countries including India, but the drug is still under review in Canada, Australia, and Europe. OGIVRI™ is the first approved biosimilar for HERCEPTIN®, which made $6.7 billion in sales in 2016. It is unclear when OGIVRI® will make it to market: the product is subject to the terms of a global settlement and license agreement reached between Mylan and Genentech in March in which Mylan agreed to withdraw its pending IPRs. Although the terms of the agreement have not yet been made public, Mylan will be able to market OGIVRI™ worldwide, except in Japan, Brazil, and Mexico.

On December 11 ADMELOG® (insulin lispro), biosimilar to Lilly's HUMALOG®, was approved December 11, 2017, after receiving tentative approval in September. The first approved follow-on insulin product, ADMELOG® will be available in early 2018, with pricing information released at that time. Although patent protection on HUMALOG® has expired, Lilly could seek to enforce a remaining patent covering its injection device.

Pfizer's IXIFI™ (infliximab-qbtx), biosimilar to Janssen's REMICADE® was approved December 13, 2017 for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. IXIFI™ joins two other infliximab biosimilars: Merck's RENFLEXIS®, and Hospira's INFLECTRA®. Because Hospira – Pfizer's subsidiary – has been marketing INFLECTRA® since October 2016, Pfizer announced that it would not commercialize IXIFI™, and is "currently evaluating its strategic options." In February 2016, Sandoz acquired the rights to Pfizer's infliximab biosimilar throughout the European Economic Area.

On November 9, 2017, FDA approved Dynavax Technologies' HEPLISAV-B™ (Hepatitis B Vaccine, Recombinant [Adjuvanted]), the first new hepatitis B vaccine to come to market in more than 25 years. Unlike previous vaccines which required three shots over six months – such as GlaxoSmithKline's ENGERIX-B®– HEPLISAV-B™ requires only two doses over one month. Launch is expected in the first quarter of 2018, and pricing information is not yet available.

Legislative Developments

As part of the tax overhaul bill, Congress has changed the tax credit for developing treatments for rare diseases. By way of background, the Orphan Drug Act of 1983 provides incentives, including tax credits, longer market exclusivity, and clinical research subsidies, to ease the burden of developing drugs for rare diseases (diseases affecting fewer than 200,000 people). The law Pub. L. 115-97, Part V, Subpart A, Sec. 13401, cuts the orphan drug credit from 50% to 25%. This change is effective for taxable years beginning after December 31, 2017. According to an October 2017 report released by QuintilesIMS Institute, sales of orphan drugs exceeded $36 billion last year, or 7.9% of drug spending in the U.S.

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