Biosimilars Market Update

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With You Today

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BPCIA Litigation and Patent Dance

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“Blind” Infringement Suits

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BPCIA Patent Dance Statute

Not later than 20 days after the Secretary notifies the [aBLA] applicant that the application has been accepted for review, the [aBLA] applicant … shall provide to the reference product sponsor a copy of the application …, **and such other information** that describes the **process or processes used to manufacture** the biological product that is the subject of such application; and … **may** provide to the reference product sponsor additional information requested by or on behalf of the reference product sponsor.

42 U.S.C. § 262(*l*)(2)(A)-(B)

Disclosure of Manufacturing Information

- Issue: What is required of a biosimilar applicant to comply with subsection (*l*)(2)?
- Some biosimilar applicants have taken the position that producing the aBLA alone complies with the statute
- Biologic manufacturer left to file allegedly "blind" infringement suit without information on manufacturing other than what is found in the aBLA
- Increasing strategy in view of *Sandoz v. Amgen* decision, holding that the patent dance is optional
- No court has definitively ruled on how to interpret the "and such other information" clause of subsection (*l*)(2)(A)

Amgen v. Hospira (epoetin alfa)

- Amgen's complaint alleged that Hospira violated the BPCIA by not providing additional manufacturing information
  - Amgen further alleged that it could not assess infringement of certain of its process patents due to this "violation"
- District court denied Hospira's motion to dismiss, which argued that there is no private right of action for alleged violations of the BPCIA
- But district court also denied Amgen's motion to compel discovery into Hospira's manufacturing processes, since such information was irrelevant due to Amgen's failure to assert process patents
  - After Amgen appealed, Federal Circuit found it had no jurisdiction over the appeal of the interlocutory discovery order

Declaratory Judgment Complaints

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Declaratory Judgment Complaints by Biosimilar Applicants

- Issue: When can a biosimilar applicant file a declaratory judgment (DJ) action?
- District courts have dismissed DJ complaints filed by Amgen, Celltrion, and Teva, each of which sought declarations of non-infringement or invalidity regarding their proposed biosimilar products
  - *Amgen v. Genentech* (bevacizumab): Court granted Genentech's motion to dismiss, finding that the BPCIA does not allow for DJ actions until notice of commercial marketing is provided
  - *Celltrion v. Genentech* (rituximab, trastuzumab): Court granted Genentech's motions to dismiss because Celltrion did not complete all steps of the patent dance before filing

Patent Thickets and Case Management

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Patent Thickets

- Biologics manufacturers have vast patent portfolios on their products:
  - Molecule
  - Formulations
  - Upstream processes
  - Downstream processes
  - Methods of use
- Tens or more than a hundred patents may cover a given biologic product
- Patent-holders may assert claims based on any or all of these patents against biosimilar applicants, depending on the outcome of the patent dance

AbbVie v. Boehringer Ingelheim (adalimumab)

- **74** asserted patents
- BI pursuing an "unclean hands" defense, alleging:
  - AbbVie "engaged in a **pattern** of pursuing **numerous overlapping and non-inventive patents** for the purpose of developing a '**patent thicket**,' using the patenting process itself as a means to seek to **delay competition** against its expensive and lucrative adalimumab product. That strategy has generated … **more than 100 patents**."
  - Many of the asserted patents "share common specifications and have overlapping and nearly identical claims"
  - These patents "do not represent innovation, but rather are attempts to claim methods of treatment, methods of production, and formulations derived from the prior art for the purpose of **creating a patent thicket or estate that competitors must**, as AbbVie has publicly stated, **'contend with' to sell the active ingredient**" in Humira, which was covered by a patent that expired in December 2016.

AbbVie v. Boehringer Ingelheim (adalimumab)

- To support its "unclean hands" defense, BI sought discovery of R&D documents dated outside the default six-year period under the local rules
- The court **rejected** BI's argument that the case is "unusual, given the number of patents and claims at issue, and the evolution of a '**patent thicket**' over a lengthy period of time"
- But the Court ordered AbbVie to produce documents "for the time preceding the six-year period" regarding R&D because "[r]esearch and development information that leads in a plausible and logical fashion to 'conception and reduction to practice'" is relevant to the litigation

Case Management

- With patent thickets resulting in a high number of patents asserted in a given case, courts are looking at ways of narrowing the issues
- *Genentech v. Amgen* (D. Del.) (bevacizumab):
  - Court directed the parties to reduce the number of asserted patents from 26 to no more than 8 by a date certain
  - Parties agreed to "an initial phase of discovery" whereby the parties would take depositions of each other's corporate designees under FRCP 30(b)(6)
  - Court would like to "make an early determination" regarding whether Genentech can seek damages for activity that Amgen argues is protected by the safe harbor
  - Trial set for June 1, 2020
  - In a memorandum order regarding case management: "The court is a limited resource. Every set of litigants is entitled to use its fair share of this resource – but only its fair share. The litigants in this action are coming perilously close to exceeding that limit."

Safe Harbor

Safe Harbor Statute

It shall **not** be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention … **solely for uses reasonably related** to the **development and submission of information** under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1)

$70 Million Damages Award to Amgen

- In September 2017, a Delaware federal jury found that Hospira infringed one of Amgen's Epogen/epoetin alfa (EPO) patents and awarded Amgen $70 million in damages
- Some portion of each of the batches accused of infringement were used for testing for purposes of submitting an aBLA to FDA
- Jury agreed with Amgen in finding that 21 of Hospira's biosimilar EPO batches were produced to create a stockpile of commercial product, and not protected by the safe harbor of § 271(e)(1)

Delaware Court Affirmed Jury Verdict for Amgen

- Hospira filed a post-trial motion for judgment as a matter of law that the accused batches were protected under the safe harbor and that damages can be no greater than $1.5 million per batch, if sold
- In late August, Delaware judge issued an opinion denying Hospira's motion: "A reasonable jury could have concluded that fewer than all of the batches were protected by the safe harbor defense."
- On October 3, 2018, Hospira filed a notice of appeal to the Federal Circuit
  - Appeal docketed as Case No. 19-1067 on October 11
  - Deadline for Hospira to file its opening brief is December 10 (based on the docketing date)

Labeling Carve-Outs and Infringement Claims

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Carve-Out Legal Authority

- No “same labeling” requirement for biosimilars
- No legal provision limiting carve-outs to indications or other conditions of use protected by patents or exclusivity
- No “use codes” that would define the parameters of a carve-out
- FDA’s Biosimilars Labeling Guidance specifically allows a biosimilar applicant to seek licensure for fewer than all of the RP’s approved indications or conditions of use

Carve-Out Legal Issues

- Do biosimilarity studies in protected indications need to be described in labeling?
  - FDA says in most cases biosimilarity studies do not need to go on labeling
- Will FDA use a "less safe or effective for the remaining conditions of use" standard for biosimilar carve-outs?
- Can biosimilarity labeling use a "shades of gray" approach to get around use patents (rather than complete carve-outs)?
  - What does it mean for a condition of use to be "previously approved"?
- Should the Purple Book identify biosimilarity or interchangeability by indication?
- Will FDA allow an expedited pathway for subsequent approval of carved-out indications?

Immunex v. Sandoz (etanercept)

- Sandoz submitted an aBLA seeking approval for indications for psoriatic arthritis and plaque psoriasis, but later withdrew those indications
- FDA ultimately approved a label that did not contain indications for psoriatic arthritis and plaque psoriasis
- In litigation, Immunex asserted a patent covering the carved-out methods of use and moved for summary judgment of infringement, arguing:
  - The original act of submitting an aBLA seeking approval of the psoriatic arthritis and plaque psoriasis indications (including with clinical trial data for plaque psoriasis) constitutes infringement under § 271(e)(2)(C)
  - Irrelevant whether Sandoz subsequently withdrew those indications from review because infringement has already occurred

Immunex v. Sandoz (etanercept)

- The court issued a sealed order on August 21, which is likely a decision on Immunex's motion
  - A public version of the order is still not available
- Trial begin on September 11, 2018 and concluded on September 25, 2018
  - Neither of the patents asserted at trial were the psoriasis treatment patent that was the subject Immunex's motion
  - This likely means that either the court denied Immunex's motion or granted summary judgment of non-infringement, such that Immunex did not assert the psoriasis patent at trial

Recent Notable Victories

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Big wins for biosimilar applicants!

- **Celltrion won summary judgment of non-infringement in litigation regarding its infliximab biosimilar**
  - No infringement under the doctrine of equivalents—Janssen's only theory of infringement—because the range of equivalents necessary to cover Celltrion's biosimilar product ensnares material in the prior art
- **Federal Circuit affirmed judgment for Apotex that its pegfilgrastim and filgrastim biosimilar candidates do not infringe Amgen's protein refolding method patent**
  - But Amgen has since sued Apotex over the filgrastim/pegfilgrastim products based on newly-issued patents
- **Sandoz won summary judgment of non-infringement of Amgen's protein purification patent based on its filgrastim/pegfilgrastim candidates**
  - Amgen's appeal is pending at the Federal Circuit

Antitrust Issues

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Patent Litigation Settlements

- By settling patent lawsuits and other disputes, biologics manufacturers can orchestrate launch timing for biosimilar competition
- As one example, AbbVie has settled claims regarding its Humira/adalimumab patents with multiple parties, resulting in different launch dates for adalimumab biosimilars in the U.S. that are far behind European launch dates:

Biosimilar Manufacturer	European Launch Date	U.S. Launch Date
Amgen	October 16, 2018	January 31, 2023
Samsung Bioepis	October 16, 2018	June 30, 2023
Mylan	--	July 31, 2023
Sandoz	October 16, 2018	September 30, 2023
Fresenius Kabi	First half of 2019	September 30, 2023

FTC and DOJ Disclosure of Biosimilar Settlements

- Under "Patent Right to Know Drug Prices Act" (S. 2554), Reference Product Sponsors and biosimilar applicants must file patent settlement agreements with the Federal Trade Commission ("FTC") and the U.S. Department of Justice ("DOJ") for review
  - Signed into law on October 10
  - Imposes the same FTC and DOJ disclosure requirements currently in place for ANDA litigation settlements
- "SUPPORT for Patients and Communities Act" (H.R. 6), a bill primarily focused on the opioid crisis, made certain changes to the FTC disclosure requirement
  - Closed loophole in prior bill that only required disclosure for biosimilar applicants that provided a statement under section § 262(*l*)(3)(B)(ii)(I) in the patent dance
  - Extended disclosure requirement to agreements between two biosimilar applicants regarding the exclusivity period for the first interchangeable biosimilar under § 262(k)(6)
  - Signed by President on October 25, 2018

Remicade Antitrust Suits

- On September 20, 2017, Pfizer filed an antitrust lawsuit against Johnson & Johnson in the Eastern District of Pennsylvania
- Complaint alleges that J&J engaged in an anticompetitive scheme to protect its Remicade (infliximab) product upon Pfizer's launch of its competing biologic Inflectra (infliximab-dyyb) in 2016
- According to a brief filed by the Biosimilars Council, J&J's response to the Inflectra launch included:
  - Contracts with insurers that either (1) require them to deny coverage for Inflectra or (2) impose unreasonable preconditions (like a "fail first" requirement) governing coverage for Inflectra
  - Arrangements through which J&J only provides rebates on other products if insurers agree not to cover Inflectra
- On August 8, 2018, the Court denied J&J's motion to dismiss finding the allegations in the complaint sufficient to state a claim for antitrust injury

Remicade Antitrust Suits

- On June 6, 2018, retailers Walgreens and Kroger, direct purchasers, and indirect purchasers of Remicade filed their own antitrust suit against J&J
  - Complaint alleges that J&J's tactics have allowed it to retain market share despite lower cost biosimilar competition from Pfizer (Inflectra) and Merck (Renflixis)
  - "[E]ven though Pfizer's and Merck's products are significantly less expensive than Remicade and have no clinically meaningful differences from them, the overall price of infliximab has actually increased since the entry of these two additional competitors."
- Court recently denied motion to compel arbitration of the suit based on provision in distribution agreements with plaintiffs-direct purchasers

Remicade Antitrust Suits

- In most recent earnings call, J&J said that it has retained approximately 94% volume share on infliximab despite biosimilar competition
  - Regarding the antitrust suits, Chairman and CEO Alex Gorsky stated that "[t]here is really no update on that. So, we'll wait and see, but it's not something that concerns us giv[en] the contracting practices that we employ and how that is on par with others in the industry."

PTAB Updates

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Tribal Immunity Still a Hot Topic

- In March, PTAB denied Allergan and St. Regis Mohawk Tribe's motion to terminate IPRs regarding Restasis patents based on sovereign immunity
- In July, a panel of the Federal Circuit affirmed, holding that "tribal sovereign immunity cannot be asserted in IPRs"
- Allergan and the Tribe filed for panel rehearing and rehearing *en banc*, both of which were denied on October 22
  - The mandate will issue October 29
  - Allergan and Tribe expected to appeal to Supreme Court
- Meanwhile, Sen. Tom Cotton (R-AR) and a bipartisan group of cosponsors introduced the Preserving Access to Cost Effective Drugs Act (S. 2514), which would permit the PTO and ITC to review patents regardless of any claim of tribal sovereign immunity made as part of sham transactions

Constitutionality of IPRs on Pre-AIA Patents

- PTAB issued a final written decision finding one of Genentech's pre-AIA patents unpatentable
  - IPR was filed by Hospira
- Genentech appealed to the Federal Circuit, which, among other things, challenges the constitutionality of retroactively applying *inter partes* review to a patent that issued prior to the enactment of the AIA
- Federal Circuit has directed the Attorney General to inform the court whether the government intends to intervene in Genentech's constitutional challenge
- In unopposed motions, which the Federal Circuit granted, the Attorney General moved to "exercise its statutory right to intervene in this appeal under 28 U.S.C. § 2403(a) to defend the constitutionality of the Act of Congress that appellant challenges."
- Responsive briefs from Hospira and the United States are due November 5

New (Old) Claim Construction Standard

- Earlier this year, PTO issued notice of proposed rulemaking to change the claim construction standard applied by the PTAB in post-grant proceedings
- On October 10, PTO announced a final rule replacing the "broadest reasonable interpretation" standard with the standard applied in federal district courts and ITC proceedings as articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005)
- Final rule also states that "any prior claim construction determination concerning a term of the claim in a civil action, or a proceeding before the International Trade Commission ('ITC'), that is timely made of record in an IPR, PGR, or CBM proceeding will be considered."
- Rule takes effect on **November 13** and applies to all IPR, PGR, and CBM petitions filed on or after that date

Regulatory and FDA

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Transitional Biologics

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Regulatory Status of Proteins

- BPCIA revised the statutory definition of "biological products" to explicitly include proteins (but exclude "chemically synthesized polypeptides")
- This was necessary because, historically, many proteins have been regulated and approved as "drugs" under the FFDCA
  - *E.g.*, insulin, human growth hormone, hyaluronidase, etc.
- BPCIA also required all biological products to be approved via BLAs, not NDAs, 505(b)(2) applications, or ANDAs

Regulatory Status of Proteins

- BPCIA says:
  - NDAs, 505(b)(2) applications, and ANDAs can continue to be submitted for most proteins until March 23, 2020
  - Approved NDAs, 505(b)(2) applications and ANDAs will be "deemed" to be BLAs on March 23, 2020
- FDA Draft Guidance issued March 14, 2016
  - FDA will not approve a pending NDA, 505(b)(2) application, or ANDA for a protein product after March 23, 2020
  - Applicants will need to re-file as BLAs

Problems with FDA's Approach

- Creates "regulatory dead zone" of several years
  - Reasonable applicants will not submit NDAs, 505(b)(2) applications, or ANDAs for months or years before March 23, 2020 because of risk they will not be approved by then
  - No ability to submit biosimilar application until after March 23, 2020
- Re-filing requirement issues:
  - Highly disruptive to ongoing, or even completed, reviews
  - Could require payment of significant new user fee (@$2M)
  - Could result in lengthy new BsUFA review goal (10 months)
  - Could require initiation of **patent dance**
- Arguably inconsistent with the statute
  - Congress allowed submissions until March 23, 2020
  - No statutory basis to deny approval

Many Unresolved Issues

- Will approved 505(b)(2) applications become aBLAs or full BLAs?
  - What criteria will FDA use to decide?
- Will transitioned Reference Products get 12 years of exclusivity?
  - FDA says no, but this issue may be decided by the courts
- Will resubmitted aBLAs be subject to the patent dance provisions?
  - Probably, and this may be exactly why FDA adopted its policy

Umbrella Exclusivity

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Reference Product Exclusivity

- Two Types:
  - 4 Year: No aBLA can be **submitted** for 4 years **after "first licensure"** of the reference product
  - 12 Year: No aBLA can be **approved** for 12 years **after "first licensure"** of the reference product
- Pediatric exclusivity can extend these exclusivity periods for 6 months
- Date of "first licensure" and RP exclusivity expiry date (RP exclusivity plus pediatric exclusivity, if any) are published in the Purple Book for some biological products

Limitations on RP Exclusivity

- 4- and 12-year exclusivity provisions DO NOT APPLY to:
  - A supplement for the biological product that is the RP; or
  - A subsequent application (BLA) filed by the same sponsor or manufacturer of the biological product that is the RP (or a licensor, predecessor in interest, or other related entity) for:
    - A non-structural change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    - A structural modification that does not result in a change in safety, purity, or potency
- These limitations are intended to make it harder for RP sponsors to "game the system" regarding exclusivity

Umbrella Exclusivity

- What is it?
  - Created by FDA in the Hatch-Waxman context
  - Line extensions are protected by any residual NCE or 3-year exclusivity left for the initial product
  - Policy Goal: encourage continued innovation
- Does Umbrella Exclusivity apply to RP exclusivity?
  - No similar statutory "hook" as in Hatch-Waxman
  - Explicit limitations arguably prohibit umbrella policy for biologics
  - Congress could have concluded that risks of "gaming the system" outweigh interest in encouraging innovation

REMS as a Barrier to Generic Development

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REMS as a Barrier to Generic Development

- On May 17, FDA announced that is had received numerous inquiries from generic companies indicating that they would like to develop generic versions of marketed drugs, but have been unable to obtain necessary samples of the reference listed drug (RLD)
- Inability of generic company to access RLD samples typically occurs when brand products are subject to limited distribution in connection with a Risk Evaluation and Mitigation Strategy (REMS)
- REMS is an FDA program implemented to ensure that a specific drug's benefits outweigh its risks
- According to FDA, "brand drug sponsors may use these limited distribution arrangements, whether or not they are REMS-related, as a basis for blocking potential generic applicants from accessing the samples they need."

FDA Response

- FDA published a list of RLDs and RLD sponsor companies for which FDA has received an inquiry regarding the inability of generic companies to obtain RLD samples
- In July, FDA Commissioner Gottlieb issued a statement on "new policies to reduce the ability of brand drug makers to use REMS programs as a way to block timely generic drug entry, helping promote competition and access."
- According to the statement, REMS program is allowing brand companies to delay generic entry in two ways:
  - By allowing brands to restrict sales of their drug, thus preventing generic companies from obtaining enough samples to run bioequivalence testing
  - Generic companies must negotiate with brand companies to develop a single shared REMS program
- Two draft guidances released to address the issue

FDA Draft Guidances on REMS

- *Development of a Shared System REMS*: describes general principles and recommendations to assist sponsors in developing shared REMS programs, to facilitate negotiations between brand and generic companies
- *Waivers of the Single, Shared System REMS Requirement*: describes when and how the FDA will consider waiving the single, shared system requirement, and how generic applicants can request a waiver; waiver allowed where:
  - The burden of forming a single shared system outweighs the benefits of having one, or
  - An aspect of the REMS is covered by a patent or is a trade secret and the generic applicant certifies that it sought a license for use of that aspect and was unable to obtain one

Stay up-to-date on biosimilars news!

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