Biosimilars at the Bar: Legal Issues

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Topics to Cover

- Update on *Sandoz v. Amgen* and open questions
- Considerations on tentative licensure following *Sandoz*
- Discovery disputes under BPCIA & considerations
- IPR evolution in biosimilar space

Patent Challenges

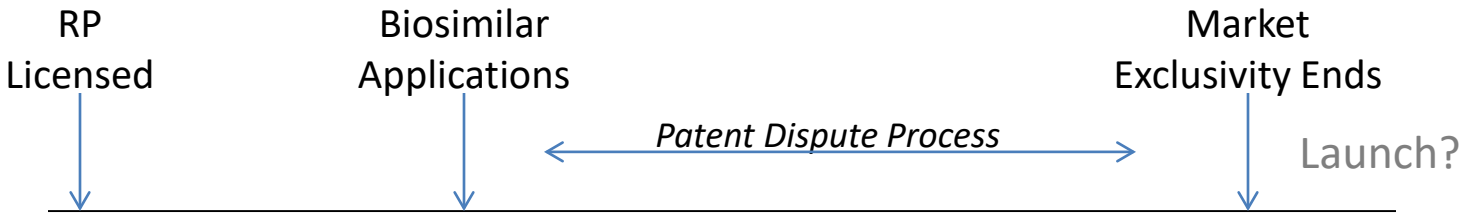
Approved Biosimilar	Litigation	PTAB
Humira (Amjevita/Cyltezo)	AbbVie v. Amgen (DED) (status conf. 10/2/2017) U.S. Pat. Nos. 8,663,945; 8,911,964; 8,916,157; 8,961,973; 8,986,693; 9,096,666; 9,220,781; 9,272,041; 9,359,434; and 9,365,645 AbbVie v. Boehringer Ingelheim (DED) (filed 8/2/2017) U.S. Pat. Nos. 8,926,975; 9,018,361; 9,090,867; 9,096,666; 9,255,143; 9,266,949; 9,272,041; and 9,546,212	7 other patents challenged via IPR
Enbrel (Erelzi)	Immunex v. Sandoz (NJD) (expert discovery) U.S. Pat. Nos. 8,063,182; 8,163,522; 7,915,225; 8,119,605; and 8,722,631	1 patent challenged via IPR
Neupogen (Zarxio)	Amgen v. Sandoz (CAND) U.S. Pat. No. 6,162,427 (exp.)	
Remicade (Inflectra/Renflexis)	Janssen v. Celltrion (MAD) (motion to dismiss) U.S. Pat. Nos. 6,284,471; and 7,598,083 Janssen v. Samsung Bioepis (NJD) (filed 5/17/2017) U.S. Pat. Nos. 7,598,083; 6,900,056; and 6,773,600	Ex parte re-exam for US 6,284,471 8 patents challenged via IPR

Patent Challenges

FDA Accepted aBLA	Litigation	PTAB
Neupogen (Grastofil)	Amgen v. Apotex (FLSD) (consolidated with below) U.S. Pat. Nos. 8,952,138 and 6,162,427 (exp.)	
Neulasta (LA-EP2006/Lapelga/CHS-1701)	Amgen v. Apotex (FLSD) (terminated 9/6/2016) U.S. Pat. Nos. 8,952,138 and 5,824,784 (exp.) Amgen v. Sandoz (CAND) (expert discovery) U.S. Pat. Nos. 8,940,878 and 5,824,784 (exp.) Amgen v. Coherus (DED) (filed 5/10/2017) U.S. Pat. No. 8,273,707	1 patent challenged via IPR
Epogen (Retacrit)*	Amgen v. Hospira (DED) (trial 9/18/2017) U.S. Pat. Nos. 5,856,298 and 5,756,349	
Avastin (ABP 215)	Genentech v. Amgen (DED) (dismissed) moving through the patent dance	1 patent challenged via IPR

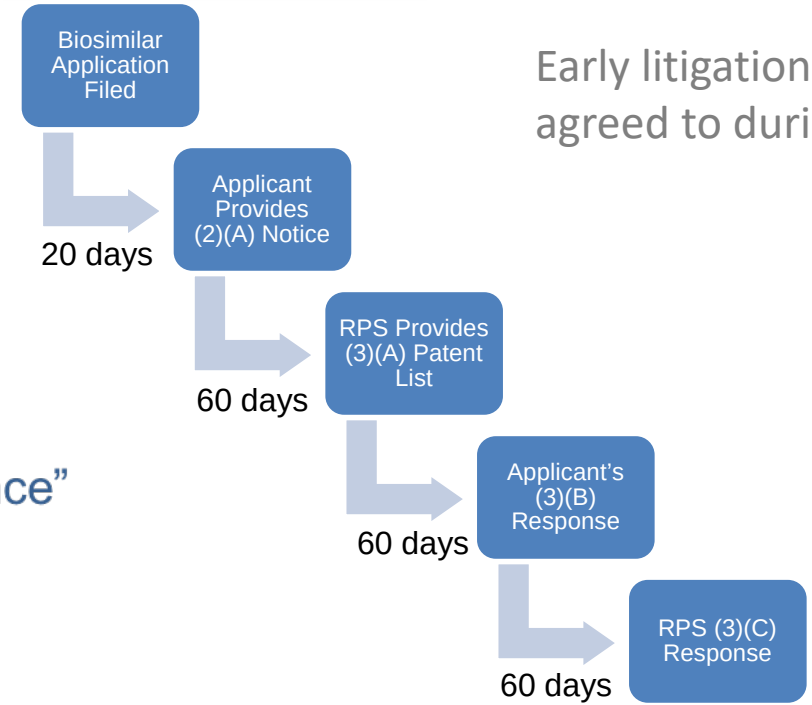
Biologics Price Competition & Innovation Act

- Abbreviated pathway to FDA licensure for follow-on alternatives to biologics
- Timing
  - Applications may not be submitted until 4 years after RP licensed
  - Licenses “may not be made effective” until 12 years after RP licensed



Patent Dispute Process

Early Phase Litigation



Early litigation proceeds on patents agreed to during negotiations

"Patent Dance"

Negotiation
If parties disagree, Applicant selects number of patents at issue
A selection of 0 means that RPS may choose 1 patent

Patent Dispute Process

- Applicant provides Notice of Commercial Marketing. (42 U.S.C. § 262 (*l*)(8)(A))
- Late litigation: Before the first commercial marketing, the reference product sponsor ("RPS") may seek a preliminary injunction prohibiting the commercial manufacture or sale of the biosimilar product until the court decides issues of patent validity, enforcement, and infringement.
  - Late litigation can proceed on any patent included on one of the initial "lists" provided by the RPS or Applicant that is not included on the early phase negotiated lists.

Notice of Commercial Marketing

- The subsection (k) applicant ***shall provide*** notice to the reference product sponsor (RPS) not later than 180 days before the date of the first commercial marketing of the biological product ***licensed under subsection (k)***.

- Failure to Provide Notice of Commercial Marketing
  - RPS may bring Declaratory Judgment action for patent infringement, validity or enforceability (42 U.S.C. § 262(l)(9)(B))

Amgen Inc. v. Sandoz Inc.
No. 2015-1499 (Fed. Cir. July 23, 2015) (Neupogen®)

- Complying with 42 U.S.C. § 262 (*l*)(2)(A) (providing aBLA and manufacturing process) is not mandatory because BPCIA provides a remedy.
- The Applicant can provide effective notice of commercial marketing only ***after*** the FDA has licensed (approved) the biosimilar product.
- Where the Applicant fails to provide its aBLA and manufacturing information, the 180-day notice of commercial marketing is mandatory; in this case, Sandoz may not market Zarxio before 180 days from March 6, 2015, *i.e.,* September 2, 2015.
- If Applicant provides the aBLA and manufacturing information but fails to provide Notice of Commercial Marketing - RPS can seek a declaratory judgment. (42 U.S.C. § 262(*l*)(9)(B))

Petition for Certiorari

- After petition for *en banc* rehearing denied, Sandoz petitions Supreme Court (Feb. 16, 2016).
- Questions presented:

  Whether **notice of commercial marketing given before FDA licensure is effective?**

  Whether treating **Section 262(*l*)(8)(A) as a standalone requirement and creating an injunctive remedy** that delays all biosimilars by 180 days after approval is improper?
- Federal Circuit erred by holding "than an applicant 'may only give effective notice of commercial marketing *after* the FDA has licensed its product."
- Federal Circuit erred by "creating a new remedy . . . an injunction against commercial marketing until 180 days after post-approval notice is given."

Petition for Certiorari

- Amgen opposes petition for certiorari
  - Amgen argues that the Federal Circuit was correct – "notice of commercial marketing is effective only after FDA licensure of the Applicant's product under subsection (k)."
- Amgen files conditional cross-petition in March 2016 to introduce other "patent dance" questions into appeal
  - Is an Applicant required by 42 U.S.C. § 262(l)(2)(A) to provide the Sponsor with a copy of its biologics license application and related manufacturing information, which the statute says the Applicant "shall provide," and, where an Applicant fails to provide that required information, is the Sponsor's sole recourse to commence a declaratory-judgment action under 42 U.S.C. § 262(l)(9)(C) and/or a patent-infringement action under 35 U.S.C. § 271(e)(2)(C)(ii)?

Petition for Certiorari

- On January 13, 2017, Supreme Court granted Sandoz's petition and Amgen's cross-petition, consolidating case nos. 15-1039 and 15-1195.
- Represents first time Supreme Court weighs in on BPCIA passed in 2010
- Oral argument held on April 26, 2017

Sandoz Inc. v. Amgen Inc. et al.
No. 15-1039 (S. Ct. June 12, 2017)

- **Unanimous** decision; opinion authored by Justice Thomas
- Reversed Federal Circuit on the simpler issue of when notice of commercial marketing must be provided
- Biosimilar applicant may provide notice of commercial marketing (intent to launch) **before** FDA licenses aBLA
  - Amgen's arguments "cannot overcome the statute's plain language."
  - "[T]he applicant may provide notice either before or after receiving FDA approval."
  - Consequently, the applicant can provide notice before the 12-year period has ended.
  - So Federal Circuit erred in issuing injunction preventing Sandoz from launching until 180 days after licensure, and relatedly, Amgen's state law unfair competition claim also fails because it was predicated on the argument that the BPCIA prohibits pre-licensure notice.

Sandoz Inc. v. Amgen Inc. et al.
No. 15-1039 (S. Ct. June 12, 2017)

- Agreed with Federal Circuit on the more complex issue of whether a federal injunction is available to force the applicant's disclosure of aBLA
- Amgen (RPS) is **not** entitled to an injunction requiring Sandoz to provide its aBLA and manufacturing information.
  - The statute specifies a "remedy" for failure to provide these information to RPS → the RPS can seek an immediate declaratory judgment patent action under Sec. 262(l)(9)
  - The applicant cannot seek a declaratory judgment action before it launches – it must wait to be sued by the RPS
  - The federal remedy for Amgen is that it got control over the timing/content of patent litigation because Sandoz failed to provide the aBLA/manufacturing information
  - This is the "sole remedy" <u>at least in federal law</u>

Sandoz Inc. v. Amgen Inc. et al.
No. 15-1039 (S. Ct. June 12, 2017)

- But remanded to Federal Circuit to determine state law remedies

  "There is no dispute about how the federal scheme actually works, and thus nothing for us to decide as a matter of federal law. The mandatory or conditional nature of the BPCIA's requirements [under §262(l)(2)(A)] matters only for purposes of California's unfair competition law, which penalizes 'unlawful' conduct. Whether Sandoz's conduct was 'unlawful' under the unfair competition law is a state-law question, and the court below erred in attempting to answer that question by referring to the BPCIA alone."

  - If California law treats Sandoz's noncompliance with §262(l)(2)(A) as unlawful, then the lower court must also determine whether the BPCIA preempts the state law remedy (and whether Sandoz has forfeited any such preemption defense).

Sandoz On Remand

- Amgen asserted that Sandoz engaged in "unlawful" conduct under CA's Unfair Competition Law Code § 17200 *et seq.*, where "unfair competition" includes "unlawful" or "unfair" or "fraudulent" business acts or practices. Amgen predicated state law claims on Sandoz's failure to provide aBLA-related information under § 262(l)(2)(A) and providing notice of commercial marketing prior to licensure by FDA
  - Law provides broad reach over conduct
  - Intent irrelevant
  - "Unlawful" act is one that violates some other law, including federal statutes, federal regulations, state statutes, state regulations, prior case law, local ordinances, standards of professional conduct.

Sandoz On Remand

- Supreme Court has now decided that pre-licensure notice of commercial marketing is not unlawful so that particular conduct is not unlawful under CA law
- In the now-vacated opinion, Federal Circuit determined that Sandoz's compliance with § 262(l)(2)(A) was conditional and not mandatory, so failure to comply with this section would not be "unlawful"
- But Supreme Court opinion treats § 262(l)(2)(A) as a "requirement", e.g.:
  - "Section 262(l)(2)(A)'s requirement that an applicant provide the sponsor with its application and manufacturing information is not enforceable by an injunction under federal law"
  - "Sandoz failed to disclose the requisite information under §262(l)(2)(A), and was accordingly subject to the consequence specified in §262(l)(9)(C)"
  - "The first question presented by these cases is whether §262(l)(2)(A)'s requirement—that the applicant provide its application and manufacturing information to the sponsor—is itself enforceable by injunction"
- Accordingly, Sandoz's failure to comply with this disclosure requirement *could* be a violation of the federal statute satisfying the state law unfair competition claim

Sandoz On Remand

- Federal Circuit requests supplemental briefing on remand
- The Federal Circuit vacated its July 2015 opinion, reinstated the appeal, and directed the parties to file further briefing on whether (1) the BPCIA preempts additional remedies under state law for an applicant's failure to comply with § 262(l)(2)(A); (2) whether Sandoz has waived any preemption defense; and (3) whether California law would treat noncompliance with § 262(l)(2)(A) as unlawful under California the unfair competition code
  - Sandoz and Amgen filed on 8/28
  - Solicitor General to file amicus brief by 9/11
  - Responses due within 10 days of filings

Sandoz On Remand – Supplemental Briefing Ongoing

- Amgen Supplemental Briefing
  - Federal Circuit should reverse the district court dismissal of Amgen's state law claims and remand for further proceedings
  - Pointed to the Supreme Court's language in opinion to support its argument that Sandoz's failure to provide aBLA was a violation of the BPCIA
  - Sandoz waived any preemption defense, and in any event, the BPCIA does not preempt state law remedies for the applicant's failure to comply with 42 U.S.C. § 262(l)(2)(A)

Sandoz On Remand – Supplemental Briefing Ongoing

- Sandoz Supplemental Briefing
  - Argued for Federal Circuit to exercise its discretion to remand to district court so state law claims can be evaluated in the first instance and appealed together
  - Federal Circuit should affirm the dismissal of Amgen's state law claims as preempted by the BPCIA under field and conflict preemption
  - Amgen's unfair competition claims fail under California state law – unless Sandoz's conduct was unlawful as a matter of federal law (which is precluded by Supreme Court decision), then Sandoz's conduct cannot form a basis for this state law claim
  - Amgen abandoned its conversion claim; in any event, it would fail as a matter of law because Amgen failed to establish that withholding of aBLA was a wrongful act and that it had an exclusive right to possession of its approved Neupogen license in view of the 12-year exclusivity expiring and an applicant's reliance on publicly-available information about the reference product in its aBLA

Sandoz Inc. v. Amgen Inc. et al.
No. 15-1039 (S. Ct. June 12, 2017)

- Other remedies/consequences for noncompliance?
  - Court also suggests (FN 2) that a district court can consider the applicant's noncompliance in the "balance of equities" for a preliminary injunction… so an injunction under federal law could still issue that takes into account the applicant's noncompliance while patent case is pending
- Opinion leaves open the question of whether disclosure of the aBLA and manufacturing information is required – will remain open until the Federal Circuit considers Amgen's state law unfair competition claims on remand
- Appears to be a win for earlier biosimilar entry, but uncertainty remains around the mandatory nature of disclosure provision (and remedies for noncompliance) for all actors and how lower courts will decide on preliminary injunctions

Justice Breyer: Further FDA Role in Interpreting BPCIA?

- Just when FDA thought it was out, the Court pulls it back in…
- Justice Breyer's concurrence raises interesting questions as to whether FDA may revisit the Court's interpretation of these provisions and reach a different interpretation following agency rulemaking
- The concurrence points out that FDA has the Congressional authority under the statute to interpret the same provisions and, after further experience administering the BPCIA, may opt to "depart from, or to modify" the Court's interpretation
- Will FDA have cause or desire to reconsider the Court's interpretation of these patent provisions? At present, it seems unlikely.

“Tentative” License for Biosimilars?

- Federal Circuit doubled down on post-licensure notice of commercial marketing in *Amgen v. Apotex* (Neulasta®), No. 2016-1308 (Fed. Cir. July 5, 2016) in an attempt to address criticism of its *Amgen v. Sandoz* decision, that requiring notice post-licensure effectively extends by 180 days the 12-year exclusivity term of the RP:

  “[W]e have been pointed to no reason that the FDA may not issue a license before the 11.5-year mark and deem the license to take effect on the 12-year date—a possibility suggested by § 262(k)(7)(A)’s language about when the FDA approval may ‘be made effective.’”

“Tentative” Licensure for Biosimilars?

- Federal Circuit suggested that the text of BPCIA provides statutory authority to FDA to provide an alternative solution in the form of pre-effective date approvals.
  - FDA can tentatively license a biosimilar any time after the aBLA is submitted and still comply with § 262(k)(7)(A), which provides that biosimilar approval “may not be made effective . . . until the date that is 12 years after the date on which the reference product was first licensed.”
- Effectively invited FDA to create a process akin to the “tentative approval” process for generic drugs under the Hatch-Waxman Act.
- **But, in view of Supreme Court’s July opinion in *Sandoz v. Amgen*, there is little urgency at present for FDA to pursue a tentative approval process. The Supreme Court’s opinion does not foreclose such an option in the future, however.**

Recent Ruling on BPCIA Discovery Dispute

- *Amgen Inc. v. Hospira, Inc.* (Fed. Cir. Aug. 10, 2017) (Before Dyk, Bryson, and Chen, J.)
- The applicant "shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), *and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application*," § 262(l)(2)(A).
- In 2014, Hospira filed aBLA for biosimilar version of Amgen's Epogen®. Hospira provided aBLA to Amgen but not other separate manufacturing information, despite Amgen seeking information the cell culture medium used by Hospira during manufacture.
- Amgen did not include its cell-culture medium patents on its (l)(3)(A) patent list so Hospira was not sued on those.
  - The (3)(A) list should include patents for which the RPS "believes a claim of patent infringement could be reasonably asserted" by the RPS
- Amgen claimed it could not assess the reasonableness of asserting those patents without cell-culture medium information from Hospira; concerned about Rule 11

Recent Ruling on BPCIA Discovery Dispute

- Amgen sought discovery during litigation on composition of Hospira's cell culture medium, which Hospira refused
- District court denied Amgen's motions to compel because this information was irrelevant to the asserted patents
- Amgen 2016 appeal to Federal Circuit raised jurisdictional questions – recent Federal Circuit decision held it lacked jurisdiction to hear interlocutory appeal because the district court decision was not a collateral order and Amgen was not entitled to mandamus under the All Writs Act

Recent Ruling on BPCIA Discovery Dispute

- List it or lose it – limited options for RPS to pursue if patents are not listed and, like here, the RPS sponsor did not include state law claims to support an injunction to pursue the manufacturing information
  - Federal Circuit: no Rule 11 sanctions for “holding or asserting a mistaken belief in good faith” when listing patents for the (3)(A) list
  - “[T]he reasonableness requirement of paragraph (l)(3)(A) does not preclude a sponsor from listing a patent for which an applicant has not provided information under paragraph (l)(2)(A).”

Current BPCIA Discovery Disputes

- AbbVie v. Amgen (DED)
- Amgen sought discovery regarding AbbVie's patent dance with other biosimilars
- AbbVie responds to Amgen's discovery request
  - Amgen chose the scope
  - BPCIA does not require or suggest that Congress intended for Courts to allow disclosure of patent exchange materials to 3rd parties
  - Relevance of the patent exchange material with 3rd party is at best marginal and does not satisfy burden of production
- Awaiting ruling

IPRs and Standing

- A potential biosimilar applicant must have standing to seek relief in Court
- Anyone has standing to challenge patents via IPR
- IPR is popular route to "clear a patent path"
- Phigenix, Inc. v. ImmunoGen, Inc., 845 F.3d 1168 (Fed. Cir. 2017)
  - Phigenix filed an IPR petition challenging validity of all claims of U.S. Patent No. 8,337,856 (assigned to Immunogen, Inc.)
  - Final written decision PTAB upheld validity of '856 patent claims
  - Phigenix appealed PTAB decision to the Federal Circuit
  - Federal Circuit dismissed stating that "Article III requires that a party invoking jurisdiction of a federal court suffer an 'injury in fact.' and that 'Phigenix has suffered no such injury'."

Upcoming Supreme Court Review of IPR

- In June, Supreme Court granted certiorari in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, Case 16-712 (U.S. 2017) to consider "whether inter partes review – an adversarial process used by the Patent and Trademark Office (PTO) to analyze the validity of existing patents – violates the Constitution by extinguishing private property rights through a non-Article III forum without a jury."
  - Oil States owns the '053 patent and Greene's filed an IPR, which resulted in PTAB holding the patent invalid based on prior art. On appeal to the Federal Circuit, the court ignored the constitutional questions raised by Oil States and affirmed the PTAB in an unpublished order.
  - Oil States filed a petition for cert, asserting that IPRs violated the Seventh Amendment right to jury trials and violate Article III, section 1, because adjudication of patent rights fall within province of federal courts. It was improper for the patent to be invalidated in a non-Article III setting.

Upcoming Supreme Court Review of IPR

- Greene's and the PTO opposed the petition for certiorari
  - Congress may designate public rights for adjudication in non-Article III tribunals, something the Supreme Court has recognize – "what makes a right 'public' rather than private is that the right is integrally related to particular federal government action."
    - Congress created USPTO with special expertise in evaluating patents and directed the PTO to issue a patent under standards set by federal law
    - Patents accordingly are "public" rights
    - The USPTO's invalidation of a patent that should not have been granted is not unconstitutional
  - Seventh Amendment guarantees right to jury trial only to claims adjudicated in Article III courts; where Congress has assigned delegation to a non-Article III tribunal, Seventh Amendment poses no bar

Upcoming Supreme Court Review of IPR

- Grant of certiorari was surprising given that Supreme Court has declined to accept certiorari previously on IPR constitutionality
- Oral argument heard in October 2017 term - decision likely next summer
- A decision that the American Invents Act-created IPRs are unconstitutional would effectively eliminate IPRs as a method to “clear a path” and put at risk other post-grant administrative proceedings under the PTO

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Questions?