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Amgen v. Sandoz on appeal: The Federal Circuit Construes the BPCIA

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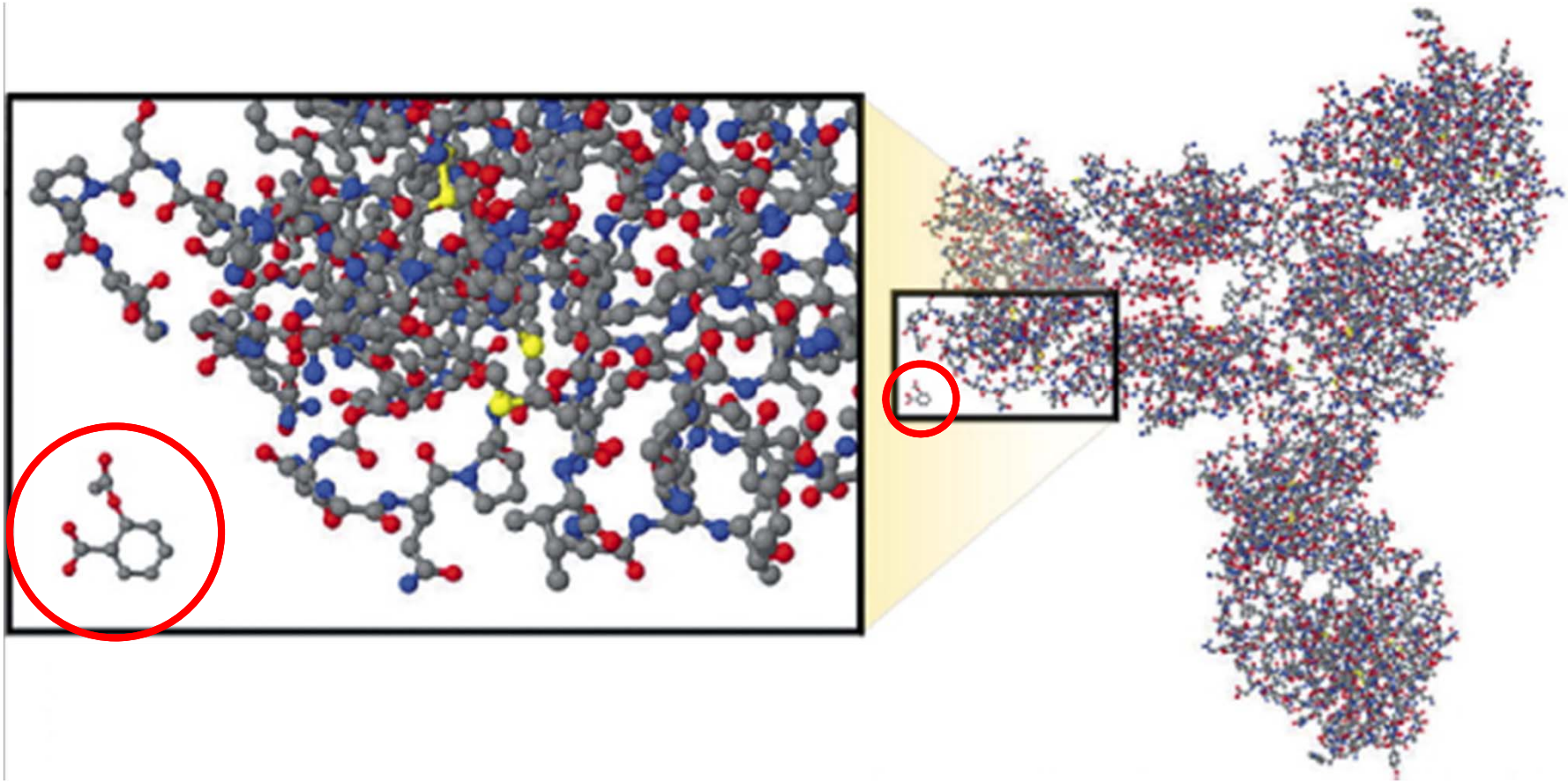
Agenda

- What is a “Biosimilar”?
- The Biologics Price Competition and Innovation Act (“BPCIA”) and the “Patent Dance”
- *Amgen v. Sandoz:* Overview of the Issues
  - Is the “Patent Dance” Optional?
  - Notice of Marketing: Before or After FDA Approval?
- District Court Opinion
- July Federal Circuit Ruling
- Remaining Questions and Possibility of Appeal
- Impact and Looking Ahead
- Questions?

What Is A "Biosimilar"?

- "Biosimilar" can be thought of as a **"generic" biologic drug product.** BUT there are technical/legal differences:
- Generic drugs: small organic molecules.
  - Manufactured by chemical synthesis to have *identical* structure to brand.
  - FDA requires generic to contain *exactly the same* active as brand.
  - Hatch Waxman laws: Abbreviated FDA approval path since 1984
- Biosimilars: large, complex biologic molecules ("biotech" drugs).
  - Manufactured by fermentation (bacteria, yeast growing in a broth)
  - Small differences in fermentation/purification can lead to significant differences in structure/purity between biosimilar and brand. FDA does not require identity; instead, rigorous tests to show *high similarity.*
  - NO abbreviated approval path until Biologics Price Competition and Innovation Act (BPCIA) passed as part of "Obamacare" in 2010.

Small Molecule v. Biologic: Aspirin v. mAb



Source: Woodcock et al., Developing the Nation's Biosimilars Program (N Engl J Med 365(5) pp. 385-88)

How Is A Biosimilar Different From a Generic Drug?

- Biologics cost MUCH MORE than small molecule drugs, and are seen as the “future of the drug industry.”
- Big incentive for gov’t to enact Hatch Waxman-type abbreviated pathway for “generic” biologics.
- American biotech industry lobbied hard against duplicating Hatch Waxman scheme for biologics.
- FDA did not want to police patents as it does for generics.
- Competing gov’t, industry interests led to the BPCIA, which provides incentives for innovation, abbreviated FDA approval path, and a legal framework for resolving patent infringement suits prior to marketing.

The Biologics Price Competition and Innovation Act ("BPCIA")

- Passed as part of the Affordable Care Act, March 23, 2010
- Amended section 351 of the Public Health Service Act to create an **abbreviated licensure pathway** for biological products shown to be "biosimilar" to, or "interchangeable" with, a reference product that has already been licensed by FDA
  - "Biosimilar" biologic vs. "interchangeable" biologic vs. "generic" small molecule
  - "Section 262(k) pathway" (codified at 42 U.S.C. § 262(k))—permits a "biosimilar" product to be licensed on less than the full complement of preclinical and clinical test data normally required for a new biologic
- Patent dispute resolution pathway different from that used for small molecule drugs: the BPCIA "Patent Dance"
  - Question raised in litigation: what are the steps of the Dance, and which (if any) are mandatory?

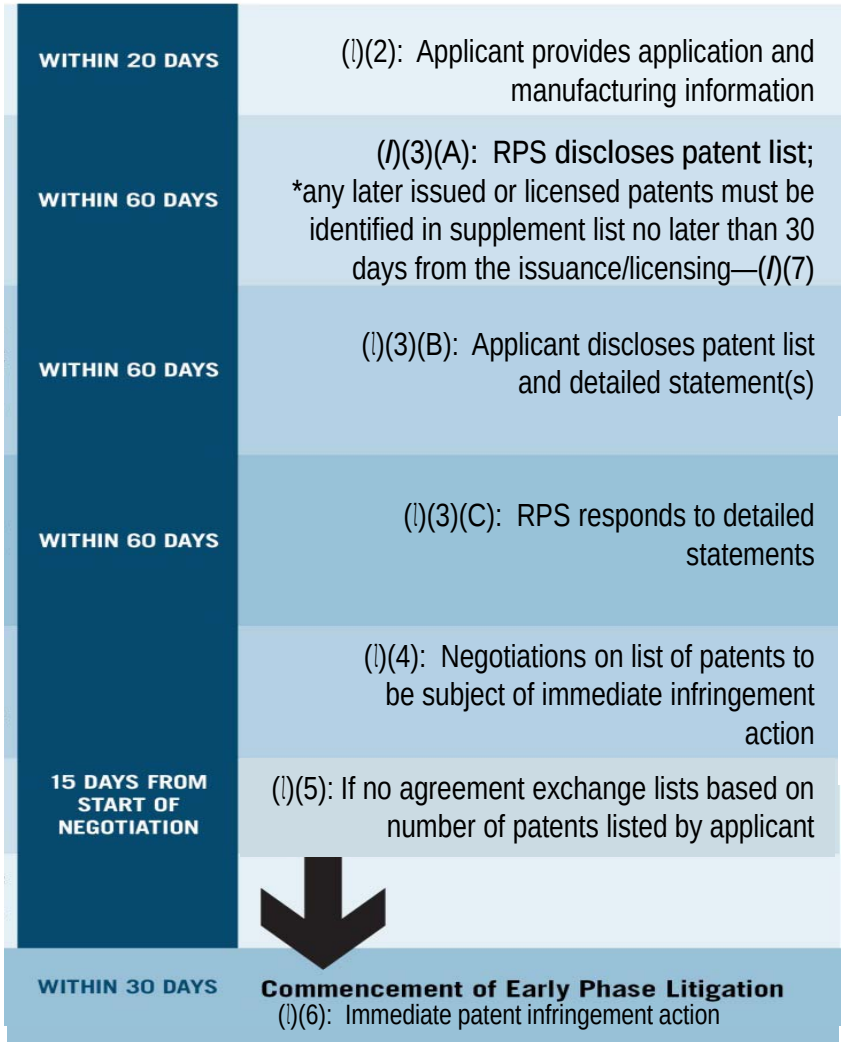
BPCIA v. Hatch Waxman

- No Orange Book or patent certifications.
- No 30-month stay of approval.
- “First-filer” exclusivity: Limited to “interchangeable” biosimilars.
- No automatic substitutability at pharmacy.
- “Patent Dance” dispute resolution pathway **much** more complex
- 180-day notice prior to commercial launch mandatory (akin to automatic 180-day TRO after FDA approval)
- Clinical trials likely required to prove biosimilarity (regulatory approval much more complex, expensive than proving bioequivalence)

The "Patent Dance": § 262(*l*) Provisions

First Wave: "Immediate Patent Infringement Action"

Applicant Notified that Biosimilar Application Accepted by FDA



(*l*)(7): RPS shall supplement (l)(3) list with later issued or exclusively licensed patents within 30 days of issuance or licensing; and applicant shall respond with detailed statement(s)

Second Wave:

"Preliminary Injunction"

(*l*)(8)(A): Applicant provides notice to the RPS not later than 180 days before the date of first commercial marketing.

(*l*)(8)(B): After receiving notice of commercial marketing, the RPS may seek a preliminary injunction on the basis of any patent that was listed under (l)(3) or (l)(7) and not included on the lists for (l)(4) or (l)(5).

Interpreting the BPCIA § 262(*l*) provisions

Pioneer case for testing and understanding the § 262(k) pathway

- First biosimilar application accepted for FDA review under § 262(k) (July 7, 2014)
- First biosimilar product approved by FDA (March 6, 2015)
- Determination of parties' rights and obligations under BPCIA § 262(*l*)

Key issues:

- (1) Whether a biosimilar applicant can elect not to disclose its biosimilar application and manufacturing information under 42 U.S.C. § 262(*l*)(2)(A), and what consequences, if any, attend that election.
- (2) Whether a subsection (k) applicant "may satisfy its obligation to give notice of commercial marketing under 42 U.S.C. § 262(*l*)(8)(A) by doing so before the FDA licenses its product," and whether such notice is "mandatory."

1. Must an applicant provide the initial disclosures under § 262(*l*), and what happens if it doesn't?

§ 262(*l*)(2)(A): **Subsection (k) application information**:

- *Not later than 20 days* after the Secretary notifies the subsection (k) applicant that *the application has been accepted* for review, *the subsection (k) applicant—(A) 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.

Amgen: The § 262(*l*) disclosure provisions are mandatory, and can be enforced through external remedies.

Amgen:

- Mandatory language: the § 262(*l*) disclosure provisions use the word "shall," refer to "information *required* under paragraph (2)(A)," and refer to non-compliance with the disclosure provisions as a "failure."
- Statutory Scheme: § 262(*l*)(9)(C) cannot be the only remedy because it does not permit the RPS to bring infringement suits for patents on methods of manufacturing, which are critical to biologics regulation.
  - § 271(e)(2) and (e)(4) don't remedy this because they are unclear on whether the RPS can bring suit for methods of manufacturing patents.
- Congressional intent / Policy: Unless the disclosure of manufacturing information is mandatory under § 262(*l*)(2), there is no way for a reference product sponsor to know which patents it can reasonably assert.

Sandoz: The § 262(*l*) provisions are optional, and the alternatives are spelled out in the BPCIA and conforming amendments.

Sandoz:

- "Shall" is not so restrictive—for each step under § 262(*l*), the statute itself provides the consequences of choosing an alternative route.
- 42 U.S.C. § 262(*l*)(9)(C) and 35 U.S.C. § 271(e) clearly contemplate that applicants may choose not to provide the initial disclosure under §262(*l*)(2), and these provisions provide the only remedies available for the RPS when the applicant chooses this alternative route.
  - In other words, the BPCIA permits applicants to *choose* the level of certainty they want regarding patent infringement issues before they launch their products.
- The RPS does not need the applicant to provide its manufacturing information in order for the RPS to bring an infringement suit.

Statutory consequences for failure to follow the dance

If the applicant does not…	***Then the RPS may…***
• Provide its application and manufacturing information within 20 days of notification of FDA acceptance per *(l)*(2)(A)…	➢ Bring a declaratory judgment action asserting "***any patent*** that claims the biological product or a use of the biological product."
• Provide a detailed statement in response each patent listed by the RPS, as provided in (*l*)(3)(B)(ii), (*l*)(7)(B)…	➢ Bring a declaratory judgment action asserting any patent listed by the RPS under (*l*)(3) or (*l*)(7).
• Notify the RPS of the number of patents the applicant will list under (*l*)(5), or does not simultaneously exchange the list of patents the applicant believes should be the subject of an immediate action for infringement per (*l*)(5)…	➢ Bring a declaratory judgment action asserting any patent listed by the RPS under (*l*)(3) or (*l*)(7).
• Provide the Secretary with notice and a copy of a Complaint for patent infringement filed by the RPS per (*l*)(6)(C)…	➢ Bring a declaratory judgment action asserting any patent listed by the RPS under (*l*)(3) or (*l*)(7).
• Provide notice to the RPS at least 180 days before the date of first commercial marketing per (*l*)(8)(A)…	➢ Bring a declaratory judgment action asserting any patent listed by the RPS under (*l*)(3) or (*l*)(7).

- ***If the RPS does not*** disclose a patent on its list in (*l*)(3) or (*l*)(7), ***then the RPS may not*** bring an action for that patent under 35 USC § 271(e).
- ***If the RPS does not*** bring suit within 30 days of agreement on a patent listed under *(l)*(4), or within 30 days of the exchange of lists under *(l)*(5), ***then the RPS*** is limited to the remedy of a reasonable royalty.

2. When can a biosimilar applicant provide effective notice that it will market in not less than 180 days?

§ 262*(l)* 8) Notice of commercial marketing and preliminary injunction.

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

When do the 180 days begin to run?

- **Sandoz**:
  - Immediately upon service of notice.
  - The term "applicant" in § 262*(l)*(8)(A) shows that notice can be served by someone with an application still pending before FDA.
  - If the "notice" provision is interpreted so that the 180 days begin to run only after FDA approval, then the notice provision would be converted to a de facto *exclusivity* provision, providing an additional 6 months of exclusivity.
- **Amgen**:
  - Not until after FDA approval.
  - The term "licensed" in § 262*(l)*(8)(A) shows that notice can be served only as to a product that has been approved by FDA.
    - Prior litigation: *Sandoz v. Amgen*
  - "Applicant" is a defined term under in § 262*(l)*, which encompasses a successful applicant who has obtained FDA approval.

Amgen v. Sandoz: N.D. Cal. Weighs In

March 19, 2015: N.D. Cal. Order Denying Amgen's Motions for Preliminary Injunction and Judgment on the Pleadings

- 1. An RPS cannot force a biosimilar applicant to dance:
  - The 262(*l*) provisions provide a "carrot of a safe harbor for applicants," but "contain[] no stick to force compliance" if the applicant chooses to forgo that safe harbor and invite immediate litigation.
- 2. Biosimilar applicants can give the required notice of commercial marketing *before* FDA approval.
  - To hold otherwise "would tack an unconditional extra six months of market exclusivity onto the twelve years reference product sponsors already enjoy under 42 U.S.C. § 262(k)(7)(A)."
  - "Had Congress intended to make the exclusivity period twelve and one-half years, it could not have chosen a more convoluted method of doing so."

Amgen v. Sandoz: Fed. Cir. Hearing (June 3, 2015)

Fed. Cir. Hearing: June 3, 2015

- Split seemed likely, with predicted victory for Sandoz on the first question, and division and uncertainty on the second question:
- J. Newman:
  - 1. Frequent, pressing challenges to Sandoz (isn't Sandoz cherry-picking which elements of the BPCIA "count"?) vs. few softballs to Amgen
  - 2. If notice isn't mandatory, how can an RPS be assured that it will know about an infringing product application?
- J. Lourie & J. Chen:
  - 1. Wary about reading subsection (*l*)(9) out of the statute, and what a remedy would look like on remand.
  - 2. Wary of granting additional exclusivity. But, if FDA approval isn't the earliest point at which notice may be given, then when? Wary of permitting an applicant to provide notice at a time when "commercial marketing" of the proposed biosimilar is merely "aspirational" and speculative.

Amgen v. Sandoz: Fed. Cir. Opinion (July 21, 2015)

Fed. Cir. Split Opinion: July 21, 2015

- Split: disclosure steps are not mandatory; notice may be required, and can be given only after FDA approval.

Holding	J. Newman	J. Lourie	J. Chen
1. Biosimilar applicants can choose not to disclose aBLA and manufacturing info., subject only to immediate suit for infringement by RPS.	✗	✓	✓
2. Notice of commercial marketing is mandatory, and can be given only after FDA approval of the biosimilar product.	✓	✓	✗

Amgen v. Sandoz: Fed. Cir. On "Patent Dance"

No procedural right to compel compliance with the disclosure requirements of the patent dance (*l*)(2)(A)

- although the plain language of the "shall" provision itself might support Amgen's reading of the statute, other provisions in the BPCIA and in 35 U.S.C. § 271(e)(2)(C)(ii) "indicate that 'shall'…does not mean 'must.'"
- → Sandoz did not violate the BPCIA, state unfair competition laws by not disclosing its aBLA and manufacturing information by the statutory deadline

BPCIA provides sole consequences for failure to disclose:

§ 262(*l*)(2)(A): **Subsection (k) application information**:

- *Not later than 20 days* after the Secretary notifies the subsection (k) applicant that *the application has been accepted* for review, *the subsection (k) applicant—(A) 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*)(9)(C): **Subsection (k) application not provided:**

- If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), *the reference product sponsor, but not the subsection (k) applicant*, may bring an action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of *any patent that claims the biological product or a use of the biological product*.

Conforming Amendments: 35 U.S.C. § 271(e)

35 U.S.C. § 271(e)(2)(C): creates the technical act of infringement for jurisdiction: It shall be an act of infringement to submit—

- (i) with respect to a patent that is identified in the list of patents described in section 351(*l*)(3) of the Public Health Service Act (including as provided under section 351(*l*)(7) of such Act), an application seeking approval of a biological product, or
- (ii) if the applicant for the application fails to provide the application and information required under section 351(l)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act,

if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(4): Remedies for an act of infringement under (2)

- Injunctive relief
- Damages/other monetary relief
- Permanent injunction (only if final court decision before FDA approval of biosimilar)

Amgen v. Sandoz: Fed. Cir. On 180-Day Notice

Subsection (k) applicant can give effective notice of commercial marketing only ***after*** FDA has licensed its product

- "biological product ***licensed*** under subsection (k)" vs. "the biological product that is the subject of" the biosimilar application
- Notice after FDA approval "ensures the existence of a fully-crystallized controversy regarding the need for injunctive relief."
- → injunction extended through September 2, 2015

Remaining Questions

- Is notice of commercial marketing mandatory for all biosimilar applicants, or only for applicants that opt out of the disclosure provisions?
  - J. Lourie: an applicant *must* provide notice of commercial marketing *if* it opts out of the disclosure provisions
    - Unlike the disclosure provision of (*l*)(2)(A), the (*l*)(8)(A) notice provision lacks any corresponding provision that contemplates non-compliance with that step or provides any consequence for failure to provide notice, so non-compliance is not an option for (*l*)(8) notice.
    - Although (*l*)(9)(B) provides that the RPS may bring a declaratory judgment action for failure to comply with certain patent dance steps including the notice provision, that provision applies *only after the applicant has already complied with the disclosure provisions* of (*l*)(2)(A).
  - J. Newman: "I agree with the court that notice of issuance of the FDA license is mandatory, and that this notice starts the 180-day stay of commercial marketing….Thus I join Part…(B)(II)…of the court's opinion."

Remaining Questions

Meaning of "FDA approval"—does tentative approval count?

- J. Lourie:

  "[R]equiring FDA licensure before notice of commercial marketing does not necessarily conflict with the twelve-year exclusivity period of §262(k)(7)(A). It is true that in this case, as we decide infra, Amgen will have an additional 180 days of market exclusion after Sandoz's effective notice date; that is because Sandoz only filed its aBLA 23 years after Amgen obtained FDA approval of its Neupogen product. … That extra 180 days will not likely be the usual case, as aBLAs will often be filed during the 12-year exclusivity period for other products."

- Statute: § 262(k)(7) **Exclusivity for reference product**
  - **(A) Effective date of biosimilar application approval**. Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a).
  - **(B) Filing period** An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).

Possibility of Appeal?

- Key date: September 2, 2015
  - Panel: Sandoz's180-day notice period for commercial launch did not start running until the date of approval, March 6, 2015 → injunction extended through Sept. 2, 2015
  - Unlikely either side could get *en banc* review of the panel's decision before Sept. 2, 2015:
    - Losing party has 30 days to petition for rehearing
    - Panel has 10 working days to vote on panel rehearing
    - Members of *en banc* court have 10 working days to request a response to the petition
    - After filing of the response, 10 working days to call for vote on rehearing *en banc*
    - If *en banc* review is granted: time for briefing + oral argument

Possibility of Appeal?

- Amgen's hope for an appeal: **injunction** to keep Sandoz off the market beyond Sept. 2, 2015:
  - From the District Court: could be granted only on patent grounds, not BPCIA grounds
  - From the Fed. Cir.: could be granted only if the court thinks that ***despite the panel's decision*** Amgen is likely to prevail on its "patent dance" argument at some higher level. (unlikely on timing and substance)
  - From the Supreme Court: highly unlikely to issue an injunction granting relief that two lower courts have already denied

Possibility of Appeal?

After September 2:

- As long as Sandoz is on the market, Amgen could continue to pursue an injunction to knock it off the market for failure to engage in the "patent dance."
- → If a rehearing petition is on file by September 2 but has not yet been publicly ruled upon, the case could continue—even all the way up to the Supreme Court; the parties would have 90 days to petition the Supreme Court following a denial of rehearing by the Fed. Cir.
  - But given the novelty of the issues presented in this case, the Supreme Court likely will not step in to take this case.

Impacts of Split Opinion and Looking Ahead

- Impact on strategic choices: Do biosimilar applicants have any incentive to avoid the dance if opting out means that they can't give notice of commercial marketing until after approval?
- How does this impact use of IPRs?

Other Cases to Watch

- *Janssen v. Celltrion*, No. 15-cv-10698 (D. Mass., filed Mar. 6, 2015).
  - Similar issues
  - Different approach by Janssen: private right of action to seek a court order forcing the applicant to follow the patent dance.
- *Amgen v. Apotex*, No. 15-cv-61631 (S.D. Fla., filed Aug. 6, 2015)
  - first biosimilars litigation in which parties have "danced" through the entire "first wave"
  - Amgen seeking a d.j. that Apotex's "notice" is "ineffective" because its product has not yet been licensed by FDA.
  - Trial scheduled to begin July 11, 2016

Questions?

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