



Webinar Series: Biosimilars

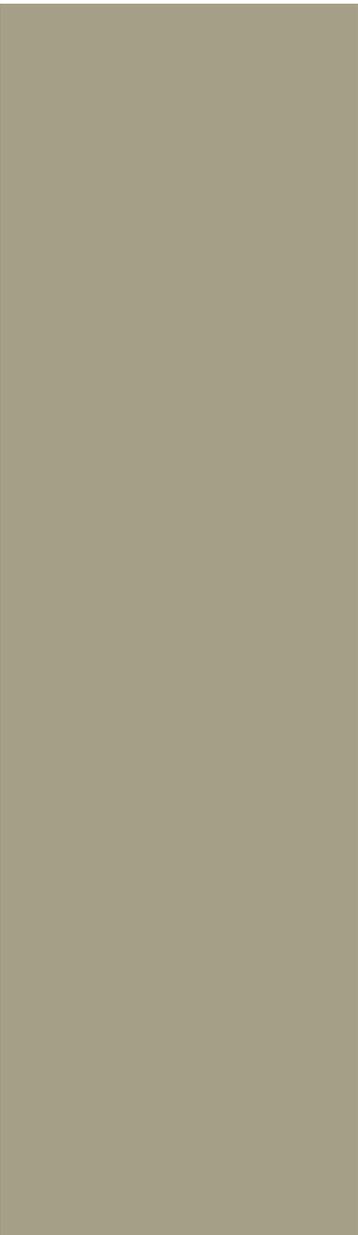
Biologic Litigation: Past, Present & Future



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Biologics Litigation: Past, Present and Future

BPCIA

- The **Biologics Price Competition and Innovation Act of 2009 (BPCIA)** was passed as part of the Affordable Care Act and signed into law in March 2010
- BPCIA creates an **abbreviated licensure pathway for biological products** shown to be biosimilar to or interchangeable with an FDA-licensed reference product
- The courts and FDA are **tackling uncharted legal and regulatory issues** surrounding implementation of the legislation

FDA Approves Two Biosimilars

In September 2015, FDA approved first biosimilar:

- Sandoz's Zarxio® as biosimilar to Amgen's Neupogen® (filgrastim)

In April 2016, FDA approved second biosimilar:

- Celltrion's Inflectra® as biosimilar of Janssen's Remicade® (infliximab)
- First biosimilar monoclonal antibody approved

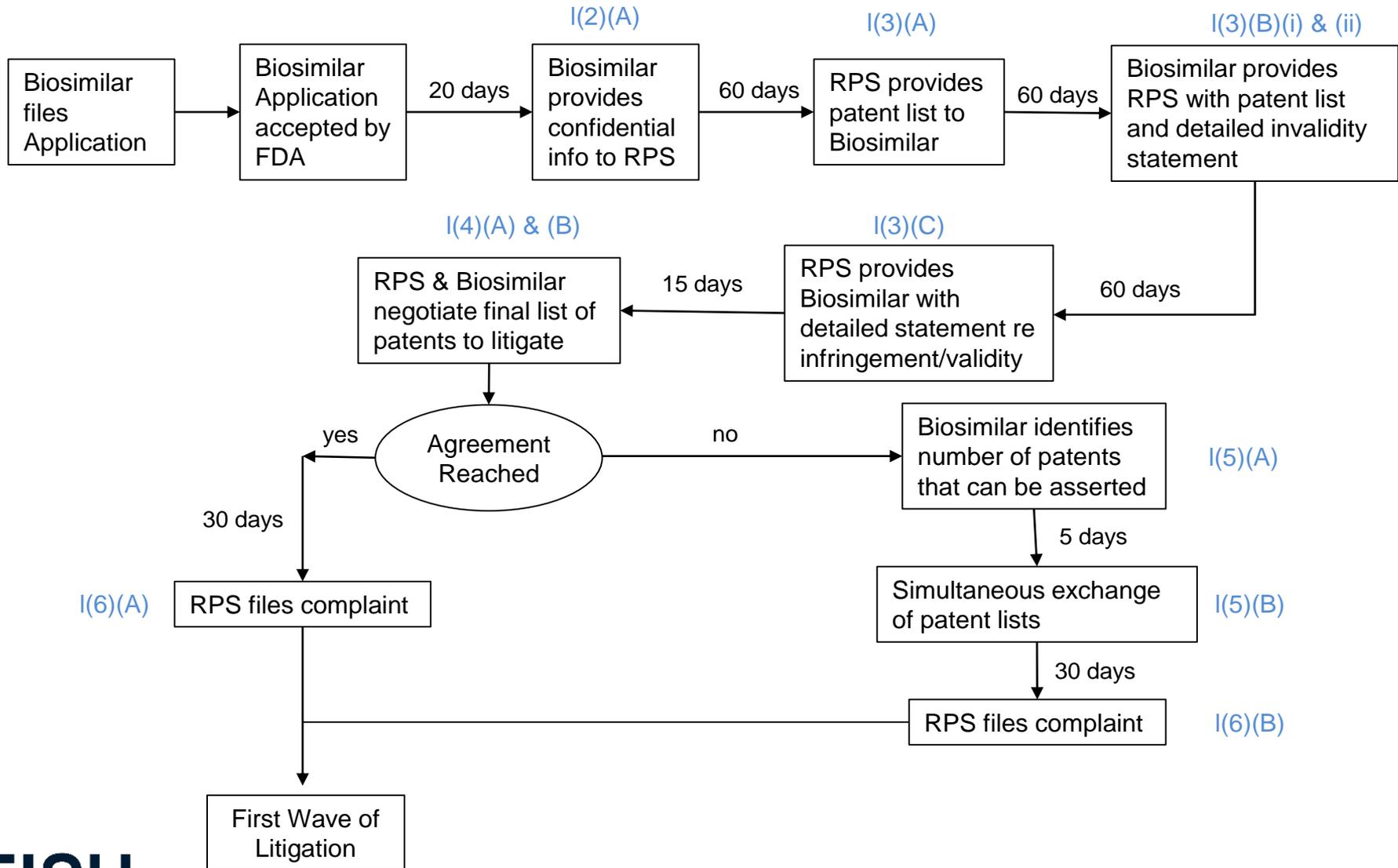
FDA has received additional biosimilar applications, including:

- Apotex's biosimilar to Amgen's Neulasta® (the long-acting formulation of Neupogen®)
- Hospira's biosimilar to Amgen's Epogen® and Janssen's Procrit®.
- Sandoz's biosimilar to Immunex's Enbrel®

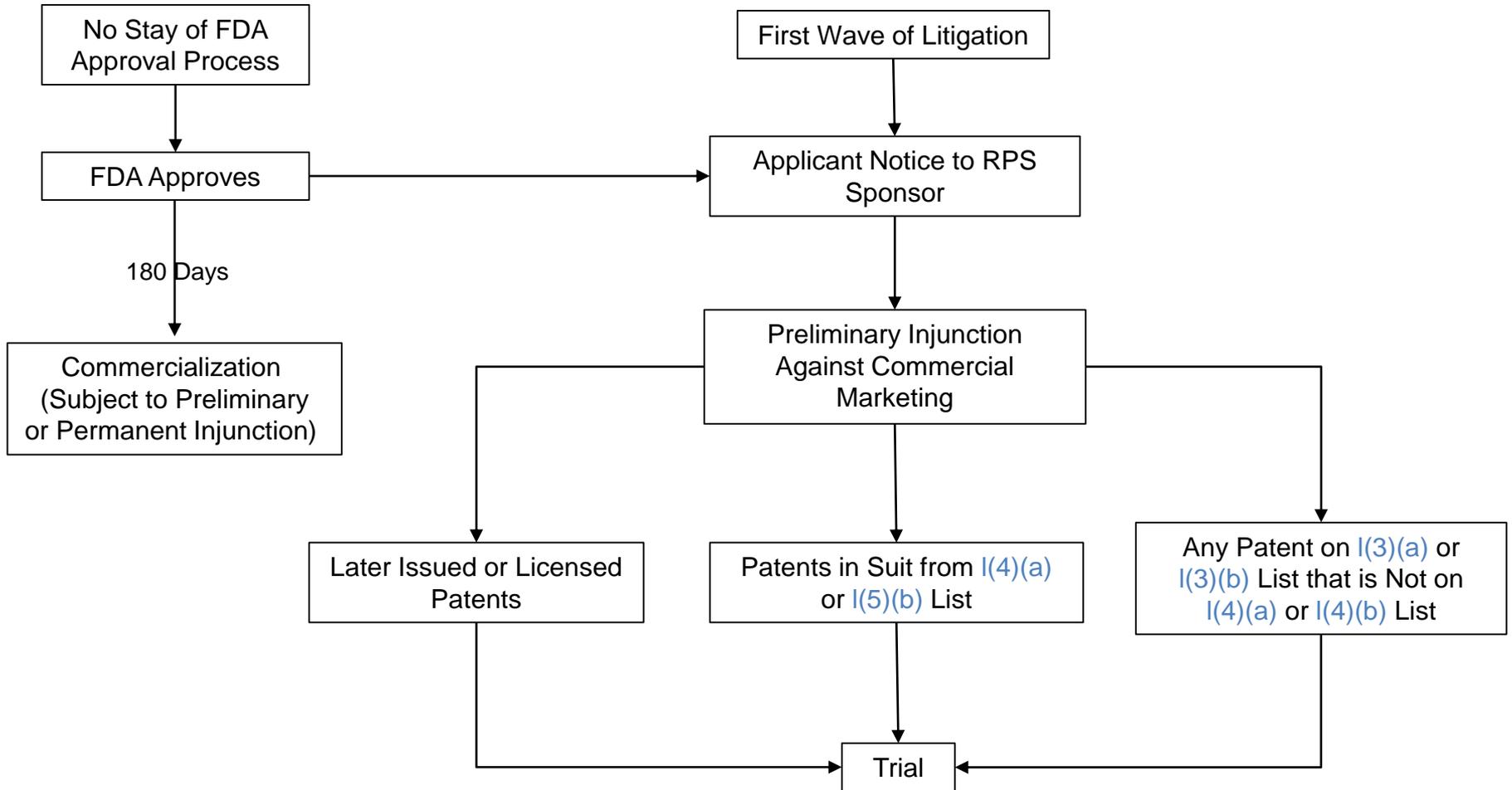
Significant Patents Will Expire Soon

Type of biologic	Brand name/active ingredient/description	US patent expiry	Sales (2013-2016; billions)	Biosimilar?
Humanized antibody	Avastin (bevacizumab) ; VEGF antibody	2019	\$6.1	
	Herceptin (trastuzumab) ; HER 2 receptor mAb	2019	\$6.8	
	Humira (adalimumab) ; TNF blocker	2016	\$10.7	Amgen; Cohera; Novartis/Sandoz
Non-humanized antibody	Erbitux (cetuximab) ; EGF receptor antagonist	2018	\$2.0	
	Remicade (infliximab) ; TNF blocker	2018	\$9.8	Celltrion (Remsima)
	Rituxan (rituximab) ; CD20-directed cytolytic antibody	2018	\$7.8	Novartis/Sandoz
Non-antibody biologics	Aranesp (darbepoetin alfa) ; Erythropoiesis-stimulating agent	2024	\$1.9	
	Enbrel (etanercept) ; TNF blocker	2028	\$8.9	Sandoz
	Epogen (epoetin alfa) ; human erythropoietin	Expired	\$2.0	Hospira
	Neulasta (pegfilgrastim) ; Leukocyte growth factor	2015	\$5.8	Apotex
	Neupogen (filgrastim) ; Human erythropoietin	Expired	\$2.0	Sandoz (Zarxio); Apotex; Hospira
	Lantus (insulin glargine) ; Insulin	Expired	\$7.9	

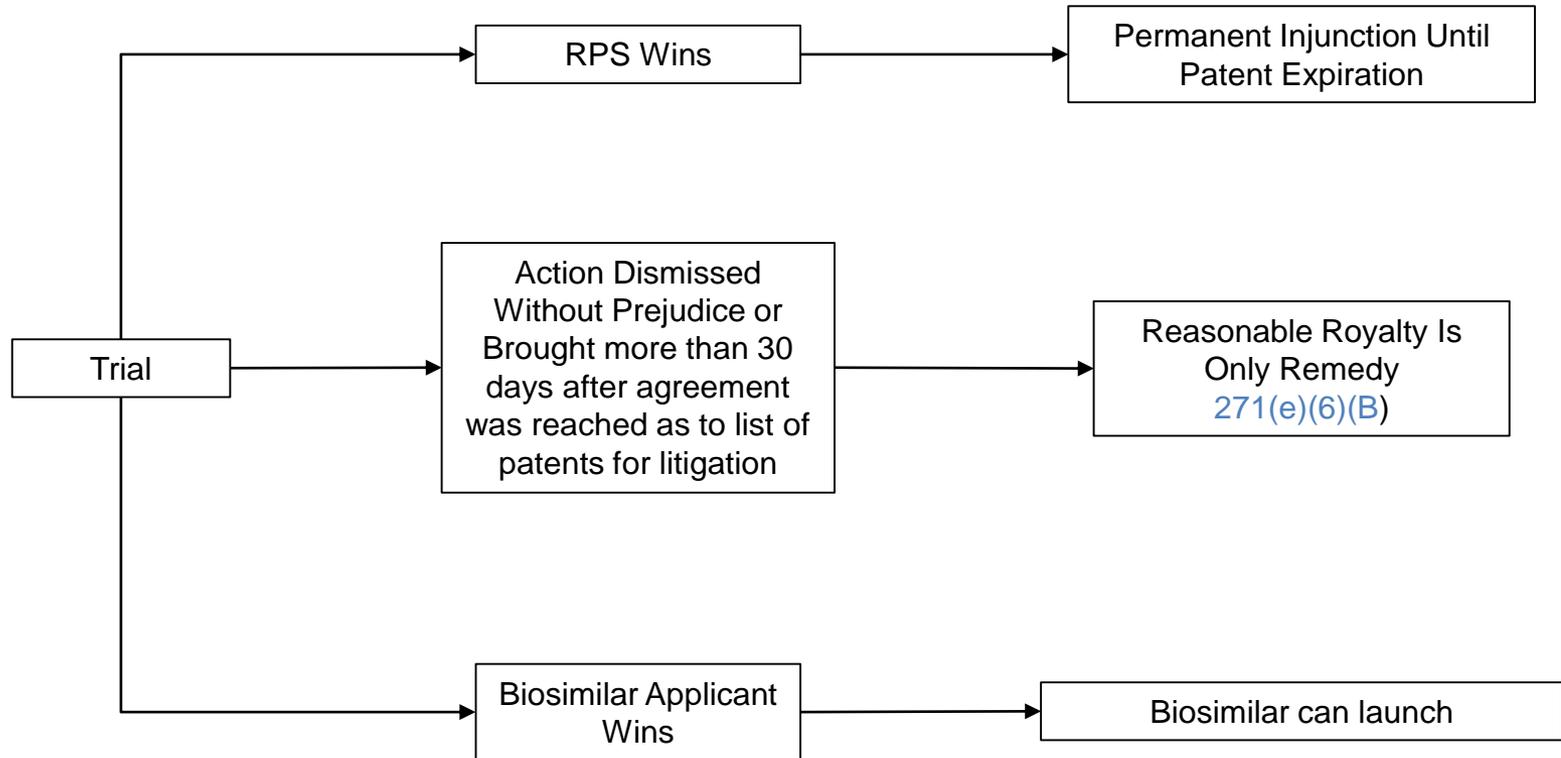
The BPCIA Patent Dance-First Wave



The BPCIA Patent Dance-Second Wave



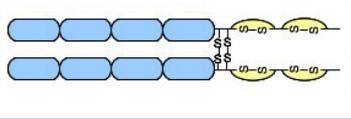
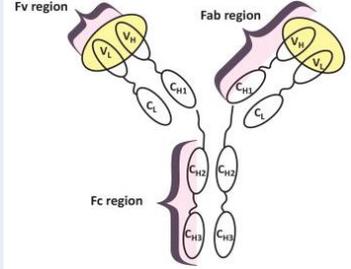
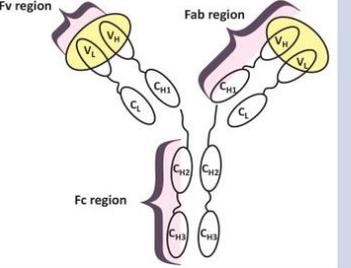
The Patent Dance Framework Under BPCIA





BPCIA Past Litigation: Jurisdictional Issues

Past Litigation

Biologic		Case	Keywords/issues
Enbrel® (etanercept)		<p><i>Sandoz Inc. v. Amgen Inc.</i> (2014-1693 Fed. Cir. 2014)</p>	<p>Does biosimilar applicant need a BPCIA application on file to be able to file DJ? DJ Jurisdiction?</p>
Remicade® (infliximab)		<p><i>Celltrion Healthcare Co. v. Kennedy Trust for Rheumatology Research</i> (14-CV-2256 S.D.N.Y. 2014)</p> <p><i>Janssen Biotech v. Celltrion Healthcare</i> (15-CV-10698 D. MA 2015)</p>	<p>Does biosimilar applicant need a BPCIA application on file to be able to file DJ? DJ Jurisdiction?</p> <p>Can applicant challenge the validity of patent against non-RPS first?</p>
Remicade® (infliximab)		<p><i>Hospira v. Janssen</i> (14-CV-7049 S.D. N.Y. 2015)</p>	<p>Can biosimilar applicant seek DJ of invalidity immediately after filing aBLA?</p>

Sandoz Inc. v. Amgen Inc., No. 13–2904 (N.D. Cal. 2014)

Background: **Enbrel®**; Sandoz hadn't yet filed biosimilar application but Phase III trials were ongoing

- Sandoz files DJ complaint; Roche patents created a "cloud of legal uncertainty" over its drug product
- Amgen Motion to Dismiss; no statutory authority to consider a patent dispute involving a biosimilar product until appropriate time under BPCIA; and no case or controversy
- Sandoz's opposition to MTD: controversy is real and immediate

ND Cal granted MTD

- BPCIA's patent exchange provision governed the dispute and preclude lawsuit outside of the statutory framework
- Rejected Sandoz's argument that §262(l)(8) allowed Sandoz to file a DJ action upon biosimilar's notice of commercial marketing
- Sandoz failed to demonstrate a case or controversy

Fed. Cir. affirmed dismissal only on case/controversy issue



Celltrion Healthcare Co., Ltd. v. Kennedy, No. 14-2256 (S.D.N.Y. 2014)

Background: Janssen is the RPS for biologic **Remicade®**; Kennedy is patent owner but is not RPS; Celltrion did not invoke patent litigation provisions of BPCIA

- Celltrion files DJ complaint vs. Kennedy; alleged that patents were invalid
- Kennedy filed a motion to dismiss; no case or controversy; BPCIA does not permit DJ without an application pending; no application has yet been filed (although Celltrion was in discussions with FDA regarding a potential application)
- Celltrion's opposition to MTD: Kennedy has asserted patents against others previously; Celltrion had spent lots of time and \$\$\$ on its biosimilar (clinical trials completed)



SDNY granted MTD

- FDA approval too far away (no application then on file);
- Kennedy had not expressed a clear intent to enforce its patents
- BPCIA is the appropriate mechanism to deal with this issue - “Even if the Court were to find that Celltrion had engaged in sufficient meaningful preparation to market Remsima and that the threat of injury was sufficiently demonstrable, the Court would still exercise its discretion to decline to hear this case in light of the existence of the BPCIA statutory framework for the resolution of patent disputes in the licensing of biosimilars.”
- Celltrion should follow BPCIA framework (v. Janssen)



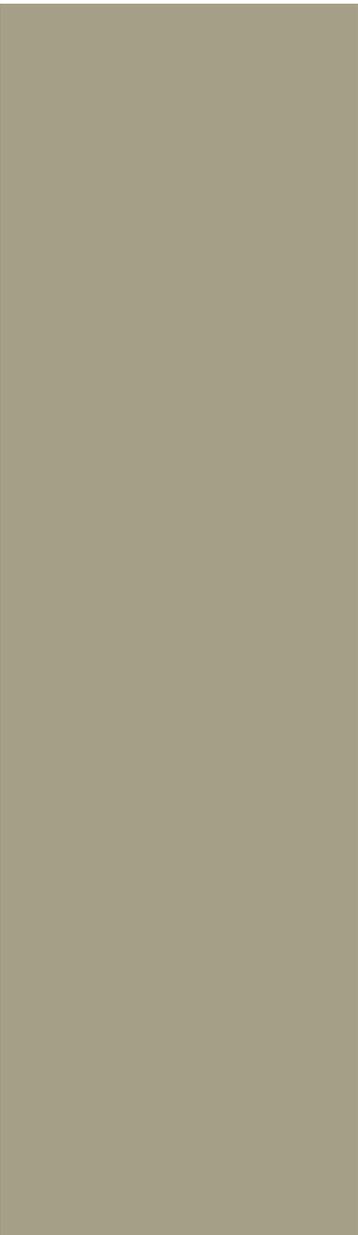
© 2005 GS

Background: Celltrion files aBLA referencing Janssen's **Remicade®**;
Hospira enters into agreement to co-market drug with Celltrion

Hospira seeks DJ patents are invalid; argues since it did not file the aBLA it does not need to abide by the BPCIA patent dance procedures

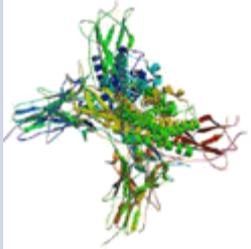
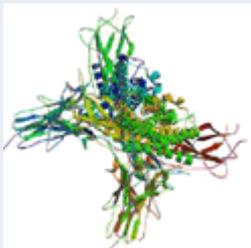
- Case dismissed for lack of case or controversy
- Court reasoned adjudicating this case would enable any biosimilar developer to partner with another distributor and thereby skirt the dispute resolution procedures of the BPCIA Congress purposefully enacted for address these conflicts





BPCIA Litigation: First BPCIA Interpretation

First Statutory Interpretation

Biologic		Case	Keywords/issues
Neupogen® (filgrastim)		<i>Amgen v. Sandoz</i> (2015-1499 Fed. Cir. 2015)	Is the patent dance required? When can biosimilar applicant give 180 notice of commercialization?
Neulasta® (pegfilgrastim)		<i>Amgen v. Apotex</i> (15- cv-61631 S.D. Fla. 2015)	If biosimilar applicant complies with patent dance, when can 180 day notice be given?

Amgen Inc. v. Sandoz Inc.

Background: **Neupogen®**; Sandoz and Amgen failed to agree on confidentiality provisions attendant to exchange of biosimilar application under BPCIA

- Amgen files DJ complaint (October 2014) on Sandoz's failure to follow the BPCIA disclosure procedures
- Sandoz's 180-day notice of commercial marketing is premature because the notice was "before" being "licensed" by FDA (42 U.S.C. § 262(l)(8))

N.D. Cal. denies Amgen's PI

- Disclosure of biosimilar application is optional
- 180-day notice can be provided before FDA approval



Amgen Inc. v. Sandoz Inc.

Federal Circuit

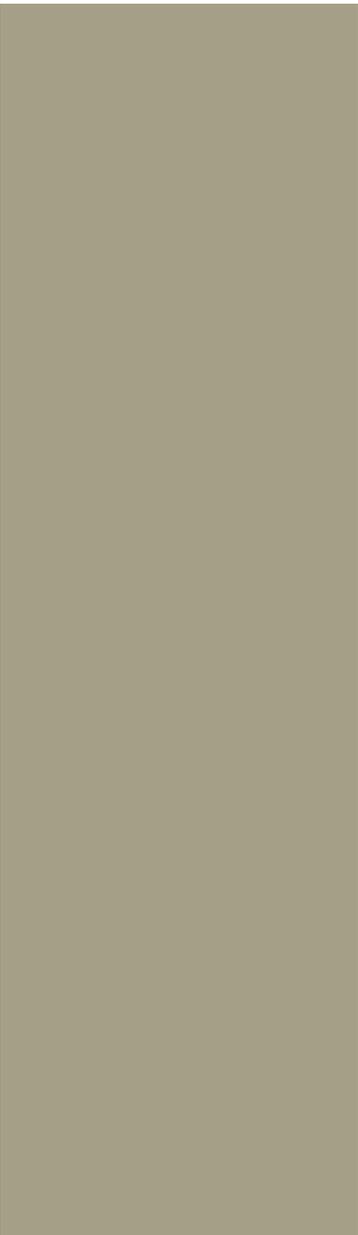
A divided panel ruled:

- 1) the information exchange and “**patent dance**” **procedures were optional** and that a biosimilar applicant could choose not to engage in them; but
 - 2) the 180-day notice requirement was mandatory, at least for applicants who had opted out of the patent dance, and that **only a notice given *after* FDA approved the aBLA would be effective** to start the 180-day clock
- Federal Circuit denied rehearing
 - Petition for certiorari submitted by Sandoz appealing notice decision
 - Amgen opposed cert. and added in conditional cross issue that dance should not be optional
 - Sandoz launched at risk in September 2015 at 15% discount
 - Pending patent infringement lawsuit re Amgen’s U.S. Patent No. 6,162,427, which claims a method of using filgrastim

Post *Amgen v. Sandoz*

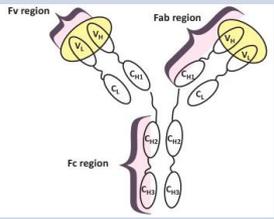
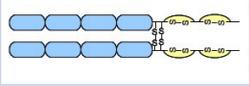
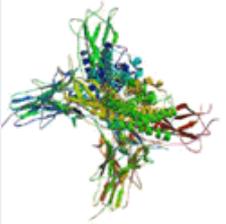
- *Amgen v. Apotex*, Case No. 15-cv-61631 (S.D. Fla. 2015)
 - First wave of dance complete
 - Amgen and Apotex reached agreement upon a list of patents that should be the subject of a first wave of patent litigation
 - *Is the notice provision optional in instances where the applicant does comply with the provisions of 262(l)(8)(2) (i.e., the patent dance)?*
 - ***District Court held notice of commercialization can only be given after FDA approves drug, even if applicant complies with provisions of patent dance***
 - Appealed to the Fed. Cir. and oral arguments were held earlier this month





BPCIA Present Litigation: “Some Dance” Cases

Present Litigation

Biologic		Case	Keywords/issues
<p>Remicade® (infliximab)</p>		<p><i>Janssen Biotech v. Celltrion Healthcare</i> (15-CV-10698 D. MA 2015)</p>	<p><i>Is the refusal to participate in the negotiation process of 262(l)(4) and (5) contrary to text of statute?</i></p>
<p>Epogen® (epoetin alfa)</p>		<p><i>Amgen v. Hospira</i> (15-CV-839 D. Del. 2015)</p>	<p><i>Is the refusal to participate in the negotiation process of 262(l)(4) and (5) contrary to text of statute?</i></p>
<p>Enbrel® (etanercept)</p>		<p><i>Immunex Corp. v. Sandoz Inc.</i> (16-CV-1118 D.N.J. 2016)</p>	<p><i>Is the refusal to participate in the negotiation process of 262(l)(3)(C), (l)(4) and (l)(5) contrary to text of statute?</i></p>
<p>Neulasta® (pegfilgrastim)</p>		<p><i>Amgen v. Sandoz</i> (16-CV-1276 D.N.J. 2016)</p>	<p><i>Is the refusal to participate in the negotiation process of 262(l)(3)(C), (l)(4) and (l)(5) contrary to text of statute?</i></p>

Background: **Remicade®**

- Celltrion produced its application, including manufacturing information (the completeness of which Janssen disputes), within the statutory 20-day window
- Janssen served its patent list
- Celltrion provided a detailed statement in response, and agreed that all of the patents identified by Janssen would be the subject of the first wave of litigation
- Janssen (RPS) files DJ complaint Re '083 and '471 patents, among others; faults Celltrion/Hospira for
 - Failing to provide complete manufacturing info
 - Failing to participate in good faith negotiations, which forced Janssen to file suit to preserve its statutory rights
 - Trial set for February 2017



FDA approves Celltrion's biosimilar in April 2016

- Celltrion provided second notice of commercialization for October 2, 2016
 - 180 days from FDA approval
- Janssen sends letter to Court on April 12th requesting expedited trial date of September 2016 on '083 patent only
- Alleges Celltrion's cell culture media, used to make the biosimilar infringes is '083 patent under the doctrine of equivalents
- Celltrion sends reply letter to Court on April 18th
 - Will only delay launch if required by Fed. Cir. ruling in *Amgen v. Apotex*
 - Points out Janssen's infringement theory rests on DOE; Celltrion avoids literal infringement 12 different ways
 - Open to earlier dispositive hearing if both patents are involved

Background: **Enbrel®**

- Sandoz provided Immunex with access to its aBLA and manufacturing information and later supplemented additional manufacturing info
- Immunex served its patent list
- Sandoz “agreed” to the list and waived its right to receive a statement by Immunex pursuant to 1(3)(C) and declared negotiations pursuant to 1(4) and (5) unnecessary
- Immunex files DJ complaint in Feb. 2016
 - *Can applicants waive portions of the patent dance?*
 - *Is the refusal to participate in the negotiation process of 262(1)(4) and (5) contrary to text of statute?*

Note Sandoz behaved similarly in *Amgen v. Sandoz* (D. N.J. 16-cv-1276) regarding Neulasta® patent dance negotiations

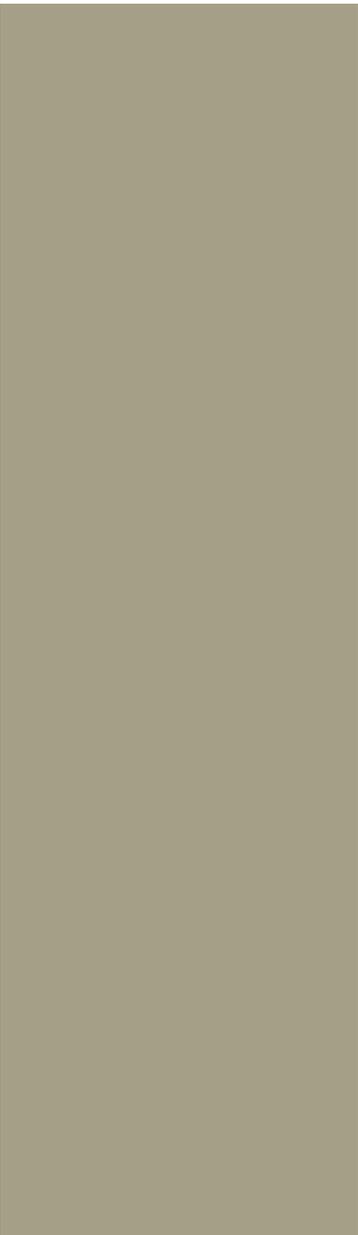
Summary of Current BPCIA Holdings

- Likely no “case or controversy” until applicant files aBLA (*Sandoz v. Amgen* (2904 case), *Celltrion v. Kennedy*)
- BPCIA also precludes DJ jurisdiction in suit against solely patent owner that does not include RPS (*Celltrion v. Kennedy*)
- BPCIA precludes DJ jurisdiction in suit by co-manufacturer that does not include aBLA applicant) against RPS (*Hospira v. Janssen*)
- Patent dance is optional (*Amgen v. Sandoz*)
- Notice of commercial marketing only effective after FDA approves aBLA (*Amgen v. Sandoz*)
 - This is true even if applicant participates in the patent dance (*Amgen v. Apotex*)

BPCIA: Current and Future Litigation

Because this area of law is new and complicated, there are many open legal questions:

- What and how much “other information” as required in 351(l)(2)(A) must an applicant provide to engage in the patent dance?
- What are the ramifications if the RPS does not in good faith agree to terms for exchange of BLA’s confidential information?
- What are the ramifications of a BLA only partially engaging in the patent dance?
- If “reasonable royalties” are the exclusive remedy, what is the date of the hypothetical negotiation?



IPRs and Biologics

IPRs and Biologics

Biologics IPRs

- A number of biosimilar makers have turned to IPR to challenge innovator patents prior to submitting their biosimilar applications to the FDA
- Examples include
 - Boehringer Ingelheim
 - IPR2105-00415, -417, -418 challenging patents covering Rituxan®
 - Hospira
 - IPR2013-00365 challenging patents covering dosing regimens for administering erythropoietin (EPO) IPR2013-00365 challenging Eprex (epoetin alfa), a biologic used to treat anemia
 - Amgen
 - IPR2015-01514, -1517 challenging patents covering Humira®
- Hedge fund manager Kyle Bass filed IPR2015-01792 targeting Hoffman-La Roche's U.S. Patent 8,163,522 covering the biologic Enbrel®
 - Denied institution March 2016

IPRs and Biologics

Biologics IPRs

- Biosimilar manufacturers view IPRs as advantageous
 - Provide for a sort of freedom to operate analysis
 - Claims are construed with the broadest reasonable interpretation
 - Generally broader claim construction than district court
 - No presumption of patent validity
 - Invalidity need be proved only by “preponderance of the evidence”
 - As opposed to “clear and convincing evidence”
 - Decisions rendered faster
 - Allows for patent certainty when litigation under Biologics Price Competition and Innovation Act of 2009 (BPCIA) is premature

Case Study

Boehringer Ingelheim

- Developing a biosimilar of Biogen and Genentech's antibody product Rituxan®
- Early adopter of IPR in lieu of BPCIA litigation
- Boehringer filed IPR petitions in December 2014 challenging three patents covering Rituxan®
 - Patents do not expire until 2020 or later

Case Study

Boehringer Ingelheim

- Strategy has mixed results
 - IPR2015-00417 instituted on all claims of 7,976,838 patent
 - IPR2015-00415 not instituted on half of challenged claims of 7,820,161 patent
 - IPR2015-00418 filed against 8,329,172 patent not instituted
- Board's decision not to institute IPR for all claims in '161 and '172 patents leaves those patents for BPCIA litigation
 - Board's decision likely strengthens these patent claims

Should IPRs Not Apply to BioPharma?

In July 2015, a group of 80 House members signed a letter urging the addition of language to H.R.9 to exempt certain biopharmaceutical patents from IPR review



July 15, 2015

Chairman Chuck Grassley
Senate Judiciary Committee
224 Dirksen Senate Office Building
Washington, DC 20510

Ranking Member Patrick Leahy
Senate Judiciary Committee
224 Dirksen Senate Office Building
Washington, DC 20510

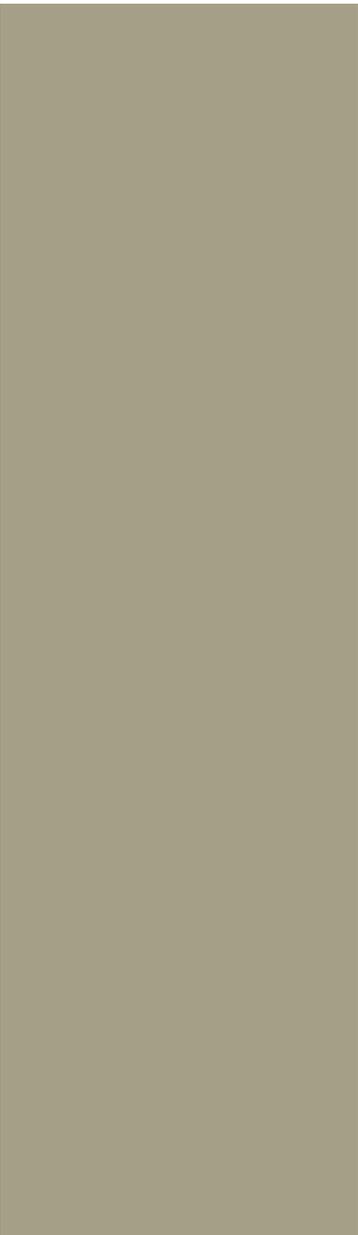
Chairman Robert Goodlatte
House Judiciary Committee
B351 Rayburn House Office Building
Washington, DC 20515

Ranking Member John Conyers
House Judiciary Committee
2138 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Grassley, Ranking Member Leahy, Chairman Goodlatte, and Ranking Member Conyers –

We write to express our support for changes to H.R. 9, the Innovation Act, and S. 1137, the PATENT Act, to preserve the integrity of the Drug Price Competition and Patent Term Restoration Act (commonly referred to as Hatch-Waxman) and the Biologics Price Competition and Innovation Act (BPCIA) by exempting certain biopharmaceutical patents on approved medicines from the *inter partes review* (IPR) process at the Patent and Trademark Office (PTO), and to rebut several erroneous statements that have been made about these proposals. Unfortunately, these statements disregard the intent behind both the America Invents Act (AIA) and the patent resolution frameworks established under Hatch-Waxman and BPCIA, and contain a number of false statements about the impact of failing to correct this unintended consequence of the AIA. We are writing to set the record straight.

Hatch-Waxman and BPCIA were established by Congress as separate patent resolution frameworks for biopharmaceutical patents in order to achieve two key objectives: 1) to increase the ability of generic and biosimilar manufacturers to offer consumers lower cost versions of off-patent medicines, and 2) to preserve incentives for the discovery and development of new, innovative medicines. In fact, as the Supreme Court has stressed, one of the "key features" of the Hatch-Waxman Act was the establishment of "special procedures for identifying, and resolving, related patent disputes" including the paragraph IV



Questions?

FISH.

Thank you!



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