October 13, 2016

Webinar Series: Biosimilars

Update on Biologics Litigation and IPRs

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Southern California
Office

FISH.
FISH & RICHARDSON

Overview

- Biosimilars Series
  - Introduction to the area of biosimilars
  - Explore key developments and trends
- CLE Credit
  - Contact: Jane Lundberg
    - lundberg@fr.com
- Materials will be made available
  - fr.com/industries/life-sciences
- Follow us on Twitter @FishRichardson
  - #fishwebinar

Save the Date:

Life Sciences IP Summit

November 3, 2016

Sofitel
Redwood City, CA

Background

Previous Webinars:

- Biosimilars 101
- Biosimilars 102 – Litigation: Planning and Strategy
- Biosimilars & IPR
- Biosimilars Litigation: Past, Present, and Future

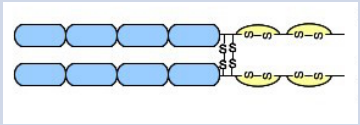
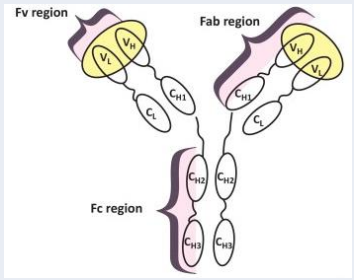
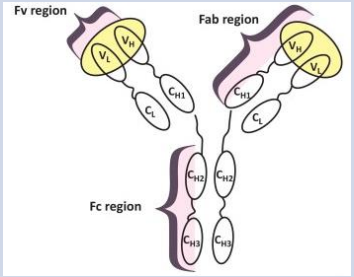
BPCIA

- 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

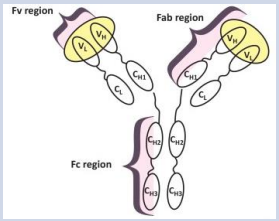
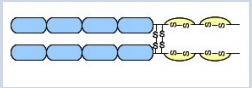
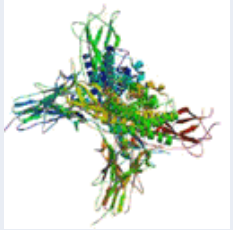
- BPCIA **creates an abbreviated licensure pathway for biological products** shown to be biosimilar to or interchangeable with an FDA-licensed reference product

- The courts and FDA are **tackling uncharted legal and regulatory issues** surrounding implementation of the legislation

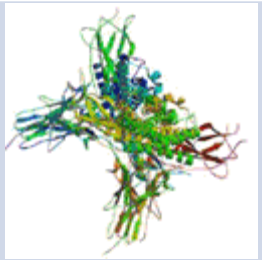
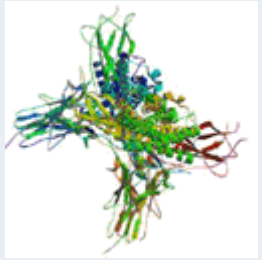
Past Litigation

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

Present Litigation

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

First Statutory Interpretation

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

First Statutory Interpretation

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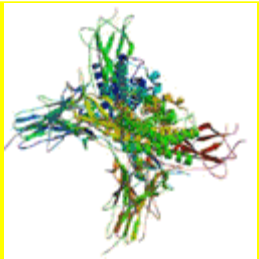
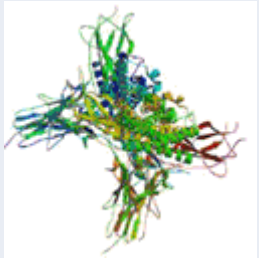
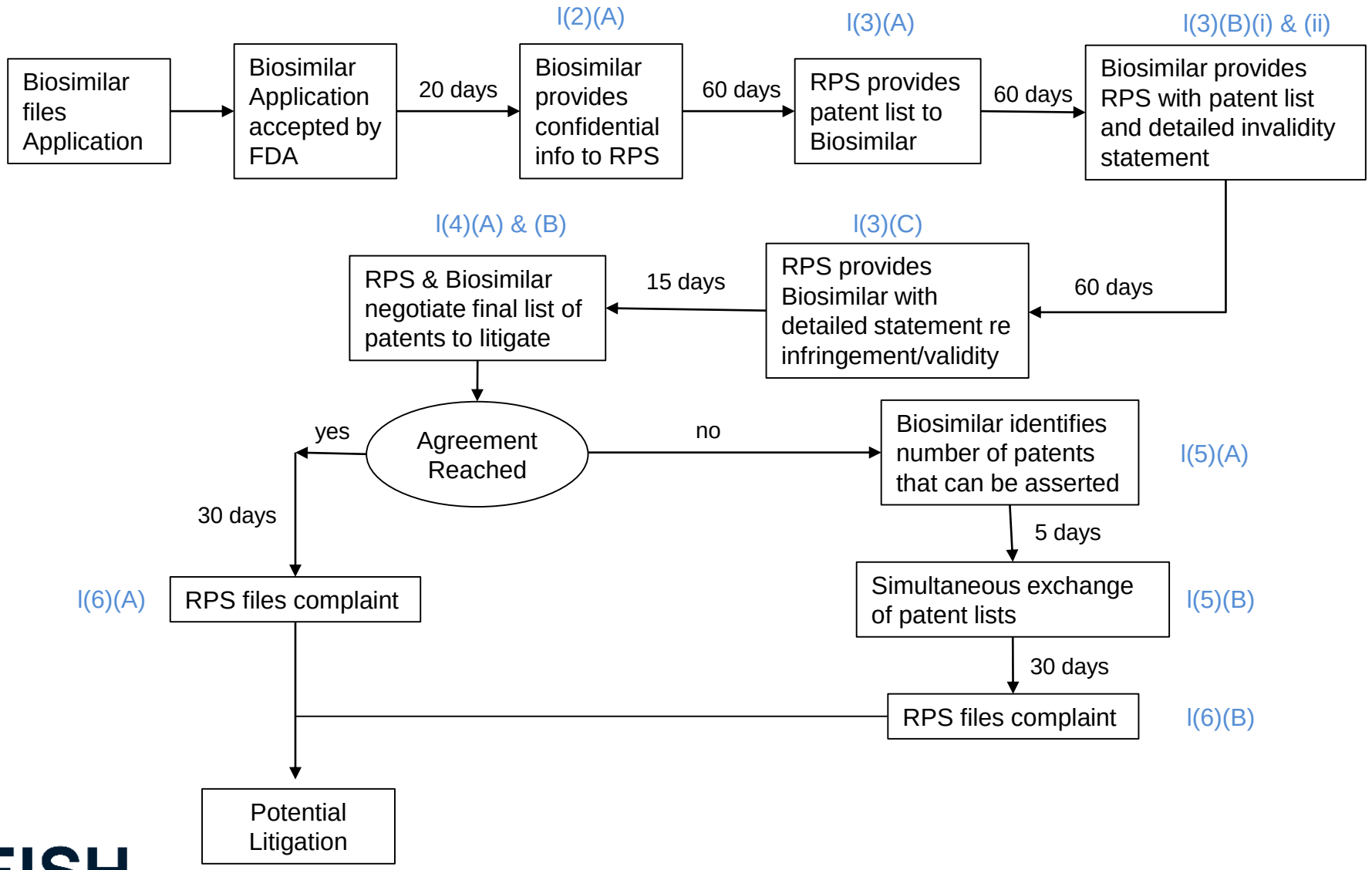
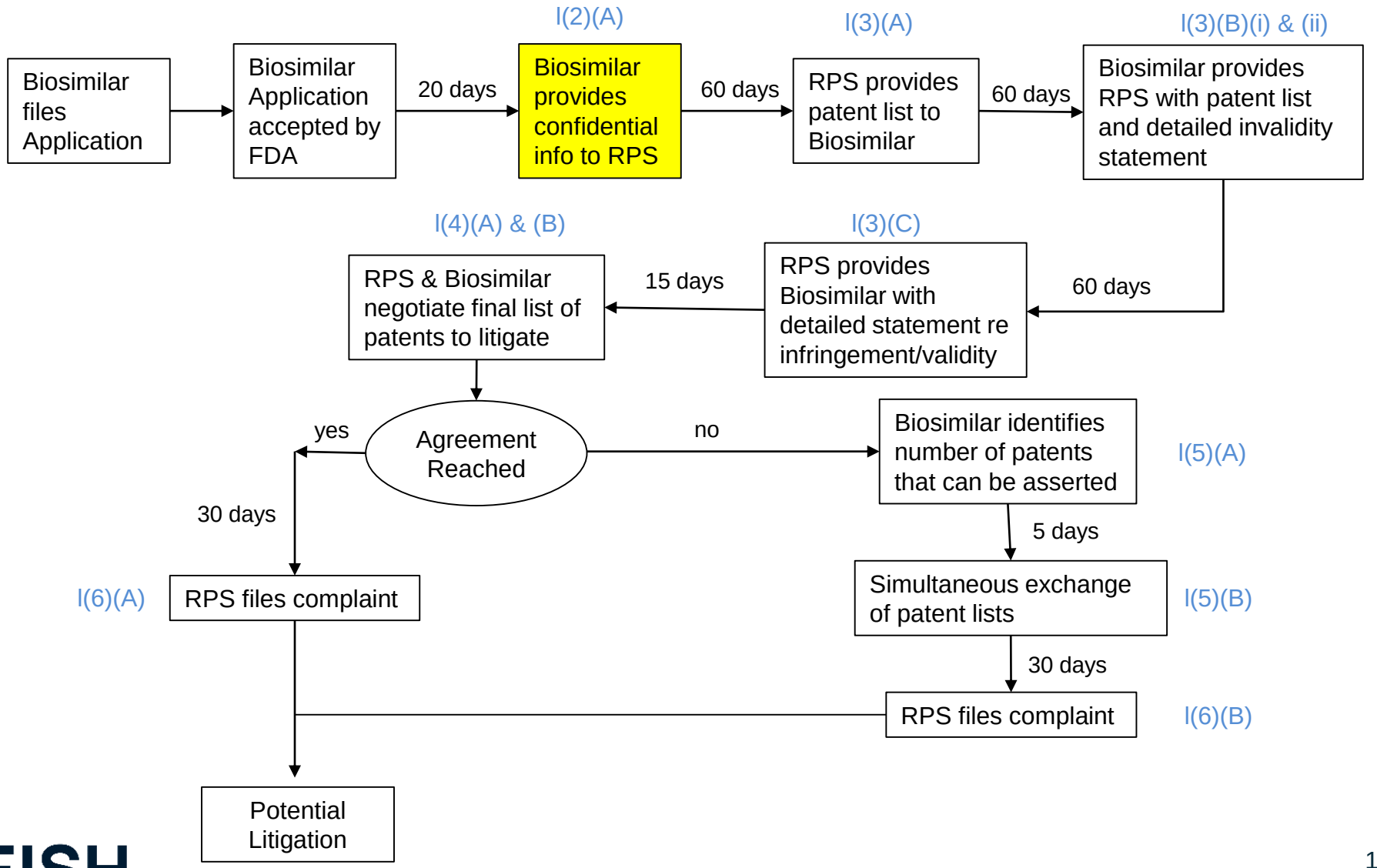
Neupogen® (filgrastim)		*Amgen v. Sandoz* (2015-1499 Fed. Cir. 2015)	Is the patent dance required? When can biosimilar applicant give 180 notice of commercialization?
Neulasta® (pegfilgrastim)		*Amgen v. Apotex* (15-cv-61631 S.D. Fla. 2015)	If biosimilar applicant complies with patent dance, when can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

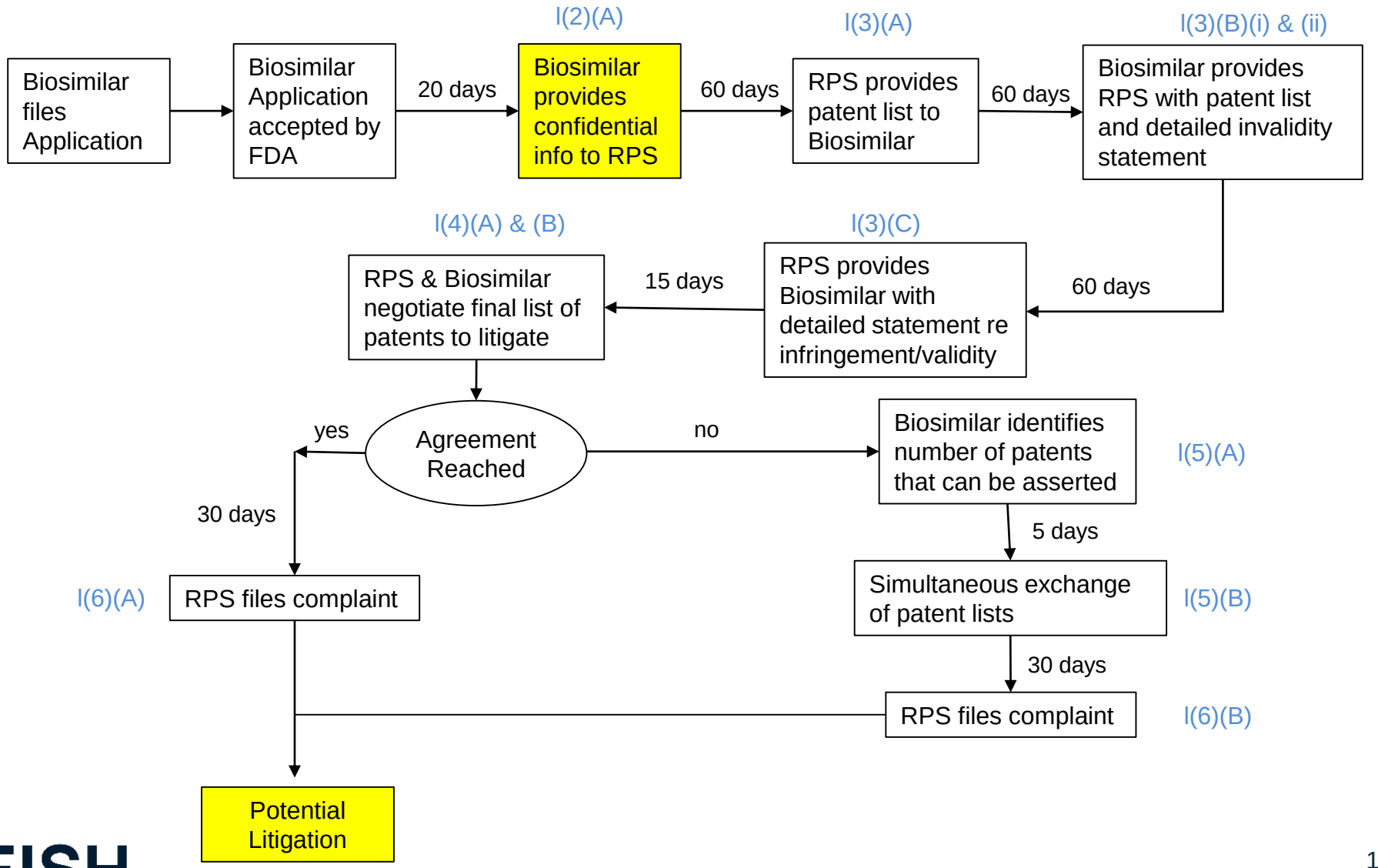
The BPCIA Patent Dance



The BPCIA Patent Dance



The BPCIA Patent Dance



When “Shall” means “May”

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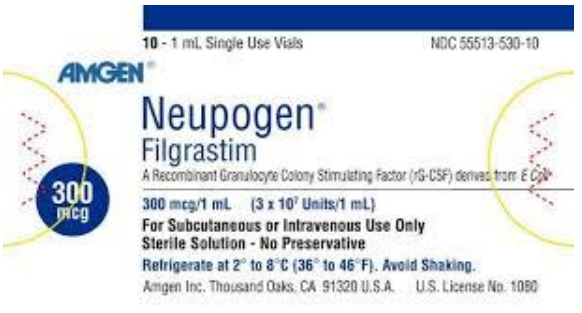
Amgen Inc. v. Sandoz Inc.

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; also asserted a state law cause of action for conversion based on Sandoz's use of Amgen's information related to safety, purity, and potency; alleged patent infringement.
- Amgen files PI motion (February 2015) to block commercial manufacture, use, offer to sell, sale within the United States, or importation into the United States:
  - BPCIA says "shall" disclose application (42 U.S.C. § 262(l)(2)).
  - Sandoz's 180-day notice of commercial marketing is premature because the notice was not "before" being "licensed" by FDA (42 U.S.C. § 262(l)(8)).
  - Provide a copy of the application, complete patent exchange process, provide notice of commercial marketing.



Amgen v. Sandoz, No. 3:14-cv-04741-EDL (ND Cal)

Amgen Inc. v. Sandoz Inc.

- Sandoz's opposition to MTD
  - As remedies exist for failure of applicant to provide biosimilar application, BPCIA does not mandate disclosure.
  - Amgen is still able to assert its patents and can do so immediately.
  - 180 day notice of commercial manufacturing does not first require FDA approval.
  - No irreparable harm
    - Sandoz offered application with "industry standard" confidentiality obligations but Amgen refused.
    - Amgen had right to sue immediately after expiration of 20 day period to disclose application but instead waited 3 months.
    - Any economic harm can be compensated with monetary damages.

Amgen Inc. v. Sandoz Inc.

NDCA denies Amgen's PI

- Disclosure of biosimilar application is optional
  - "Shall" does not always mean mandatory particularly where the law provides remedies for failure to comply.
- 180-day notice can be provided before FDA approval
  - "Licensed" does not require FDA approval prior to 180-day notice.
  - "Before" modifies "first commercial marketing" not "licensed" thus must give notice "before" marketing.
  - Waiting until FDA approval will give RPS an additional 6 months exclusivity not intended by BPCIA.
- PI Denial
  - Amgen only raised "speculative" notions of irreparable harm.
  - Amgen did not provide any proofs of infringement.

Amgen Inc. v. Sandoz Inc.

Federal Circuit

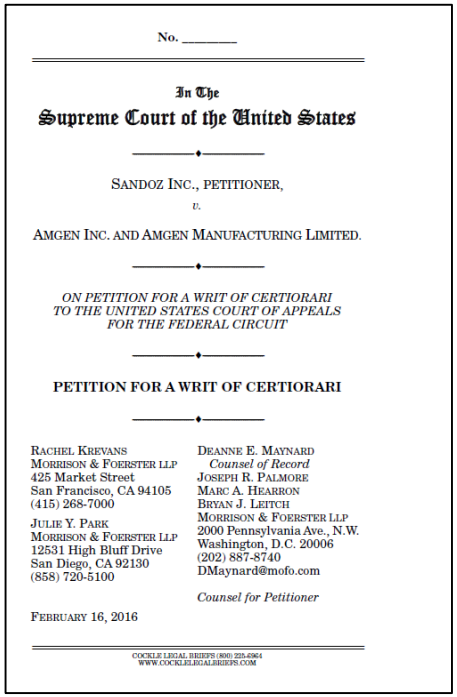
A divided panel ruled:

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.

- According to the Court, Sandoz's opt-out did not violate the BPCIA or constitute unfair competition, leaving patent infringement as Amgen's only remedy, but Sandoz's July 8, 2014, notice was ineffective since its application was unapproved at that time.
- Federal Circuit denied rehearing.

Not the end of it . . . Sandoz appealed



No. _____

In The
Supreme Court of the United States

SANDOZ INC., PETITIONER,
v.
AMGEN INC. AND AMGEN MANUFACTURING LIMITED.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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Counsel for Petitioner

FEBRUARY 16, 2016

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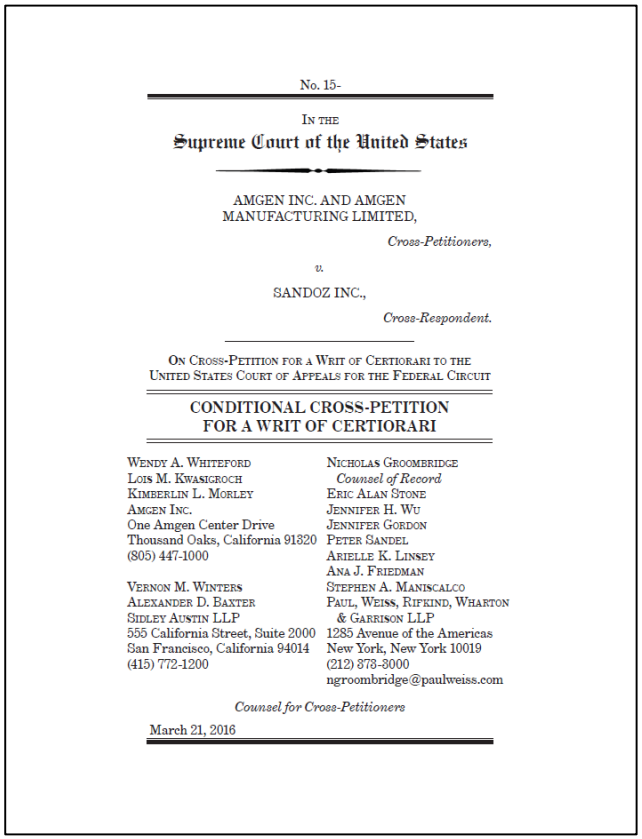
Issue:

(1) Whether notice of commercial marketing given before Food and Drug Administration (FDA) approval can be effective; ***and***

(2) Whether, in any event, it is improper to treat Section 262(*l*)(8)(A)—the Biologics Price Competition and Innovation Act of 2009's "Notice of commercial marketing" provision which states that a biosimilar applicant shall provide notice to the incumbent seller of the biological product "not later than 180 days before the date of the first commercial marketing of the biological product licensed under" an abbreviated pathway for biosimilars—as a stand-alone requirement and creating an injunctive remedy that delays all biosimilars by 180 days after approval.

Amgen cross-appealed



No. 15-

IN THE
Supreme Court of the United States

AMGEN INC. AND AMGEN MANUFACTURING LIMITED,
Cross-Petitioners,

v.

SANDOZ INC.,
Cross-Respondent.

ON CROSS-PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CONDITIONAL CROSS-PETITION FOR A WRIT OF CERTIORARI

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Counsel for Cross-Petitioners

March 21, 2016

Issue:

(1) Whether a biosimilar applicant ("Applicant") is required by 42 U.S.C. § 262(l)(2)(A) to provide the reference product sponsor ("Sponsor") with a copy of its biologics license application and related manufacturing information, which the statute says the Applicant "shall provide;" and

(2) Whether, where an Applicant fails to provide that required information, the Sponsor's sole recourse is to commence a declaratory judgment under 42 U.S.C.(l)(9)(C) and/or a patent-infringement action under 35 U.S.C. § 271(e)(2)(C)(ii).

Timing

Feb 16 2016	Petition for a writ of certiorari filed. (Response due March 21, 2016)
Mar 21 2016	Brief amicus curiae of Biosimilars Council filed.
Mar 21 2016	Motion for leave to file amici brief filed by Apotex, Inc., et al.
Mar 21 2016	Brief amici curiae of Hospira, Inc, et al. filed.
Mar 21 2016	Brief of respondents Amgen Inc., et al. in opposition filed.
Mar 21 2016	Brief amicus curiae of Mylan, Inc. filed.
May 31 2016	DISTRIBUTED for Conference of June 16, 2016.
May 31 2016	Reply of petitioner Sandoz Inc. filed. (Distributed)
Jun 20 2016	The Solicitor General is invited to file a brief in this case expressing the views of the United States.

Implications

- Potential far reaching strategic implications for biosimilar applicants and originators
  - Whether to dance or not
    - What must be exchanged as part of the dance?
  - Whether notice of commercial marketing is necessary and when
    - Before or after approval

IPRs Challenging Biologic Patents

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Biologics patents challenged in IPR

HUMIRA® adalimumab

Rituxan® Rituximab

Herceptin® trastuzumab

Enbrel® etanercept

AVASTIN® bevacizumab

TYSABRI® (natalizumab)

Neulasta® (pegfilgrastim)

ORENCIA® (abatacept)

Biologics IPRs – the current players for BIG drugs

Drug	Global Sales in 2014	First IPR, filer, and date
Humira	$13 billion	IPR 2015-01514; Amgen; filed 6/26/2015
Rituxan	$7.3 billion	IPR2015-00415; Boehringer Ingelheim; filed 12/15/2014
Herceptin	$6.6 billion	IPR2014-00676; Phigenix; filed 4/22/2014
Enbrel	$9.1 billion	IPR2015-01792; Coalition for Affordable Drugs V; filed 8/22/2015
Avastin	$7 billion	IPR2016-01771; Hospira; filed 9/9/2016
Tysabri	~$2 billion	IPR2016-0912; Swiss Pharma International; filed 4/18/2016
Gattex	Estimated $100 million	IPR2015-0990; Coalition for Affordable Drugs II; filed 4/1/2015
Ovencia	$1.4 billion	IPR2015-01537; Momenta; filed 7/2/2015
Neulasta	$4.6 billion	IPR2016-01542; Apotex; filed 8/5/2016

Biologics IPRs – the current players

Drug	Patent Owner(s)	Who challenged? Green = instituted; red = not instituted; black = awaiting decision on institution
Humira	AbbVie	Boehringer Ingelheim (2); Coherus (4); Amgen (2)
Rituxan	Genentech; Biogen	Celltrion (2; 2); Boehringer Ingelheim (3)
Herceptin	Genentech; Immunogen	Phigenix (1;1); Mylan (2); Hospira (1)
Enbrel	Hoffman-LaRoche	Coalition for Affordable Drugs V (1)
Avastin	Genentech	Hospira (1)
Tysabri	Biogen	Swiss Pharma International (3)
Gattex	NPS Pharmaceuticals (Shire)	Coalition for Affordable Drugs II (2)
Ovencia	Bristol-Myers Squibb	Momenta (1)
Neulasta	Amgen	Apotex (1)

Biologics IPRs – Final Written Decision; Herceptin (US 8,337,856)

Drug (filer)	Instituted Ground(s)
IPR2014-00676 (Phigenix)	35 U.S.C. § 103(a) 1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8. **PTAB held claims not unpatentable**
PTAB	Patent Owner provided evidence showing: • "at the time the '856 patent was filed, prior art indicated that HERCEPTIN®-maytansinoid immunoconjugates would have been expected to exhibit unacceptable levels of antigen-dependent toxicity in normal human liver tissue in patients."; • "ordinary artisans would <u>not</u> have had a reasonable expectation that any immunoconjugate, much less the claimed Herceptin®-maytansinoid immunoconjugate in particular, would be useful to treat solid tumors in humans." • "unexpected superior results as compared to closest prior art compositions, fulfilling a long-felt and unmet need, praise in the field, and commercial success", including evidence that T-DM1/Kadcyla®, the product encompassed by the claim, "fulfilled a long-felt, unmet need for an immunoconjugate capable of targeting a solid tumor in patients without excessive toxicity". Patent Owner's evidence relating to the commercial success of the product through its expert Mr. Jarosz (analyzed sales and prescription data, and marketing and promotional efforts relating to the product) was compelling. Patent Owner's secondary consideration evidence was not expected, and that the unexpected results were commensurate in scope with claim 8.

Biologics IPRs – Grounds instituted; Humira – (US 8,889,135)

Drug (filer)	Instituted Ground(s)
IPR2016-00409 (BI)	35 U.S.C. § 103(a) 1. A method for treating rheumatoid arthritis in a human subject, comprising administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13 -15 days for a time period sufficient to treat the rheumatoid arthritis, wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7 …

Biologics IPRs – Grounds instituted; Humira – (US 8,889,135)

Drug (filer)	Instituted Ground(s)
IPR2016-00172 (Coherus)	35 U.S.C. § 103(a) 1. A method for treating rheumatoid arthritis in a human subject, comprising administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13 -15 days for a time period sufficient to treat the rheumatoid arthritis, wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7

Biologics IPRs – Grounds instituted; Humira- US 9,017,680

Drug (filer)	Instituted Ground(s)
IPR2016-00188 (Coherus)	35 U.S.C. § 103(a) 1. A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising: administering to said patient, in combination with methotrexate, a human anti-TNFα antibody, wherein the human anti-TNFα antibody is administered subcutaneously in a total body dose of 40 mg once every 13-15 days, and wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7 ….

Biologics IPRs – Grounds instituted; Humira – US 9,073,987

Drug (filer)	Instituted Ground(s)
IPR2016-00189 (Coherus)	35 U.S.C. § 103(a) 1. A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising: administering to said patient a total body dose of 40 mg of a human anti-TNFα antibody, wherein the dose is administered subcutaneously from a 40 mg dosage unit form once every 13-15 days, and wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7 …

Biologics IPRs – Grounds instituted; Gattex – US 7,056,886

IPR (filer)	Instituted Ground(s)
IPR2015-01093 (CAD2)	35 U.S.C. § 103(a) 1. A glucagon-like peptide 2 (GLP-2) formulation comprising: (a) a medically useful amount of a naturally occurring GLP-2 or an analog thereof; (b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a physiologically tolerable level; (c) L-histidine; and (d) a bulking agent selected from the group consisting of mannitol and sucrose.
IPR2015-00990 (CAD2)	35 U.S.C. § 103(a) 46. A GLP-2 formulation comprising: (a) about 0.1 to about 50 mg/ml of a GLP-2 peptide or an analog thereof; (b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a pharmaceutically tolerable level; (c) about 0.5 to about 1% L-histidine; and (d) about 2 to about 5% mannitol.

Biologics IPRs – Grounds instituted; Ovencia – US 8,476,239

IPR (filer)	Instituted Ground(s)
IPR2015-01537 (Momenta)	35 U.S.C. § 103(a) 1. A stable formulation suitable for subcutaneous administration comprising at least 100mg/ml CTLA4Ig molecule, a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof and a pharmaceutically acceptable aqueous carrier, wherein the formulation has a pH range of from 6 to 8 and a viscosity of from 9 to 20 cps, and the weight ratio of sugar:protein is 1.1:1 or higher.

Cabilly II patent IPRs; US 6,331,415

IPR (filer)	Ground(s)
IPR2015-01624(Sanofi-Aventis; Regeneron)	Instituted under 35 U.S.C. § 103 on claims 1-4, 11-12, 14, 18-20 and 33; **terminated**
IPR2016-00383 (Genzyme)	**Institution denied**
IPR2016-00460 (Genzyme)	Instituted on same grounds as Sanofi/Regeneron; joined to IPR2015-01624; **terminated**
IPR2016-00710 (Mylan)	Instituted on same grounds as Sanofi/Regeneron
IPR2016-01373 (Merck)	Asserted different § 103 grounds regarding claims 1-4, 11-12, 14-20, and 33; decision on institution pending
IPR2017-00047 (Merck)	Asserts same grounds as Mylan and seeks joinder; decision on institution pending

Interesting PTAB decision in biologics space

Daiichi Sankyo v Alethia (**IPR2015-00291**); US Patent 8,168,181

- Use of “lack of written description” in IPR context
- Patent claims directed to methods of using genus of antibodies in order to treat bone resorption; priority application failed to disclose any antibodies with the claimed functional properties or common structural features required to show possession of the claimed genus
- PTAB held that patent claims not entitled to earlier priority date as priority application failed to provide written description support for claimed genus
- Claims were found unpatentable under 35 USC § 102(a) based on a reference that otherwise would not have been prior art if the priority claim had been upheld

Questions?

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Thank you!

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A replay of the webinar will be available for viewing at fr.com/industries/life-sciences.