



Webinar Series: Biosimilars

Recent and Upcoming BPCIA Guidance
from the Federal Circuit and the Supreme
Court



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Overview

- Biosimilars Series
 - Introduction to the area of biosimilars
 - Explore key developments and trends
- CLE Credit
 - Contact: Jane Lundberg
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- Materials will be made available
 - fr.com/industries/life-sciences
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Upcoming
Biosimilars
Webinars

1:00 PM ET
August 16, 2017
November 16, 2017



Background



FISH.

Biologics Price Competition and Innovation Act

- Enacted in 2010 as part of the Affordable Care Act
- Provides an abbreviated regulatory pathway for biosimilars and interchangeables
- Lays out a patent dispute resolution framework
- Similarities and differences with the Hatch-Waxman framework

Stats to Date

- 5 FDA approved biosimilars
 - Zarxio (Neupogen biosimilar, Sandoz)
 - Amjevita (Humira biosimilar, Amgen)
 - Inflectra (Remicade biosimilar, Pfizer)
 - Erelzi (Enbrel biosimilar, Sandoz)
 - Renflexis (Remicade biosimilar, Samsung Bioepis)
- 2 commercially launched biosimilars
 - Zarxio
 - Inflectra
- No interchangeables approved to date
- 19 litigations thus far involving biologics/biosimilars and the BPCIA

SCOTUS: *Amgen v. Sandoz*

Amgen v. Sandoz

- Background: Neupogen®
- Divided Federal Circuit 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 approval of the aBLA would be effective to start the 180-day clock
- Sandoz launched at risk in September 2015 at a 15% discount
- SCOTUS granted *certiorari* review

SCOTUS: The Issues

- 1) Whether a biosimilar applicant is required by 42 U.S.C. § 262(l)(2)(A) to provide the RPS with a copy of its aBLA and related manufacturing information, which the statute says the applicant “shall provide;” and
- 2) When an applicant fails to provide that required information, is the sponsor's sole recourse to commence a declaratory judgment 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)
- 3) Whether notice of commercial marketing given before FDA approval can be effective; and
- 4) Whether, in any event, it is improper to treat Section 262(l)(8)(A) – the “Notice of commercial marketing” provision ... as a stand-alone requirement and as creating an injunctive remedy that delays all biosimilars by 180 days after approval.

The Amici

- Biosimilars Council
- Apotex Inc.
- Hospira Inc.
- Mylan Inc.
- **United States**
- Adello Biologics, LLC
- Pharmaceutical Care Management Association
- Apotex Inc.
- America's Health Insurance Plans
- AARP Foundation
- Coherus Biosciences
- AbbVie Inc.
- Janssen Biotech
- Biotechnology Innovation Organization
- Genetech
- Eleven Professors

United States Amicus Brief

- Recommended that SCOTUS grant certiorari petition
- Generally sided with biosimilar applicant, Sandoz
 - notice of commercial marketing prior to FDA approval is consistent with § 262(l)(8)(A);
 - injunctive relief is not available for a failure to provide notice under § 262(l)(8)(A) because nothing in the BPCIA creates a cause of action to enforce the notice provision; and
 - if a biosimilar applicant fails to engage in the patent dance, a RPS's sole recourse is an immediate patent-infringement action.

Oral Arguments

- The attorneys:
 - Seth Waxman (WilmerHale) represented Amgen, the reference product sponsor.
 - Deanne E. Maynard (Morrison & Foerster LLP) represented Sandoz, the biosimilar manufacturer
 - Anthony Yang, the assistant to the solicitor general

Questions from the Bench

- FDA's role in interpreting and applying the BPCIA

20 JUSTICE KENNEDY: But Justice Breyer's
21 question and my question is the same. The FDA is
22 involved in -- intimately, page 32A of the brief, the
23 subsection (k) application information. Not later than
24 20 days after the secretary notifies the applicant that
25 the application has been accepted, the applicant shall
1 provide.

2 Now, this -- this means that the agency
3 gives the notice for 20 days. And it seems to me,
4 certainly, it would be within its authority, or it would
5 be a sensible thing for it to say -- and they have a
6 regulation -- if you don't do that and we've told you to
7 do that, we're going to delay the review process.

Questions from the Bench

- FDA's role in interpreting and applying the BPCIA

5 JUSTICE BREYER: All right. Now, we are
6 being asked to interpret very technical provisions that
7 I find somewhat ambiguous and am operating in a field I
8 know nothing about. But it's going to have huge
9 implications for the future. So why isn't the way to go
10 about this case to ask the agency to issue some
11 regulations? Then when we see their interpretation, you
12 all will be able to argue that their interpretation
13 exceeds the statutory delegation. And by doing that, we
14 would have a better picture.

Questions from the Bench

- Interplay between state and federal law

18 JUSTICE GORSUCH: All right. Well, let me
19 know where I get it wrong, but -- or at least I
20 understand that's the primary position of -- of your
21 side. But Amgen sought relief under State law and --
22 and I -- I didn't take -- take it that Petitioner argued
23 preemption in any way, shape, or form. So where does
24 that leave us? (1) (9) might otherwise be the exclusive
25 -- or almost exclusive mechanism, but what happens when
1 we have a claim under State law that no one's argued is
2 preempted?

Questions from the Bench

- Good faith basis for bringing suit without access to the application

3 JUSTICE SOTOMAYOR: Could it -- could the
4 company with the product file a declaratory-judgment
5 action when they don't know what you're going to do? Do
6 they have a good-faith basis for believing you're going
7 to infringe if they don't have the application to look
8 at until they get discovery?

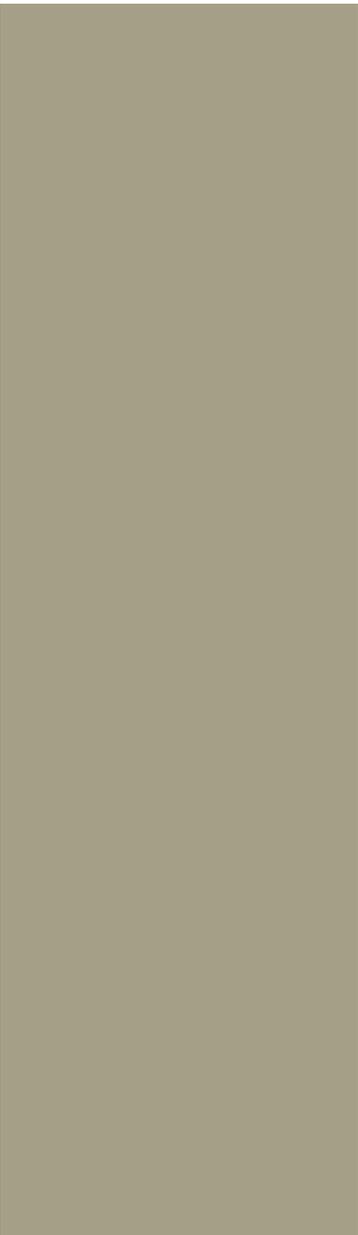
Questions from the Bench

- Good faith basis for bringing suit without access to the application

21 CHIEF JUSTICE ROBERTS: But it doesn't know
22 the specifics of the biosimilar. I mean, by definition,
23 the biosimilar is similar; it's not identical. And
24 whether or not it infringes might have something to do
25 with the ways in which it is different.

Status Quo (for now)

- Decision expected by end of June 2017
- Despite the uncertainty surrounding SCOTUS interpretation of the BPCIA dance and notice provision, parties are still litigating
 - *Amgen v. Coherus* (May 10, 2017)
 - *Janssen v. Samsung Bioepis* (May 17, 2017)



Federal Circuit Cases

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Federal Circuit: Amgen v. Hospira

- Drug at issue: **Epogen®** biosimilar
- BPCIA action filed September 2015 in D. Delaware
- Appeal Issue according to Amgen: “[t]he issue on appeal is not whether the discovery Amgen seeks is relevant; rather, the issue is whether Amgen is nevertheless entitled to the discovery as a matter of law under the BPCIA, even though it is irrelevant to the pending patent claims.”
- Fully briefed; oral arguments held April 3, 2017



Federal Circuit: Amgen v. Hospira

Background of the case

- Patent Dance:
 - Hospira produced its aBLA during the patent dance
 - Amgen claimed Hospira refused to produce other manufacturing information as required under the BPCIA (262(l)(2)(A))
 - Amgen did not list any cell culture patents on its 3(A) list
- District Court
 - Amgen sought discovery into additional manufacturing to identify other infringed patents
 - Hospira refused the discovery
 - Amgen moved to compel
 - Judge Andrews of D. Delaware denied the motion to compel
- Amgen appealed

Federal Circuit: Amgen v. Hospira

Background of the case, cont.

Federal Circuit:

- Motion to Dismiss the Appeal Based on Lack of Jurisdiction:
 - The Federal Circuit denied Hospira's motion to dismiss the appeal, but left open the question of jurisdiction
- Merits Briefing:
 - Amgen: denial of discovery "threatens to undermine the entire balance of the BPCIA"
 - Hospira: this is a simple discovery dispute governed by FRCP 26
- Oral Argument:
 - Panel: Dyk, Bryson, Chen

Federal Circuit: Amgen v. Apotex

- Drug at issue: **Neulasta®** and **Neupogen®** biosimilars
- BPCIA action filed October 2015 in the Southern District of Florida
- First completed BPCIA litigation on the merits of a patent dispute
- District court found that Apotex's biosimilar manufacturing processes did not infringe U.S. Patent 8,952,138
- Amgen's appeal:
 - Claim construction issues
 - Whether pre-litigation representations made by the biosimilar manufacturer are binding for the infringement analysis under the BPCIA
- Briefing completed in January 2017; Oral arguments not yet scheduled
- IPR instituted on the patent-at-issue in February 2017

Federal Circuit: Amgen v. Apotex

Background of the case:

- '138 patent:

1. A method of refolding a protein expressed in a non-mammalian expression system and present in a volume at a concentration of 2.0 g/L or greater comprising:

- (a) contacting the protein with a refold buffer comprising a redox component comprising

- a final thiol-pair ratio having a range of 0.001 to 100 and
 - a redox buffer strength of 2 mM or greater

- and one or more of:

- (i) a denaturant;
- (ii) an aggregation suppressor; and
- (iii) a protein stabilizer;

- to form a refold mixture;

- (b) incubating the refold mixture; and

- (c) isolating the protein from the refold mixture.

Federal Circuit: Amgen v. Apotex

Background of the case, cont.:

- Apotex's Claim Construction Position:
 - "Refold mixture" = A mixture formed from contacting the protein and the refold buffer"
 - Argued that "a protein is present at a concentration of 2.0 g/L or greater *after dilution in a refold mixture.*"

Claim Term	Court's Construction
"refold mixture"	A mixture formed from contacting (1) the volume in which the concentration of protein is 2.0g/L or greater with (2) the refold buffer. The refold mixture has a high protein concentration, where "high protein concentration" is at or above about 1g/L protein.

Federal Circuit: Amgen v. Apotex

Background of the case, cont.:

- Apotex's representations
 - In 262(l)(3)(B) statements, said refold mixture was 0.9-1.4 g/L of filgrastim
 - In rebuttal case, stated that its refold mixture had a washed inclusion-body concentration of 0.9-1.4 g/L, but 2/3 was water and therefore total protein was 0.3-0.5 g/L
- Amgen response:
 - aBLA did not limit protein concentration to non-infringing range
 - Washed inclusion-body concentration should equal protein concentration
 - 262(l)(3)(B) statements should be given weight
- District Court adopted Apotex's final theory in finding non-infringement

Federal Circuit: Amgen v. Apotex

Background of the case, cont.:

- Potential implications for future BPCIA litigants:
 - (1) is the infringement analysis in a BPCIA litigation governed by the disclosures in the aBLA?
 - (2) are statements made by biosimilar applicants under 42 U.S.C. § 262(l)(3)(B) of the BPCIA “optional pre-litigation letters” or binding party admissions?

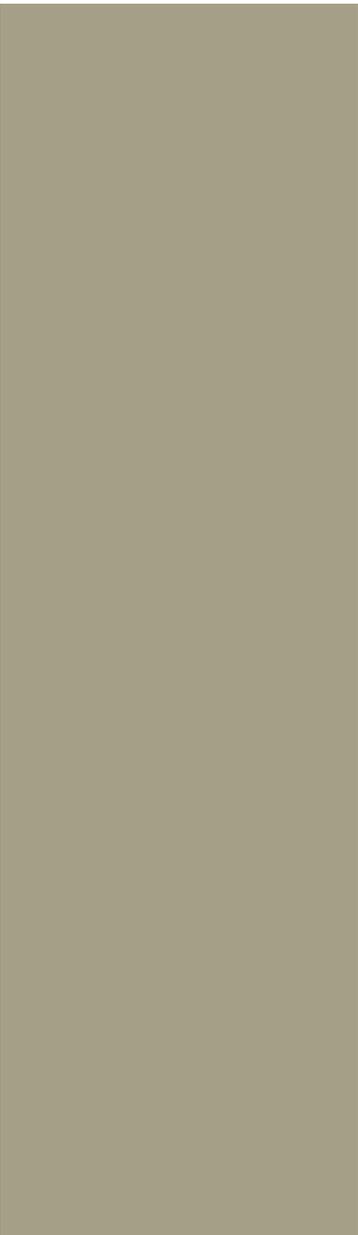
Federal Circuit: Janssen

- *Janssen v. Celltrion* and *In re Janssen*
 - The two appeals “will be considered companion cases and assigned to the same merits panel for oral argument.”
- Drug at issue: **Remicade®** biosimilar
- BPCIA action filed March 2015 in D. Massachusetts
- District court ruled that U.S. Patent 6,284,471 was invalid for double patenting
- PTAB also found ‘471 patent invalid for double patenting
- Awaiting reply brief in *In re Janssen* (due June 6, 2017); oral arguments not yet scheduled

Federal Circuit: Janssen

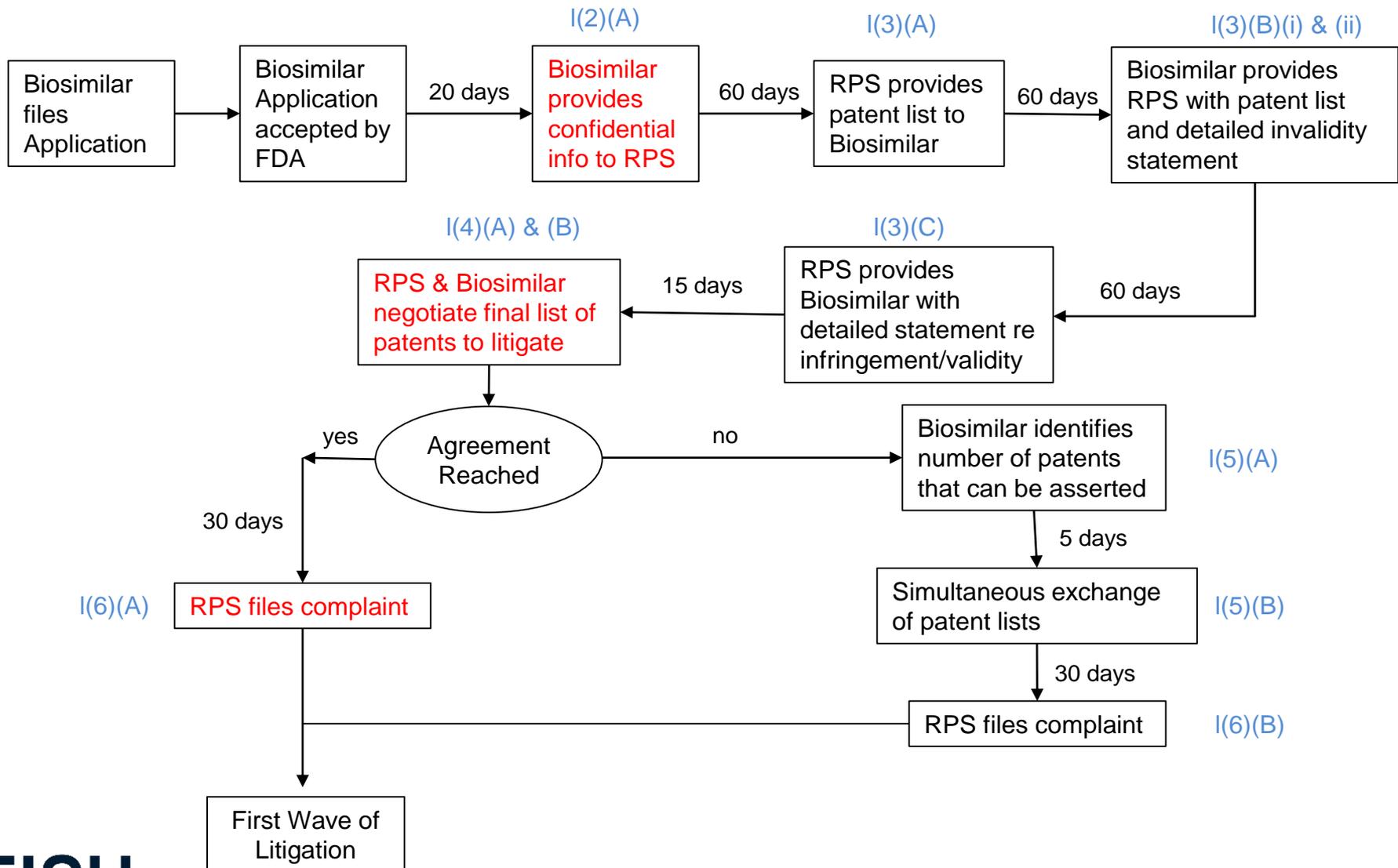
Background of the case:

- District court granted Janssen's motion to amend protective order
 - Janssen could use information produced by Celltrion under the PO to file a new case against HyClone, a third party cell culture media supplier for Celltrion's biosimilar product
- District court granted Celltrion's motion for summary judgment that all claims of the '471 patent are invalid for obviousness-type double patenting (August 2016)
 - *Gilead* theory re later issued, earlier expiring patents
 - "Safe Harbor" theory re 35 U.S.C. § 121
- District court entered partial final judgment of invalidity of the '471 patent (September 2016)
- Janssen appealed invalidity rulings to the Federal Circuit



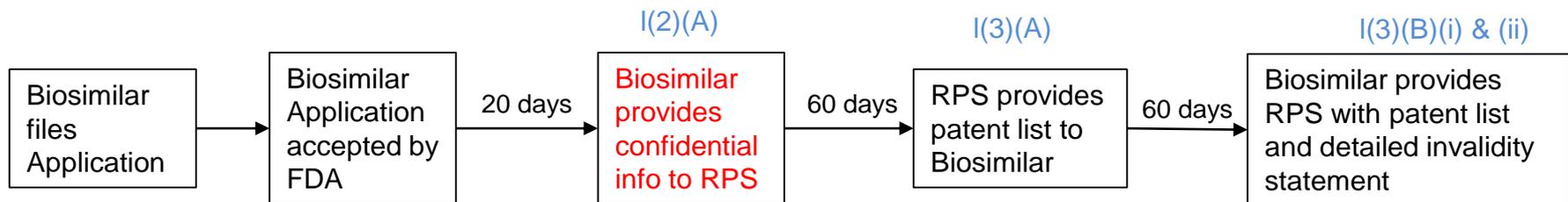
Other Pending Issues

The BPCIA Patent Dance-First Wave



Scope of Information Provided under 2(a)

- § 262(l)(2)(A):
 - 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 **shall provide to the [RPS] a copy of the [abbreviated biologic license application (aBLA)]** 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 the [aBLA.]**



Scope of Information Provided under 2(a)

- Subsection (k) applicants have taken different views about what constitutes sufficient disclosure under this section of the statute
 - The type and amount of information disclosed has varied between BPCIA cases
- Versions of aBLA submissions
 - File transfer links to electronic files in eCTD format
 - Remote access to a Sandoz-hosted database of TIFF images, modified to include added confidentiality designation
 - Immunex took issue with Sandoz's refusal to provide it with local access. Immunex alleged that Sandoz failed to satisfy § 262(l)(2) because (1) review of the disclosed information was supposedly burdensome and (2) the information disclosed (including the aBLA) was purportedly not in an unaltered state.

Scope of Information Provided under 2(a)

- Manufacturing Information
 - In the dispute over infliximab, Celltrion provided Janssen with a copy of its entire aBLA but refused to disclose information relevant to the manufacture of its biosimilar.
 - In Amgen's dispute with Hospira over epoetin alfa, Hospira turned over its entire aBLA
 - over 507 native files as well as 747,000 additional pages of information concerning Hospira's product and the process employed to make it
 - In Genentech's dispute with Amgen over bevacizumab, Genentech sought a declaratory judgment and an accompanying order that Amgen's § 262(l)(2)(a) disclosure of its aBLA (which omitted manufacturing information) was insufficient.

Standing Issues and Section 6(a)

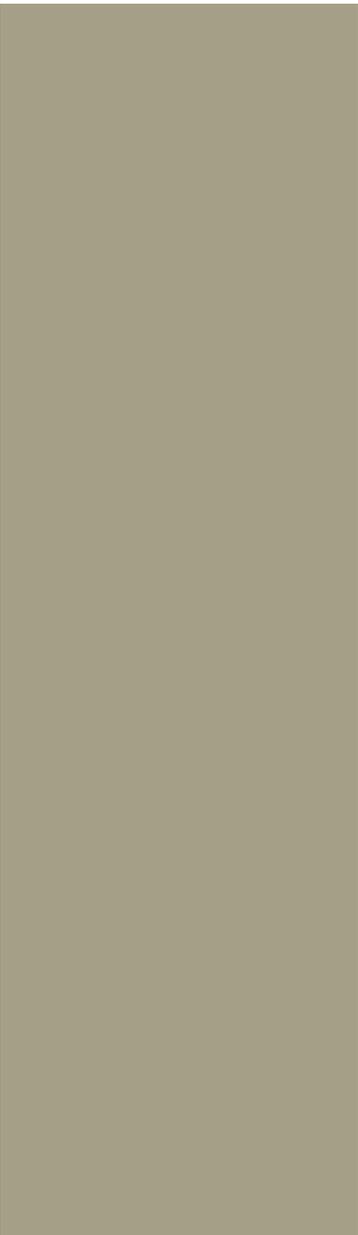
- § 262(l)(6)(A): 30 day window for filing a complaint under the BPCIA
- § 271(e)(6)(B): if a suit is brought later than 30 days or dismissed without prejudice, then “the sole and exclusive remedy” is a reasonable royalty
- *Janssen v. Celltrion*
 - Standing issues, with potential ramifications for damages
 - Celltrion short-circuited the patent dance by skipping the negotiation steps of § 262(l)(4)(A) and (5)
 - Court held that only the list of patents that emerge from the properly completed BPCIA “are potentially subject to the reasonable royalty damages limitation.”
 - Thus, the 30-day clock was never triggered.
 - Janssen can cure standing without being limited to a reasonable royalty

Skipping Parts of the Dance

- Parties who have started the patent dance are skipping steps
 - Waiving negotiation process of 262(l)(4) and (5)
 - E.g., *Amgen v. Sandoz* (Neulasta®); *Immunex v. Sandoz* (Enbrel®); *Amgen v. Hospira* (Epogen®)
- What are the ramifications (if any) for skipping parts of the patent dance?
 - 30 day clock of § 271(e)(6)(B) to file a lawsuit not triggered if parties short circuit the patent dance
 - 35 U.S.C. §271(e)(6) will not limit damages to a reasonable royalty for any proven infringement
 - Other potential ramifications

BPCIA and *TC Heartland* Decision

- 28 U.S.C. § 1400(b) provides that “[a]ny civil action for patent infringement may be brought in the judicial district where the defendant resides, or where the defendant has committed acts of infringement and has a regular and established place of business”
- *TC Heartland* holds “that a domestic corporation ‘resides’ only in its State of incorporation for the purposes of the patent venue statute”
- Impacts BPCIA cases similar to other patent cases
 - In addition to state of incorporation, Defendant can be sued, for example, in the state where headquarters or manufacturing plants are located
- *TC Heartland* does not directly affect non-US companies



IPR Litigation

IPR Petitions Filed

<i>Drug</i>	<i>2013</i>	<i>2014</i>	<i>2015</i>	<i>2016</i>	<i>2017</i>	<u>Total by Drug</u>
Avastin (bevacizumab)	0	0	0	1	0	1
CroFab (crotalidae polyvalent immune fab)	0	1	1	0	0	2
Dupixent (dupilumab)	0	0	0	0	1	1
Elaprase (idursulfase)	0	0	1	0	0	1
Enbrel (etanercept)	0	0	1	0	0	1
Epogen / Procrit (epoetin alfa)	1	0	0	0	0	1
Gattex (tedeglutide)	0	0	2	0	0	2
Herceptin (trastuzumab)	0	0	0	2	11	13
Humira (adalimumab)	0	0	7	1	6	14
Kadcyla (ado-trastuzumab emtansine)	0	2	0	0	0	2
Myozyme / Lumizyme (alglucosidase alfa)	3	0	0	0	0	3
Neulasta (pegfilgrastim)	0	0	0	1	0	1
Orencia (abatacept)	0	0	1	0	0	1
Rituxan (rituximab)	0	3	2	2	7	14
Tysabri (natalizumab)	0	0	0	3	0	3
Cabilly Patent	0	0	2	4	0	6
Unknown product	0	0	0	1	3	4
<u>Total by Year</u>	4	6	17	15	28	70

Challenges to Herceptin Patent

- Genentech's US 6,407,213
 - Challenged by three IPR petitions
 - Mylan filed 2 petitions on August 30, 2016 (IPR2016-01693 and IPR2016-01694)
 - Genentech and Mylan reached a settlement
 - Both IPRs were terminated after Patent Owner's Preliminary Response but prior to a decision on institution
- Celltrion and Teva filed a third petition May 8, 2017 (IPR2017-01374)
 - Asserted grounds are identical to those set forth in IPR2016-01693
 - Celltrion and Teva had the benefit of being able to review the Patent Owner's Preliminary Response prior to making their own filing

IPR Challenging Humira Patent

- IPR2016-00172
 - *Coherus v. AbbVie*, challenging US 8,889,135, which is directed to a method for treating rheumatoid arthritis

IPR2016-00172
Patent 8,889,135 B2

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–5 (collectively, “the challenged claims”) of U.S. Patent No. 8,889,135 B2 (Ex. 1001, “the ‘135 patent”). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner demonstrates, by a preponderance of evidence, that claims 1–5 are unpatentable.

- First time any Humira patent in AbbVie’s portfolio was invalidated in the United States



Questions?

FISH.

Thank you!



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