



Webinar Series: Biosimilars

Biosimilars: A Year in Review



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Overview

- Biosimilars Series
 - Introduction to the area of biosimilars
 - Explore key developments and trends
- CLE Credit
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- Materials will be made available
 - fr.com/industries/life-sciences
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Today's Topics

- Update on US Market for Biosimilars through 2017
- Biosimilar Litigation in 2017
- Trends in Biologic IPRs in 2017
- Issues to Watch for in 2018



US Biosimilar Market as of 2017

US Biosimilars Market

Biosimilar Drug	Biologic Drug	Biosimilar Code Name	FDA Approval Date	Time from aBLA Acceptance to Approval	Actual or Intended Commercial Launch Date
Ixifi® (Pfizer)	Remicade® (Johnson & Johnson)	Infliximab-qbtx	December 13, 2017	8 months	No launch intended
Ogivri® (Mylan)	Herceptin® (Genentech & Roche)	Trastuzumab-dkst	December 4, 2017	11 months	Confidential under license agreement
Mvasi® (Amgen & Allergan)	Avastin® (Roche)	Bevacizumab-awwb	September 14, 2017	10 months	
Cyltezo® (Boehringer Ingelheim)	Humira® (AbbVie)	Adalimumab-adbm	August 26, 2017	7 months	
Renflexis® (Samsung Bioepis/ Merck)	Remicade® (Johnson & Johnson)	Infliximab-abda	April 21, 2017	13 months	July 24, 2017
Amjevita® (Amgen)	Humira® (AbbVie)	Adalimumab-atto	September 23, 2016	8 months or less	Will not launch until 2023 per settlement
Erelzi® (Sandoz)	Enbrel® (Amgen)	Etanercept-szsz	August 30, 2016	13 months	
Inflectra® (Pfizer/ Celltrion)	Remicade® (Johnson & Johnson)	Infliximab-dyyb	April 5, 2016	20 months	November 28, 2016
Zarxio® (Sandoz)	Neupogen® (Amgen)	Filgrastim-sndz	March 6, 2015	10 months	September 15, 2015

US Biosimilars Market

Pending aBLAs

- 14 pending aBLA applications
 - 6 related to Neulasta/Neupogen®
 - 2 related to Rituxan®
 - 3 related to Herceptin®
 - 1 related to Humira®
 - 1 related to Remicade®
 - 1 related to Epogen®
- No interchangeables approved to date, but 14 applications have been filed from 9 different companies

Pricing of Biosimilars in the US

- Current Pricing:
 - Small molecule generics often discount 85% below brand name drugs
 - Zarxio® launched at 15% discount off Neupogen® in 2015
 - Inflectra® launched at 15% discount off Remicade® in 2016
 - Renflexis® launched at 35% discount off Remicade® in 2017
- Potential Reasons for Lack of Cost Reduction
 - Only three commercialized biosimilars
 - Discounts greater than 15% usually don't occur until a second competitor arrives on the market
 - Trouble gaining traction in US market
 - Inflectra® captured less than 4% of US market for Remicade®

Pricing of Biosimilars in the US

First US Biosimilar Antitrust Suit

- In September 2017, Pfizer sued Janssen Biotech and its parent Johnson & Johnson (J&J) in E.D. PA.
- Pfizer alleged that J&J sought to preserve a monopoly over the Remicade® (infliximab) market through anticompetitive discounts and rebates along with exclusionary contracts.
- Pfizer alleged that such behavior undermined the purpose of the BPCIA—namely, to reduce the cost of biologic therapeutic drugs.
- J&J has denied any wrongdoing and recently filed a motion to dismiss Pfizer’s complaint.
- Trial anticipated in early 2020.
- Similar class action suits also pending in Pennsylvania.

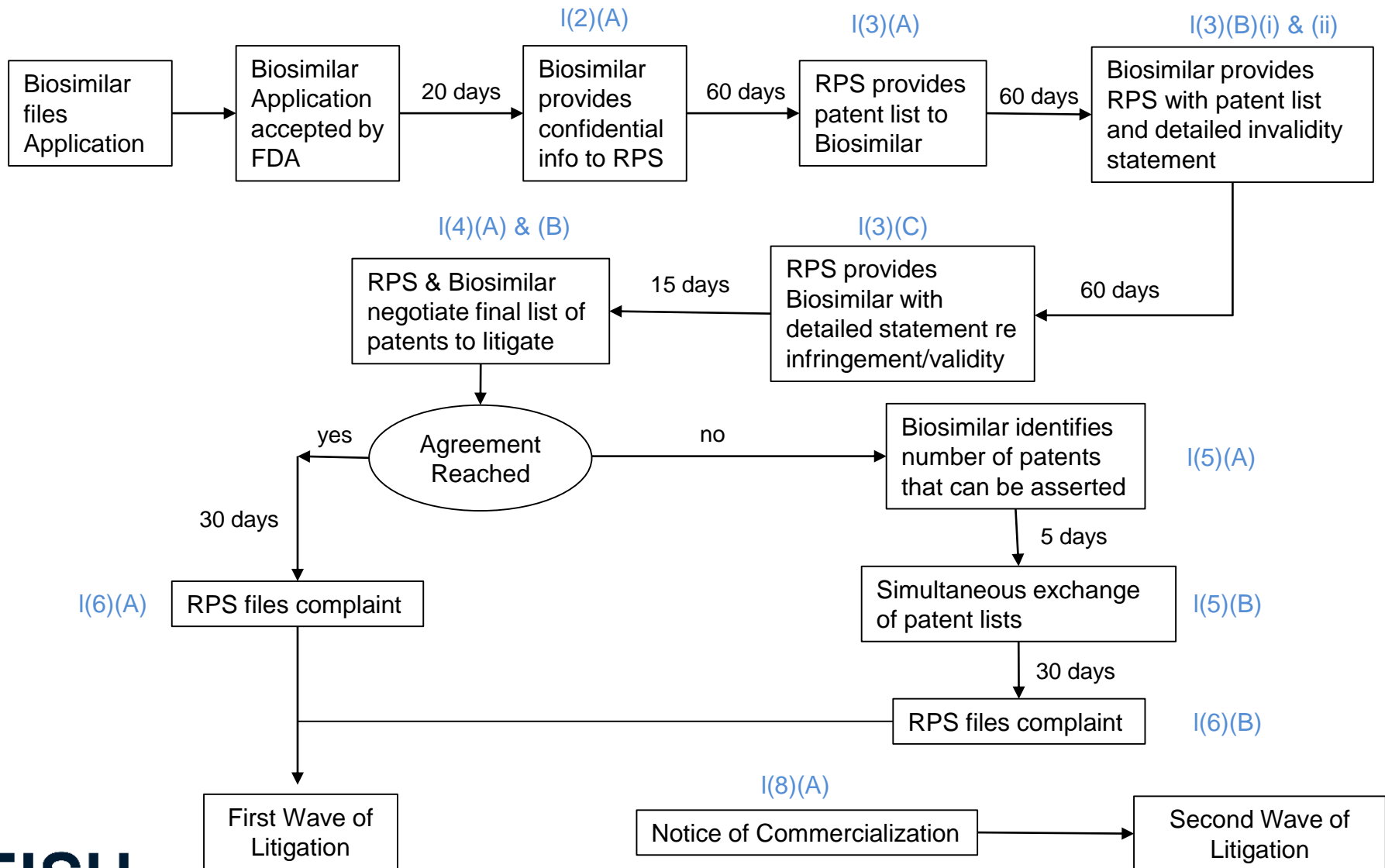
FDA Draft Guidance on Interchangeables

- January 17, 2017: FDA draft guidance on biosimilar interchangeability.
 - Recommends switching studies to show that patients can alternate between the biologic and interchangeable safely.
- May 19, 2017: Comment period closed.
 - 53 filed comments by brand companies, biosimilar companies, healthcare providers, insurers, and other interested organizations.
- FDA has not committed on when or if it will finalize this guidance, but has committed to:
 - Provide draft guidance related to post-approval manufacturing changes by March 31, 2019 and
 - Publish revised draft guidance applicable to biosimilars and interchangeables on “Good Review Management Principles and Practices for PDUFA Products” by the end of fiscal year 2018.

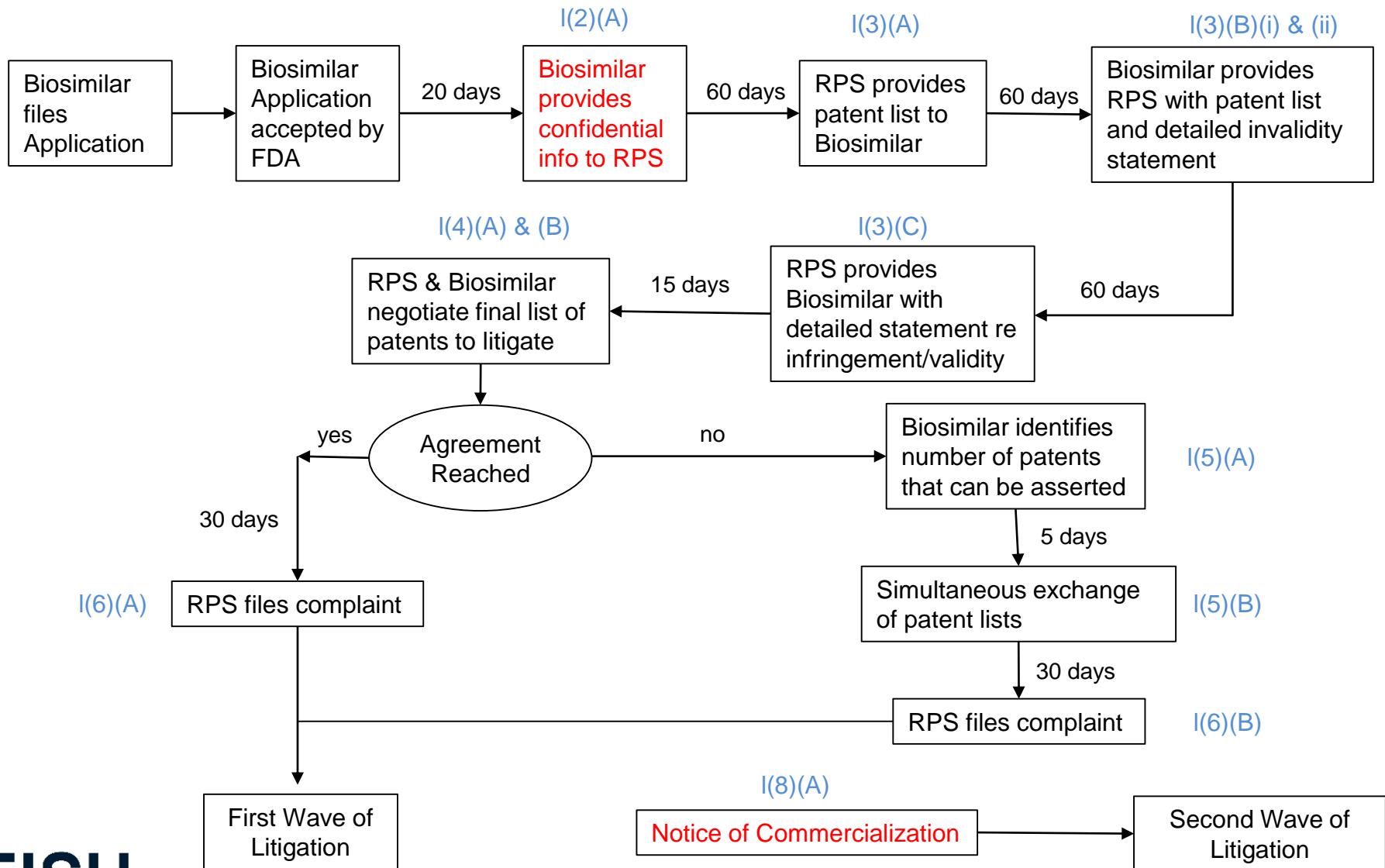


2017 BPCIA Litigation

The BPCIA Patent Dance



The BPCIA Patent Dance



Amgen v. Sandoz: SCOTUS

SCOTUS Issue #1: Enforcement of Patent Dance, § 262(l)(2)(A)

- Is the requirement that a biosimilar applicant provide aBLA and manufacturing information to the reference product sponsor enforceable by an injunction under federal law?
 - No.

SCOTUS Issue #2: Notice of Commercial Marketing, § 262(l)(8)(A)

- Must the biosimilar applicant give notice to the manufacturer after, rather than before, obtaining a license from the FDA for its biosimilar?
 - No.

Amgen v. Sandoz: SCOTUS Issue #1

42 U.S.C. §262(1)(2)(A):

Within 20 days after FDA has accepted a biosimilar application for review, the applicant “shall provide to the reference product sponsor a copy of the application . . . and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application.”

42 U.S.C. §262(1)(9)(C):

If the applicant “fails to provide the application and information required under paragraph (2)(A),” only the reference product sponsor “may bring an action . . . for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product.”

Amgen v. Sandoz: SCOTUS Issue #1

- § 262(1)(2)(A) information exchange is not enforceable by injunction under federal law.
- § 262(1)(9)(C) provides the exclusive federal remedy for an applicant's failure to turn over its BLA and manufacturing information.
- The presence of this remedy coupled with the absence of other remedies suggest Congress did not intend for other federal remedies to enforce the disclosure requirement.
- Remand to Federal Circuit to decide if an injunction is available under state law to enforce § 262(1)(2)(A).

Amgen v. Sandoz: SCOTUS Issue #2

- An applicant may provide notice of commercial marketing before obtaining a license.
 - 42 U.S.C. §262(l)(8)(A):

“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).”
 - § 262(l)(8)(A) contains a single timing requirement of 180 days before marketing.
 - “Commercial marketing” is the point in time by which the product must be licensed; product need not be licensed at the time notice is given.

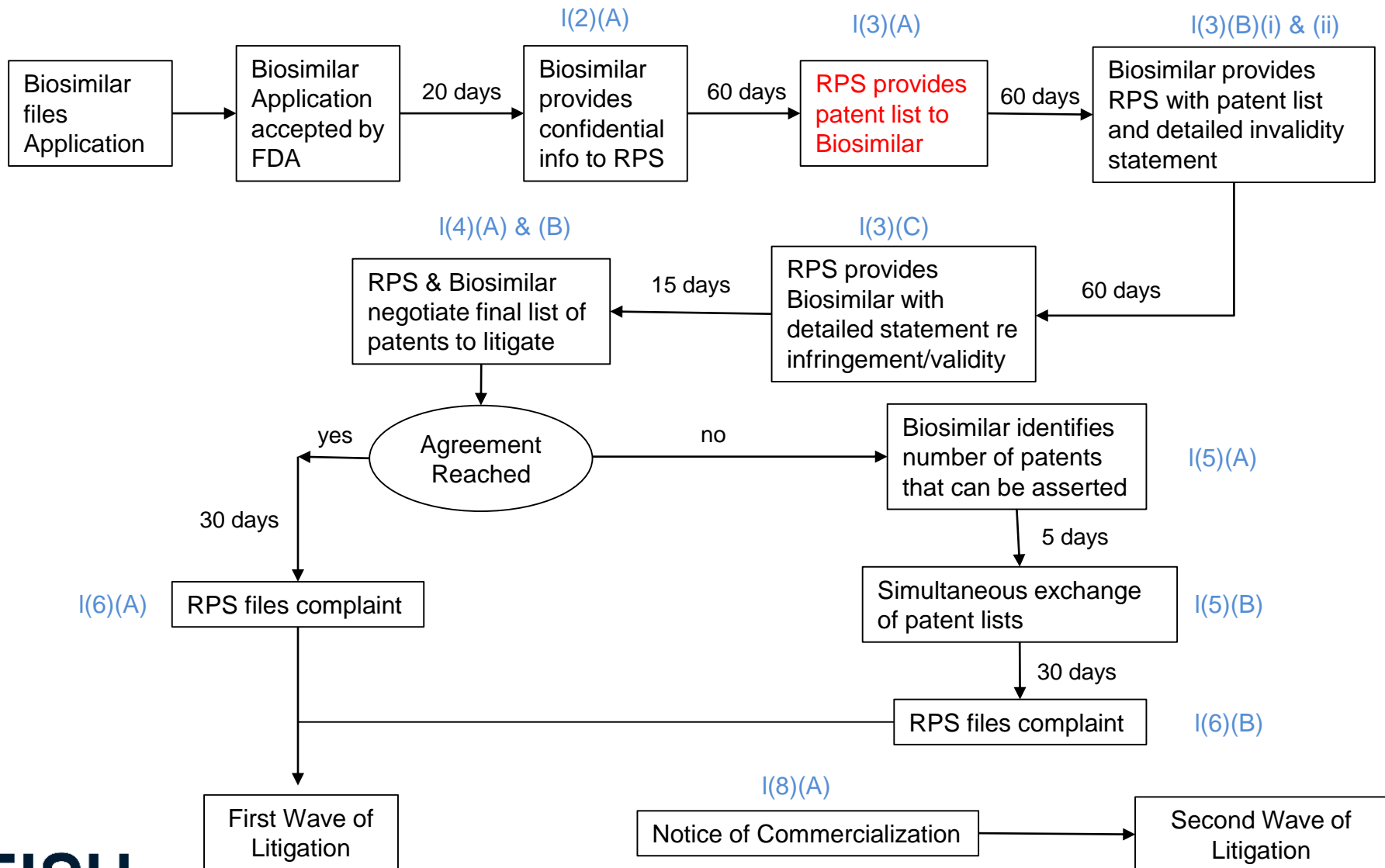
Amgen v. Sandoz: Other Takeaways

²In holding that §262(l)(9)(C) represents the exclusive remedy for an applicant's failure to provide its application and manufacturing information, we express no view on whether a district court could take into account an applicant's violation of §262(l)(2)(A) (or any other BPCIA procedural requirement) in deciding whether to grant a preliminary injunction under 35 U. S. C. §271(e)(4)(B) or §283 against marketing the biosimilar. See *Winter v. Natural Resources Defense Council, Inc.*, 555 U. S. 7, 20 (2008) (court should consider "balance of equities" in deciding whether to grant a preliminary injunction).

Amgen v. Sandoz: Update

- **June 12, 2017:** SCOTUS Opinion
- **December 14, 2017:** Federal Circuit ruled that the BPCIA preempted any state law remedies for an applicant's failure to comply with 2(A).
- **December 19, 2017:** N.D. Cal. District Court ruled on summary judgment that the accused Neupogen[®] and Neulasta[®] biosimilars did not infringe the one remaining patent-in-suit.
- **January 8, 2018:** Final judgment entered in N.D. Cal. District Court.

The BPCIA Patent Dance



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.”



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 (CAFC-16-2179).

Federal Circuit: *Amgen v. Hospira*

Federal Circuit Ruling – August 10, 2017

- Dismissed for lack of jurisdiction.
 - “Run-of-the-mill discovery dispute” that was not “effectively unreviewable.”
- No entitlement to mandamus under the All Writs Act.
 - No “clear and undisputable” right to relief.
 - Federal Rules of Civil Procedure apply in BPCIA litigation.
 - Information sought is outside the scope of discovery.
- Amgen would not have faced sanctions for mistakenly listing potentially infringed patents on its 3(A) list.
 - Analogies to *Hoffman La-Roche* in Hatch-Waxman context.

Federal Circuit: *Amgen v. Hospira*

Key Takeaways

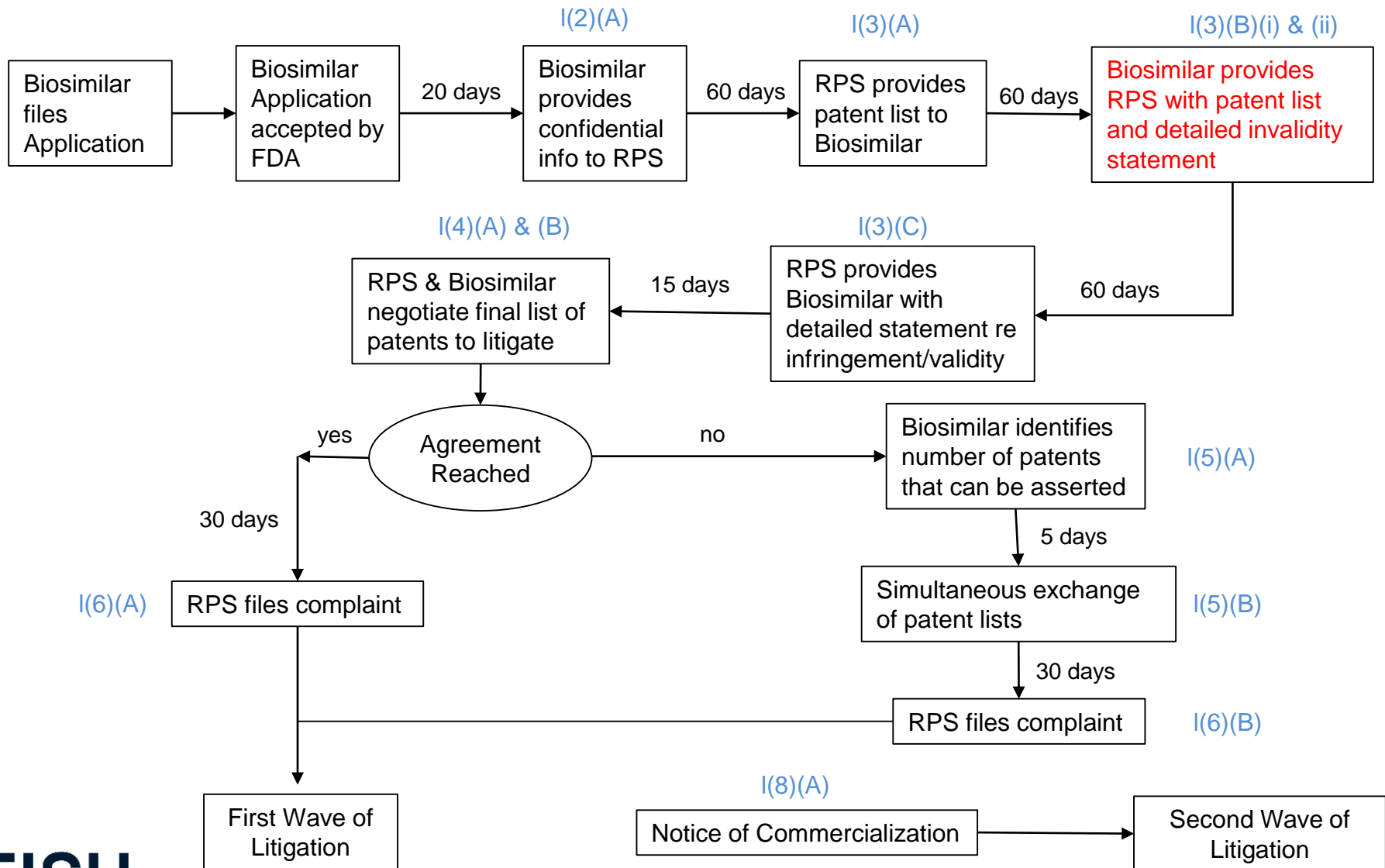
- RPS cannot sue on some patents and obtain unrelated discovery to sue on other patents.
- RPS will not face sanctions for mistakenly listing patents on a 3(A) list if biosimilar applicant refuses to produce necessary information.

Amgen v. Hospira, cont.

First BPCIA Damages Award

- On September 22, 2017, a Delaware jury awarded Amgen \$70 million for Hospira's infringement of an Amgen patent covering the manufacture of Epogen[®].
- Interesting facts:
 - Patent was expired by time of trial.
 - The biosimilar was neither FDA approved nor launched.
 - First infringement damages awarded under the BPCIA.

The BPCIA Patent Dance



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 (CAFC-17-1010):
 - Claim construction issues.
 - Whether pre-litigation representations made by the biosimilar manufacturer are binding for the infringement analysis under the BPCIA.

Federal Circuit: *Amgen v. Apotex*

Background of the Case:

- In 262(1)(3)(B) statements: Apotex said its refold mixture was 0.9-1.4 g/L of filgrastim, but claim required 2 g/L.
- Court's subsequent claim construction only required "about 1 g/L" protein.
- In rebuttal case: Apotex 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:
 - 262(1)(3)(B) statements should be given weight.
 - aBLA did not limit protein concentration to non-infringing range.
- District Court adopted Apotex's final theory in finding non-infringement.

Federal Circuit: *Amgen v. Apotex*

Federal Circuit Ruling – November 13, 2017

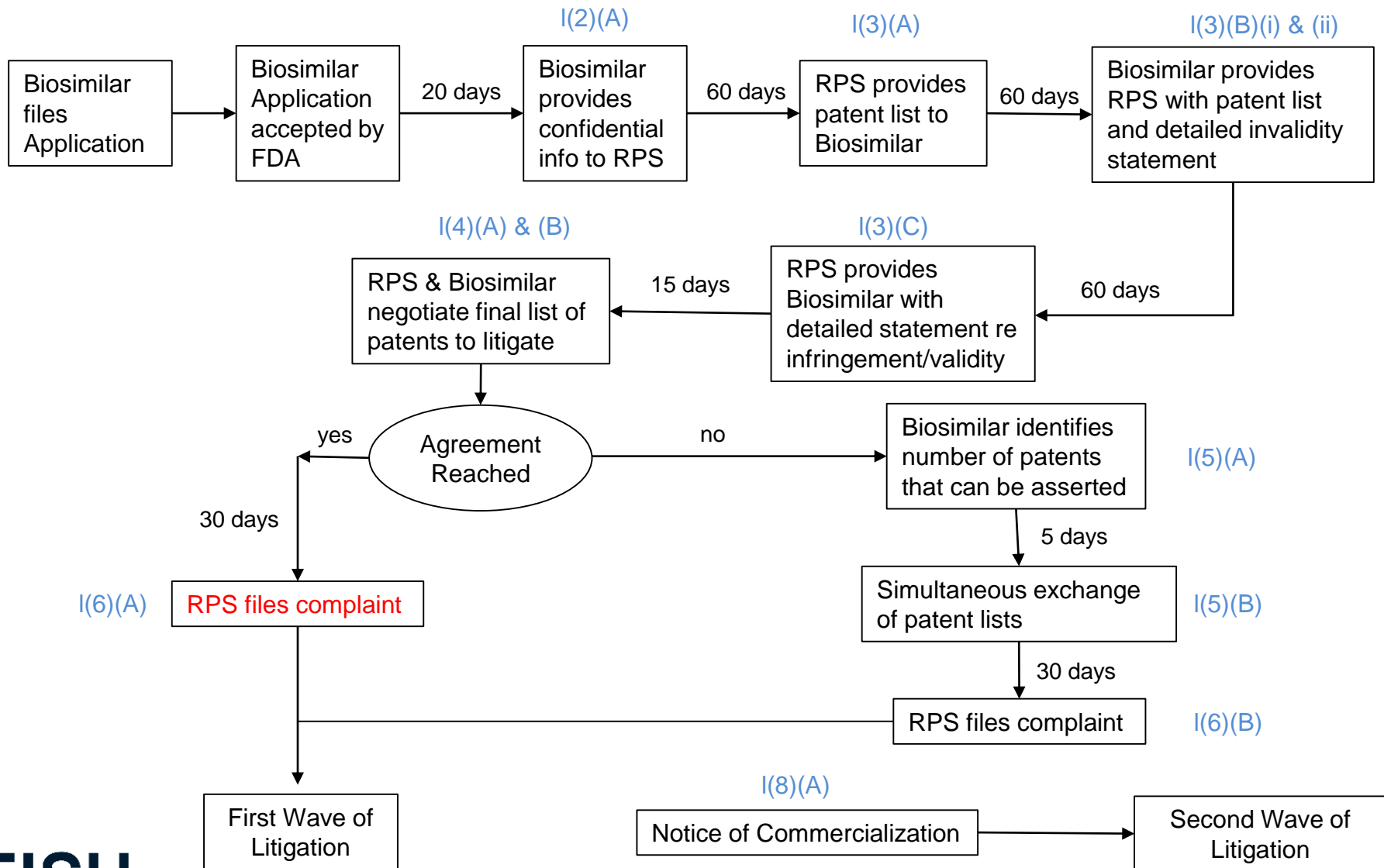
- Affirmed non-infringement.
- Held that “statements in the pre-litigation letters are party admissions and have *some* probative weight.”
 - But district court here properly considered them and found them outweighed by other evidence showing the letters were inaccurate.
- Implicitly agreed that *Sunovion/Glaxo* framework applies in BPCIA context.

Federal Circuit: *Amgen v. Apotex*

Key Takeaways

- Statements made by biosimilar applicants under 42 U.S.C. § 262(l)(3)(B) of the BPCIA have probative weight and are considered in an infringement analysis, but can be outweighed by other evidence.
- Infringement analysis in a BPCIA litigation is likely governed by the disclosures in the aBLA:
 - Per *Sunovion*: if aBLA explicitly authorizes a parameter within the scope of the claims, then that limitation is met as a matter of law.
 - Per *Glaxo*: If the aBLA is silent on a parameter, the court looks to extrinsic evidence to resolve infringement.

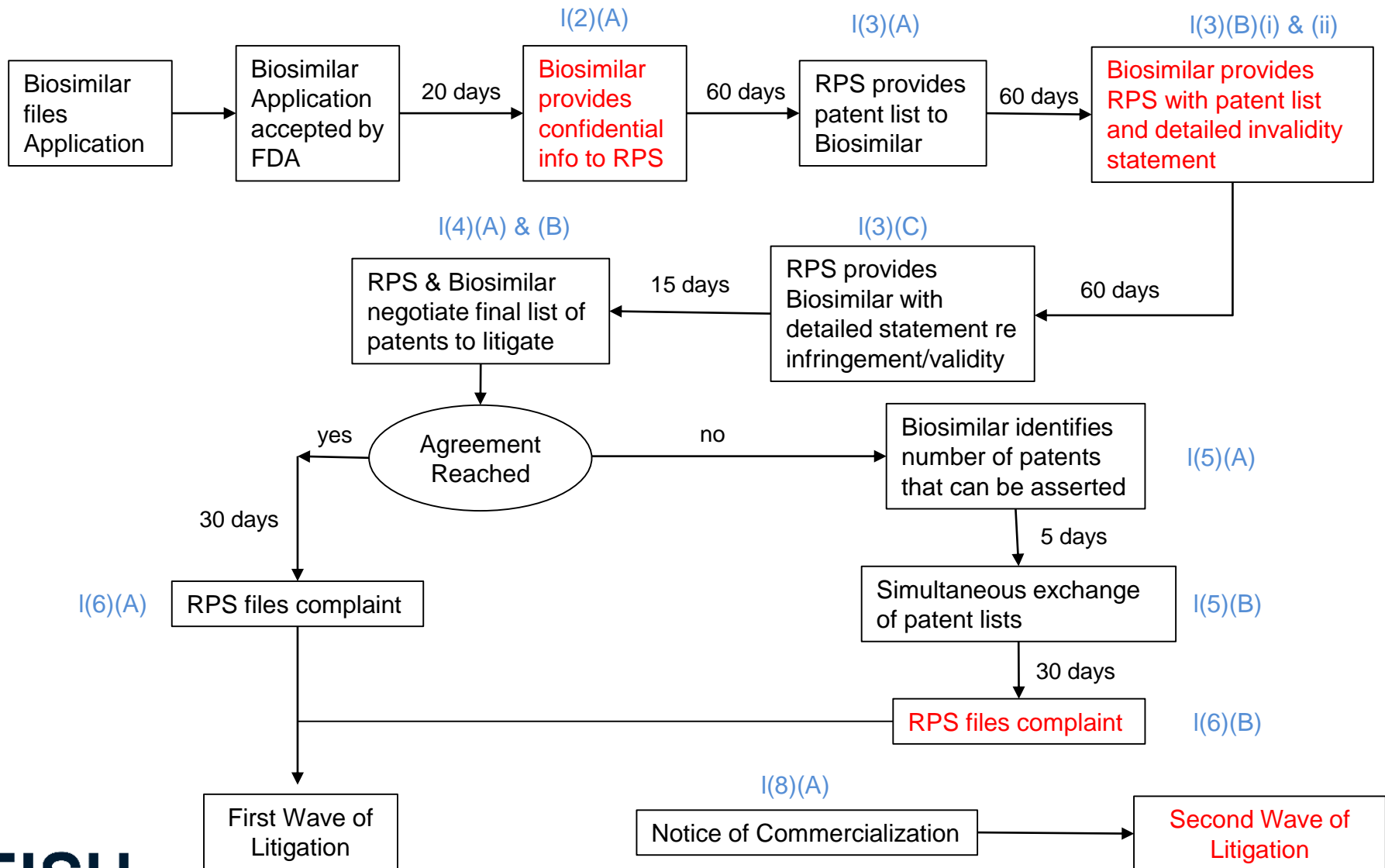
The BPCIA Patent Dance



District Court: *Janssen v. Celltrion*

- § 262(l)(6)(A): Following patent dance, 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).
 - March 2, 2017: District Court ruled that only the list of patents that emerge from the properly completed BPCIA “are potentially subject to the reasonable royalty damages limitation.”
 - The 30-day clock was never triggered.
 - Janssen could cure standing without being limited to a reasonable royalty

The BPCIA Patent Dance – Many Questions Remain



District Court: *Genentech and Amgen*

- 2017 lawsuits relating to Amgen's biosimilar of Genentech's **Avastin®**:
 - *Genentech v. Amgen* (D. Del. 1:17-cv-00165)
 - *Amgen v. Genentech* (C.D. Cal. 2:17-cv-07349)
 - *Genentech, v. Amgen* (D. Del. 1:17-cv-01407)
 - *Genentech, v. Amgen* (D. Del. 1:17-cv-01471)
- Extensive ongoing motion practice raising many issues:
 - Amgen provided only its aBLA – did it comply with 2(A)?
 - Did Amgen properly engage in the negotiation steps of the patent dance?
 - Can Amgen, as a biosimilar applicant, provide notice of commercial marketing and bring a DJ action in the middle of the patent dance?
 - Should Genentech's later filed Delaware actions be transferred to California?
 - Are biosimilar applicants bound by representations regarding commercial launch dates made during the patent dance?

District Court: *Amgen v. Coherus*

- Drug at issue: **Neulasta®** biosimilars
- BPCIA action filed May 2017 in D. Del.
- R&R dated 12/7/17 recommended granting Coherus' motion to dismiss:
 - Patent at Issue is directed to a process of purifying proteins.
 - Only infringement theory is DOE, but prosecution history estoppel bars DOE here.
 - Recommends dismissal with prejudice (no leave to amend).
- Amgen has objected to the R&R, raising BPCIA-related pleading issues:

“[B]ecause of the constraints [on using confidential information in an aBLA] placed on pleadings by the Biologics Price Competition and Innovation Act (“BPCIA”) [at § 262(l)(1)(F)], Amgen’s pleading contains as much factual support as permitted. Even if the Court finds Amgen’s pleading factually insufficient, Amgen should be permitted to file an amended complaint under seal to address any shortcomings.”



Other 2017 BPCIA Litigation

Federal Circuit: *Janssen*

- *Janssen v. Celltrion* (17-1120) and *In re Janssen* (17-1257):
 - 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.
- Briefing completed June 2017; oral arguments held October 3, 2017.

Active Pre-2017 District Court Litigations

Case	Reference Biologic	Current Status
<p><i>Janssen v. Celltrion</i></p> <p>(D.Mass. 15-cv-10698; 16-cv-11117; 17-cv-11008)</p>	<p>Remicade® (infliximab)</p>	<ul style="list-style-type: none"> • Invalidity of '471 patent on appeal • Jury trial in 2018 • Numerous motions pending, including motions to exclude expert testimony and Hospira's summary judgment motion for noninfringement
<p><i>Immunex v. Sandoz</i></p> <p>(D.N.J.16-cv-1118)</p>	<p>Enbrel® (etanercept)</p>	<ul style="list-style-type: none"> • Consent PI entered • Trial scheduled for April 17, 2018
<p><i>Janssen v. Hyclone</i></p> <p>(D.Utah 16-cv-00071)</p>	<p>Remicade® (infliximab)</p>	<ul style="list-style-type: none"> • Stayed pending completion of trial in <i>Janssen v. Celltrion</i> or other disposition at district court level

District Court Litigations Filed in 2017

Case Name	Filing Date	Drug at Issue	Number of Patents
Genentech v. Amgen (D. Del. 1:17-cv-00165)	2/15/2017	Avastin®/Mvasi® (bevacizumab)	0 (alleged violations of BPCIA)
Amgen v. Coherus (D. Del. 1:17-cv-00546)	5/10/2017	Neulasta®/CHS-1701 (pegfilgrastim)	1
Janssen v. Samsung Bioepis Co., Ltd. (D. N.J. 2:17-cv-03524)	5/17/2017	Remicade®/ Renflexis® (infliximab)	3
Janssen v. Celltrion (D. Mass. 1:17-cv-11008)	5/31/2017	Remicade®/Inflectra® (infliximab)	1
AbbVie al v. Boehringer Ingelheim (D. Del. 1:17-cv-01065)	8/2/2017	Humira®/Cyltezo® (adalimumab)	8
Amgen al v. Mylan (W.D. Pa. 2:17-cv-01235)	9/22/2017	Neulasta®/MYL-140H (pegfilgrastim)	2

District Court Litigations Filed in 2017, cont.

Case Name	Filing Date	Drug at Issue	Number of Patents
Amgen v. Genentech, (C.D. Cal. 2:17-cv-07349)	10/6/2017	Avastin®/Mvasi® (bevacizumab)	27 (declaratory judgment)
Genentech, v. Amgen (D. Del. 1:17-cv-01407)	10/6/2017	Avastin®/Mvasi® (bevacizumab)	25
Genentech, v. Amgen, (D. Del. 1:17-cv-01471)	10/18/2017	Avastin®/Mvasi® (bevacizumab)	25
Genentech, v. Pfizer, Inc. (D. Del. 1:17-cv-01672)	11/17/2017	Herceptin®/PF-05280014 (trastuzumab)	40
Genentech v. Sandoz (D. N.J. 2:17-cv-13507)	12/21/2017	Rituxan®/Rixathon® (rituximab)	24

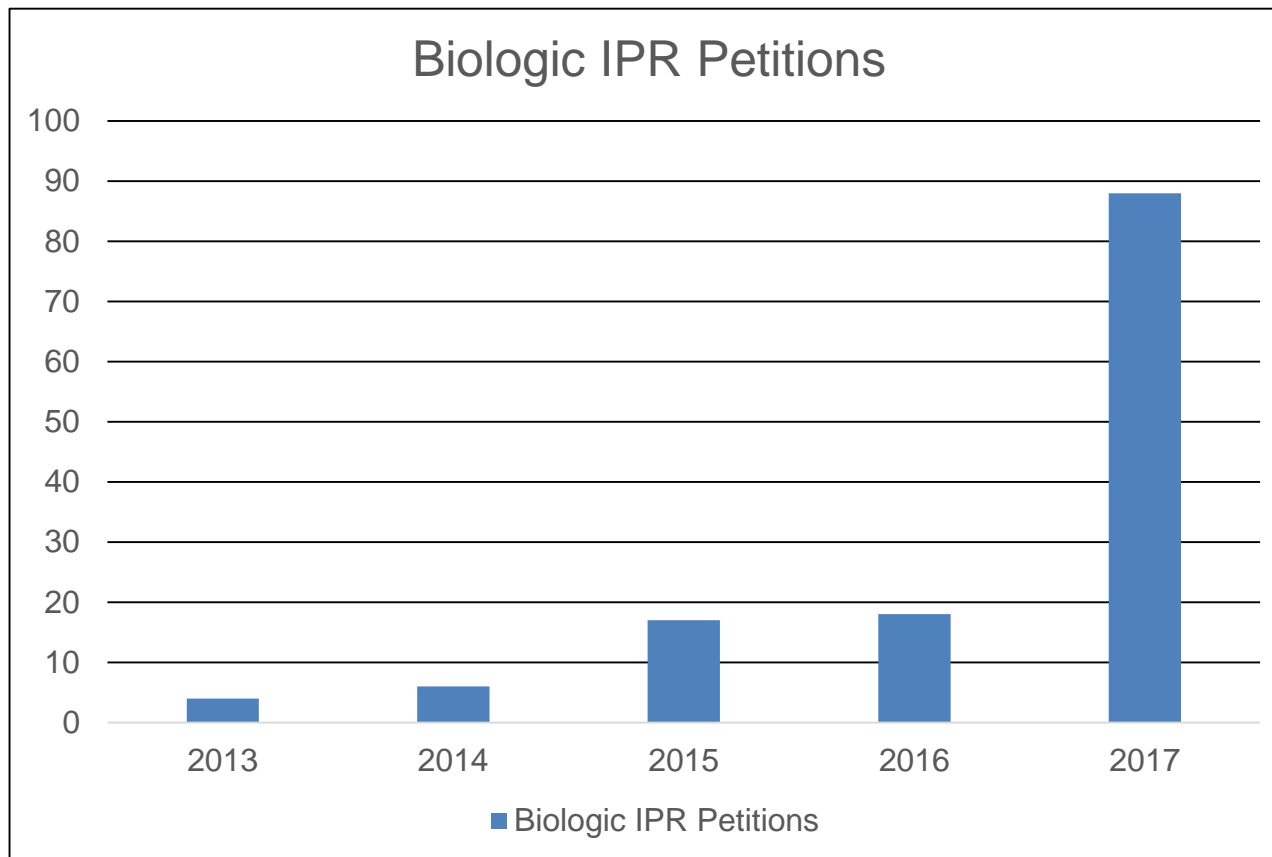
District Court Litigations to Date in 2018

Case Name	Filing Date	Drug at Issue	Number of Patents
Celltrion, Inc. et al v. Genentech, Inc. et al, (N.D.Cal. 3-18-cv-00274)	1/11/2018	Herceptin®/Herzuma® (CT-P6) (trastuzumab)	38
Celltrion, Inc. et al v. Genentech, Inc. et al, (N.D.Cal. 3-18-cv-00276)	1/11/2018	CT-P10/ Rituxan® (rituximab)	37
Genentech v. Celltrion (D. Del. 1-18-cv-00095)	1/12/2018	Herceptin®/Herzuma® (CT-P6) (trastuzumab)	40
Genentech v. Celltrion (D.N.J. 1-18-cv-00574)	1/12/2018	CT-P10/ Rituxan® (rituximab)	40



2017 Biologic IPR Petitions

Biologic IPR Petitions



IPR Petitions Filed

<i>Drug</i>	<u>IPR PETITIONS FILED</u>					<u>Total by Drug</u>
	<i>2013</i>	<i>2014</i>	<i>2015</i>	<i>2016</i>	<i>2017</i>	
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	3	3
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	17	19
Humira (adalimumab)	0	0	7	1	8	16
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	10	17
Tysabri (natalizumab)	0	0	0	3	0	3
Cabilly Patent	0	0	2	4	0	6
CSL830	0	0	0	0	1	1
Lantus (insulin glargine)	0	0	0	0	2	2
Unknown product	0	0	0	1	5	6
<u>Total by Year</u>	4	6	17	15	46	88

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.



Predictions for 2018

FISH.

What to Watch for in 2018

- FDA:
 - Approval decisions on 17+ pending aBLA applications.
 - Approval of the first interchangeable?
 - Revised draft guidance applicable to biosimilars and interchangeables on “Good Review Management Principles and Practices for PDUFA Products.”
- Pricing
 - Approval of more biosimilars and judicial scrutiny may lead to lower prices.
- Many active district court litigations.

What to Watch for in 2018

- Unclear if number of biologic IPRs will continue to grow as rapidly.
- Factors affecting IPR filings:
 - Supreme Court's ruling in *Oil States*
 - Court is analyzing whether post-grant patent practice, including IPRs, is unconstitutional.
 - Argument held in November 2017; decision expected by spring.
 - Increased IPR fees
 - The petitioning fee for challenging up to 20 claims will increase by \$6,500.
 - IPR post-institution fees will also increase, but only by \$1,000.

Thank you!



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