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Training Academy Session # 26

What You Need to Know About the Biologics Price Competition and Innovation Act (BPCIA)

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Session Overview

- Background
- Abbreviated Pathway
- Patent Dance Litigation
- Recent Case Law

Background Information

The **Biologics Price Competition and Innovation Act (BPCIA)** was signed into law by President Obama on March 23, 2010, as part of the Patient Protection and Affordable Care Act (commonly known as Obamacare).

The BPCIA aims to **increase competition** in the biologics market, potentially leading to **lower prices** for these costly drugs.

It established an expedited approval process for biosimilars—products akin to generic drugs for biologics—and introduced a framework to resolve patent disputes between biosimilar manufacturers and original product sponsors (RPSs).

Source: www.fda.gov/drugs/biosimilars/biosimilar-product-information

Background Information

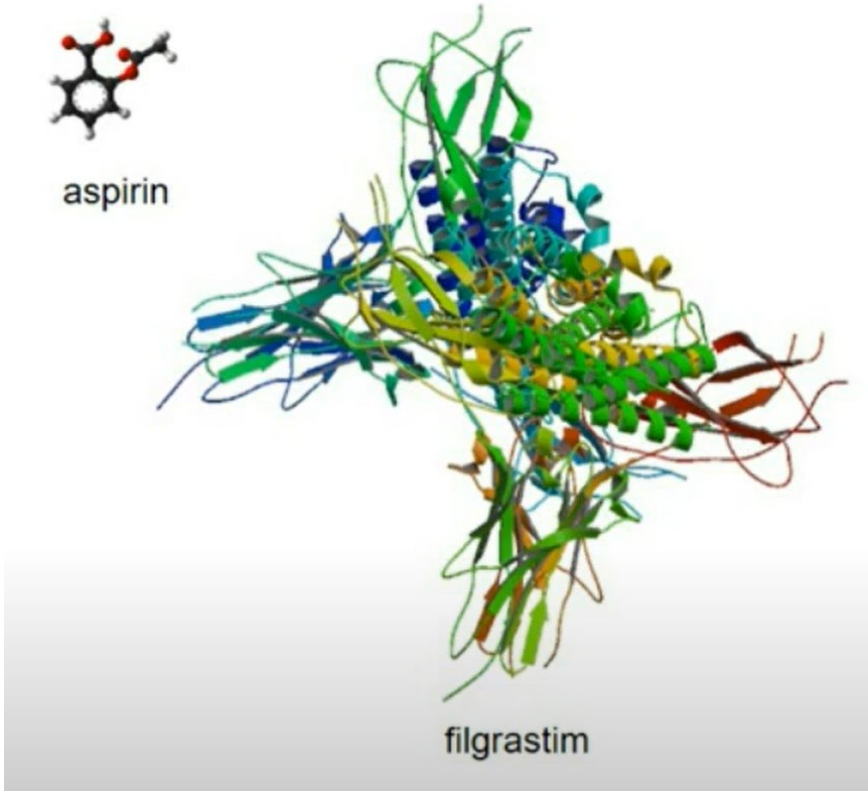
A **biosimilar** is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product in safety, purity, and potency. *See 42 U.S.C. §§ 262(a)(2)(C)(i)(l), 262(k)(2)(A)(iii), 262(l).*

A **biological product** means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine … applicable to the prevention, treatment, or cure of a disease or condition of human beings. *See 42 U.S.C. § 262(i)(1).*

Source: FDA website

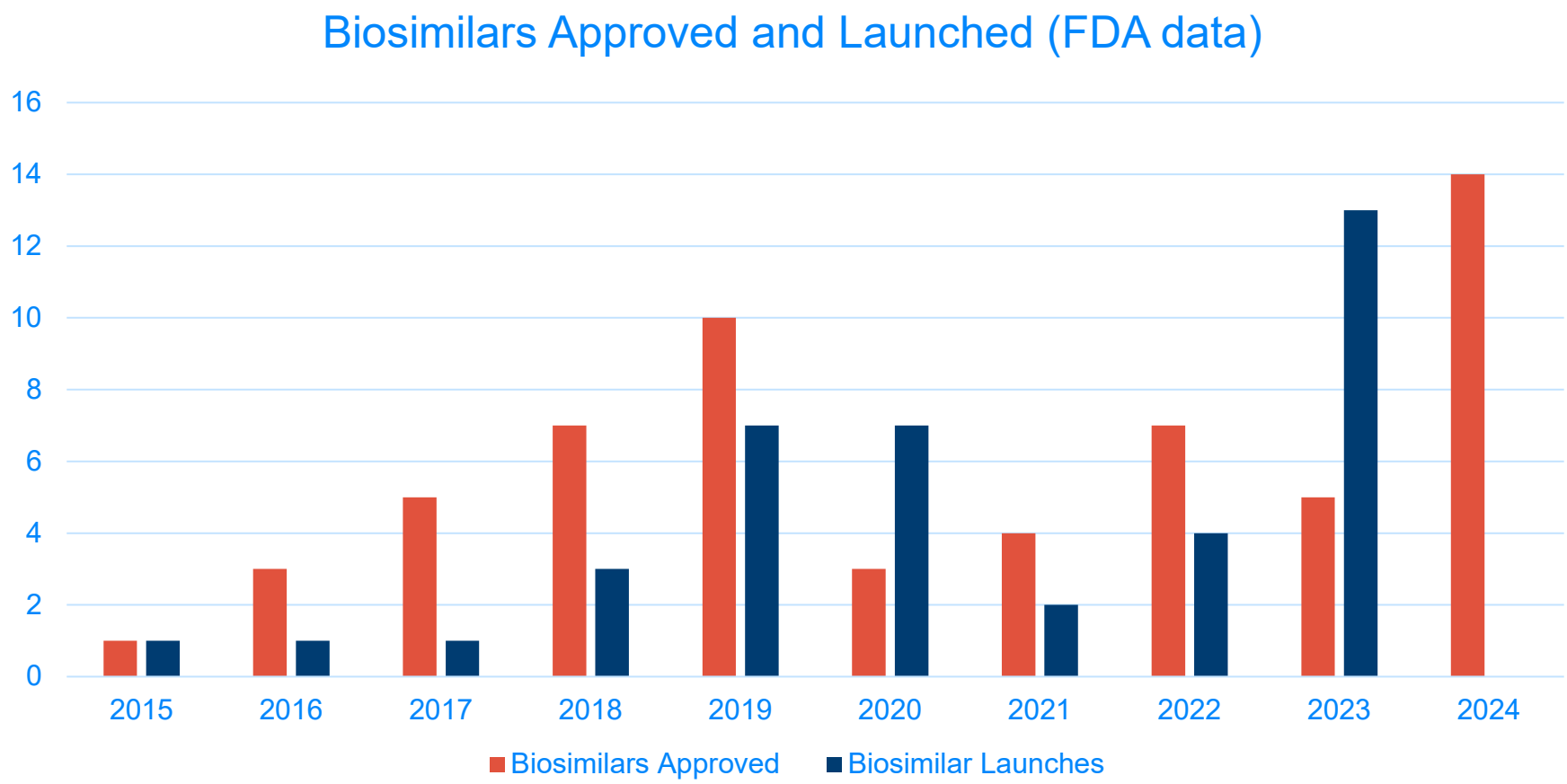
Background Information

In contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material – human, animal, or microorganism – are complex in structure, and thus are usually not fully characterized. Biological products are typically large, complex molecules (*e.g.*, antibodies and proteins, such as insulin and filgrastim) and not small chemical molecules (*e.g.*, aspirin).



Source: FDA website

Biosimilar Approvals/Launches



Source: www.fda.gov/drugs/biosimilars/biosimilar-product-information

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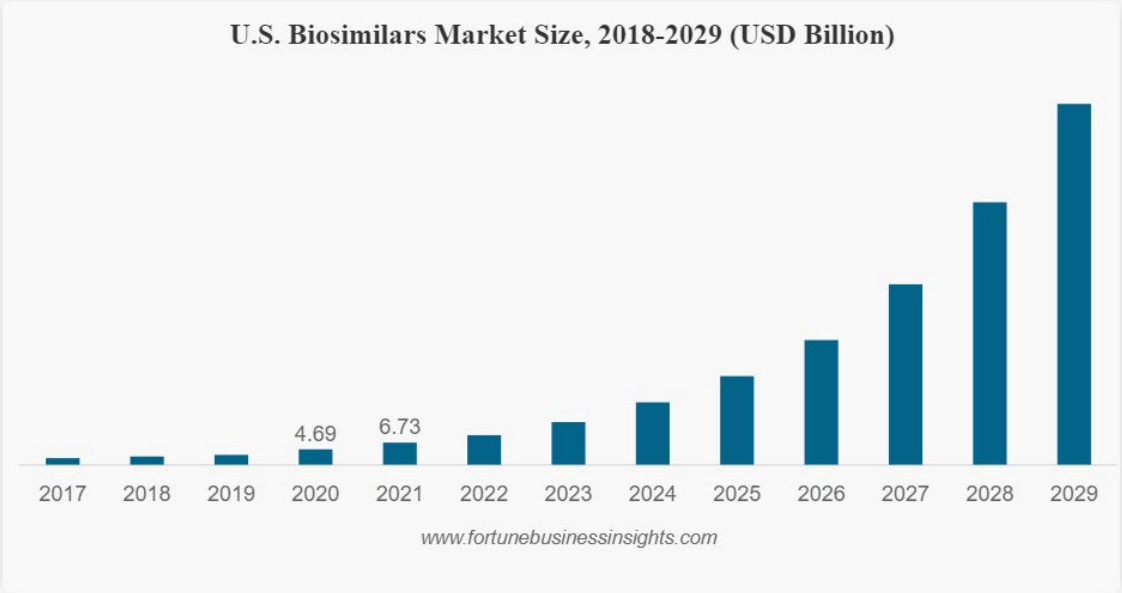
Projected Market Size of Biosimilar Industry

Since its enactment, the BPCIA has significantly contributed to the rapid growth of the U.S. biosimilar industry. In 2021, the U.S. biosimilar market was valued at approximately $6.73 billion, and it is **projected to reach nearly $100.75 billion by 2029**, reflecting increased adoption and acceptance of biosimilar therapies across various healthcare settings.



Source: https://www.fortunebusinessinsights.com/industry-reports/u-s-biosimilars-market-100990

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Example: Humira and the Biosimilar Amjevita

The year 2023 marked a significant milestone with a record of 13 biosimilar launches, including nine highly anticipated Humira® (adalimumab) biosimilars. AbbVie's Humira® first hit the market in 2003 and has since generated an astounding $200 billion in revenue, making it the world's top-selling drug between 2012 and 2020. Despite the FDA approving the first Humira® biosimilar (Amgen's Amjevita™) in 2016, biosimilars could only enter the U.S. market in 2023 due to settlement agreements between biosimilar manufacturers and AbbVie.

Source: Amgen website

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Abbreviated Pathway for Biosimilars

Default pathway for approval is by showing the new biologic is, among other things, "safe, pure, and potent." *See 42 U.S.C. § 262(a)(2)(C)(i)(I).*

BPCIA established an alternative, abbreviated pathway for biosimilar sponsors to obtain FDA approval for their products. This streamlined process allows manufacturers to reference existing clinical trial data from the approved reference product (RP), reducing the amount of additional information and studies required compared to traditional biologic applications. However, biosimilar applicants must ensure that their products share the same route of administration, dosage form, strength, and indications as the RP to qualify under this pathway.

- **Under the abbreviated pathway, the applicant must show that its product is "highly similar" to the reference product and that there are no "clinically meaningful differences" between the two in terms of "safety, purity, and potency."** *See 42 U.S.C. §§ 262(i)(2)(A), 262(i)(A)(B), 262(k)(2)(A)(i)(I).*

Source: www.fda.gov/drugs/biosimilars/biosimilar-product-information

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Hatch-Waxman Versus BPCIA Litigation

	Hatch-Waxman Litigation (small molecules)	BPCIA Litigation (biologics)
How does applicant provide notice of its application?	Paragraph IV notice with Offer of Confidential Access	Patent dance – provides confidential information
When does applicant provide position?	Paragraph IV notice	Patent dance – statement
Which patents are litigated?	Orange Book	Patent dance – patent lists
Does suit automatically stay approval	30-Month stay	RPS may seek preliminary injunction

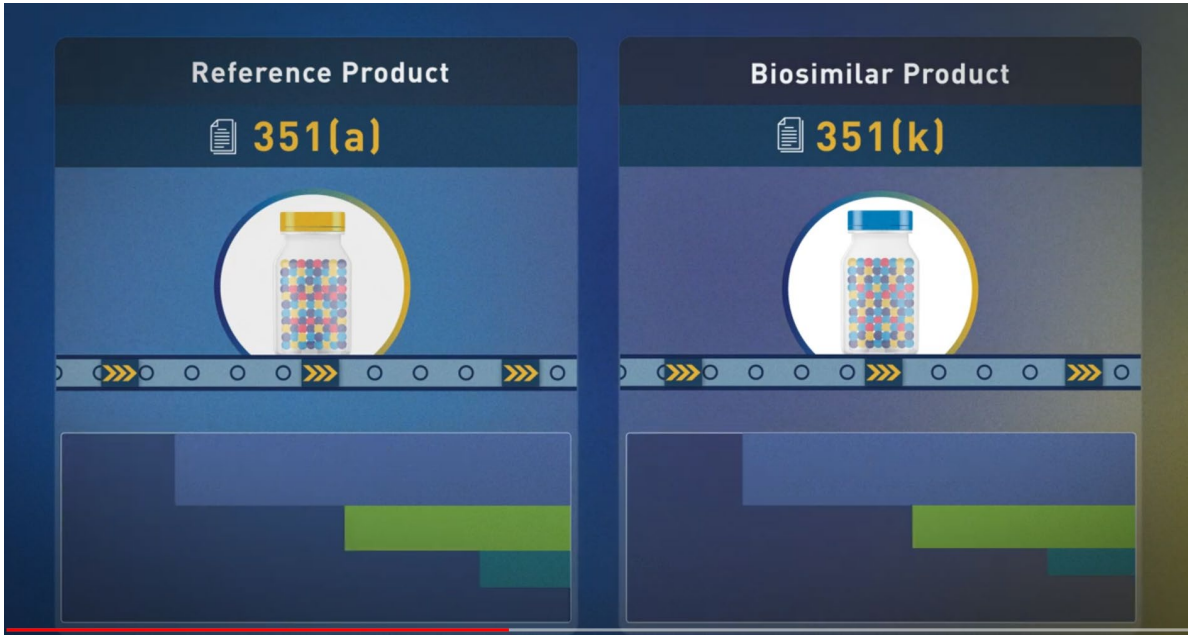
*FDA website

351(k) Application

- A biosimilar product is approved in a **351(k) application** (42 U.S.C. § 262(k)) under an abbreviated approval pathway
- Biosimilar may rely in part on FDA's determination of safety and effectiveness for the reference product, which greatly reduces clinical trial burden
- Biosimilar applicant must provide data that
  - establishes that the proposed biosimilar product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components"
  - provides an assessment of toxicity
  - includes a clinical study that
    - assesses immunogenicity and pharmacokinetics
    - Demonstrates safety, purity, and potency in at least one condition for which the reference product is used

351(k) Application

Biosimilars must be shown to be (a) highly similar to and have (b) no clinically meaningful differences from the reference product in terms of safety and effectiveness.



Source: www.fda.gov/biosimilars

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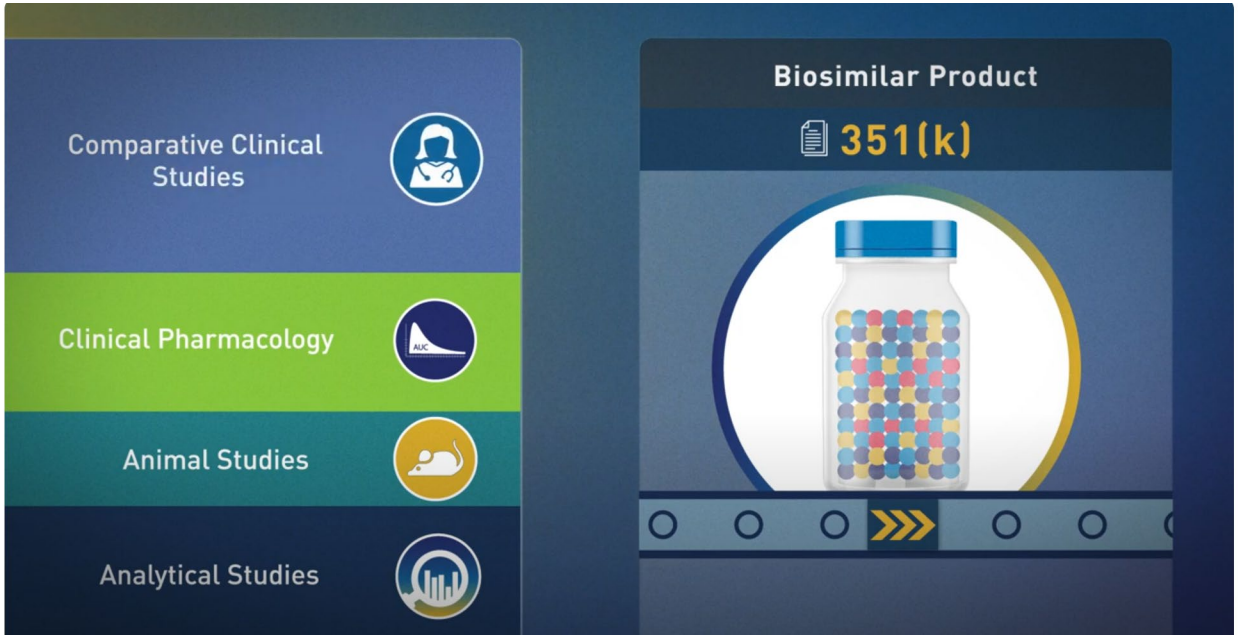
351(k) Application

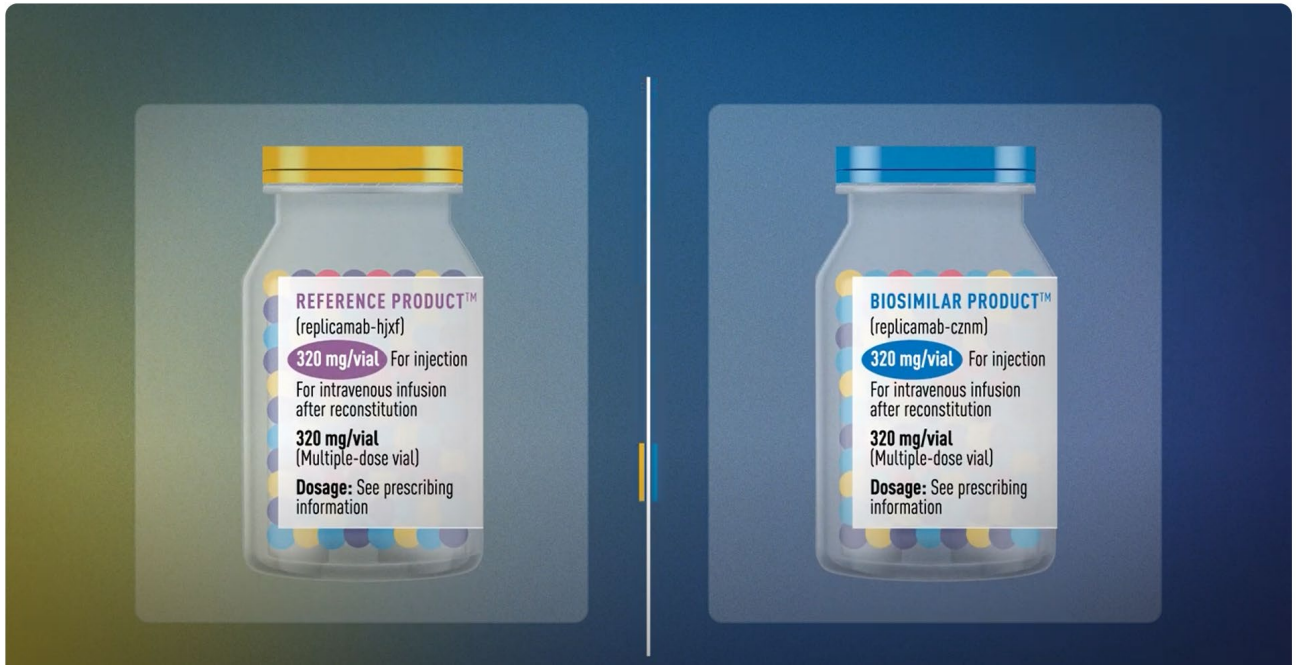
Manufacturers rely on (a) analytical studies, (b) animal studies, (c) clinical pharmacology, and (d) comparative clinical studies.



Source: www.fda.gov/biosimilars

351(k) Application

Biosimilars must have the same mechanism of action, route of administration, dosage form, and strength as the reference product.



Source: www.fda.gov/biosimilars

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FDA Review & Approval

- **If a proposed biosimilar product is highly similar** to the reference product and the totality of evidence supports its biosimilarity, it is possible for the biosimilar manufacturer to **seek approval for some or all indications for which the reference product is licensed, without directly studying those indications**.
- Timing issues and exclusivity period:
  - Biosimilar applicant may not submit a 351(k) application until 4 years after the reference product is first licensed
  - FDA may not license a biosimilar until 12 years after the reference product is first licensed.
    - *See 42 U.S.C. §§ 262(k)(7)(A), 262(k)(7)(B), Sandoz Inc. v. Amgen Inc.,* 582 U.S. 1, 10-11 (2017).
- This procedure provides innovators with **12 years of market exclusivity from the date of RP approval**, during which time the FDA cannot approve a biosimilar referencing that product.

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Step-by-Step Process of the BPCIA Approval:

1. **Development & Preclinical Testing**: Biosimilar developers conduct research and preclinical testing to generate data supporting similarity to the reference product.

2. **Investigational New Drug Application (IND)**: The developer submits an IND to the FDA, allowing human clinical trials to begin.

3. **Clinical Trials**: The developer conducts clinical trials to demonstrate biosimilarity to the reference product.

4. **351(k) Biologics License Application (BLA)**: The developer submits a 351(k) BLA to the FDA, which includes data on safety, purity, and potency, comparing the biosimilar to the reference product.

Source: https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

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Step-by-Step Process of the BPCIA Approval:

5. **FDA Review & Approval**: The FDA reviews the 351(k) application, focusing on biosimilarity, and may request additional data or clarification.

6. **Patent Dance**: The biosimilar applicant and the reference product sponsor (**RPS**) exchange patent information to identify potential patent disputes.

7. **Patent Litigation**: If necessary, litigation may occur to resolve patent disputes before market entry.

8. **Final Approval & Market Entry**: Once all requirements are met, the FDA grants final approval, allowing the biosimilar to enter the market. However, note that the BPCIA provides a 12-year exclusivity period for the reference biologic. If a biosimilar is approved while patent litigation is still ongoing, the biosimilar manufacturer may choose to launch "at risk," meaning they could face significant damages if the court later finds that they infringe a valid patent.

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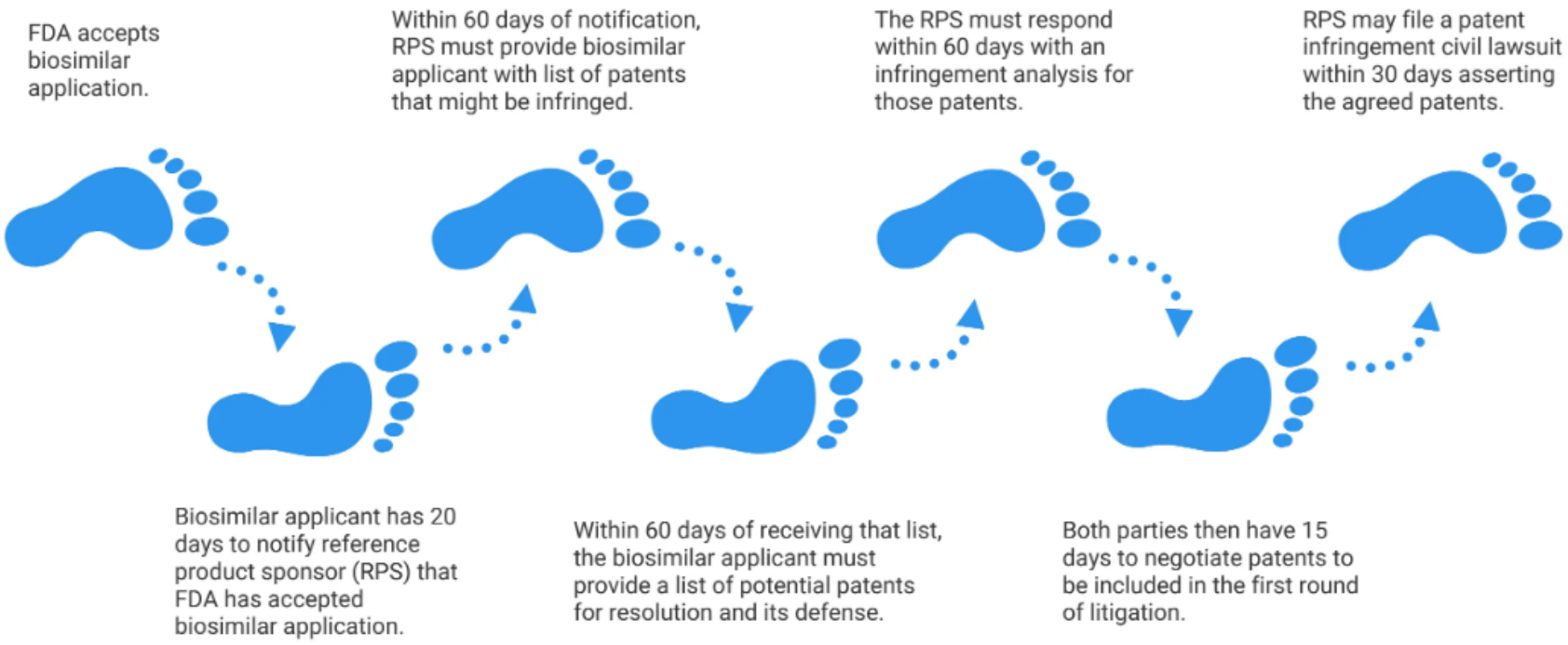
BPCIA Patent Disputes

- **Patent Dance**: The **BPCIA outlines a structured mechanism for resolving patent disputes** between biosimilar manufacturers and reference product sponsors

- The patent resolution framework may end in one or more litigations or alternative proceedings such as inter partes review (IPR) before the U.S. Patent and Trademark Office

The patent dance provides biosimilar applicants with some degree of control over the timing of litigation filings. The entire process typically take approximately 245 days, excluding any time required for litigation.



Source: https://www.centerforbiosimilars.com/view/the-inner-workings-of-the-bpcia-patent-dance

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Patent Dance – Step-by-Step Overview

1. **Biosimilar Application Submission**: The biosimilar applicant submits an application to the FDA, notifying the RPS within 20 days. A copy of the 351(k) application and "such other information that describes the process or processes used to manufacture the biological product that is the subject of such application" should be provided to the RPS. However, this requirement could come into conflict with applicant's right in trade secret and proprietary information.

2. **RPS Patent List (42 U.S.C. § 262(l)(3)(A))**: Within 60 days, the RPS provides the biosimilar applicant with a list of patents believed to be infringed. The RPS must also identify which of the patents if any that the RPS is willing to license to the applicant.

Source: https://www.centerforbiosimilars.com/view/the-inner-workings-of-the-bpcia-patent-dance

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Patent Dance – Step-by-Step Overview

3. **Biosimilar Response (42 U.S.C. § 262(l)(3)(B))**: The applicant has 60 days to respond, listing patents that they will not challenge and those they believe are invalid, unenforceable, or not infringed.

4. **RPS Reply (42 U.S.C. § 262(l)(3)(C))**: The RPS has 60 days to respond to the biosimilar applicant's assertions with respect to its infringement and validity position.

5. **Patent List Negotiation (42 U.S.C. § 262(l)(4))**: Both parties have 15 days to negotiate which patents will be litigated.

Source: https://www.centerforbiosimilars.com/view/the-inner-workings-of-the-bpcia-patent-dance

Patent Dance – Step-by-Step Overview

6. **Litigation Phase (42 U.S.C. § 262(l)(6))**: The RPS files an infringement suit on the agreed patents within 30 days of negotiation.

7. **If the parties cannot agree** on a list of patents within 15 days after exchanging their lists, each party then has 5 days to unilaterally list the patents that they believe should be subject to immediate litigation. The RPS can immediately bring a patent infringement lawsuit against the biosimilar applicant for any of the patents on the final, unresolved lists.

8. **Litigation Outcome**: Although the FDA can approve a biosimilar before all patent disputes are resolved, the final decision on whether a biosimilar can be marketed before all litigation is concluded can depend on factors such as issuance of preliminary injunctions and settlement discussions.

Source: https://www.centerforbiosimilars.com/view/the-inner-workings-of-the-bpcia-patent-dance

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Patent Dance – Step-by-Step Overview

9. **Second Litigation (42 U.S.C. § 262(l)(8))**: RPS may file a second litigation following notice of commercial marketing not later than 180 days before marketing (42 U.S.C. § 262(I)(8)(A)) vis-à-vis any patent on the patent list that was not litigated in the first litigation.

- **What happens if the biosimilar applicant does not participate?**
  - If biosimilar applicant never sends the application information at Step 1:
    - RPS can bring a declaratory judgment action for infringement on any patent, and biosimilar applicant cannot bring any declaratory judgment action (42 U.S.C. § 262(l)(9)(C))
  - If biosimilar applicant sends the initial info then stops participating:
    - RPS can bring a declaratory judgment action for infringement on any patent that RPS identified in its list, and biosimilar applicant cannot bring any declaratory judgment action (42 U.S.C. § 262(l)(9)(B))

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Advantages of Engaging in the Patent Dance

1. **Early Resolution of Patent Disputes**: Patent dance provides a structured way for biosimilar applicant and RPS to identify and resolve patent issues before the biosimilar product is marketed.

2. **Controlled Litigation**: The parties can agree on which patents to litigate, potentially narrowing the scope of litigation and reducing costs.

3. **Market Certainty**: Both parties gain clarity on the patent landscape, which can lead to more predictable timelines for biosimilar market entry.

Compliance with the Patent Dance

1. **Not Mandatory**: The biosimilar applicant can choose not to engage in the patent dance. However, opting out may have consequences, such as the RPS being able to immediately sue for patent infringement on any patent that could have been part of the dance.
   - An applicant must give notice at least 180 days before the first commercial marketing, which may be either before or after receiving FDA approval. *Sandoz Inc. v. Amgen Inc.,* 582 U.S. 1, 29-30 (2017).

2. **Strategic Choice**: Engaging in the patent dance can delay litigation, provide negotiation opportunities, and possibly lead to settlement before expensive litigation begins.

3. **The decision to engage** in the patent dance depends on the strategic goals of the biosimilar applicant and the RPS.

Disadvantages in the Patent Dance

1. **Disclosure of Information**: The biosimilar applicant must disclose detailed information about their product and manufacturing process to the RPS, which could potentially expose sensitive information.

2. **Potential for Increased Litigation**: Engaging in the patent dance can result in a larger number of patents being litigated, as the RPS may identify and assert multiple patents.

3. **Time-Consuming**: The process involves multiple rounds of exchange and negotiation, which can delay the resolution of patent disputes and the biosimilar's market entry.

Benefits of Opting Out of the Patent Dance

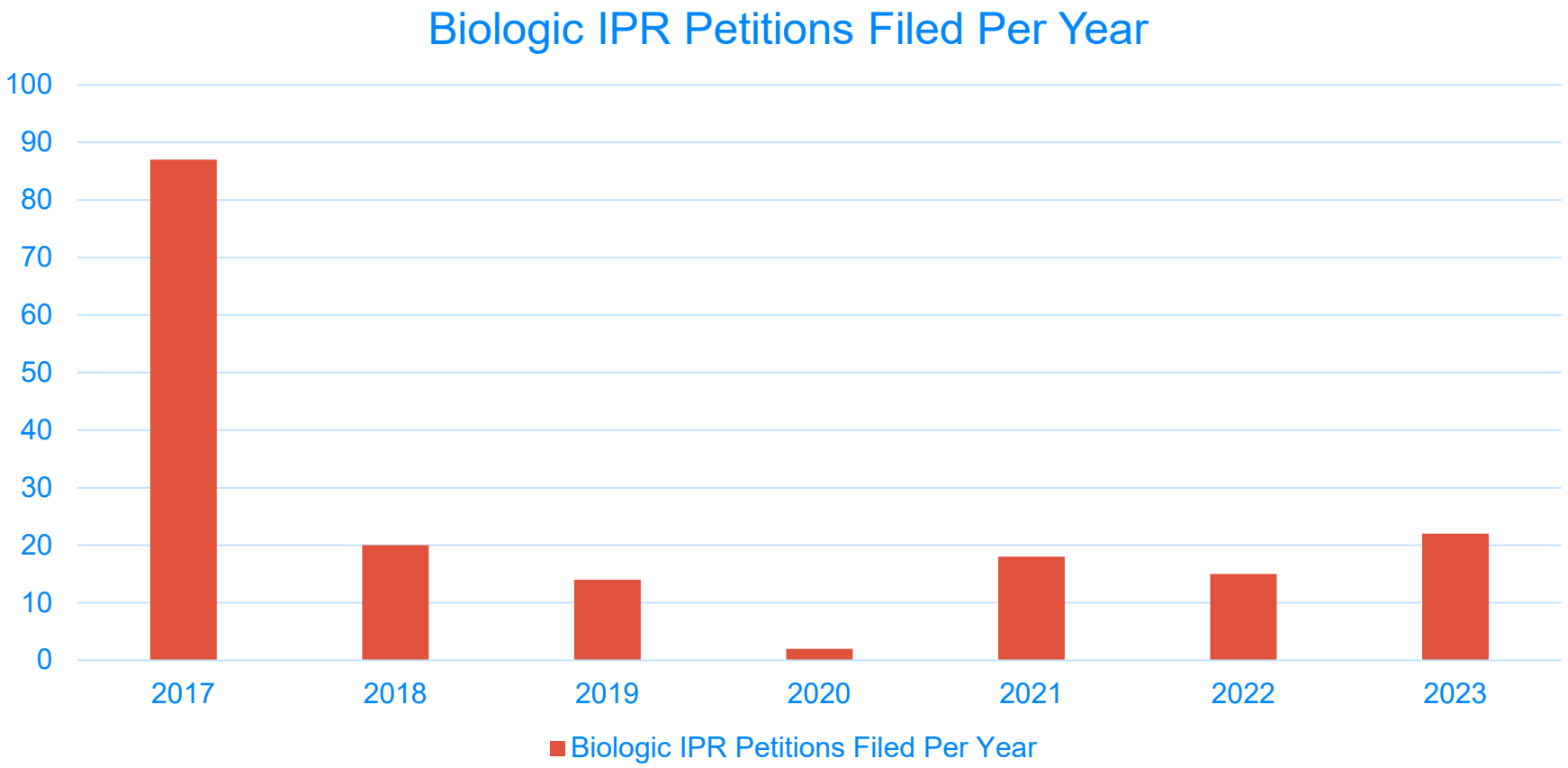
1. **Faster Market Entry**: Without engaging in the patent dance, the biosimilar applicant might avoid delays associated with prolonged negotiations and exchanges.

2. **Reduced Disclosure**: The applicant does not have to disclose detailed information about their product to the RPS, maintaining more confidentiality.

3. **Strategic Litigation**: The RPS may be limited in the number of patents they can assert initially, potentially reducing the complexity and cost of litigation.

- Opting out of the patent dance can be a strategic choice for biosimilar applicants who prefer to avoid early disclosure and are prepared for the possibility of immediate litigation.

Biosimilar Post-Grant Challenges at the PTAB



Source: https://www.uspto.gov/patents/ptab/statistics

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Inter Partes Review (IPR) action at PTAB

Strategic Considerations:

- A biosimilar applicant can initiate an IPR at the PTAB to challenge the validity of patents that the reference product sponsor (RPS) asserts during the patent dance under the BPCIA.

- Biologic and biosimilar activity at the PTAB increased in 2023 compared to 2022, with 22 IPR petitions and two PGR petitions filed, up from 15 IPR petitions and two PGR petitions in the previous year. Notably, 2023 saw the highest number of filings in this area since the record-setting 87 IPR petitions filed in 2017.

- The decision to initiate an IPR as part of the patent dance strategy depends on various factors, including the strength of the patents in question, the cost-benefit analysis of litigation versus IPR, and the timing of the biosimilar's anticipated approval and market launch. Companies often weigh these considerations in conjunction with their overall strategy for challenging the reference product's patent portfolio.

Biologics Price Competition and Innovation Act (BPCIA)

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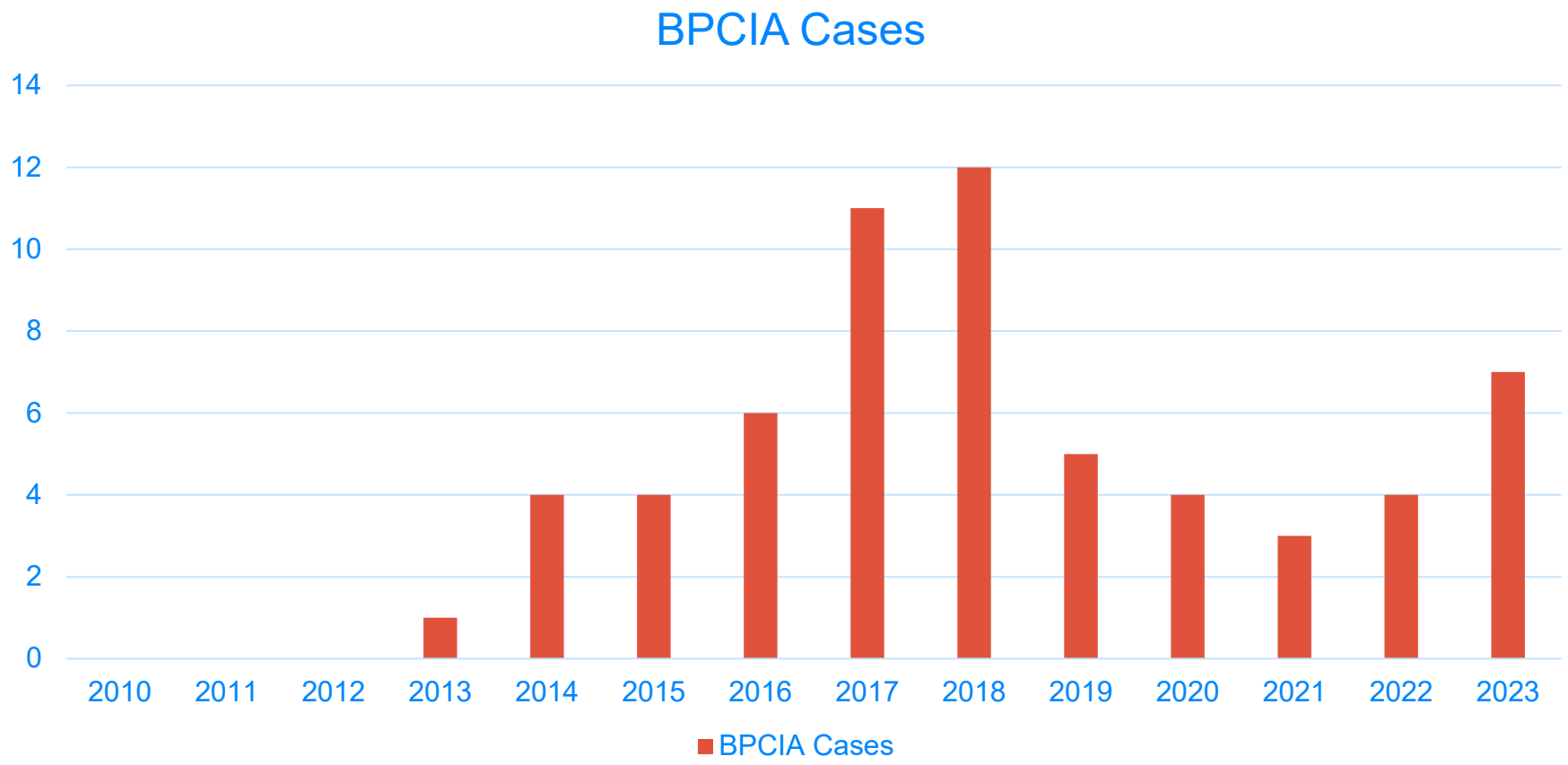
BPCIA Cases Filed Since BPCIA Enactment



Source: https://www.bigmoleculewatch.com/bpcia-patent-litigations/

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BPCIA – District Court Litigation

- Since the enactment of the BPCIA in 2010, District Courts have presided over more than 60 cases under its framework.
- Many cases involve repeated litigation between the same parties over the same biosimilar products.
- Common for RPS to initiate an infringement lawsuit, while the biosimilar developer simultaneously files a separate declaratory judgment action, leading to parallel legal battles, highlighting the complexity and strategic litigation approaches seen in BPCIA cases

Key Case Law:
Sandoz Inc. v. Amgen Inc., 582 U.S. 1 (2017)

- The Supreme Court affirmed the Federal Circuit's holding that the "patent dance" is optional but reversed the Federal Circuit's ruling regarding the 180-day notice.

- Court held that biosimilar applicants may give notice of commercial marketing either *before* or *after* receiving FDA approval. *Sandoz Inc. v. Amgen Inc.*, 582 U.S. at 29-30.

Sandoz Inc. v. Amgen Inc., 582 U.S. 1 (2017)

Litigation History

- **District Court**:
  - Amgen sued Sandoz in the NDCAL for failing to comply with the Biologics Price Competition and Innovation Act (BPCIA)'s "patent dance" and for prematurely providing notice of commercial marketing prior to the eventual FDA approval of its biosimilar in 2015.
  - Amgen brought suit to compel Sandoz to comply with the patent dance framework.

- **Federal Circuit**: Issued a split decision, ruling that the "patent dance" was optional but that Sandoz's notice of commercial marketing was ineffective until the FDA licensed the biosimilar.

- **Supreme Court**: Court ruled unanimously in favor of Sandoz, deciding that the "patent dance" is indeed optional, and biosimilar makers can give notice of commercial marketing before FDA approval.

Sandoz Inc. v. Amgen Inc., 582 U.S. 1 (2017)

Practice Tips

- **Optional Patent Dance**: Biosimilar applicants can strategically choose to bypass the patent dance, potentially accelerating the path to market but risking immediate litigation.
- **Notice of Commercial Marketing**: The Supreme Court clarified that notice of commercial marketing can be provided before FDA approval, allowing biosimilar manufacturers to manage the timing of market entry more effectively.
- **Litigation Risks**: Both parties should prepare for early litigation if the patent dance is bypassed, balancing potential market advantages against the costs and uncertainties of immediate legal challenges.

Amgen Inc. v. Hospira, Inc., 944 F.3d 1327 (Fed. Cir. 2019)

Case History:

- Amgen sued Hospira, alleging that Hospira's biosimilar, which referenced Amgen's **Epogen®** (epoetin alfa), infringed on two of Amgen's patents.
- The key issue was whether biosimilar batches prepared by Hospira fell within the safe harbor provisions of the Patent Act
- Federal Circuit found substantial evidence supported jury determination of infringement by batches not within the safe harbor

Janssen Biotech, Inc. v. Celltrion Healthcare Co., 296 F. Supp. 3d 336 (D. Mass. 2017)

- Janssen, the maker of **Remicade®** (infliximab), sued Celltrion and Hospira over their biosimilar **Inflectra®**.
- Celltrion argued that Janssen lacked standing because the assignment document included all of Johson & Johnson's then-existing affilates
- The Federal Circuit held that the evidence demonstrated appropriate standing for Janssen

Apotex Inc. v. Amgen Inc., 827 F.3d 1052 (Fed. Cir. 2016)

- Apotex sought to market a biosimilar version of Amgen's **Neulasta®** (pegfilgrastim) and engaged in the BPCIA's patent dance.
- After completing the patent dance, Apotex argued that it did not need to provide Amgen with a 180-day notice of commercial marketing before launching its biosimilar, since it had followed the patent dance process.
- Amgen disagreed, asserting that the 180-day notice is mandatory, even if the patent dance is followed.
- Federal Circuit held that the 180-day notice of commercial marketing is required even when the patent dance has been fully completed, emphasizing that this notice is critical for allowing the RPS time to seek a preliminary injunction to resolve outstanding patent disputes
- The ruling effectively delayed Apotex's ability to launch its biosimilar by requiring it to provide the 180-day notice, giving Amgen more time to challenge any remaining patent issues.

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Genentech, Inc. v. Immunex R.I. Corp., *964 F.3d 1109* (Fed. Cir. 2020)

- Genentech filed a TRO seeking to enjoin Immunex for failing to comply with the BPCIA notice requirements
- Federal Circuit affirms district court's denial of the TRO
- Section 262(l)(8)(A) requires a biosimilar applicant to provide notice of commercial marketing 180 days before launch
- Immunex amended its application two times after the notice
- Court holds that the applicant, after providing notice, need not provide additional notices after each subsequent amendment

Key Takeaways Across Cases:

These rulings emphasize several critical points for biosimilar applicants and reference product sponsors under the BPCIA:

1. **Full Disclosure in Patent Dance**: Biosimilar applicants must provide comprehensive information about their manufacturing processes during the patent dance to ensure transparency and compliance

2. **180-Day Notice Requirement**: Even when the patent dance is followed, the 180-day notice of commercial marketing is required, ensuring that reference product sponsors have sufficient time to address any patent issues

3. **Strategic Considerations**: Compliance with the BPCIA's procedural requirements is crucial in biosimilar litigation. Failure to meet disclosure obligations or notice requirements can delay biosimilar market entry and expose applicants to litigation risks and damages

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