New York Intellectual Property Law Association:
Hot Topics and Issues in the Biosimilars Space

PATENT LITIGATION AND STRATEGY UNDER THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

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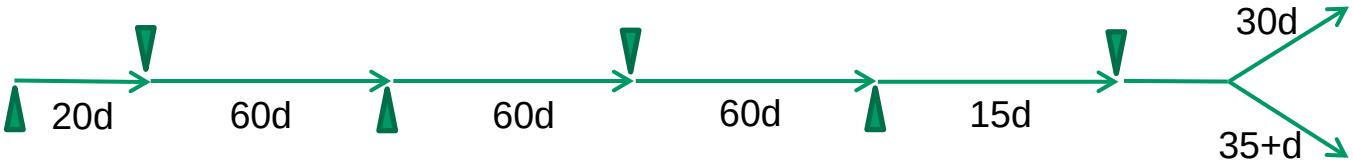
BPCIA Process, Early Phase

Applicant gives RPS aBLA & manufacturing info, 42 USC 262(l)(2)

Applicant gives invalidity, unenforceability, and non-infringement contentions (and optionally its patent list), 262(l)(3)(B)

If agreement reached, RPS files infringement action on agreed upon patents, 262(l)(6)(A)

Negotiation ends



FDA accepts "subsection k" application ("aBLA")

RPS gives its patent list, 262(l)(3)(A)

RPS gives infringement contentions & responds to applicant contentions, 262(l)(3)(C), and negotiations begin over which listed patents will be litigated, 262(l)(4)

If no agreement :
- parties exchange lists of patents, 262(l)(5)(B)
- RPS' list no longer than applicant's (but may include 1 patent if applicant lists none)
- RPS files infringement action on listed patents, 262(l)(6)(B)

Biosimilar POV

- BPCIA sets out a regulatory and dispute resolution framework for follow-on biologics or biosimilars inspired by the one the Hatch-Waxman Act uses for small-molecule generics, but has many differences.
- A biosimilar producer does not know what patents it may be sued on because there is no list.
- The “branded” product may be covered by many more patents than in a typical Hatch-Waxman scenario.
- Some of those patents may be licensed-in by the branded producer and not owned or controlled by the branded company.
- The branded company gets to decide which patents to sue you on so you won’t necessarily get a free-and-clear pathway even if you win the case.
- The amount of information you need to provide the branded company before they tell you which patents is burdensome and troubling.

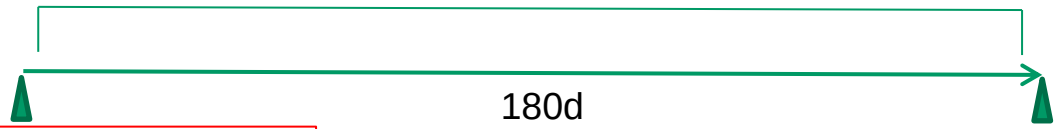
WHY ARE THE STAKES SO HIGH?

- BPCIA has an application and approval process that requires significant up-front time and investment
- Average cost of bringing a biosimilar to market is estimated to be between $100MM and $200MM
  - Compare: Average cost of bringing small-molecule generic is estimated to be between $1MM AND $5MM
- Generally, it is scientifically difficult to prove equivalence between a follow-on biologic and a reference product.
- As stated by the Congressional Research Service:

"In contrast to chemical drugs, which are small molecules and for which the equivalence of chemical composition between the generic drug and innovator drug is relatively easy to determine, a biologic, such as a protein, is much larger in size and much more complex in structure …. In many cases, current technology will not allow complete characterization of biological products and additional clinical trials may be necessary before FDA would approve a follow-on biologic."

BPCIA Process, Later Phase

Before first commercial marketing, RPS may seek preliminary injunction on patents issued/licensed after the Early Phase and those on the 262(l)(3) lists not already in litigation, 262(l)(8)(B)



Applicant "shall provide" notice to RPS at least 180 days before first commercial marketing of biologic "licensed under subsection (k)," 262(l)(8)(A)

Date of first commercial marketing

Federal Circuit Interprets the BPCIA

Amgen v. Sandoz, 794 F.3d 1347 (Fed. Cir. 2015) addressed 3 issues:

1. Must the applicant provide its aBLA and manufacturing info?

    - No, the applicant is not required

2. If an applicant not provide its aBLA and manufacturing info, must it provide 180 days notice of commercial manufacturing?

    - Yes, such an applicant is required to give notice

3. Can the applicant provide 180 days notice of commercial manufacturing effective before FDA licensure?

    - No, notice is only effective if given after FDA licensure

Fractured Federal Circuit Opinion

	Lourie*	Newman	Chen
Applicant not required to provide aBLA	✓	✗	✓
Applicant that does not provide aBLA must give 180 days notice	✓	✓	✗
180 days notice only after FDA licensure	✓	✓	✓

Authored the precedential opinion

"Shall" Does Not Mean Must in Paragraph (l)(2)(A)

- The "applicant ***shall provide***" the RPS the aBLA and manufacturing info, 262(l)(2)(A)

- "Shall" cannot be read in isolation. BPCIA contemplates an applicant may fail to disclose and sets forth the ***only*** remedies:

  - If "applicant ***fails to provide the application and information required under paragraph (2)(A)***, the [RPS], but not the subsection (k) applicant, may bring" a D.J. action on "any patent that claims the biological product or a use of the biological product," 262(l)(9)(C)

  - "It shall be an act of infringement to submit . . . an application seeking approval of a biological product" if the applicant "***fails to provide the application and information required under [paragraph] (l)(2)(A)***," 35 USC 271(e)(2)(C)(ii)

- "[M]andating compliance with (l)(2)(A) in all circumstances would render [these provisions] superfluous . . ."

“Shall” Means Must in Paragraph (l)(8)(A)

- The “applicant ***shall*** provide notice to [RPS] not later than 180 days before the date of the first commercial marketing,” 262(l)(8)(A)

- Unlike (l)(2)(A), “we do not find any provision in the BPCIA that contemplates, or specifies the consequence for, noncompliance with paragraph (l)(8)(A) here . . .”
- If applicant complies with (l)(2)(A), but not (l)(8)(A), BPCIA permits the RPS to file a D.J. action on any patent on the (l)(3)(A) list. *See* 262(l)(9)(B). But this “does not apply in this case, where Sandoz did not comply with (l)(2)(A) to begin with.”
- “[W]here, ***as here, [the] applicant completely fails to provide its aBLA and the required manufacturing information to the RPS*** . . . the requirement of paragraph (l)(8)(A) is mandatory.”
- Federal Circuit enjoined Sandoz from marketing for the requisite days
- Sandoz petitioned the Supreme Court on Feb. 17 to review the marketing notice determination

Marketing Notice Only After Licensure

- The "applicant shall provide notice to [RPS] 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)

- Sandoz argued "licensed" means only the product be licensed at time of marketing; it does not limit the timing of notice

- "[O]nly (l)(8)(A) refers to the product as 'the biological product licensed under subsection (k).'" Other paragraphs refer "to the product as 'the biological product that is the subject of' the application . . . If Congress intended (l)(8)(A) to permit effective notice before the product is licensed, it would have used the 'subject of' language.'"
- "Giving notice after FDA licensure, once the scope of the approved license is known and the marketing . . . is imminent, allows the RPS to effectively determine whether, and on which patents, to seek a preliminary injunction . . ."

Notice Loophole is Closed

Amgen v. Apotex, 15-cv-61631 (S.D. Fla. Dec. 9, 2015) (Cohn, J.)

- Apotex disclosed aBLA and manufacturing info, but refused to give marketing notice arguing notice is mandatory under *Sandoz* only if applicant does not disclose
- Amgen moved to enjoin Apotex from marketing until 180 days after FDA licensure
- District court held notice is ***required in call cases***: "Nothing in the statute or the *Sandoz* decision leads to or supports" Apotex; "scenario proposed by Apotex would result in confusion and uncertainty, as well as inconsistent results"
- But what about D.J. action remedy in (l)(9)(B)?
- Granted preliminary injunction based on stipulation of irreparable harm, balance of hardships, and public interest
- Appealed to Federal Circuit, fully briefed on Feb. 12

Private Enforcement of Notice Requirement?

Amgen v. Hospira, 15-cv-839 (D. Del.)

- Hospira disclosed aBLA, but allegedly not manufacturing info; Hospira refused to give marketing notice
- Amgen filed D.J. seeking Hospira to comply with (l)(8)(A), Hopsira moved to dismiss for no private cause of action
- Hospira:

  - Congress provided sole remedy in (l)(9)(B) of D.J. of infringement, validity, enforceability

- Amgen:

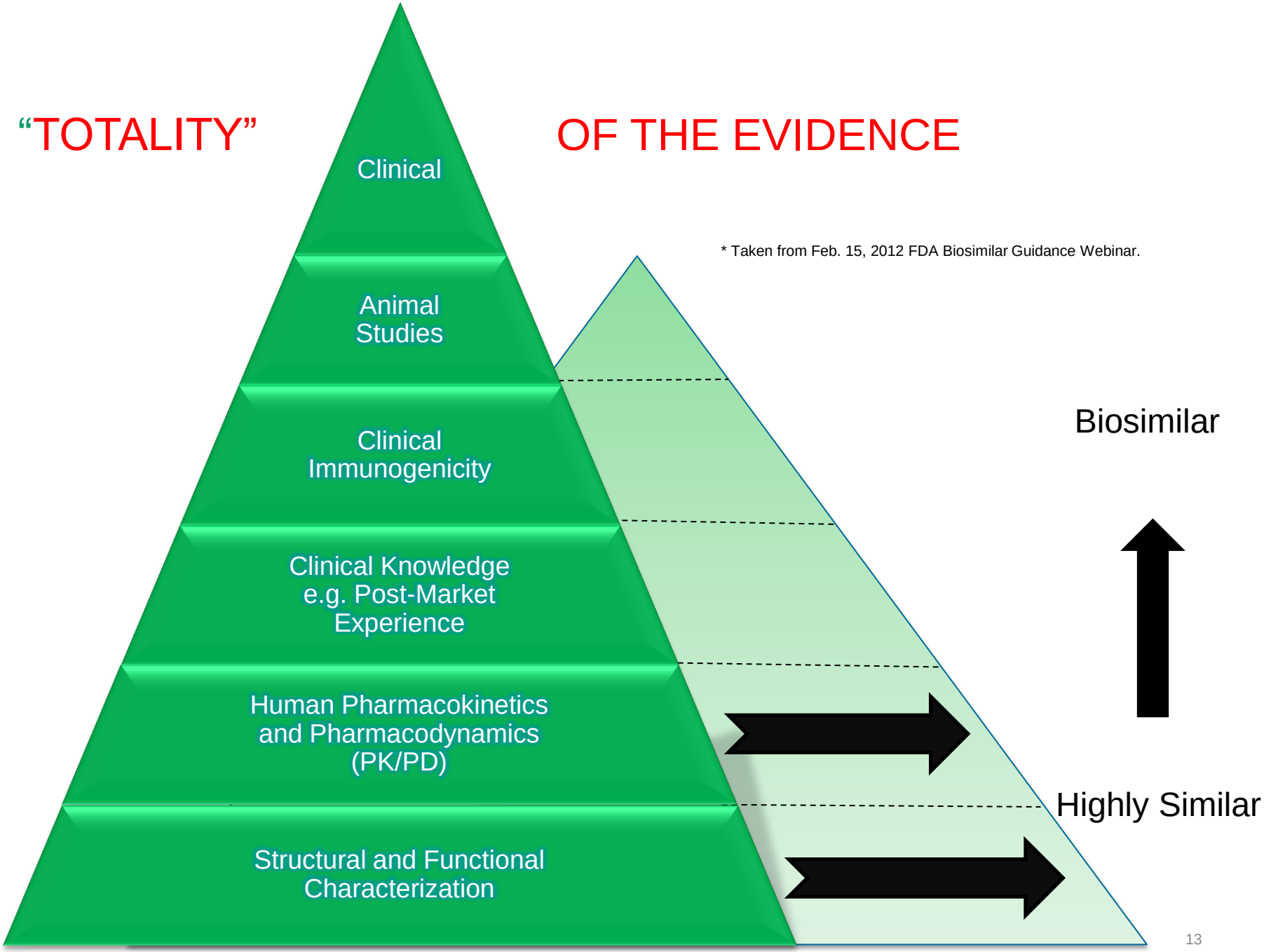
  - (l)(9)(B) not applicable here – Hospira did not comply with (l)(2)(A)
  - Federal Circuit enforced the requirement in *Sandoz*
  - Congress created implied cause of action as requirement benefits a particular class (RPSs) and it would not otherwise be enforced

- District court heard oral arguments on Feb. 16

WHAT DOES “BIOSIMILARITY” MEAN?

- Means that follow-on biologic is “highly similar” to reference product, notwithstanding minor differences in clinically inactive components
- Application must demonstrate required biosimilarity through:
  - analytical studies;
  - animal studies; *and*
  - a human clinical study or studies that are sufficient to demonstrate the follow-on biologic is “safe, pure and potent.”
- Ultimate question: How close does the proposed follow-on biologic compare to the reference product?

“TOTALITY” OF THE EVIDENCE



* Taken from Feb. 15, 2012 FDA Biosimilar Guidance Webinar.

FIRST PRINCIPLES

- BPCIA passed before recent spate of Section 101 cases.

- *Mayo v. Prometheus* (2012) changed the game, or did it?

- Safe Harbor cases:
  - *Classen Immunotherapies, Inc. v. Biogen Idec*, 659 F.3d 1057 (Fed. Cir. 2011).

  - *Classen* limited by *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, 686 F.3d 1348 (Fed. Cir. 2012).

BPCIA IS SUPPOSED TO PROVIDE A “FASTER” PATHWAY

YES, THE PRIOR SLIDE WAS BLANK ON PURPOSE

"INTERCHANGEABLE"

- Means that follow-on biologic "may be substituted for the reference product without the intervention of the healthcare provider who prescribed the medication."
- Application must show that the follow-on biologic "can be expected to produce the same clinical results as the reference product in any given patient" and, if administered more than once, the "risk in terms of safety or diminished efficacy of alternating or switching" between the products is "not greater than the risk of using the reference product without such alternation or switch."
- BPCIA provides incentives to the first biosimilar applicant to demonstrate interchangeability by providing a period of exclusivity during which no other product can be deemed interchangeable with the reference product.
- This period of exclusivity ends on the earliest of:
  - One year after first commercial marketing;
  - If no expedited patent litigation suit is brought against that applicant under the PHSA § 351(l), 18 months after approval;
  - if an expedited patent litigation suit is brought against that applicant under PHSA § 351(l), 18 months after final decision on all patents-in-suit (or dismissal); or
  - if an expedited patent litigation is brought against that applicant under PHSA § 351(l) and still pending, 42 months after approval.

DATA EXCLUSIVITY FOR THE REFERENCE PRODUCT

- No application can be filed until *4 years* after the date the reference product was first licensed.
- No application can be approved until *12 years* after the date the reference product was first licensed.
- Pediatric exclusivity: can extend 4 and 12 year periods for 6 months each.

What damages for stayed patent?

Janssen v. Celltrion & Hospira, 15-cv-10698 (D. Mass.)

- Janssen moved to stay with respect to its '471 patent under reexam
- Defendants:

  - Janssen seeks to circumvent BPCIA, which limits remedy to reasonable royalty if lawsuit is not filed within 30 days or, if timely, "not prosecuted to judgment in good faith," 35 USC 271(e)(6)

  - Defendants face undue prejudice and tactical disadvantage

  - If stay is entered, Janssen should agree to be limited to reasonable royalty

- Janssen:

  - A stay, warranted by the stay factors, does forfeit right to lost profit damages

  - 271(e)(6) limits damages only for patents on negotiated (l)(4) or (l)(5)(B) lists, and does not apply here because defendants "consented to Janssen's patent list" and did not engage further in the patent dance

- Motion to stay is pending

WHAT IS AN RPS TO DO?

- Get patents
  - •Targets, therapeutic agents, methods of use, formulations, cell lines, drug delivery, manufacturing or production processes, starting materials, vectors, technology platforms, treatment methods, etc.
- Get more patents, particularly improvements that extend the patent portfolio protection.
- Get patent term extensions, track expiration dates.
- Determine which patents should be included in the Patent Dance, considering:
  - Scope of claim coverage
  - Potential participation of co-owner(s)/licensor(s)
  - Survivability of claims over prior art
  - Nexus between patent claims and RSP's commercial product to support lost profit damages and injunctive relief
  - What if the aBLA Applicant does not engage or engage fully in the Patent Dance.
- Determine which patents should be held back from immediate litigation for follow-on litigation after notice/FDA approval.
- Track sales, patenting process and aBLA filings to be prepared for preliminary and permanent injunctive relief during litigation.
- Monitor FDA publications on biosimilars to prepare for applicants who do/don't disclose aBLA and manufacturing data.

WHAT IS A BIOSIMILAR PROSPECTOR TO DO?

- In picking target(s) for biosimilar application(s), identify all relevant patents:
  - Targets, therapeutic agents, methods of use, formulations, cell lines, drug delivery, manufacturing or production processes, starting materials, vectors, technology platforms, treatment methods, etc.
  - Particular focus on manufacturing or production method patents
  - Create internal “Orange Book” listing
  - Determine expiration dates and potential patent term extensions
- Consider data exclusivity period
- Map-out positions regarding validity, enforceability and/or non-infringement
- Consider whether to pursue own biologic license application (BLA)
  - Need only demonstrate that the biologic be “safe, pure, and potent”
  - Avoid risk and unpredictability of BPCIA patent dispute resolution procedures

BIOSIMILAR APPLICANT STRATEGIES (CONTINUED)

- Select patents for immediate litigation
  - Number of patents
  - Which patents?
    - Strength and expiration dates
    - Potential co-plaintiffs and venue
  - Take advantage of elaborate dance of patent list exchanges; likely have significant power due to its ability to set an upper limit on how many patents can be the subject of immediate litigation
  - Does reference product sponsor indicate willingness to license or lack of intention to assert certain patents?
- Consider what district court(s) reference product sponsor will likely file
- Second wave litigation
  - Consider impact of remaining patents that could be asserted
  - Prepare for preliminary injunction papers in advance of 180-day notice

EARLY DAYS -- CONCLUSIONS

- BPCIA does not provide the same level of predictability as Hatch-Waxman Act.
- Need improvements in technical and regulatory procedures for determining equivalence between reference product and biosimilar.
- Will likely take several years for reference product sponsors and biosimilar applicants to work through complexities of BPCIA.
- Nature of biologics and BPCIA processes provides for opportunity for “biobetters”
  - Patents?
  - New data exclusivity?
- New in-house specialist who “does not engage” in prosecution.
  - How broadly will “relevant” in prosecution bar be read?
- Where will the preferred district courts for the immediate litigation be? Identify district courts where reference product sponsor has opportunity to complete trial in an expedited manner?
- Strategic considerations as to which patents will be immediately litigated and which will be in second wave will be of great importance.
- Will immediate litigation always be just a single patent? Or more often will asserted patents be all listed patents originally identified?
- Manufacturing or production method patents will likely play an important role.

Thank You For Your Attention!

Questions?