



New Advances and Updates in the Biologics and Biosimilars Landscape

Daniel A. Kracov, Partner, Arnold & Porter LLP and Secretary and General Counsel, FDLI
Board of Directors

Teresa Stanek Rea, Partner, Crowell & Moring LLP

Sarah Yim, Acting Director, Therapeutic Biologics and Biosimilars Staff, CDER, FDA

Moderated by **Freddy A. Jimenez**, Vice-President, Law and Compliance, Celldex
Therapeutics, Inc. and Member, FDLI Board of Directors



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Compliance, Celldex Therapeutics, Inc. and
Member, FDLI Board of Directors

FDA Biosimilars Update

FDLI Annual Conference

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Sarah Yim, M.D.

Acting Director of the Office of Therapeutic Biologics and
Biosimilars

CDER/FDA



U.S. FOOD & DRUG
ADMINISTRATION

Balancing Innovation and Competition

- FDA recognizes our important role in helping to ensure the U.S. remains a driving force in medical innovation, as well as the importance of robust and timely competition to enhance patient access and reduce cost burdens on patients and our health care system.
- The FDA has and will continue to play a critical role in facilitating increased access to biosimilars.
 - By increasing treatment options, biosimilars can enhance competition in the market for biological products without reducing incentives to innovate.
 - Availability of biosimilar and interchangeable products that meet the FDA's robust approval standards will improve access to biological products.

Biosimilars To Date



As of April 2, 2019:

- **18** 351(k) BLAs for biosimilar products have been approved for 9 reference products.
 - **8** biosimilar products are believed to have been commercially launched
- **28 planned 351(k) submissions** (from 16 companies) have been publicly announced
- **77 programs** (for 36 different reference products) were enrolled in the **Biosimilar Product Development (BPD) Program** to discuss development of proposed biosimilar products or interchangeable products

BsUFA II and Biosimilars Action Plan

- BsUFA II Commitments October 2017
 - Advancing development of biosimilars through further clarification of the 351(k) regulatory pathway (commitments for FDA to issue guidance for industry)
 - Enhancing capacity for biosimilar regulations, including:
 - strengthen staff capacity to develop new regulations and guidance, review templates, communications to the public, and update the Purple Book
- FDA released the Biosimilars Action Plan (BAP) July, 2018 to provide information about the key actions the Agency is taking to encourage innovation and competition among biologics and the development of biosimilars.
 - The BAP is a dynamic plan that builds on the Agency's progress in implementing the approval pathway for biosimilar and interchangeable products

FDA's Biosimilars Action Plan



Key goals outlined in the BAP:

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process
2. Maximizing scientific and regulatory clarity for the biosimilar product development community
3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors
4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

BAP Deliverables: *Completed*



<i>Completed</i>	<i>Deliverable</i>
December 2018	Questions and Answers on Biosimilar Development and the BPCI Act; Final Guidance
December 2018	New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2); Draft Guidance
December 2018	Interpretation of the Deemed to be a License Provision of the Biologics Price Competition and Innovation Act; Final Guidance
December 2018	The Deemed to be a License Provision of the BPCI Act: Questions and Answers; Draft Guidance
December 2018	Definition of the Term Biological Product; Proposed Rule
December 2018	Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020
March 2019	Nonproprietary Naming of Biological Products – Update; Draft Guidance

BAP Deliverables: *Upcoming*



<i>BAP Goal</i>	<i>Deliverable</i>
Goal 2	Considerations in Demonstrating Interchangeability with a Reference Product; Final Guidance (user fee goal date of May 17, 2019)
	Revised draft guidance on comparative analytical assessments (user fee goal date of May 21, 2019)
	Biosimilar and Interchangeable Insulins; Part 15 Public Hearing (May 13, 2019)
	Draft guidance providing clarity to biosimilar applicants who seek approval for fewer than all conditions of use for which a reference product is licensed
	Develop an enhanced version of the Purple Book for biological products
	Evaluate FDA's regulations regarding the submission and review of BLAs to ensure that they account for current practices and authorities
	Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act; Final Guidance
Goal 3	New communication materials to educate providers and patients about biosimilars

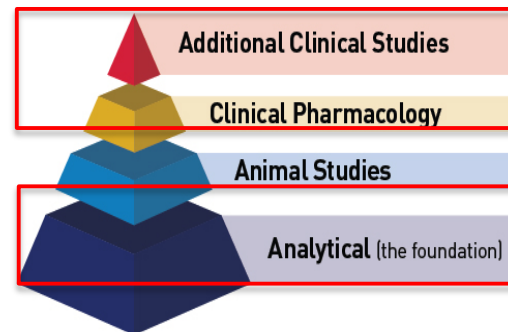
Development and Approval of Biosimilar Products

- The goal of a biosimilar development program is to establish biosimilarity between proposed product and reference product, not to re-establish safety and effectiveness.
- The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity.
- The **data package** required for approval of a biosimilar or interchangeable product is quite **extensive**.
 - As part of the demonstration of biosimilarity, the manufacturer may rely, in part, on FDA's previous determination of safety and effectiveness for the reference product for approval.
 - This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

Biosimilar Products: Data for Approval

Adequate data in the marketing application to support that the proposed product is **biosimilar** to the US-licensed reference product

- Proposed product must be **highly similar** to the US-licensed reference product notwithstanding minor differences in clinically inactive components
 - Comparative analytical data (**structural and functional analysis/characterization**) - the foundation
 - Analytical data is more **sensitive** than clinical data in detecting differences between products, should differences exist
 - A biosimilar product with highly similar structure and function to the reference product should **behave** like the reference product (i.e., have **similar efficacy and safety** as the reference product)
- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.
- This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.



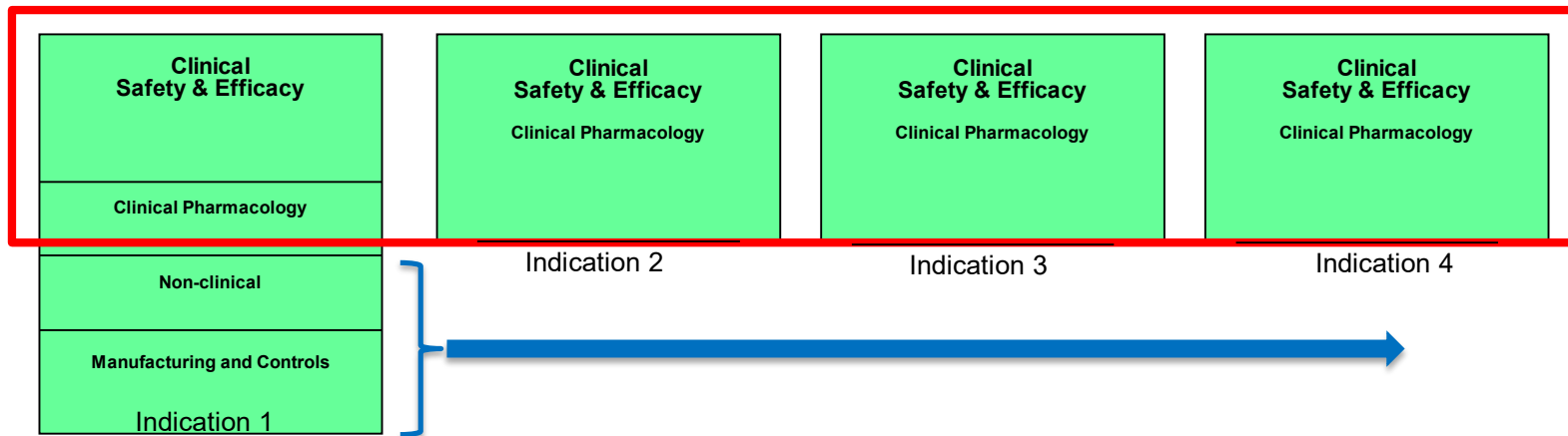
Key Points: Abbreviated Approval Pathway

- The abbreviated licensure pathway **does not mean that a lower approval standard is applied** to biosimilar or interchangeable products than to originator biological products.
 - The ability to rely on FDA’s previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program. This is what is meant by an **abbreviated** licensure pathway.
 - Extrapolation is one key component of the abbreviated licensure pathway

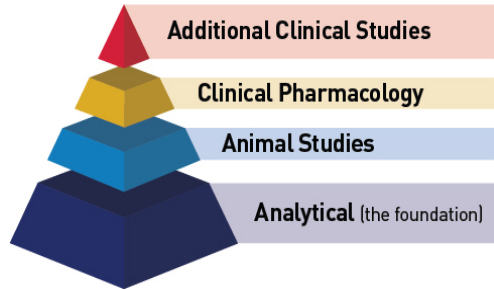
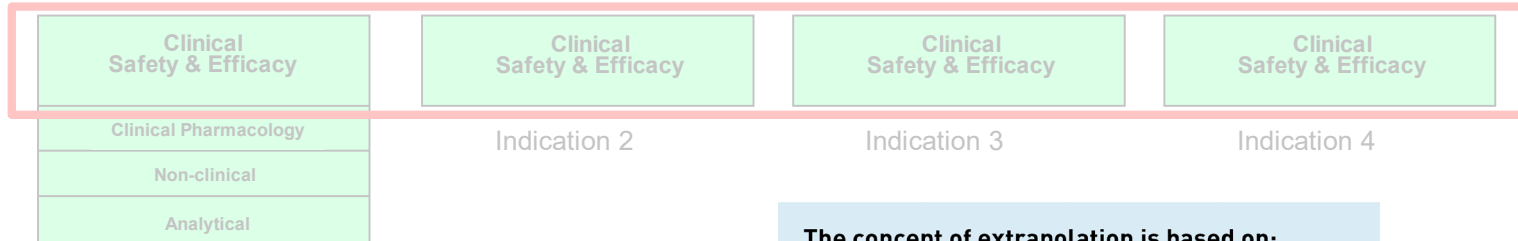
Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- FDA guidance outlines factors to consider, including:
 - MoA in each condition of use
 - PK and biodistribution in different patient populations
 - Immunogenicity in different patient populations
 - Differences in expected toxicities in each condition of use and patient population

Extrapolation Considerations: “Stand-alone” Drug Development



Extrapolation Considerations: “Stand-alone” vs. Biosimilar Development



The concept of extrapolation is based on:

- ✓ All available data and information in the biosimilar application
- ✓ FDA’s previous finding of safety and efficacy for other approved indications for the reference product
- ✓ Knowledge and consideration of various scientific factors for each indication

Biosimilar extrapolation is based on all available data in the 351(k) BLA and FDA’s finding for the reference product, not from the indication(s) studied for the biosimilar to other non-studied indications

Nonproprietary Naming April 2019

FDA's draft updated naming policy is intended to provide regulatory transparency and predictability regarding nonproprietary naming for biological products, while ensuring safe use and pharmacovigilance for patients that receive biological products.

- Unique nonproprietary names are needed for safety and suffixes will increasingly become the norm for biological products. New biological products that are within the scope of the guidance (both 351(a) and (k)) will contain suffixes.
- Applying a suffix to **already licensed** products is not necessary to achieve the goals of safe use and pharmacovigilance.
- This updated policy avoids the undue, extensive burden associated with retrospective application of the naming convention, and avoids risk of adverse patient safety issues, patient/ provider confusion, drug shortages, and supply chain disruption, because names rarely change after approval.
- FDA does not believe that the lack of suffixes for older originator products will hamper uptake of biosimilars and is committed to educating providers, patients, and others about the safety and effectiveness of biosimilars.
- FDA is continuing to consider the format of the suffix for interchangeable biological products.

Nonproprietary Naming April 2019



The guidance states that products:

- **Newly licensed under 351(a) of the PHS Act (stand-alone BLA):** Nonproprietary name consists of core name and unique suffix
- **Newly licensed under 351(k) of the PHS Act (biosimilar and interchangeable products):** Nonproprietary name consists of core name and suffix
- **Already licensed under 351 (a) of the PHS Act without a suffix in its nonproprietary name:** Nonproprietary names of already-licensed products without suffixes will not be changed to add a suffix
- **Transition Biological Products:** Nonproprietary names of already- licensed products will not be changed to add a suffix
- **Vaccine Products:** FDA is reconsidering whether vaccines should be within the scope of the naming convention

Nonproprietary Naming April 2019



Biological Product Type	Nonproprietary (Proper) Name
Newly licensed under 351(a) of the PHS Act (stand-alone BLA)	Nonproprietary name consists of core name and unique suffix
Newly licensed under 351(k) of the PHS Act (biosimilar and interchangeable products)	Nonproprietary name consists of core name and suffix
Already licensed under 351 (a) of the PHS Act without a suffix in its nonproprietary name	Nonproprietary names of already-licensed products without suffixes will not be changed to add a suffix
Transition Biological Products	Nonproprietary names of already- licensed products will not be changed to add a suffix
Vaccine Products	FDA is reconsidering whether vaccines should be within the scope of the naming convention

Thank you for your attention.

**For more information, go to
www.fda.gov/biosimilars**



Key FDA Issues

New Advances and Updates in the
Biologics and Biosimilars Landscape

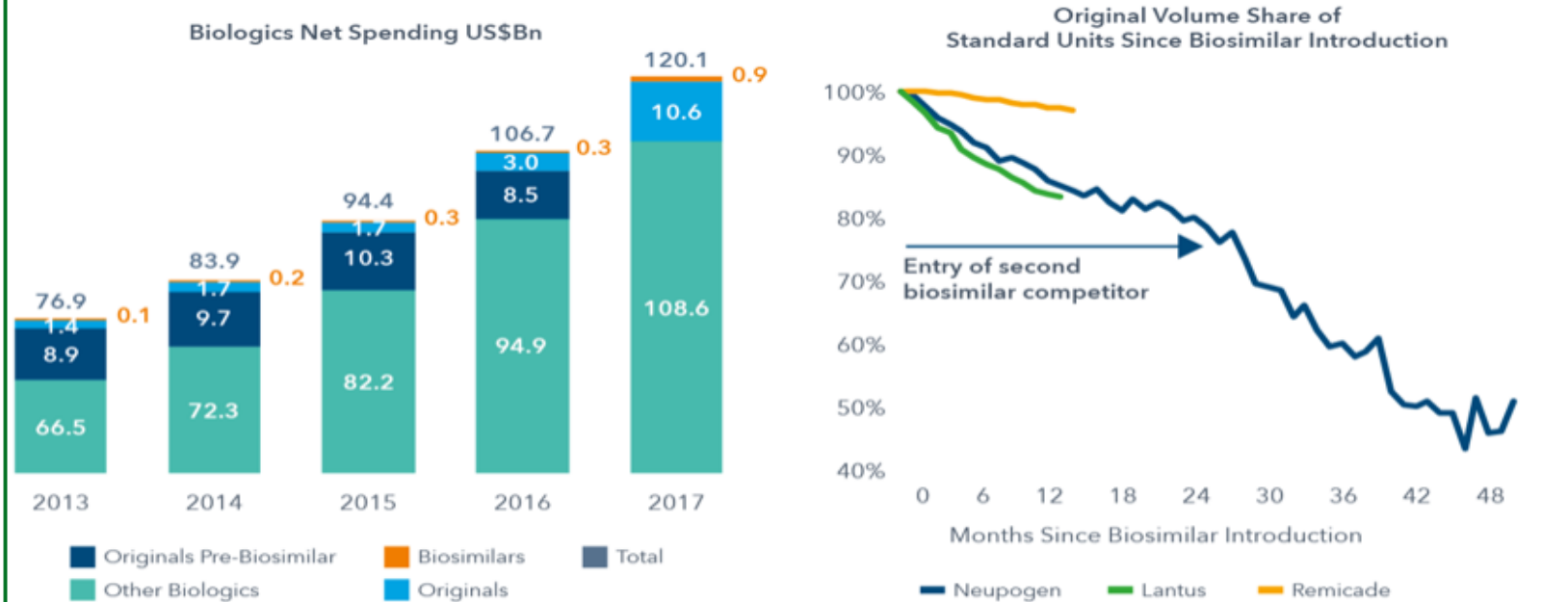
Dan Kracov

Arnold & Porter

daniel.kracov@arnoldporter.com

May 2, 2019

Impact of Biosimilars



Source: IQVIA National Sales Perspectives, IQVIA Institute, Dec 2017

Chart notes: Biologics are defined by IQVIA as clearly identifiable molecules of biologic origin, including but not limited to products created with recombinant DNA technology and without necessarily adhering to classifications by regulatory bodies, which are sometimes inconsistent with this approach. Biosimilars are abbreviated biologic approvals made with reference to an original biologic and demonstrating similarity to the reference product. Non-original products approved outside the official biosimilar pathway have been noted as "biosimilar". Original biologics that have later faced competition have been shown separately in the chart based on whether or not they are facing competition in that period. Includes all medicines in both pharmacy and institutional settings.

Report: Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022, Apr 2018

“More transparent pricing signals would encourage the rapid market uptake of lower cost products, and force manufacturers to better establish the real value of their products relative to price, including through innovative payment contracts. But payors are going to have to decide what they want: The short-term profit goose that comes with the rebates, or in the long run, a system that functions better for patients, providers, and those who pay for care.

Payors are going to have to decide this as well:

Do they want to continue to benefit from monopoly rents today, or help generate a vibrant biosimilar market that can help reset biologic pricing – and drug pricing more generally - through competition.

These are binary choices. You can’t have your cake – or in this case, your rebates – and a vibrant market for biosimilar competition too.”

- Former FDA Commissioner Scott Gottlieb, M.D., “Capturing the Benefits of Competition for Patients” AHIP National Health Policy Conference (March 7, 2018)

DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Office of Inspector General

42 CFR Part 1001

RIN 0936-AA08

Fraud and Abuse; Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Manager Service Fees

AGENCY: Office of Inspector General (OIG), Department of Health and Human Services (HHS).

ACTION: Proposed rule.

HHS Advances Payment Model to Lower Drug Costs for Patients

The International Pricing Index (IPI) Model would lower costs for physician-administered drugs by resetting Medicare payments based on international prices and introducing competition



Grassley, Klobuchar Introduce Legislation to Permit Personal Importation of Rx Drugs from Canada

Jan 09, 2019

WASHINGTON – Senate Finance Committee Chairman Chuck Grassley of Iowa and Sen. Amy Klobuchar of Minnesota today introduced the Safe and Affordable Drugs from Canada Act of 2019, which would permit the importation of prescription drugs from approved pharmacies in Canada.

Medicare and Medicaid Programs; Regulation To Require Drug Pricing Transparency

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Proposed rule.

SUMMARY: This proposed rule would revise the Federal Health Insurance Programs for the Aged and Disabled by amending the Medicare Parts A, B, C and D programs, as well as the Medicaid program, to require direct-to-consumer (DTC) television advertisements of prescription drugs and biological products for which payment is available through or under Medicare or Medicaid to include the Wholesale Acquisition Cost (WAC, or “list price”) of that drug



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3:20 PM EDT | APR 19, 2019 | BIOCENTURY | POLITICS, POLICY & LAW

Thin U.S. biosimilars market fuels proposals to regulate biologics prices

WHY ACADEMICS ARE CALLING FOR REPLACING BIOSIMILARS WITH PRICE REGULATION

BY STEVE USDIN, WASHINGTON EDITOR



TEXT SIZE
A A A



Frustration over the failure of biosimilars to slash the costs of decades-old biologics has prompted a group of policy analysts to suggest abandoning attempts to copy biologics. Because the sole purpose of biosimilars is to reduce prices, they suggest regulating the prices of biologics that have lost exclusivity rather than spending over \$150 million to develop a single biosimilar.

The proposal, published in *Health Affairs*, is attracting attention, including pushback from former FDA Commissioner Scott Gottlieb and from manufacturers who say it is too early to give up on biosimilars.

BIOSIMILARS ACTION PLAN: Balancing Innovation and Competition

July 2018

Some Key Issues

- Purple Book enhancements
- Education and industry communications about biosimilars
- Nomenclature
- Obtaining reference product for testing

Some Key Issues (cont'd.)

- Bridging studies and ex-U.S. reference products
- Extrapolation parameters
- Demonstrating interchangeability

Some Key Issues (cont'd.)

- Umbrella exclusivity for reference products
- Transition provision issues



New Advances and Updates in the Biologics and Biosimilars Landscape

- **Litigation involving the Patent Dance**
- **Interpretation of BPCIA provisions by the courts**

Teresa Stanek Rea
Crowell & Moring LLP
TRea@crowell.com

Hatch Waxman vs. BPCIA

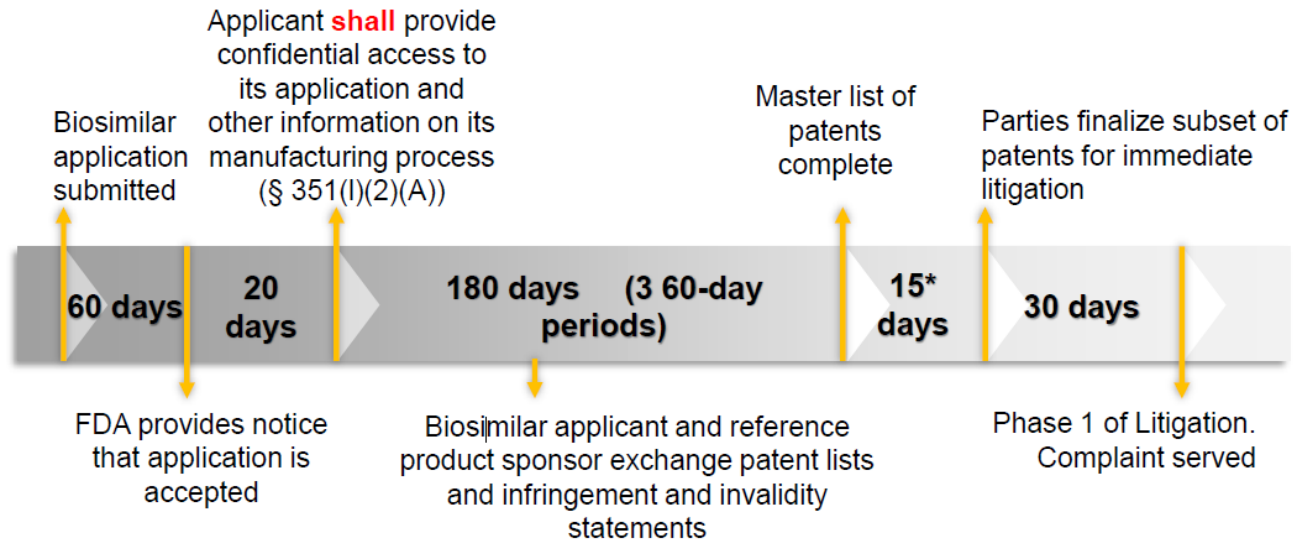
Hatch-Waxman

- Brand's patents listed in Orange Book
- Paragraph IV certification
- Notice Letter → suit within 45 days
- Automatic 30-month stay
- No process patents

BPCIA

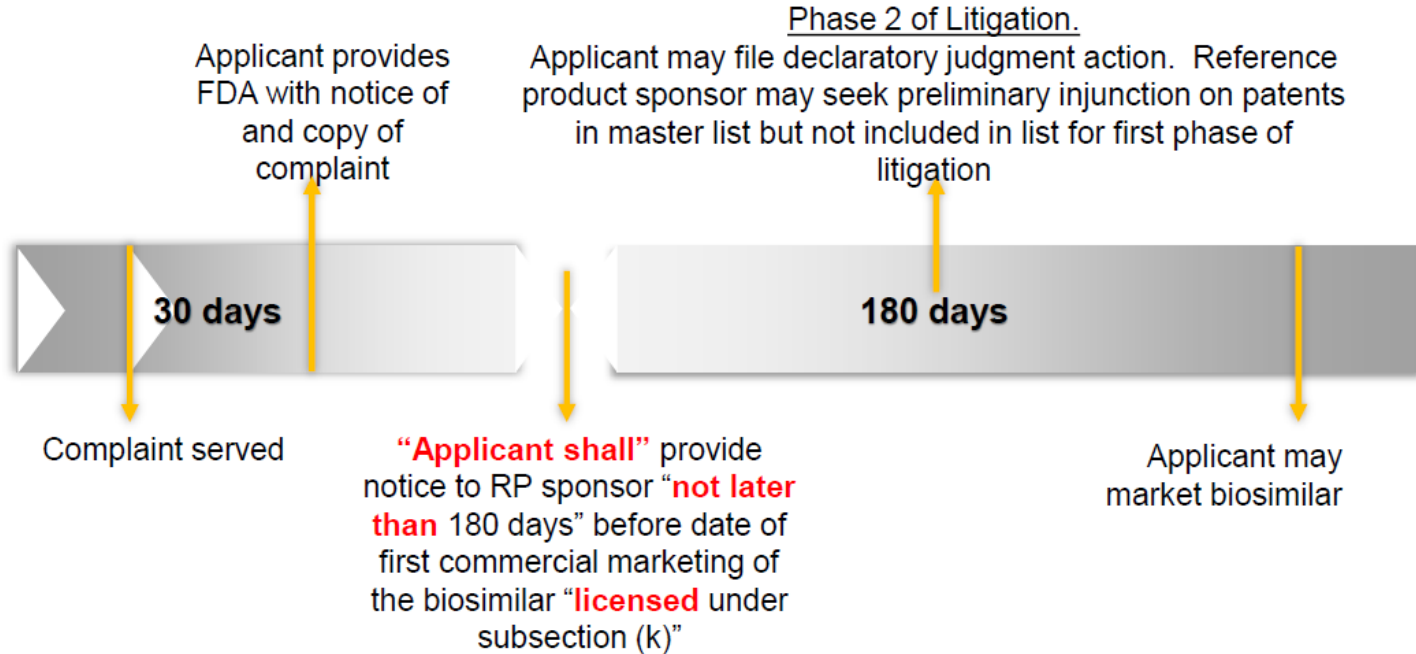
- No Orange Book; patent lists
- No Paragraph IV certification—
notifying sponsor is optional (until
notice of commercial marketing)
- Optional notice to reference product
sponsor → suit after patent dance
- No automatic 30-month stay
- Process patents available

Patent Litigation Process Overview



* If parties don't agree within 15 days, alternate procedure kicks in & time extends

Patent Litigation Process Overview



Limitations on Declaratory Judgment Actions

- **Section 351(I)(9)(A):** If applicant provides the application and information required under paragraph (2)(A), **neither party may bring a DJ** on patent validity, infringement, or enforceability until 180-day notice received
- **Section 351(I)(9)(B):** If applicant fails to complete specified actions (e.g., respond to RP sponsor list of patents), **RP sponsor** but not applicant **can bring DJ** regarding a patent in RP sponsor's initial list
- **Section 351(I)(9)(C):** "If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the **reference product sponsor**, but not the subsection (k) applicant, **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 Underlying Facts

- Sandoz filed biosimilar application referencing Amgen's Neupogen (filgrastim)
- Sandoz **did not provide** Amgen with the **biosimilar application** and **manufacturing process information** and asserted that Amgen was entitled to sue Sandoz under § 351(l)(9)(C)
- No patent exchanges
- Sandoz provided notice of commercial marketing upon FDA acceptance of the biosimilar application

Amgen v. Sandoz (N.D. Cal. 2015)

- Amgen sued Sandoz for patent infringement, unfair competition, and conversion
- Amgen alleged that Sandoz violated the BPCIA by **failing to provide confidential access** to its application and process information and by giving a premature, ineffective notice of commercial marketing before licensure of the biosimilar
- Sandoz alleged **patent dance is optional** and **180-day notice** was valid
- District court found for Sandoz on both issues

Federal Circuit's Decision

- A divided panel affirmed the district court's finding that the patent dance is optional
- “The ‘**SHALL**’ provision in [section 351(l)(2)(A)] cannot be read in isolation” and “BPCIA explicitly contemplates that a subsection (k) applicant might fail to disclose the required information by the statutory deadline”
- “[W]hen a [biosimilar] applicant fails the disclosure requirement, [section 351(l)(9)(C)] and 35 U.S.C. § 271(e) expressly provide the only remedies as those being based on the claim of patent infringement”

Federal Circuit's Decision (cont'd)

- A divided panel reversed the district court's 180-day notice holding
- Notice can only be given after FDA licenses biosimilar, "at which time the product, its therapeutic uses and its manufacturing processes are fixed"
- 180-day notice is mandatory, at least in cases where applicant fails to provide its application

Supreme Court's Decision

- Section 351(l)(2)(A) may not be enforced by an injunction under federal law
- Court focused on 351(l)(9)(C)
 - “The presence of [this provision], coupled with the absence of any other textually specified remedies, indicates that **Congress did not intend sponsors to have access to injunctive relief**, at least as a matter of federal law, to enforce the disclosure requirement”
 - The Federal Circuit must determine on remand if an injunction to enforce section 351(l)(2)(A) is available under state law

Supreme Court's Decision (cont'd)

- A biosimilar applicant may provide notice of commercial marketing before or after FDA approval of the biosimilar
- Section 351(l)(8)(A) states that the applicant “shall provide notice to the [RP sponsor] not later than 180 days before the date of the first commercial marketing **of the biological product licensed under subsection (k)**”
- The Court interpreted the **phrase to modify “commercial marketing”** — not “notice” — stating that “commercial marketing” is the point in time by which the biosimilar must be “licensed”

Federal Circuit Decision on Remand

- **Held:** BPCIA preempts state law claims predicated on an applicant's failure to comply with section 351(l)(2)(A)
 - Field preemption: “The field here is biosimilar patent litigation,” and “the federal government has fully occupied this field”
 - Conflict preemption:
 - “Amgen seeks through state law to impose penalties on Sandoz unavailable under the BPCIA”
 - Also stated that compliance with 50 state laws on torts and unfair competition might “dramatically increase the burdens” on biosimilar applicants

What Patents Should Be Listed?

“[T]he [RPS] shall provide to the subsection (k) applicant . . . a list of patents for which the [RPS] *believes* a claim of patent infringement *could reasonably be asserted*”

42 U.S.C. §262(l)(3)(A)

- **Considerations for RPS in creating 3A patent list**

- Only listed patents can be the source of a preliminary injunction under 42 U.S.C. §262(l)(8)(B)
- Potential litigation tension through asserting multiple patents directed to similar technology (*e.g.*, formulation patents having different priority dates that cover the same biosimilar product)
- Potential implicit admission that unlisted patents could never reasonably be asserted

Potential Consequences of Not Listing?

- *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052, 1058 (Fed. Cir. 2016)
 - “If a patent that the [RPS] should have included . . . ‘was not timely included,’ then the owner of that patent may not sue for infringement ***under 35 U.S.C. §271*** with respect to the biological product at issue.”
- *Amgen Inc. v. Hospira, Inc.*, 866 F.3d 1355, 1361 (Fed. Cir. 2017)
 - “[A] sponsor that fails to list a patent that ‘should have been included in the list described in [paragraph (l)(3)(A)] . . . may not bring an action ***under this section*** for infringement of the patent with respect to the biological product.”