



Is FDA's Biosimilars Action Plan Getting the Job Done?

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Introduction:

The Biosimilars Action Plan and Report Card

Biosimilars Action Plan

- Announced in July 2018.
- Intended to increase market competition without undermining incentives to invest in research.
- Four key areas:
 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 generic competition.

Biosimilars Action Plan

- Proposed rule adding or altering regulatory definitions:
 - Amending regulatory definition of “biological product” (21 C.F.R. § 600.3(h)) to comport with the statutory definition (42 U.S.C. § 262(i)(1)).
 - Defining “protein” as “any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.”
 - Defining “chemically synthesized polypeptide” as “any alpha amino acid polymer that is made entirely by chemical synthesis and is greater than 40 amino acids but less than 100 amino acids in size.”
- Released four new guidance documents:
 - One final and one draft guidance on development of biosimilars.
 - One final and one draft guidance on past applications that are deemed to be a license.

Biosimilars Action Plan Report Card

- One year after FDA's release of the Biosimilars Action Plan (BAP), the Biosimilars Council introduced a Report Card detailing the agency's progress in a number of stated goal areas.
- Though FDA made significant strides toward developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors, certain other areas are still developing:
 1. Maximizing regulatory clarity.
 - Enhancing the Purple Book.
 - Resolving issues with biosimilars patent litigation (the "patent dance").
 2. Improving the efficiency of biosimilar approvals.
 - Fixing the regulatory "dead zone" for insulin products.

Biosimilars Action Plan Report Card

In July of 2018, the U.S. Food and Drug Administration (FDA) released the Biosimilars Action Plan (BAP). The plan detailed key actions to promote innovation and competition among biologics and enhance the development of biosimilars, potentially lowering costs for patients and payors. At the one year mark, the agency has made significant progress with the BAP, but more can be done to ensure biosimilars are approved as efficiently as possible.

BAP INITIATIVE	STATUS	DETAILS
Improve the efficiency of the biosimilar and interchangeable product development and approval process.		
Application review templates for 351k Biologics License Applications (BLAs)	●	No new application review templates.
Develop an index of critical quality attributes for use in comparing biosimilars to reference products	●	No updated index of critical quality attributes for use in comparing proposed biosimilars to certain reference products since 2016.
Develop effective communications to improve understanding of biosimilars among patients, clinicians and payors.		
Outreach Campaign	●	An outreach campaign launched in September 2018 outlining steps to educate and inform physicians, pharmacists, and patients about biosimilars and interchangeability.
Develop shareable one-pager and video communications for patient audiences	●	Videos and graphics have been created and shared on social media beginning in Fall 2018.
Webinar on labeling and prescribing biosimilar and interchangeable products	●	A webinar titled "Biosimilar and Interchangeable Products in the U.S.: Scientific Concepts, Clinical Use, and Practical Considerations" was hosted in December 2018.
Maximize scientific and regulatory clarity for the biosimilar product development community.		
Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009	●	Final guidance was released December 2018. However, the policy announced in the Final Guidance (and the delay in issuing it) led to a "regulatory dead zone", slowing development of products affected by the guidance.
Guidance on Considerations in Demonstrating Interchangeability with a Reference Product	●	Final guidance was released in May 2019 which allows the use of non-U.S. reference product in development.
Guidance on Statistical Approaches to Evaluate Analytical Similarity	●	FDA issued revised draft guidance that reflects significant improvements over the previous withdrawn draft.
Guidance on Reference Product Exclusivity for Biological Products	●	Draft guidance issued in 2014 and FDA continues to update the Purple Book with exclusivity information, although gaps remain.
Guidance on processes and considerations related to post-approval manufacturing changes for biosimilar biological products	●	FDA provided limited guidance in a single Q&A in a 2018 draft guidance document, which references a final 2005 ICH guidance on comparability testing.
Develop an enhanced Purple Book to include a modernized, interactive user experience	●	No action has been taken to enhance the Purple Book.

● No Formal Action Taken ● Action In Progress ● Action Completed



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Maximizing Regulatory Clarity:

Enhancing the Purple Book

The Purple Book

- A list of biological products licensed by the FDA.
- Includes information regarding
 - Licensing date.
 - Whether the FDA evaluated the biological product for reference product exclusivity under § 351(k)(7).
 - Whether the biological product is considered biosimilar or interchangeable with a reference product.
- Does not include information regarding
 - Patents covering the innovator product or potential biosimilar products.
 - Exclusivity periods.

The Purple Book

- Unlike the Hatch-Waxman Act for small molecules, the Biologics Price Competition and Innovation Act (BPCIA) does not mandate that FDA publish the Purple Book for biosimilars and interchangeables – the publication is voluntary.
- Severely lacks information on and an administrative record of the date of first licensure and exclusivity period for each biological product.
- Does not include any record of relevant patents or patent families that may be asserted to cover a biosimilar, necessitating costly research for developers exploring biosimilars or interchangeables.
 - This necessitates the “patent dance” parties must partake in during litigation.
- All of this has generated uncertainty in the biosimilars and interchangeables landscape, as developers struggle to make better-informed decisions about their investments.

The Purple Book

- Formatting:
 - Simple PDF document.
 - Separate documents for licensed biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).
- Each list is updated independently.
 - The CDER list was last updated on 10/8/2019.
 - The CBER list was last updated on 4/24/2019.

The Purple Book – CDER Sample

Center for Drug Evaluation and Research

List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date

BLA STN	PRODUCT (PROPER) NAME	PROPRIETARY NAME	DATE OF LICENSURE (mo/day/yr)	DATE OF FIRST LICENSURE (mo/day/yr)	REFERENCE PRODUCT EXCLUSIVITY EXPIRY DATE (mo/day/yr)	INTERCHANGEABLE (I)/ BIOSIMILAR (B)	WITHDRAWN
125118	abatacept	Orencia	12/23/05	NA	NA		
103575	abciximab	ReoPro	12/22/94	NA	NA		
125274	abobotulinumtoxinA	Dysport	04/29/09				
125057	adalimumab	Humira	12/31/02	NA	NA		
761071	adalimumab-adaz	Hyrimoz	10/30/18			B	
761058	adalimumab-adbm	Cyltezo	08/25/17			B	
761024	adalimumab-atto	Amjevita	09/23/16			B	
761059	adalimumab-bwwd	Hadlima	07/23/19			B	

FDA Proposals

- In its Biosimilars Action Plan, FDA specifically committed to “[e]nhancing the Purple Book to include more information about approved biological products, including information relating to reference product exclusivity determinations.”
- “The enhanced Purple Book will provide a modernized, interactive user experience. As part of the Purple Book enhancements, the FDA will also continue its commitment under the BsUFA II goals letter to publish information about newly approved or withdrawn BLAs and about reference product exclusivity determinations.”
 - FDA, *Biosimilars Action Plan: Balancing Innovation and Competition* (July 2018).
- No action has yet been taken.

Legislative Proposals

- Biologic Patent Transparency Act (“BPTA”) (S. 659)
 - Introduced March 2019
 - Sponsored by Senators Susan M. Collins (R-ME) and Tim Kaine (D-VA).
 - Requires manufacturers of approved products to disclose and list patents for which a claim of patent infringement “could reasonably be asserted by the holder.”
 - Would include patents provided in the first-asserted patents list of the “patent dance.”
 - Requires codification of the Purple Book in a single, searchable list detailing biosimilarity and interchangeability as well as approved indications and exclusivity periods/extensions.
 - Stated goals:
 - To encourage manufacturers to apply for patents sooner.
 - To promote the development and use of generic drugs.
 - To standardize publication of the Purple Book by the FDA.

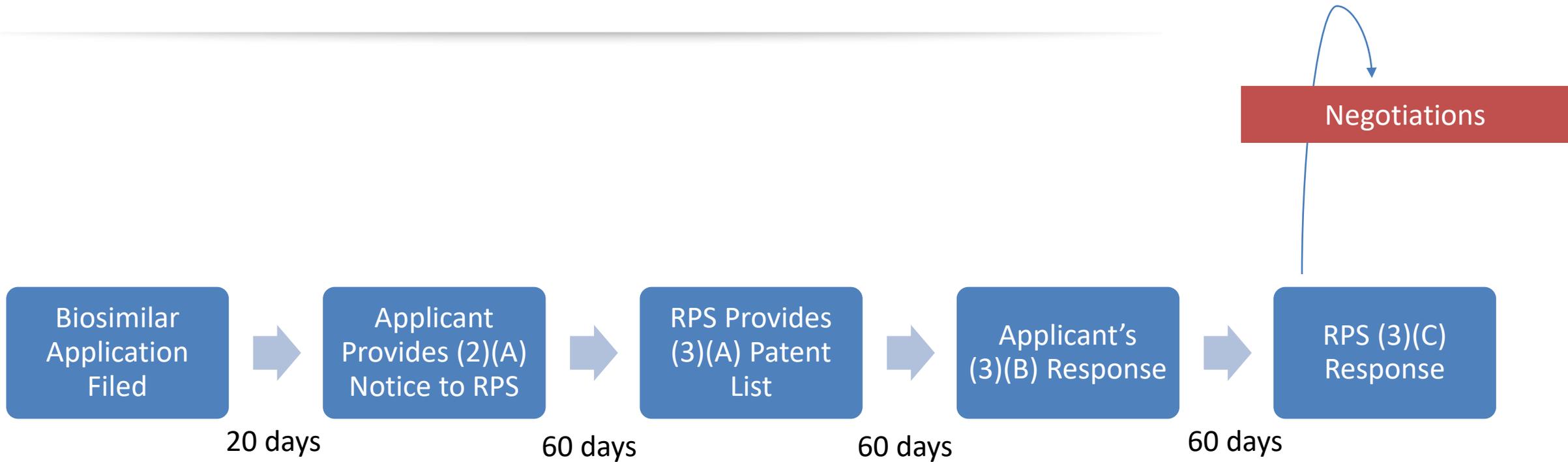
Legislative Proposals

- Purple Book Continuity Act of 2019 (H.R. 1520):
 - Introduced March 2019; passed unanimously in the House May 2019.
 - Sponsored by Rep. Anna Eshoo (D-CA).
 - Proposes amending the Public Health Service Act (“PHS” Act) to create a searchable, electronic database for all biological products
 - Requires FDA to publish patents associated with approved biological products no later than 30 days after the “patent dance” has begun.
 - Requires a clear listing of exclusivity periods for each biological product.
 - Provides an online, searchable tool for biosimilars and interchangeables.
 - Requires routine updates by FDA.

Maximizing Regulatory Clarity:

Resolving Issues with Biosimilars Patent Litigation (The “Patent Dance”)

The “Patent Dance”



The “Patent Dance”

- Negotiations (Phase I Patent Litigation):
 - If the parties cannot agree on which patents are the subject of the immediate suit within 15 days, they must simultaneously exchange their own lists, for which the applicant determines the number of entries.
 - The RPS has 30 days to bring infringement claims regarding the patents contained in the above lists.
- Notice of Commercial Marketing (Phase II Patent Litigation):
 - Addresses those patents disclosed, but not included in Phase I.
 - The applicant must provide notice to the RPS no later than 180 days before the date of the first commercial marketing of the biosimilar.
 - Failure to comply may result in a declaratory judgment action for patent infringement, validity, or enforceability.
 - See 42 U.S.C. § 262(l)(9)(B).

Issues with the “Patent Dance”

- The framework is complicated.
 - Unlike Hatch-Waxman litigation, the BPCIA does not require reference product sponsors to list patents covering the product in the Purple Book.
 - Instead, parties must engage in a multistep exchange of lists to determine the patents at issue.
- Following *Amgen v. Sandoz*, biosimilar applicants have been opting out of the dance.
 - SCOTUS held in *Amgen* that the only federal remedy for such “opting out” is to bring a declaratory judgment action to enforce the patents.
 - This “opting out” gives more control over dispute resolution to biosimilar applicants, who may now choose whether to disclose applications and may choose to challenge the reference patents in the USPTO, where the burden for invalidity is lower and the process less consolidated.
 - But, greater uncertainty

Legislative Proposals

- Biologic Patent Transparency Act (S. 659):
 - Similar to Hatch-Waxman, would require biological product sponsors to disclose any patent for which “a claim of patent infringement could reasonably be asserted . . . if a person not licensed by the holder engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product.”
 - This provision, which remedies the concerns of Purple Book critics, would restrict the “patent dance” only to those patents timely disclosed to FDA, eliminating the need for patent list exchanges.

Legislative Proposals

- Affordable Prescriptions for Patients Act of 2019 (S. 1416):
 - Sponsored by Senator John Cornyn (R-TX).
 - Pending passage in the Senate.
 - Limits the number of certain patents that can be asserted in BPCIA litigation by allowing a reference product sponsor to “assert in the action a total of not more than 20 patents of the type described in subparagraph (b), not more than 10 of which shall have issued after” the date of the initial 3A listing.
 - The patents listed also must: “claim the biological product [or method or manufacture] that is the subject of [the application]”; be included on the 3A patent list; and “have an actual filing date of more than four years after the date on which the reference product is approved” or “include a claim to a method in a manufacturing process that is not used by the [RPS].”
 - Stated goals:
 - To streamline the process and reduce the burden of litigation.

Legislative Proposals

- Affordable Prescriptions for Patients Through Improvements to Patent Litigation Act (H.R. 3991):
 - Sponsored by Rep. Henry Johnson (D-GA).
 - Pending passage in the House.
 - Almost identical to S.1416 (as to biosimilars litigation).
 - Caps the number of a subset of patents claimed by the reference product sponsor to 20; limits 10 of those 20 patents to those issued or licensed after the sponsor's initial list is sent.
 - Stated goal:
 - To streamline the process and reduce the burden of litigation.

Improving the Efficiency of Biosimilar Approvals:

Fixing the Regulatory “Dead Zone” for Insulin Products

The Regulatory “Dead Zone”

- Though insulin is a *biological product*, it has traditionally been approved as a *drug* under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA).
- Following the BPCIA’s direction that all applications to market *biological products*, including insulin, be submitted under section 351 of the Public Health Service Act (PHS) after March 23, 2020, FDA's inaction on final guidance for both "deemed" and "biological product" definition has led to a regulatory “dead zone.”
- FDA currently recommends applicants stuck in the dead zone abandon their section 505 applications and start the process anew under section 351.

The Regulatory “Dead Zone”

- The effects of the resulting dead zone are contrary to FDA’s stated goal of keeping drug prices low and accessible to consumers.
- Resubmission under section 351 may require additional clinical studies to demonstrate that the generic insulin product does not meaningfully differ from the reference product with respect to safety, purity, or potency.
- Longer pending approval for insulin products will result in longer periods of reference exclusivity, which expire upon transition of the product to a licensed biologic.
- Though FDA stated that it “intends to assist applicants” affected by the dead zone “where feasible and appropriate,” the situation likely will cause market entry delays for insulin products, driving insulin prices up and adversely impacting consumers and payors.

Legislative Proposals

- Efforts are concentrated on exempting generic insulin applications from the section 351 mandate.
- Affordable Insulin Approvals Now Act (S. 2103):
 - Sponsored by Senators Dick Durbin (D-IL), Kevin Cramer (R-ND), and Tina Smith (D-MN).
 - Exempts applications for generic insulin products submitted under section 505 of the FDCA before December 31, 2019 and that remain unapproved as of March 23, 2020.
 - Requires the FDA to label said approved applications as licensed biological products after the March 23, 2020 transition date.
 - Would result in quicker approval of tentatively approved generic insulin products awaiting the end of reference product exclusivity.
- The Bill is awaiting approval in the Senate.

Conclusions

Has FDA kept its promises outlined in the Biosimilars Action Plan?

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