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Review Article

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The Purple Book: Evaluations, Approvals and recent updates

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Abstract

The Purple Book is an informative database of all FDA-licensed biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products. and allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research (CBER). The current article emphasizes the significance of the Purple Book and the new law, The Purple Book Continuing Act enacted about approved patented biologic products, marketing status etc. The Act codifies a number of FDA's current Purple Book practices, and imposes a new requirement for publishing the reference product sponsor's "patent lists" exchanged in the so-called "patent dance" of BPCIA biosimilar litigation. Biologics approved for 2020-21 are listed.

Keywords: CDER, USFDA, BPCIA, Biological products, Purple Book, FDA, CBER, Biosimilar product

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1. Introduction

It is apparent that a bio-pharma product manufacturer would forever and a day first look for the existence of any similar product in the market. If it is to deal from the Regulatory perspective, the concern would be to chalk out their developmental/promotional strategies error-free. To enable all the generic drugs and biologics manufacturers be acquainted with the approved generic and biologic products, the United States Food and Drug Administration (USFDA) has introduced individual comprehensive repositories such as Purple Book and Orange Book.

Biological products include medications for treating many serious illnesses and chronic health conditions, including diabetes. A biosimilar is a biological product that is highly similar to, and has no clinically meaningful differences from, a biological product already approved by the FDA (also called the reference product). This means you can expect the same safety and effectiveness from the biosimilar as you would the reference product.

An interchangeable biosimilar product may be substituted for the reference product without the intervention of the prescriber. The substitution may occur at the pharmacy, a practice commonly called “pharmacy-level substitution”—much like how generic drugs are substituted for brand name drugs, subject to state pharmacy laws, which vary by state. Biosimilar and interchangeable biosimilar products have the potential to reduce health care costs, similar to how generic drugs have reduced costs. Biosimilars marketed in the U.S. typically have launched with initial list prices 15% to 35% lower than comparative list prices of the reference products.

The Purple Book is an informative database of all FDA-licensed biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products and allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research (CBER).

In February 2020, FDA released a searchable, online database that now replaces both lists and the information of biological products, regulated by CDER including any biosimilar and interchangeable biological products, licensed (approved) by the FDA and FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by CBER. It also includes information pertaining to exclusivity if the FDA has determined that a biological product is eligible for a relevant period of exclusivity. (1)

The article focused on the significance of the Purple Book, statutory updates on the recent laws, Biologics approved and the products recalled in 2020 and 2021

On March 6, 2015, the FDA approved the first biosimilar for distribution in the United States. This is a huge approval, and an accomplishment for the pharmaceutical company, Sandoz, and their biosimilar, Zarxio (filgrastim-sndz) to offer a reduced cost alternative therapy to their expensive biologic counterparts where there have been previously been no lower-cost options. Biologic drugs play an important role in healthcare and represent $232 billion in global revenue.1 Biologic drugs represent 25% of the total global pharmaceutical market.1 The number of biologic drugs approved by the US Food and Drug Administration (FDA) continues to increase, with 12 biologic drugs included in the 46 new molecular entities approved by the FDA in 2017.A total of 6 Biosimilars were approved in 2018. Subsequently FDA released the Biosimilars Action Plan in July 2018. On Dec 1st 2018 65 programs were enrolled in the Biosimilar Product Development (BPD) Program.

CDER has received meeting requests to discuss the development of Biosimilars for 33 different reference products. Since program inception and as of December 1, 2018, 14 companies have publicly announced submission of 26 351(k) BLAs to FDA. As of December 1, 2018, fifteen 351(k) BLAs for biosimilar products have been approved. (1)

Table 1. List of FDA approved Biosimilar Products in 2019-2020 (1-3)

S.NO	Biosimilar Name	Approved date	Reference Product
1	Ontruzant (trastuzumab-dttb)	January 2019	Herceptin (trastuzumab)
2	Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)
3	Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)
4	Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)
5	Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)
6	Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)
7	Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)
8	Ziextenzo (pegfilgrastim-bmez)	November 2019	Neulasta (pegfilgrastim)
9	Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)
10	Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)
11	Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)
12	Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)
13	Riabni (rituximab-arrx)	December 2020	Rituxan (rituximab)

Table 2. List of FDA approved BLA Products in 2021

S.NO	Biosimilar Name	Approved date
1	Source Plasma (prepared by plasmapheresis)	June 25, 2021
2	StrataGraft (Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)	Jun 15, 2021
3	Prevnar 20 (Pneumococcal 20-valent Conjugate Vaccine)	June 8, 2021
4	Ryplazim (plasminogen,human-tvmh)	Jun 4, 2021
5	Abecma (idecabtagene vicleucel)	March 26, 2021
6	Breyanzi (lisocabtagene maraleucel)	Feb 5, 2021

2. Biological Product- Biosimilar product-Reference products- Interchangeable products

A Biological Product is used to diagnose, prevent, treat and cure diseases and medical conditions, may be produced through biotechnology in a living system, such as microorganism. plant or animal cell, and are often more difficult to characterize than small molecule drugs. Biological products contain Vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, monoclonal antibodies and therapeutic proteins.

A **biosimilar product** is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and has no clinically meaningful differences in terms of safety, purity and potency (safety and effectiveness) from the reference product that is generally demonstrated through human pharmacokinetic(exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

A **reference product** is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and effectiveness data. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful differences.

Interchangeable products are biosimilar products that meet additional requirements outlined by the Biologics Price Competition and Innovation Act, 2009 and ammended in the Law of Patient protection and Affordable Care Act and signed on March 23rd 2010. An interchangeable product may be substituted for the reference product without the involvement of the prescriber. FDA's high standards for approval should assure health care providers that they can be confident in the safety and effectiveness of an interchangeable product, just as they would be for an FDA-approved reference product. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated. An interchangeable product may be substituted for the reference product without the involvement of the prescriber. FDA's high standards for approval should assure health care providers that they can be confident in the safety and effectiveness of an interchangeable product, just as they would be for an FDA-approved reference product.

Reference Product exclusivity

The Public Health Service (PHS) Act under Section 351(k)(7) of provides for periods of reference product exclusivity, beginning on the date on which the reference product (as that term is defined in section 351(i)(4)) is first licensed under section 351(a) of the PHS Act. Specifically, if the reference product is determined to be eligible for the periods of reference product exclusivity under this section, a 351(k) application may not be submitted for review to the FDA until the date that is 4 years after the date on which the reference product was first licensed, and approval of a 351(k) application may not be made effective until the date that is 12 years after the date on which the reference product was first licensed.

The reference product exclusivity expiration date indicates (1) the date that is 12 years after the date on which the reference product was first licensed as described in 351(k)(7); plus (2) any pediatric exclusivity granted pursuant to section 505(A) of the FD&C Act, if applicable.

First interchangeable Exclusivity date: It is the date that FDA determines that a second or subsequent biological product is interchangeable with a reference product. (3)

3. Display of unbranded biologics

An "unbranded biologic" is not an "interchangeable biosimilar and hence it is not separately identified in the Purple Book. However, an unbranded biologic is considered by FDA to be equivalent to its brand name biological product because it is the same product as the brand name biological product under the same BLA.

4. Updation of the Purple Book

An FDA-approved biological product or updates to an approved product's information will generally be added to the Purple Book within 10 business days of approval. Newly added drugs are indicated with a letter "N", Products added in the current release with "R" and updated products with the letter "U".

5. The Purple Book-Contents

The Purple Book includes:

- The date on which a biological product was licensed under section 351(a) or 351(k) of the Public Health Service Act (PHS Act).
- Whether a biological product licensed under section 351(k) of the PHS Act has been determined by the FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product).
- The date of expiration of applicable exclusivity, if FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) of the PHS Act or exclusivity for first interchangeable biological product under section 351(k)(6) of the PHS Act.

6. Significance of the Purple Book

- The Purple Book database contains information for multiple users (e.g., patients, the general public, healthcare providers, manufacturers, and researchers). The data can be searched using two types of search options: Simple Search and Advanced Search to access a product's labeling.
- Patients and the General Public may find the Purple Book 'Simple Search' useful to find information about a biological product they are currently taking or may be prescribed and to view options for FDA-approved biosimilar and interchangeable products.
- Healthcare Providers may find the Purple Book 'Simple Search' useful to see all associated products for a biological product they prescribe or are considering prescribing for a patient, including Biosimilars and interchangeable products.
- Healthcare providers may also find the 'Advanced Search' useful to search using additional terms, including strength, dosage forms, or product presentations (e.g., Autoinjector).
- The 'Product Label' (e.g., Prescribing Information) icon/link associated with each product in the database directs users to information a healthcare provider may find useful when prescribing a product.
- Manufacturers and Researchers may find the 'Advanced Search' useful as it allows users to view and sort all available information in a table format, as well as download the results and information as an Excel, CSV or PDF file.

7. Role of the Purple Book

- All NDA approved BLAs biological products on March 23, 2020 are included in the Purple

Book database and identifies the date of initial approved under Section 505 of the FD&C Act within 10 business days of approval.

- The Purple Book lists will identify the date of first licensure and the date that reference product exclusivity (including any attached pediatric exclusivity) will expire.
- All biological products approved in NDAs that were deemed to be BLAs on March 23, 2020 (transition biological products) are included in the Purple Book Database. (2)

8. The Purple Book Continuity Act

The Purple Book Continuity Act is a component of the Omnibus Appropriations Bill enacted on December 27, 2020, in Section 325 entitled "Biological Product Patent Transparency." The Act codifies current FDA Purple Book practices, but also imposes a new patent listing requirement.

In particular, the Act add a new paragraph (9) to 42 U.S.C. 262(k), entitled "PUBLIC LISTING." The provisions requires FDA to publish a list of approved biological products, their date of licensure and application number, their licensure and marketing status, and any regulatory exclusivity periods, and to update the list every 30 days. The patent listing requirement comes under (9)(A)(iii), entitled "PATENT INFORMATION," which states:

Not later than 30 days after a list of patents under subsection (l)(3)(A), or a supplement to such list under subsection (l)(7), has been provided by the reference product sponsor to the subsection (k) applicant respecting a biological product included on the list published under this subparagraph, the reference product sponsor shall provide such list of patents (or supplement thereto) and their corresponding expiry dates to the Secretary, and the Secretary shall, in revisions made under clause (ii), include such information for such biological product. Within 30 days of providing any subsequent or supplemental list of patents to any subsequent subsection (k) applicant under subsection (l)(3)(A) or (l)(7), the reference product sponsor shall update the information provided to the Secretary under this clause with any additional patents from such subsequent or supplemental list and their corresponding expiry dates. The effective date of these provisions of the Purple Book Continuity Act is June 25, 2021.

Biological Product Patent Transparency section of the Consolidated Appropriations Act of 2021: Purple Book listing requirements added

The Act enacted on December 27, 2020 emphasizes the following requirements and published the first provision of the public listing in accordance to the Biological Product Patent Transparency Act (BPPT). (4) The section of the legislation states that following 25th June, 2021 the list is available in an electronic format under section 351(a) or 351(k) of the Public Health Service Act. Further the list to be revised every 30 days.

Prior to the BPPT, reference product sponsors and biosimilars would exchange patent lists confidentially, under strict limitations on disclosure, as an early step in the patent dance. (5) (assuming the biosimilar elected to initiate the patent dance by disclosing its aBLA and other information specified by statute). (6) Now, however, the BPPT sets up a framework for FDA to receive and publish at least the reference product sponsor's lists of patents in the Purple Book.

Under the BPCIA, if a biosimilar sponsor chooses to engage in the "patent dance," the reference product sponsor will provide an "initial list" ("(*l*)(3)(A)" or "3A" list) to that biosimilar applicant, along with a "supplemental list" ("(*l*)(7)" list) of any additional patents that issued after the time for the "(*l*)(3)(A)" list. These lists identify the specific patents that the reference product sponsor believes may be infringed by the biosimilar, should that biosimilar's BLA be approved and its product marketed.

Recent updates

Today i.e., 28th July, 2021 the U.S. Food and Drug Administration approved the first interchangeable biosimilar insulin product, indicated to improve glycemic control in adults and pediatric patients with Type 1 diabetes mellitus and in adults with Type 2 diabetes mellitus. Semglee (insulin glargine-yfgn) is both biosimilar to, and interchangeable with (can be substituted for), its reference product Lantus (insulin glargine), a long-acting insulin analog. Semglee (insulin glargine-yfgn) is the first interchangeable biosimilar product approved in the U.S. for the treatment of diabetes. Approval of these insulin products can provide patients with additional safe, high-quality and potentially cost-effective options for treating diabetes. (6)

9. Conclusion

The Purple Book proved to be an informative database of all FDA-licensed biological products regulated by the CDER, including licensed biosimilar and interchangeable products, and their reference products and allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by CBER. The current article emphasizes the significance of the Purple Book and the new law, The Purple Book Continuing Act enacted about approved patented biologic products, marketing status etc. The Act codifies a number of FDA's current Purple Book practices, and imposes a new requirement for publishing the reference product sponsor's "patent lists" exchanged in the so-called "patent dance" of BPCIA biosimilar litigation. Type 2 diabetes mellitus- Semglee (Insulin) came & approval of these insulin products can provide patients with additional safe, high-quality and potentially cost-effective options for treating diabetes.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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