



Approximate study time: 30 minutes



Level: Introductory/Intermediate



Audience: Regulatory



Category: Regulatory Submissions



Region: USA



CPD Points: 0.5

The regulation of biological medicinal products is governed by different laws from those that apply to small-molecule synthetic drugs. Producing faithful copies of therapeutic proteins is more challenging than producing generic drugs. The US legal framework for the licensure of follow-on biologics, and accompanying regulatory guidance from the Food and Drug Administration (FDA), have been established only in recent years.

We describe the provisions of the Biologics Price Competition and Innovation Act, identify criteria for licensing a follow-on biologic as 'biosimilar' or 'interchangeable', specify periods of market exclusivity that apply, and discuss patent infringement issues.

Finally, we describe the provisions of the Biosimilar User Fee Act, which authorises the FDA to collect fees from follow-on biologics sponsors, to support review activities.



Who will benefit from this module?

This module will mainly benefit regulatory affairs staff concerned with the licensure of follow-on biological products.



Learning objectives

- Outline the provisions of the Biologics Price Competition and Innovation Act
- Identify criteria for licensure of a follow-on biologic as biosimilar or interchangeable
- Specify periods of market exclusivity applicable to biological medicinal products
- Outline patent infringement issues relevant to biological medicinal products
- Access FDA guidance on development and licensure of follow-on biologics
- Outline the provisions of the Biosimilar User Fee Act

**Exclusivity for reference product**

The FDCA grants 12 years of exclusivity to license holders of new, innovative biological products, to run concurrently with patent term protection. Click on the Plus (+) icons for more information.

Reference	Withdraw	Request opportunity for hearing
No 30-day application may be submitted until 4 years from the date on which the reference product was first licensed by the FDA.	No approval of a 30-day application may be made effective until 12 years from the date on which the reference product was first licensed by the FDA.	An additional 6 months of exclusivity may be obtained for approved patents or orphan indications.

**Patent infringement issues**

**180 days' notice of marketing**

The applicant must provide reference product sponsor with 180 days' notice before commercial marketing, thus allowing the reference product sponsor to seek a preliminary injunction against the follow-on biologic entering the market. A decision by the US Supreme Court in June 2017 clarified that the applicant may give such notice before obtaining licensure of its product.

**The Purple Book**

By analogy with its 'Orange Book', which lists approved small-molecule drugs, the FDA has created a list of licensed biological products, showing any biosimilar or interchangeable products in each case - the Purple Book.

The Purple Book is available on the FDA website. Information about each product comprises:

- BL Number
- Product name
- Proprietary name
- Date of licensure
- Date of first licensure
- Reference product exclusivity expiry date
- Interchangeable or biosimilar status
- Withdrawn

A link to the Purple Book online can be found in the additional resources.

**Demonstrating interchangeability**

In May 2019 the FDA finalised guidance to assist sponsors in demonstrating the interchangeability of their product with a reference product for the purposes of submitting a 301(b) (2)(A) application or supplement.

The guidance provides an overview of important scientific considerations in demonstrating interchangeability, including:

- data and information needed
- the design and analysis of a switching study or studies
- the reference product in such a study
- developing presentations, container closure systems, and delivery device components plans for proposed interchangeable products
- establishing safety monitoring

A switching study is a clinical study to determine the impact of alternating or switching between the proposed interchangeable product and the reference product. The main purpose is to show that the risk in terms of safety or decreased efficacy is not greater than the risk of using the reference product alone.

**Non-proprietary naming of biologics**

**Suffixes**

The convention requires that a unique, FDA-designated, recognisable base name suffix, preceded by a hyphen, be appended to the core name for the product. The core name is the subject name designated by the USAN Council for the biological substance, when available. For example, Reparatim (core name) may become Reparatim-suffix. A biosimilar version of this biological medicinal might be named replicatim-suffix.

**Biosimilar User Fee Act**

The Biosimilar User Fee Act of 2012 (BUA) authorises the FDA to collect fees from follow-on biologics sponsors, to support review activities.

Fee rates are published in the Federal Register and on the FDA website.

FDA performance goal types are similar to those for the Prescription Drug User Fee Act (PDUFA), with some differences in treatment.

The second administration of the Act, applying to FY 2018 through 2022, establishes an improved fee structure for follow-on biologics, based on an Initial Biosimilar Development Fee for the first year once a sponsor begins clinical trials, an Annual Biosimilar Development Fee for subsequent years of development of the product, a Biosimilar Program Fee for sponsors to approved follow-on biologics, and an Application Fee for new applications for licensure.

**Criteria for licensure as biosimilar**

A 301(b) application must contain information demonstrating that the applicant's product meets a range of criteria for licensure. Click on the headings for the criteria.

- >Biosimilarity
- >Mechanism of action
- >Conditions of use
- >Administration, form, strength
- >Manufacture