Labeling for Biological Products

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CDER Prescription Drug Labeling Conference
December 5, 2019

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- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
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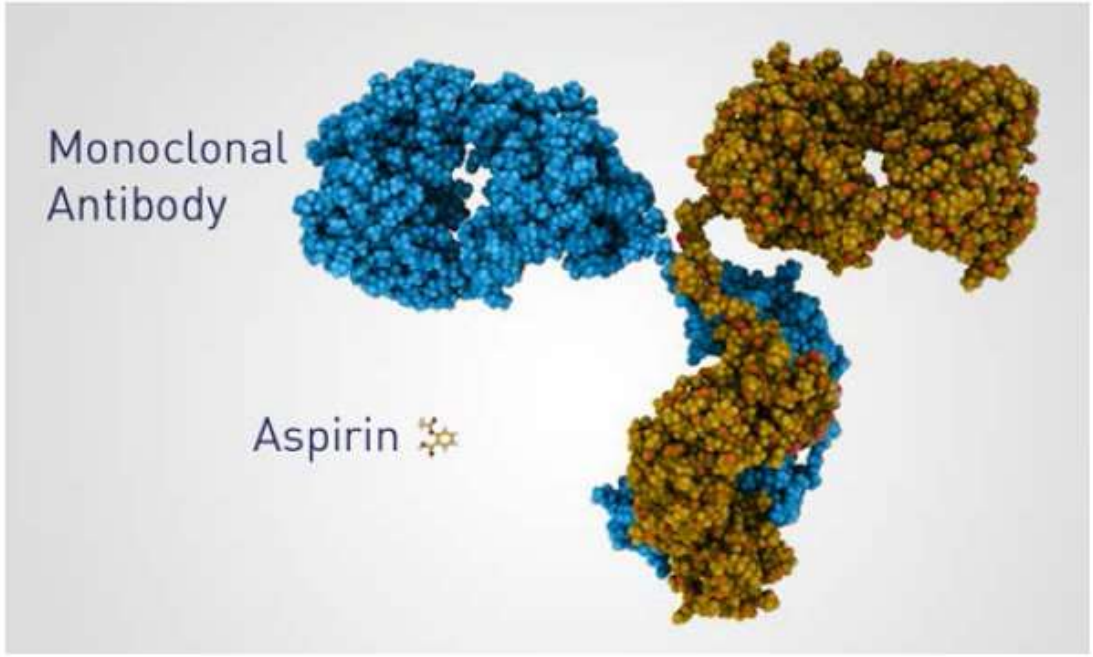
Agenda

- Background
- Labeling and Biosimilars
- Labeling and Transition Products

Background

What Are Biological Products?

- A biologic is produced in a living system such as a microorganism (yeast, bacteria), or plant or animal cells.
- Most biologics are very large, complex molecules or mixtures of molecules.
- A drug is typically a small, single version active ingredient that results from combining specific chemicals in an ordered process.



- Aspirin has 21 Atoms compared to the Monoclonal Antibody (mAb) that has 25,000 Atoms. The mAb also weighs about 800 times more than the Aspirin.

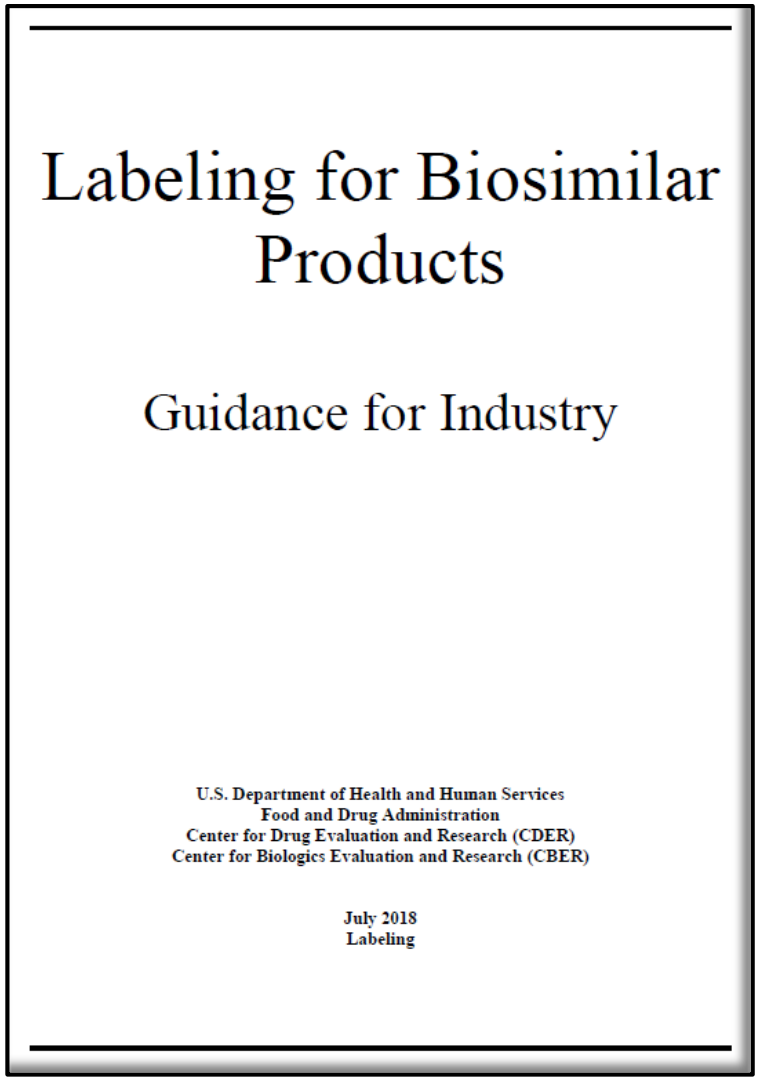
Biological Product Regulation

- **351(a) "stand alone" BLA:** contains all information and data necessary to demonstrate that the proposed biological product is safe, pure and potent

- The Biologics Price Competition and Innovation Act of 2009 (BPCI Act)
  - Created an **abbreviated licensure pathway (351(k))** for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product (originator biological product)
  - Amended the **definition of "biological product"** in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)"

Labeling and Biosimilars

Guidance



- Guidance to assist applicants in developing draft labeling for proposed biosimilar products
- Recommendations for FDA-approved Prescribing Information as well as Patient Information, Medication Guides, and Instructions for Use
- FDA intends to provide recommendations for interchangeable product labeling in future guidance

General Principles

A biosimilar product is not required to have the same labeling as its reference product, so biosimilar product labeling may differ from the reference product labeling for a variety of reasons. For example:

- A biosimilar applicant may seek licensure for fewer than all of the indications for which the reference product has been previously approved, and this difference would be reflected in product labeling.
- Labeling may include information specific to the biosimilar product, which could include differences such as preparation or storage, that do not otherwise preclude a demonstration of biosimilarity.
- Conforming to PLR and/or PLLR because the reference product labeling may not be required to conform to those requirements at the time of licensure of the biosimilar product.

General Principles

- FDA recommends that biosimilar product labeling incorporate relevant data and information from the FDA-approved labeling for the reference product, along with any appropriate modifications specific to the biosimilar product.
- FDA generally recommends that clinical data supporting the demonstration of biosimilarity not be included in biosimilar product labeling.
  - Data supporting a demonstration of biosimilarity, including the comparative clinical data, can be found in FDA's product reviews at the Drugs@FDA website.
- FDA recommends that Highlights of Prescribing Information contain a "Biosimilarity Statement" describing the meaning of approval as a biosimilar.

Biosimilarity Statement

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol

Initial U.S. Approval: YYYY

NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf).

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------

Section Title, Subsection Title (x.x) M/YYYY
Section Title, Subsection Title (x.x) M/YYYY

----------INDICATIONS AND USAGE----------

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use
Text (1)

----------DOSAGE AND ADMINISTRATION----------

- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------

Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------

- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------

- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of NEXSYMEO as been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) ofadministration described in its Full Prescribing Information.

Revised: M/YYYY

Nonproprietary Naming of Biological Products

Updated draft guidance published in March 2019

- Newly licensed under section 351(a):
  - Nonproprietary name consists of the core name and unique suffix
- Newly licensed under section 351(k):
  - Nonproprietary name consists of the core name and unique suffix
- Already licensed under section 351(a) without a suffix:
  - Nonproprietary name will not be changed to add a suffix
- Transition products:
  - FDA does not intend to apply the naming convention

Product Identification

- **Biosimilar product name**: NEXSYMEO (replicamab-cznm)
  - Information specific to the biosimilar product
  - Directive statements and recommendations for monitoring, managing, or mitigating risks
- **Reference product name**: JUNEXANT (replicamab-hjxf)
  - Clinical studies or data derived from studies with the reference product
- **Core name + "products"**: replicamab products
  - Overall risk-benefit profile of the reference product is relevant to the biosimilar product, even if a particular serious adverse reaction or other risk included in the reference product labeling may not have been reported with the biosimilar product at the time of licensure

Product Identification (Example)

Reference Product Labeling

JUNEXANT can cause acute hepatic failure. In clinical trials with JUNEXANT, 10% of patients developed elevated ALT and 5% progressed to acute hepatic failure. Evaluate ALT at baseline and monthly during treatment with JUNEXANT.

Biosimilar Product Labeling

Replicamab products can cause acute hepatic failure. In clinical trials with replicamab-hjxf, 10% of patients developed elevated ALT and 5% progressed to acute hepatic failure. Evaluate ALT at baseline and monthly during treatment with NEXSYMEO.

Considerations When Responding to Agency Comments

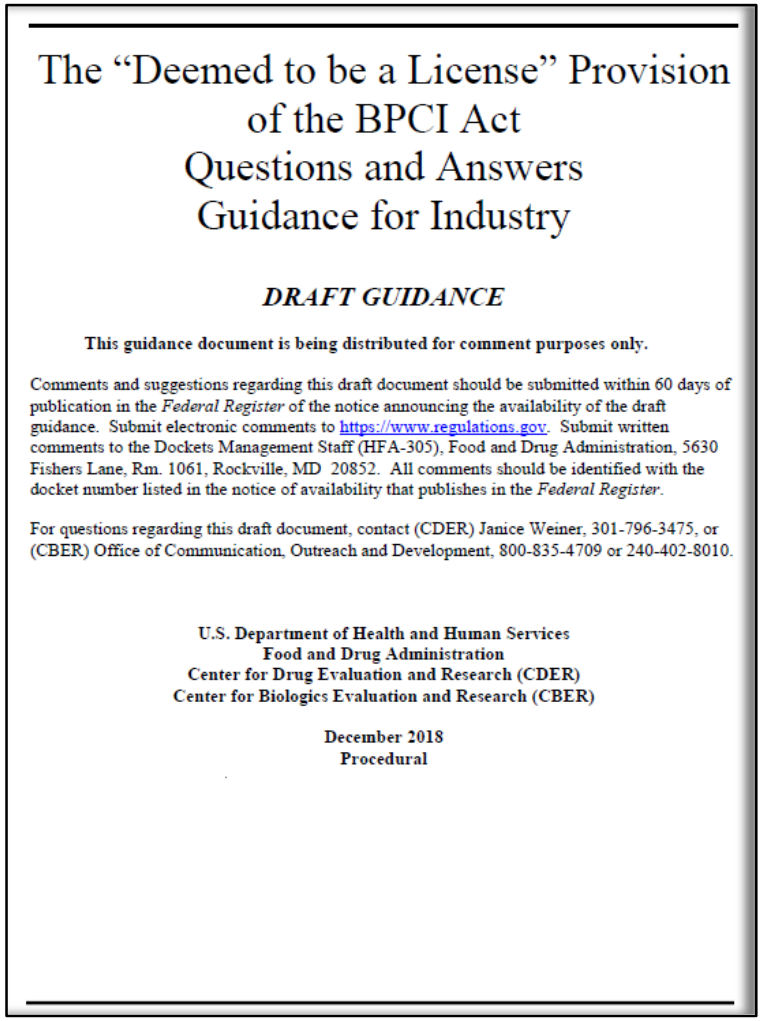
- Accept changes you agree with, including format/editorial changes
- Provide justification as a comment for changes you do not agree with (do not use the “reject” function when addressing FDA proposed changes)
- Edits you wish to propose:
  - Add via track changes and provide justification as a comment
  - Update formatting as necessary

Labeling and Transition Products

Transition Products

- Some proteins have been approved as drugs under section 505 of the FD&C Act (e.g., insulin and insulin analogs, somatropin, pancreatic enzyme products, follitropin)
- BPCI Act amended the definition of **"biological product"** in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)"
- FDA guidance explained that approved NDAs for "deemed products" will be **transitioned to 351(a) BLAs**
- Applicants can seek licensure under section 351(k) of products that are biosimilar to, or interchangeable with, transitioned reference products

Transition Products and Labeling



The "Deemed to be a License" Provision of the BPCI Act
Questions and Answers
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Janice Weiner, 301-796-3475, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2018
Procedural

- Most labeling requirements are the same for BLAs and NDAs
- There are some minor differences, as detailed in guidance
- FDA is committed to working with application holders to minimize any potential burden

Transition-Labeling Compliance Policy

- FDA has announced a compliance policy for the labeling of biological products that are the subject of deemed BLAs
  - This should minimize possible disruption and burden associated with differences in NDA and BLA labeling
- FDA does not intend to enforce BLA labeling requirements for transition products until March 23, 2025
  - If during the compliance period a deemed BLA-holder submits a supplement with proposed labeling revisions, the BLA specific labeling requirements will need to addressed before the supplement can be approved
  - FDA recommends submission of a prior approval supplement within two years after the transition date

Question

The labeling for JUNEXANT (replicamab-hjfx) states:

> Treatment with JUNEXANT increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization and death.

Which product identification term would be consistent with the Biosimilar Labeling Guidance for the labeling of NEXSYMEO (replicamab-cznm), a proposed biosimilar to JUNEXANT?

(a) JUNEXANT
(b) NEXSYMEO
(c) replicamab-cznm
(d) replicamab products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