Biosimilar Biological Products

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FDLI

Agenda

- Definitions and Background
- Biosimilar Pathway
- Related Issues (Naming, Labeling, Etc.)
- Interchangeable Biological Products
- Reference Product Exclusivity and Patent Provisions
- Transition Provisions

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- **Definitions and Background**
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Definitions and Pathways

- **Drug (FDCA § 201(g)(i))**
  - "The term "drug" means . . . articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals . . . and . . . articles (other than food) intended to affect the structure or any function of the body of man or other animals . . . ."
- **Biological Product (PHSA § 351(i))**
  - A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Question

- **Why are drugs and biologics regulated differently?**
  A. It was easier to draft biologics legislation separately
  B. Biologics were developed later in time
  C. To provide more information for us to learn
  D. Congress focused on drugs first
  E. Statutory construction rules
  F. Some other reason

History

- **Early history**
  - The Biologics Act of 1902
- **Middle history**
  - Effect of the Federal Food, Drug, and Cosmetic Act of 1938: FDCA does not affect, modify, repeal, or supersede the Biologics Act (sec. 1002(b)).
  - Effect of the Public Health Service Act (PHSA) of 1944
- **Recent history**
  - PDUFA, FDAMA harmonization, and FDAAA
  - Jurisdictional transfer of therapeutic proteins to CDER
  - Biologics Price Competition and Innovation Act (BPCIA)

History

- **Biologics reorganization**
  - Transferred to CDER
    - Monoclonal antibodies
    - Cytokines, growth factors, enzymes, and interferons
    - Proteins for therapeutic use
    - Therapeutic immunotherapies
  - Remaining in CBER
    - *Ex vivo* reagents
    - Gene therapy
    - Human and animal cells
    - Blood, blood products, plasma extenders
    - Vaccines, toxins, allergenic extracts, etc.

Applicability of FDCA to Biologics

- Investigational New Drug Application (and all related regulations) for investigational products apply
- Prescription Drug User Fee Act applies (to innovative products)
- Risk evaluation and mitigation strategy (REMS) authorities apply
- Mandatory post-approval study authority applies
- Orphan Drug Act applies

Key Regulation Counterparts

Issue	Drug Regulation	Biologics Regulation
INDs	Part 312	601.21 (says part 312 applies)
Marketing application content	314.50, 314.54, 314.94	601.2
Adverse Event Reporting	314.80	600.80
Deviation Reporting	314.81	600.14
Changes to approved application	314.70	601.12

Two Statutory Frameworks

New Drug Application (NDA)	Biologics License Application (BLA)
• Approved under the Federal Food, Drug, and Cosmetic Act (FDCA) • Small molecule drugs; peptides • Full NDAs under section 505(b)(1) of the FDCA • Follow-on applications under sections 505(j) & 505(b)(2)	• Licensed under the Public Health Service Act (PHSA) • E.g., monoclonal antibodies, fusion proteins, vaccines, gene therapies • Transition proteins previously approved under FDCA • Full BLAs under section 351(a) of the PHSA • Biosimilar applications under section 351(k)

Definitions and Pathways

- Section 351(a) BLA route:
  - Applicant shows that biological product is safe, pure, and potent
- Section 351(k)
  - "Biosimilar" – applicant shows that biological product is "biosimilar" to a single "reference product" (RP) licensed under section 351(a) of the PHSA
    - Highly similar to RP notwithstanding minor differences in clinically inactive components; and
    - No clinically meaningful differences from RP in safety, purity, and potency
  - "Interchangeable" – the product may be substituted for the RP without the intervention of the health care provider who prescribed the RP

Showing Biosimilarity

- "**Safety**" means "relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered"
- "**Purity**" means the finished product is "relative[ly] free[]" from "extraneous matter," including moisture, other volatile substances, and pyrogens
- "**Potency**" means the product's "specific ability or capacity . . . to effect a given result" based on laboratory testing or controlled clinical data
  - FDA has interpreted "potency" to include effectiveness

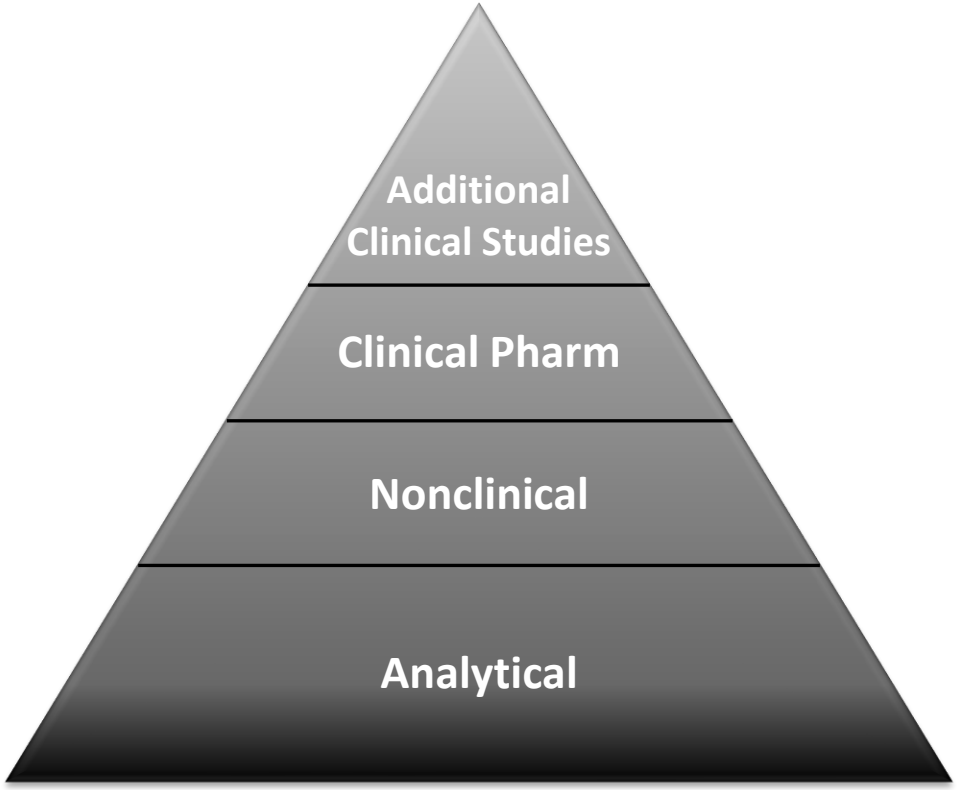
Showing Biosimilarity

- Must show biosimilarity standard is met based on:
  - Analytical studies showing biosimilar is “highly similar” to RP “notwithstanding minor differences in clinically inactive components”;
  - Animal studies; and
  - A clinical study or studies (including assessment of immunogenicity and pharmacokinetics or pharmacodynamics) sufficient to show safety, purity, and potency in 1 or more appropriate proposed conditions of use for which RP is licensed
- FDA may waive any of these data requirements upon a finding that the data are “unnecessary”

Showing Biosimilarity

- Same mechanism(s) of action (if known) as the RP
- Proposed conditions of use previously approved for RP
- Same route of administration, dosage form, and strength as RP
- Comply with good manufacturing practices (GMP)
- Consent to inspection

FDA's Approach to Biosimilarity



FDA's Approach to Biosimilarity

- Applicant should use a stepwise approach: each step should assess "residual uncertainty" about biosimilarity
- FDA uses a totality of the evidence approach to evaluating biosimilarity
  - Risk-based approach to evaluate all available data and information submitted in support of biosimilarity, including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical data

FDA's Approach to Biosimilarity

- Importance of analytical testing
  - "Extensive" structural and functional characterization is the "foundation" of a biosimilar program
  - Factors that may justify "a selective and targeted approach to animal and/or clinical studies"
    - "[R]igorous structural and functional comparisons" showing "minimal or no difference" in the products
    - Understanding of mechanism of action and clinical relevance of observed structural differences
    - Clinical knowledge of the reference product and its class
    - Availability of relevant pharmacodynamic measure(s)

FDA's Approach to Biosimilarity

- Nature and scope of clinical studies depends on residual uncertainty about biosimilarity after analytical testing
  - Comparative pharmacokinetic and pharmacokinetic studies are fundamental to demonstrate biosimilarity
  - Clinical immunogenicity assessment needed to evaluate differences in immune response
  - Comparative clinical study needed if there is residual uncertainty about whether there are clinically meaningful differences
  - Extrapolation may be acceptable to support biosimilarity for additional conditions of use

Guidance on Permitted Differences from RP

- Biosimilar applicant can obtain licensure for fewer than all RP:
  - Routes of administration (where RP is injectable);
  - Presentations (e.g., strengths, delivery devices/closures)
  - Conditions of use
- FDA may accept some differences in:
  - Formulation
  - Delivery device/container closure system
  - **But** changes cannot result in **clinically meaningful differences, different dosage form, route of administration, or new condition of use** (e.g., indication, dosing regimen) for which RP has not been approved

Use of Data from Non-U.S. Comparator

- Statute requires showing biosimilarity to a single reference product licensed by FDA under section 351(a) of PHSA
- Guidance:
  - Sponsor can provide comparative data against non-U.S. licensed comparator product to support biosimilarity
  - Need to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product
  - Generally need analytical and clinical PK/PD study directly comparing biosimilar to RP “unless it can be scientifically justified that such a study is not needed”

Interacting with FDA

- Biosimilar Initial Advisory meeting: discussion regarding whether biosimilar pathway is feasible for product, and, if so, general development advice (≤ 90 days of request; 75 days in BsUFA II)
- Four types of Biosimilar Product Development (BPD) Meetings:
  - Type 1: For otherwise stalled BPD program (≤ 30 days after request)
  - Type 2: To discuss targeted issues (≤ 75 days; 90 days in BsUFA II)
  - Type 3: In-depth data review for ongoing BPD program (≤ 120 days after request)
  - Type 4: Discuss format and content of biosimilar application (≤ 60 days after request)

User fees for Biosimilar Applications (FY 2021-2022)

User Fee Type		FY 2021	FY 2022
Biosimilar Biological Product Development (BPD) Fee	Initial BPD	$ 102,494	$ 57,184
	Annual BPD	$ 102,494	$ 57,184
	Reactivation	$ 204,988	$ 114,368
Application Fee	Clinical Data Required	$ 1,746,745	$ 1,746,745
	Clinical Data not Required	$ 873,373	$ 873,373
Program Fee		$ 304,162	$ 304,162

Biosimilars Application Review

- Biosimilar User Fee Act (BsUFA) II Goals Letter (FY 2018-2022):
  - Review and act on 90 percent of **original biosimilar application** submissions within **10 months** of the 60-day filing date
  - Review and act on 90 percent of **resubmitted original biosimilar applications** within **6 months** of receipt
  - Review and act on 90 percent of **original supplements with clinical data** within **10 months** of receipt

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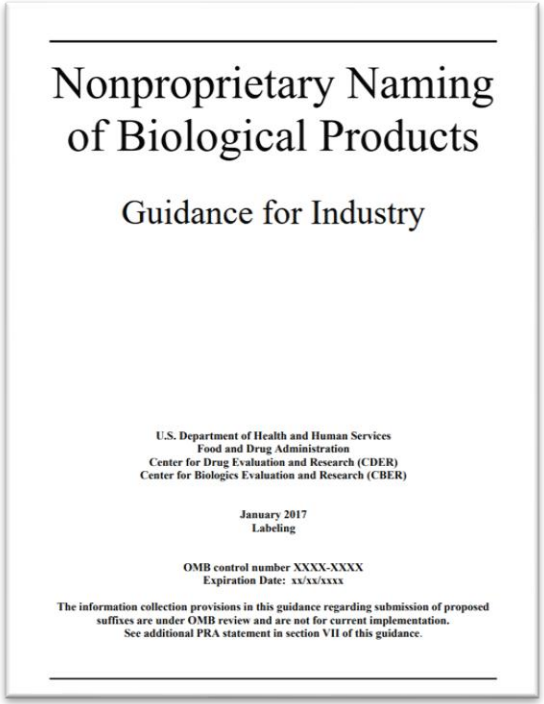
Guidance on Nonproprietary Names

- Guidance finalized in January 2017
- Goals:
  - Enhance biological product pharmacovigilance
  - Ensure safe use for biological products
  - Advance appropriate practices and perceptions regarding biological products
  - Prospective and retrospective application of naming convention



Nonproprietary Naming of Biological Products

Guidance for Industry

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)

January 2017
Labeling

OMB control number XXXX-XXXX
Expiration Date: xx/xx/xxxx

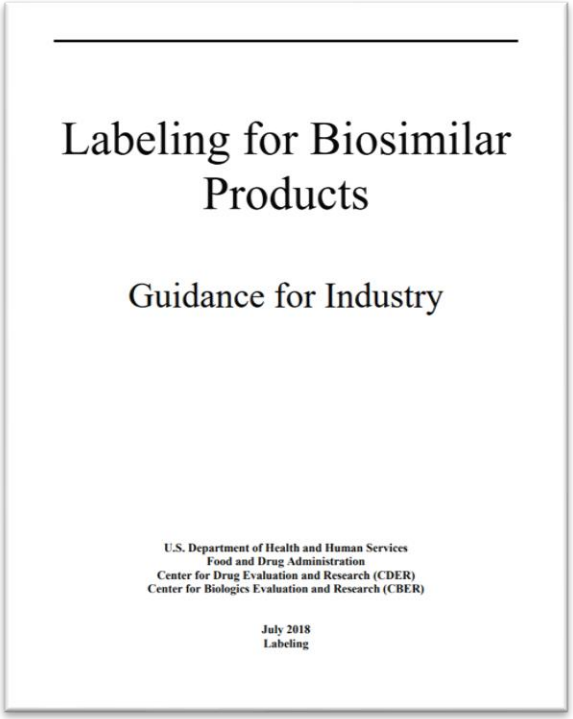
The information collection provisions in this guidance regarding submission of proposed suffixes are under OMB review and are not for current implementation.
See additional PRA statement in section VII of this guidance.

Guidance on Nonproprietary Names

- For all biological products, nonproprietary name will consist of a “core name” and a designated suffix
- FDA plans to apply this approach to all biologics prospectively and retrospectively
- Core name generally is the United States Adopted Name for RP drug substance
- Proposed suffix should be:
  - Four lowercase letters, of which at least three are distinct
  - Unique and nonproprietary
  - Devoid of meaning
  - Should not look similar to or otherwise connote the name of the license holder
- Example: “replicamab-cznm”

FDA Guidance on Biosimilar Labeling

- Guidance finalized in July 2018
- Content of biosimilar product labeling:
  - Product identification
  - Content presentation
  - Specific sections
  - Revising biosimilar product labeling


Labeling for Biosimilar Products

Guidance for Industry

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)

July 2018
Labeling

FDA Guidance on Biosimilar Labeling

- Calls for a biosimilarity statement at the beginning of the biosimilar labeling as follows:

  "[BIOSIMILAR PRODUCT'S PROPRIETARY NAME (biosimilar product's proper name)] is biosimilar to [REFERENCE PRODUCT'S PROPRIETARY NAME (reference product's proper name)] for the indications listed."*

  **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.*

FDA Guidance on Biosimilar Labeling

- Labeling will include information on comparative clinical biosimilarity studies only when "necessary to inform safe and effective use"
- Labeling should "include a description of the clinical data that supported safety and efficacy of [RP]" as described in RP labeling
  - FDA recommends that the biosimilar product name—the proprietary name if there is one—be used in biosimilar-specific labeling text
  - Nonproprietary name of RP (with its unique suffix) would be used to refer to data from the reference product, including in the clinical studies section
  - When referring to both products, use the general descriptor "[core nonproprietary name] products," e.g., "filgrastim products"

Example from Guidance

Replicamab products can cause hepatoxicity and acute hepatic failure. In clinical trials of **replicamab-hjxf**, 10% of patients developed elevated ALT or AST greater than three times the upper limit of normal and 5% progressed to acute hepatic failure. Evaluate serum transaminases (ALT and AST) and bilirubin at baseline and monthly during treatment with **NEXSYMEO** . . .

JUNEXANT *(replicamab-hjxf)* is fictional reference product

NEXSYMEO *(replicamab-cznm)* is fictional biosimilar

Postmarketing Labeling Changes

- When new information becomes available that causes information in labeling to be inaccurate, application holder must take steps to change the content of its product labeling
- Biosimilar applicant may seek licensure for an additional condition(s) of use of RP by submitting an efficacy supplement
- No same labeling requirement

Pharmacovigilance and REMS

- Postmarketing safety monitoring should have mechanisms to differentiate between adverse events associated with the biosimilar and RP
- REMS authority is applicable to biosimilars to same extent and in same manner as for innovator biologics

Pediatric Assessments

- Sponsor of a non-interchangeable biosimilar product will need to submit pediatric assessments unless FDA defers or waives
- Biosimilar sponsors may be able to use extrapolation to fulfill PREA requirements if RP labeling is adequate for given indication and applicant justifies extrapolation from RP pediatric information to biosimilar
- Interchangeable biosimilars exempt from PREA

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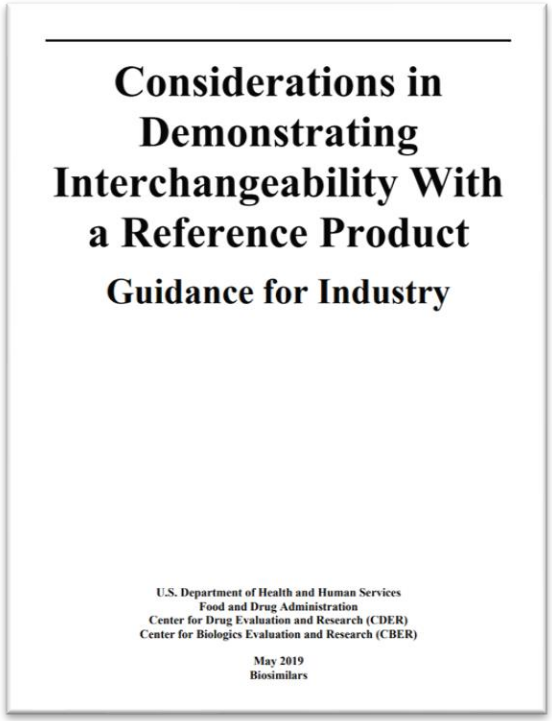
Interchangeability: Statute

- Application must show that:
  - Product is biosimilar to RP
  - Product "can be expected to produce the same clinical result as [RP] in any given patient"
  - "For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of [proposed product and RP] is not greater than the risk of using [RP] without such alternation or switch"
- The first interchangeable biosimilar for an RP is entitled to one year of exclusivity.

Guidance on Interchangeability

- Draft January 2017; finalized May 2019
- Addresses topics including:
  - Data and information needed to support interchangeability
  - Design of a switching study or studies to support such a demonstration
- Theme: FDA will evaluate data needed to show interchangeability on a case-by-case basis


Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

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)

May 2019
Biosimilars

Guidance on Interchangeability

- “FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as [RP] in all of [RP’s] licensed conditions of use”
- Sponsors may extrapolate data supporting interchangeability in one condition of use to support other conditions of use

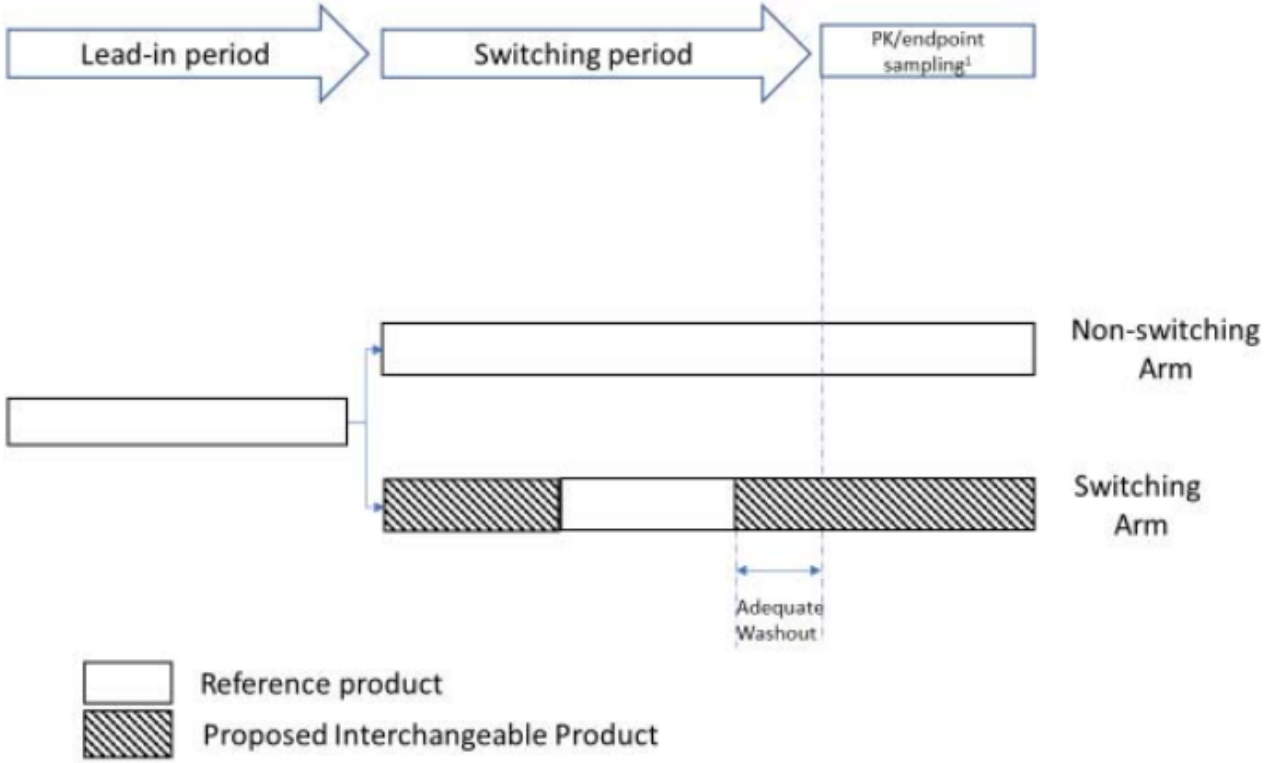
Guidance on Interchangeability

- Postmarketing data alone generally will be insufficient
- “In certain situations,” postmarketing surveillance data may be needed to support interchangeability
- “[T]here may be situations where a postmarketing study, in addition to postmarketing surveillance data” may be needed

Guidance on Interchangeability

- A switching study or studies will be expected to demonstrate interchangeability for multiple-use products
- Two designs for switching studies:
  - Dedicated switching study
  - Integrated two-part design
- Studies should assess at least three switches, with the last switch from RP to the proposed product
- Recent guidance on insulin immunogenicity

Guidance on Interchangeability



[1]Appropriate PK parameters and other endpoints (e.g., PD) also collected and analyzed in previous switch intervals.

Figure is not drawn to scale.

Guidance on Interchangeability

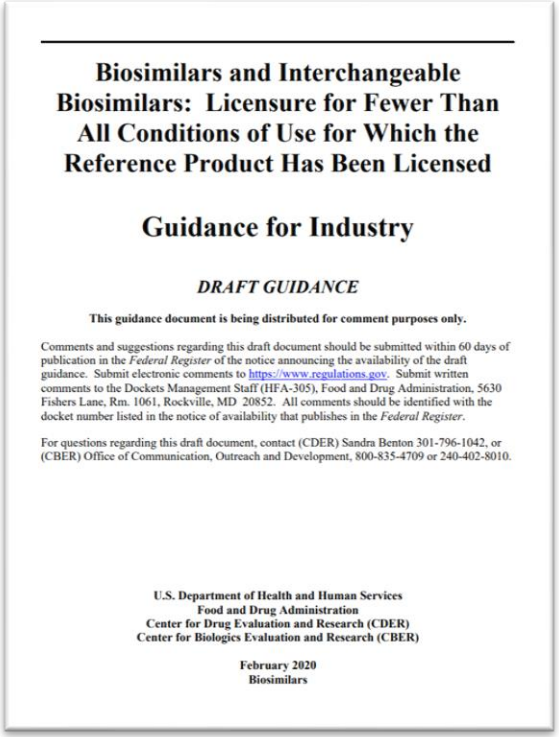
- Use of U.S.-licensed RP as comparator recommended
  - Due to “subtle differences in the levels of specific structural features (e.g., acidic variants, deamidations), process related impurities or formulation,” “multiple exposures to each product may potentially prime the immune system to recognize subtle differences in structural features between products [and] [t]he overall immune response could be increased under these conditions.”
- Sponsors will need to conduct analyses of the proposed product’s presentation to demonstrate interchangeability
  - Testing may be needed in the event of “other than minor” differences in presentation design

State Substitution Laws

- Under many state laws, only interchangeable biosimilars are automatically substitutable for the prescribed reference biologic
- Some state require prescriber notification and recordkeeping when pharmacists substitute

Draft Guidance on Labeling Carve-Outs & Carve-Ins

- Draft Guidance released February 2020
- Addresses carve-outs
- Addresses situation where 351(k) applicant seeks to add to its labeling a condition of use previously omitted
- FDA commits to expedited review



Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed

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) Sandra Benton 301-796-1042, 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)

February 2020
Biosimilars

Labeling Carve-Outs ("skinny" labels)

- A biosimilar applicant is expected to submit draft labeling that includes the conditions of use for which the applicant is seeking licensure
  - "An applicant generally may obtain licensure of a biosimilar or interchangeable for **fewer** than all of the conditions of use for which the reference product is licensed," but FDA recommends seeking licensure for all of the RP's licensed conditions of use **when possible**
  - Might not be possible due to:
    - Regulatory exclusivity
    - Patents
    - Other reasons

Skinny Labels and Induced Infringement

- 35 U.S.C. 271(b): "Whoever actively induces infringement of a patent shall be liable as an infringer."
- Example:
  - Patent claims a method of **treating Ailment A** by administering **Product X**
  - RP is Product X
    - RP labeling includes indications for treating Ailment A, Ailment B, and Ailment C
  - Biosimilar is Product X-xyza
    - Biosimilar label could state that it treats Ailment A, Ailment B, and Ailment C, or it could include only some of those indications

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Overview of Relevant Statutory Exclusivities

	Drugs Approved in NDAs	Biologics Approved in BLAs
Abbreviated Pathway(s)	ANDAs, 505(b)(2) NDAs	351(k) BLAs (biosimilars)
Statutory Exclusivity	• 5 year new chemical entity exclusivity (bar on follow-on submission) • 3 year new clinical investigation exclusivity (bar on approval) • Orphan-drug exclusivity available if rare disease or condition • Pediatric exclusivity extension	• Reference product exclusivity: 4 year and 12 year bars on 351(k) submission and approval, respectively • First licensure exception • Orphan-drug exclusivity available if rare disease or condition • Pediatric exclusivity extension

Innovator Exclusivity

*Potential for 6 month extension due to pediatric exclusivity
Note: 7 years of orphan exclusivity may also apply

“First Licensure” Provision

- Biosimilar applications may not be:
  - submitted until 4 years after first licensure of RP
  - approved until 12 years after first licensure of RP
- These provisions **“shall not apply to”**:
  - Supplement for RP
  - Subsequent BLA
    - filed by the same sponsor or “a licensor, predecessor in interest, or other related entity” for:
    - a **non-structural change**
      - that results in new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    - a **structural change**
      - that does **not** result in a change in safety, purity, or potency

Exclusivity Draft Guidance: "First Licensure"

- FDA will determine "related entity" status based on:
  - Ownership and control of companies, or
  - Engagement in "certain commercial collaborations" relating to development of the product(s) at issue
- FDA proposes to interpret "licensor" to include "entities that continue to retain . . . rights to intellectual property that covers the biological product"

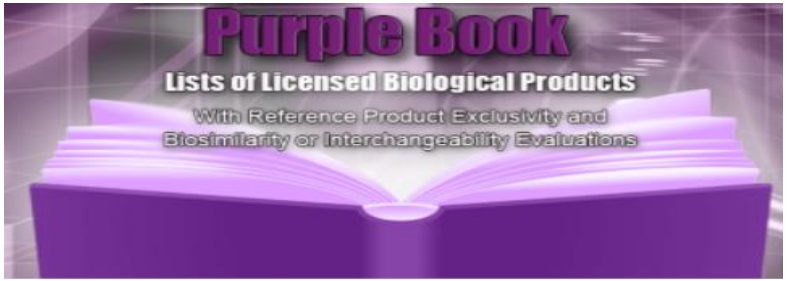
Exclusivity Draft Guidance: “First Licensure”

- **Structural Modification:**
  - “any” differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including pegylation), and infidelity of translation or transcription
- **Results in a Change in Safety, Purity, or Potency:**
  - Determination will be made on case-by-case basis and “generally” will need to be based on data
  - “The supporting information provided should include **measurable effects** (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays) clearly describing how the modification resulted in a change in safety, purity, or potency compared to the previously licensed product”
  - Presumption in case of different molecular target

Exclusivity Draft Guidance: "First Licensure"

- Burden on applicant to establish first licensure?
  - Draft Guidance describes the "information that [RP] sponsors should provide to facilitate FDA's determination of the date of first licensure"
- The "determination of the date of first licensure and of eligibility for exclusivity may not always be made at the time of licensure"

The Purple Book



- CBER and CDER list:
  - Date of licensure
  - Date of first licensure (i.e., exclusivity start date)
  - RP exclusivity expiry data
  - Biosimilar/interchangeable status
- "FDA will generally make a determination of date of first licensure for reasons of regulatory necessity and/or at the request of the 351(a) application license holder"
- Many exclusivity dates are unpopulated at this time

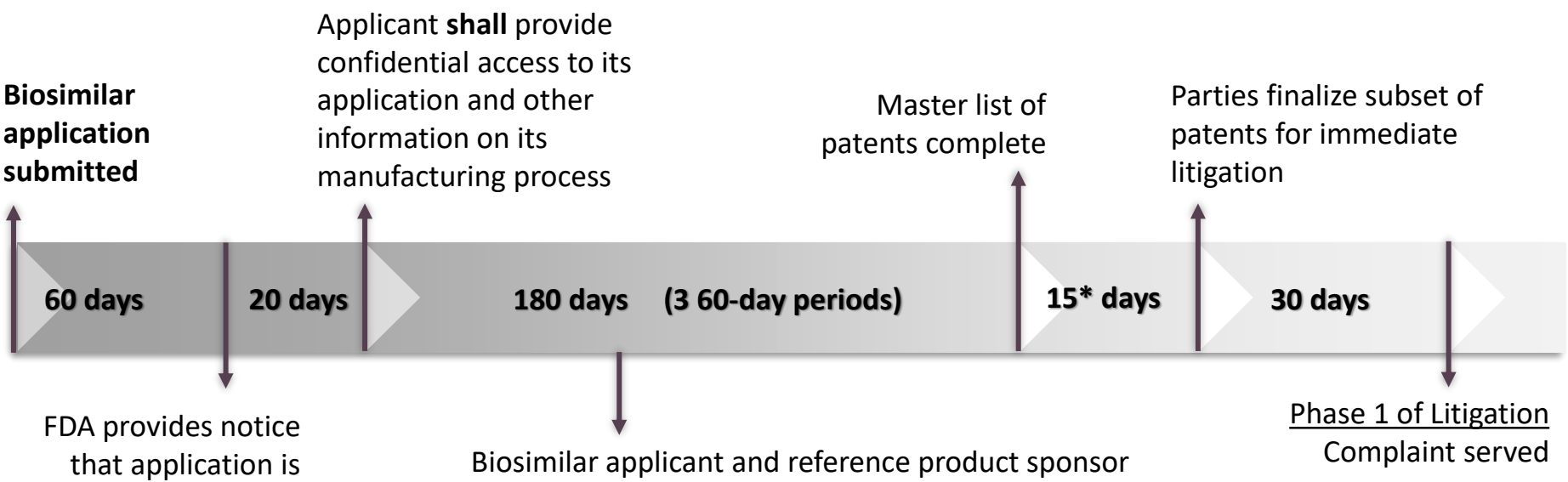
Umbrella Exclusivity

- Umbrella exclusivity: policy in which an application not eligible for its own period of reference product exclusivity under section 351(k)(7)(C) would be protected until expiry of reference product exclusivity period for the first-licensed product
  - E.g., new indications, routes, dosage forms
- If umbrella exclusivity did not apply:
  - E.g., first licensure in 2021, reference product exclusivity applies, expires 2033
    - Supplement for new indication approved in 2023 is not protected by exclusivity; biosimilar application for that indication may be immediately submitted and approved

BPCIA Patent Provisions

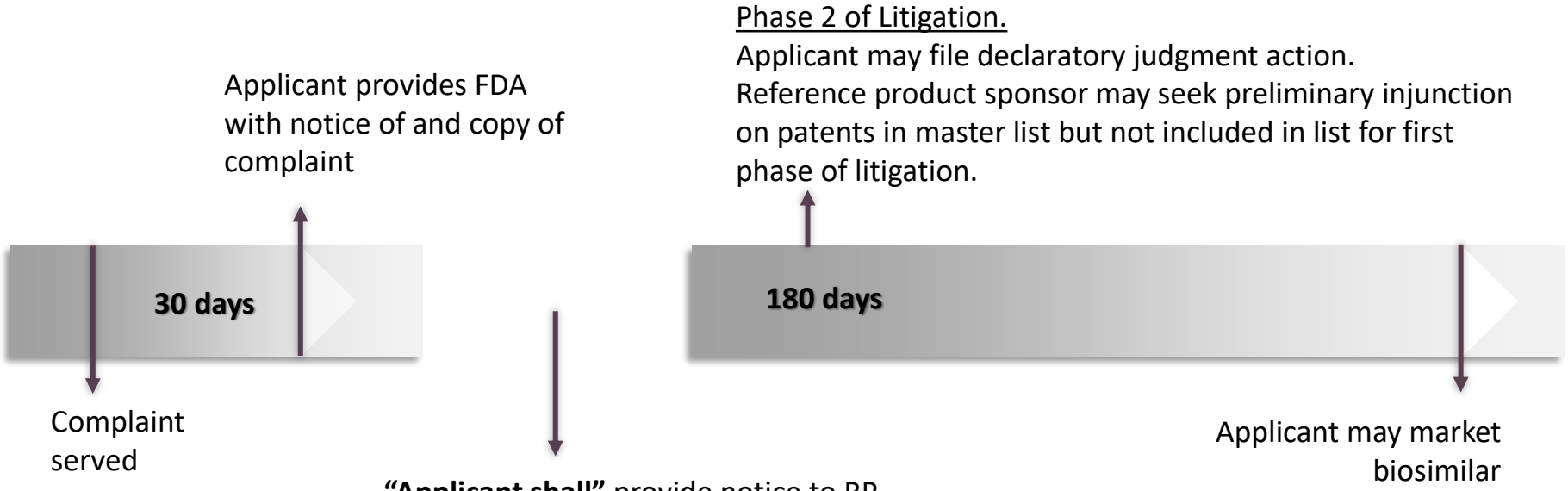
- Four stages:
  - Biosimilar applicant shares a copy of the biosimilar application and manufacturing process information with reference product sponsor
  - Parties identify potentially relevant patents and exchange statements on infringement, validity, and enforceability
  - Parties agree to subset of patents for immediate litigation
  - Not later than 6 months before market entry of the licensed biosimilar, applicant must give notice of launch and parties may engage in additional litigation
- Biological Product Patent Transparency amendments
  - FDA must publish list of patents

Patent Litigation Process Overview



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

Patent Litigation Process Overview



Use of Post-Grant and *Inter Partes* Review

- Trial proceeding conducted before the Patent Trials and Appeal Board (PTAB) at the USPTO
- Third party can file a petition challenging a patent
- Standard for proving a patent is unpatentable before the PTAB (preponderance of the evidence) is lower than an invalidity challenge in district court (clear and convincing evidence)

Use of Post-Grant and *Inter Partes* Review

- IPR is limited to the patentability of one or more claims in a patent on a ground that could be raised under 35 U.S.C. §102 (anticipation) or §103 (obviousness)
- BPCIA does not put any restrictions on the timing for filing a challenge
  - Under 35 U.S.C. § 315(b), litigants are barred from filing IPR petitions more than one year after service of a complaint for patent infringement, but there is no restriction on how early a challenger can file
- Use of IPR proceedings by biosimilar applicants to try to invalidate patents appears to be decreasing

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Transition Provisions

- BPCIA changed definition of “biological product” to include proteins (except chemically synthesized polypeptides)
  - FDA interprets “protein” as an alpha amino acid polymer with greater than 40 amino acids
- Section 7002(e) of BPCIA provides for transition of “biological products” approved under FDCA to PHSA

Transition Provisions

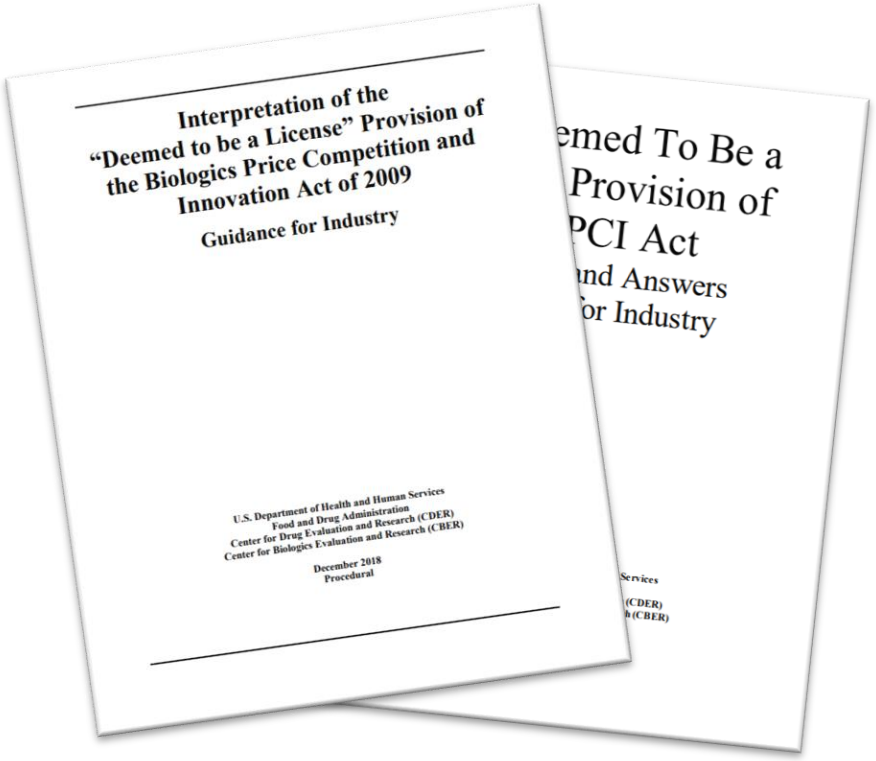
- General requirement to submit BLA for biologic under PHSA
- Key exception: Application for biologic "may be submitted" under FDCA if:
  - Biologic is in a "product class" also containing product approved under FDCA
  - Application is submitted "not later than the date that is 10 years after the date of enactment of this Act," i.e., March 23, 2020.
- "An approved application for a biological product under [the FDCA] shall be deemed to be a license . . . under such section 351 [of the PHSA] on" March 23, 2020.

Transition Provisions

- During transition period, follow-on versions of FDCA proteins must use Hatch-Waxman follow-on pathways
  - FDCA proteins do not meet definition of “reference product” for biosimilar application; not yet deemed licensed under the PHSA
  - “The term ‘reference product’ means the single biological product licensed under subsection (a) [of the PHSA] against which a biological product is evaluated in an application submitted under subsection (k)”
- FDCA proteins became reference products that can be cited in biosimilar applications as of March 23, 2020

Guidance on Deemed to Be a License Provision

- Released December 2018
  - Q&A Guidance: March 2020
- FDA interprets provision to mean that, on March 23, 2020, approved FDCA applications for biological products “will no longer exist” as NDAs and “will be replaced by” approved BLAs



Guidance on Deemed to Be a License Provision

- FDA will not finally approve an FDCA application for a biological product that remains pending or tentatively approved on March 23, 2020
  - Applications may be withdrawn and resubmitted as BLAs
- FDA recommended that applicants who plan to submit NDAs during the transition consider whether their applications may be finally approved before March 23, 2020
  - If not, FDA recommends that such applicants instead consider submitting BLAs under section 351(a) or 351(k) of the PHSA
  - Biosimilar application could be submitted “at such time as there is a biological product licensed under section 351(a) that could be a reference product”
  - Must meet statutory criteria for chosen pathway

Guidance on Deemed to Be a License Provision

- Content on exclusivity
  - Any unexpired period of Hatch-Waxman exclusivity or pediatric exclusivity for an NDA "cease[d] to have any effect" on March 23, 2020
  - Orphan exclusivity was unaffected by transition
  - FDA interprets date on which product is "deemed" licensed not to be first licensure date; no 4- or 12-year exclusivity for transitional products
- Patent issues
  - Transitional biologics were removed from the *Orange Book* on March 23, 2020
  - Provisions of FDCA governing timing of follow-on approval in light of listed patents "would no longer be relevant"
  - Implications for Hatch-Waxman patent litigation

Questions?

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