Biosimilar Biological Products

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Agenda

- Background and Definitions
- Biosimilar Pathway
- Interchangeability
- Naming and Labeling
- Reference Product Exclusivity
- Patent Provisions

BACKGROUND AND DEFINITIONS

Two Statutory Frameworks

New Drug Application

- Approved under the Federal Food, Drug, and Cosmetic Act (FDCA)
- Small molecule drugs; peptides
- Full new drug applications (NDAs) under § 505(b)(1) of the FDCA
- Abbreviated applications under §§ 505(j) & 505(b)(2)

Biologics License Application

- 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 § 351(a) of the PHSA
- Biosimilar applications under § 351(k)

Full BLA versus Biosimilar Route

- Section 351(a) BLA route:
  - Applicant shows that biological product is safe, pure, and potent
- Section 351(k) biosimilar route:
  - Applicant shows that biological product is biosimilar to a "reference product" (RP)
    - Highly similar to RP notwithstanding minor differences in clinically inactive components; and
    - No clinically meaningful differences from RP in safety, purity, and potency

Definitions

- Reference product: “the single biological product licensed under subsection [351](a) against which a biological product is evaluated in” a section 351(k) application.
- Interchangeable: “the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

BIOSIMILAR PATHWAY

Showing Biosimilarity: Statute

- 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
  - Clinical study or studies sufficient to show safety, purity, and potency for 1 or more conditions of use of RP
    - Including assessment of immunogenicity and pharmacokinetics or pharmacodynamics
- FDA may waive any of these data requirements upon a finding that the data are “unnecessary”

Other Statutory Requirements for a Biosimilar

- 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
- Consent to inspection

FDA's Approach to Biosimilarity

- Applicant should use a stepwise approach
- 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)

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

Guidance on Extrapolation

- Applicants may extrapolate clinical data supporting biosimilarity in one condition of use to support licensure in other conditions of use with “sufficient scientific justification” that addresses, e.g.:
  - Mechanism(s) of action in each condition of use;
  - PK and biodistribution in different patient populations;
  - Immunogenicity of the product in different patient populations; and
  - Differences in expected toxicities in each condition of use and patient population
- Examples thus far

Use of Data from Non-U.S. Comparator

- Statute requires that biosimilarity be shown to “a single reference product that previously has been licensed by FDA”
- 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
  - Analytical data directly comparing all 3 products and generally bridging clinical PK and/or PD study data

Interacting with FDA

- Types of meetings:
  - Biosimilar Initial Advisory (BIA): feasibility of 351(k) pathway and general advice
  - Biosimilar Biological Product Development (BPD) Type 1: necessary for an otherwise stalled development program
  - BPD Type 2: discuss specific issue, such as approach to analytics, study design or endpoints for targeted advice; no FDA review of full study reports
  - BPD Type 3: in-depth data review and advice meeting regarding an ongoing development program
  - BPD Type 4: presubmission meeting

Biosimilars Application Review

- Biosimilar User Fee Act (BsUFA) performance goals for FY 2021:
  - 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
- Advisory Committee meetings

Quiz

- How many biosimilars have been approved by FDA as of October 11, 2020?
- There were 19 total biosimilar applications filed in FY 2017 and 2018. For how many of them did FDA meet its goal to review and act within 10 months of the 60-day filing date?

Answers

- FDA has approved 28 biosimilars as of October 11, 2020
- Answer #2: 100%

Pediatric Assessments

- Assessments required for non-interchangeable biosimilar
- Guidance: FDA says requirement applies only to the extent that compliance with PREA would not result in:
  - condition of use that has not been previously approved for RP; or
  - dosage form, strength, or route that differs from that of RP
- If RP labeling has adequate pediatric information, biosimilar applicant likely can extrapolate with sufficient scientific justification
- If RP labeling lacks adequate pediatric information, see guidance re: deferrals, applicability of PREA, etc.

Pharmacovigilance and REMS

- A biosimilar product application holder must comply with requirements regarding adverse experience review, reporting, and recordkeeping (21 C.F.R. 600.80) and take steps to keep labeling up to date
- FDA has same authority for biosimilars as reference products with respect to:
  - risk evaluation and mitigation strategies; and
  - postmarketing study requirements

REMS for Biosimilars

- Special provisions on REMS for generic drugs not applicable to biosimilars
- FDA draft guidance:
  - "[W]e recommend the applicants for a [biosimilar] work together with the applicant for the product they are referencing to establish a shared system REMS"

INTERCHANGEABILITY

Interchangeability

- Section 351(i) defines “interchangeability” to mean:
  - The product may be substituted for the RP without the intervention of the health care provider who prescribed the RP
- Statutory standard
  - The biosimilar “can be expected to produce the same clinical result as the reference product in any given patient”
  - If the product is to be administered more than once to an individual: the “risk in terms of safety or diminished efficacy of alternating or switching” between the products is “not greater than the risk of” exclusively using the RP
- No interchangeability designations thus far

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

Conditions of Use for 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

Data to Support Interchangeability

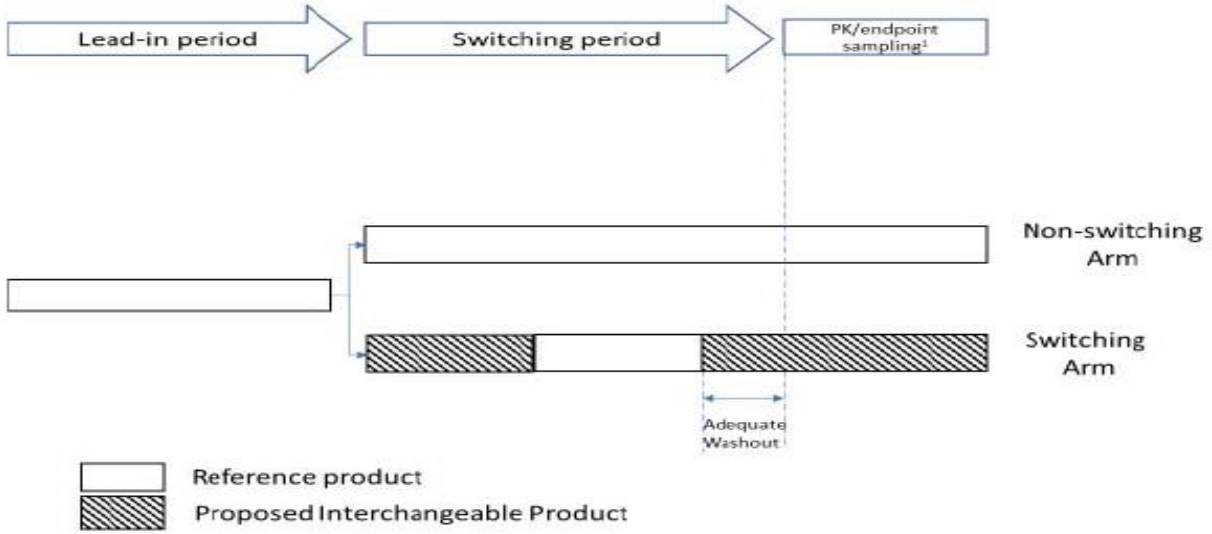
- A switching study or studies generally will be expected to demonstrate interchangeability for multiple-use products
- Postmarketing data alone generally will be insufficient
- “In certain situations,” postmarketing surveillance data may be needed to support interchangeability
- “[T]here may be situations where a postmarketing study, in addition to postmarketing surveillance data” may be needed

Switching Studies

- Two designs for switching studies:
  - Dedicated switching study
  - Integrated two-part design
- Studies should assess at least three switches
- Draft guidance on insulin immunogenicity

Switching Study Design

Example of a Switching Study Design



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

Figure is not drawn to scale.

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

Interchangeability Exclusivity

- If one biosimilar received interchangeability designation, FDA shall not license second product as interchangeable to the same reference product for any condition of use until the earlier of—
  - 1 year after first commercial marketing of first interchangeable biosimilar;
  - 18 months after--
    - a final court decision on all patents in suit under section 351(l)(6) against applicant for first interchangeable biosimilar;
    - dismissal of suit under section 351(l)(6) against such applicant; or
  - 42 months after approval of first interchangeable biosimilar if suit under section 351(l)(6) is ongoing or 18 months after such approval if applicant not sued under section 351(l)(6).

NAMING AND LABELING

Nonproprietary Names

- Issue:
  - Should biosimilars have same nonproprietary names as RPs?
  - Or should biosimilars and other biologics have distinguishable names, reflecting that the products are similar but not the same?
- BPCIA silent on naming

Nonproprietary Names

- In Aug. 2015, FDA issued:
  - Draft guidance on FDA's proposed approach for nonproprietary naming of biological products
  - Proposed rule designating nonproprietary names with suffixes for six licensed biological products
- Guidance finalized in January 2017; rule not finalized
- "Update" draft guidance released March 2019

Guidance on Nonproprietary Naming

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

FDA Implementation Plan for Suffixes

- A new section 351(a) or 351(k) applicant "should propose a suffix . . . [to be] included in the proper name designated by FDA at the time of licensure"
  - Submit ≤10 proposed suffixes and supporting analyses during IND phase or at BLA submission

Update Draft Guidance (March 2019)

- FDA does not plan to apply suffix convention retrospectively
- FDA will apply the suffix convention to interchangeable biologics
- Agency considering whether vaccines should be exempt

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)]."
  - "*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 [BIOSIMILAR PRODUCT'S PROPRIETARY NAME] has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

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 "incorporate relevant data and information from the reference product labeling, including clinical data that supported FDA's finding of safety and effectiveness of the reference product."
  - Use biosimilar product name—proprietary name if there is one—in biosimilar-specific labeling text
  - Use RP nonproprietary name to refer to RP data, including in 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*** *. . .*

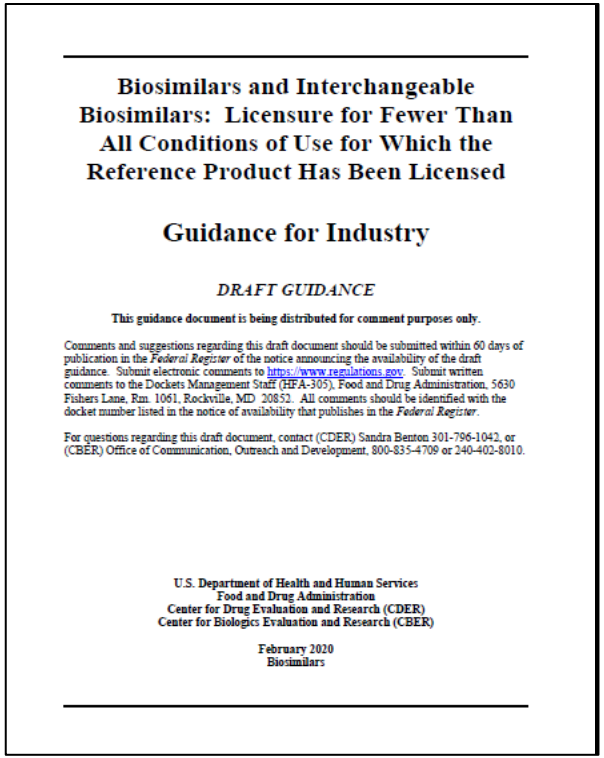
- JUNEXANT (replicamab-hjxf) is fictional reference product
- NEXSYMEO (replicamab-cznm) is fictional biosimilar

FDA Guidance on Biosimilar Labeling

- "Any specific recommendations for labeling for interchangeable products, including any interchangeability statement similar to the biosimilarity statement . . . will be provided in future guidance."

Draft Guidance on Labeling Carve-Outs and Carve-Ins

- Draft Guidance released Feb. 2020
- 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)

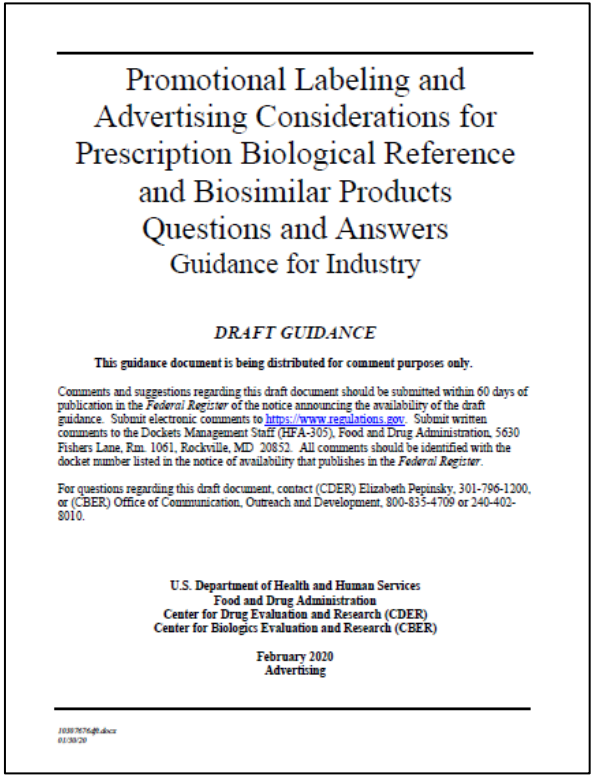
February 2020
Biosimilars

Draft Guidance on Labeling Carve-Outs and Carve-Ins

- Section 351(k) applicant may seek licensure for fewer than all of the reference product's licensed conditions of use due to:
  - Regulatory exclusivity;
  - Applicant's "own assessment" of patent protections for RP; or
  - "Other reasons"
- "To the extent practicable," FDA intends to act on section 351(k) supplements seeking licensure for additional conditions of use within 6 months of receipt
- Applicants may make "action timing request" that FDA *not* take early action on section 351(k) BLA so approval can be timed after, e.g., patent expiry

Advertising and Promotion Draft Guidance

- Released Feb. 2020
- Focuses on biosimilars, not interchangeable biologics
- Discusses considerations for presenting data and information about reference or biosimilar products in in a truthful and non-misleading way



Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products Questions and Answers

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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
Advertising

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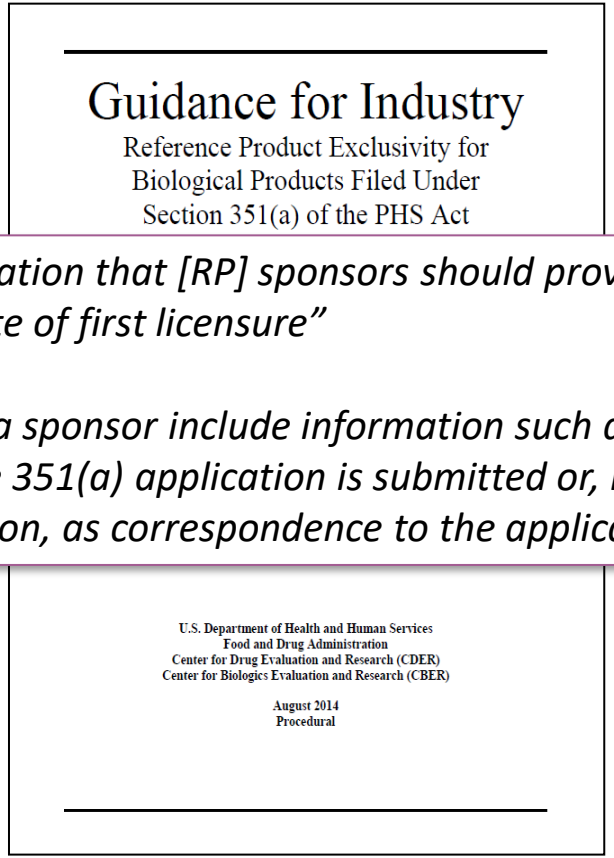
REFERENCE PRODUCT EXCLUSIVITY

Statutory Provision: Section 351(k)(7)

- **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 application filed by same sponsor or "a licensor, predecessor in interest, or other related entity" for:
    - a nonstructural change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    - a structural modification that does not result in a change in safety, purity, or potency

Exclusivity Draft Guidance



Guidance for Industry

Reference Product Exclusivity for
Biological Products Filed Under
Section 351(a) of the PHS Act

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)

August 2014
Procedural

"[D]escribes the "information that [RP] sponsors should provide to facilitate FDA's determination of the date of first licensure"

"FDA recommends that a sponsor include information such as that described in this guidance at the time the 351(a) application is submitted or, in the case of an already licensed 351(a) application, as correspondence to the application."

Recommended Content of Submissions

1. List of all licensed biological products that are “structurally related” to product for which exclusivity is sought
2. Identify products listed in #1 for which the sponsor or any related entity is the “current or previous license holder”
3. Describe structural differences between products identified in #2 and product for which exclusivity is sought
4. Include evidence of change in safety, purity, or potency between products identified in #2 and proposed product

Exclusivity Draft Guidance: “Related Entity”

- FDA proposes to interpret “licensor” to include that “entities that continue to retain… rights to intellectual property that covers the biological product”
- 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

Draft Guidance: Structural Modification

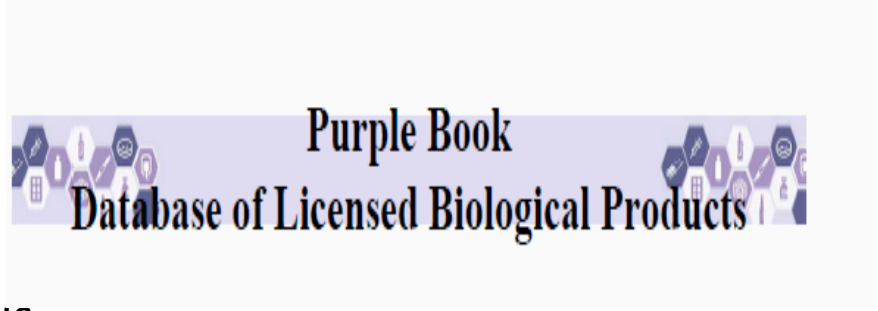
- Draft refers to “any” differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including pegylation), and infidelity of translation or transcription

Draft Guidance: Results in a Change…

- 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

The Purple Book Database

- CBER and CDER lists
  - Date of licensure
  - Date of first licensure (i.e., exclusivity start date)
  - Biosimilar/Interchangeable status



- "FDA has not made a determination of first licensure for each 351(a) biological product included in the Purple Book. The absence of a date of first licensure in the Purple Book does not mean that a biological product on the list is not, or was not, eligible for the periods of [reference product] exclusivity"

What is “Umbrella Exclusivity”?

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

FDA: Public Meeting Announced (7/25/18)

- *"FDA seeks comment on the potential application of 'umbrella exclusivity' under section 351(k)(7)."*
- *"[U]mbrella exclusivity could help shield certain biological products that would otherwise not be eligible for their own period of exclusivity . . . from biosimilar competition."*

"Umbrella" Exclusivity: FDA Questions for Public Input

- *"What considerations support recognition of umbrella exclusivity under section 351(k)(7), and what considerations disfavor recognizing umbrella exclusivity?"*
- *"How would umbrella exclusivity promote biological product innovation, and what effect would it have on market entry of biosimilars?"*
- *"What is the relevance and significance, if any, of the patent scheme in considering this issue?"*
- FDA received comment on these issues through a public meeting and docket in September 2018

Umbrella Exclusivity: The Debate

- Argument: Uncodified provision of BPCIA implicitly acknowledges
  - "If a reference product. . . has been [orphan] designated . . . for a rare disease or condition, a [biosimilar] seeking approval for such disease or condition . . . may be licensed . . . only after the expiration for such reference product of the later of—"
    - the 7-year orphan-drug exclusivity period
    - the 12-year reference product exclusivity period
- Provision is unnecessary unless umbrella exclusivity applies to a subsequent orphan indication

Umbrella Exclusivity: The Debate

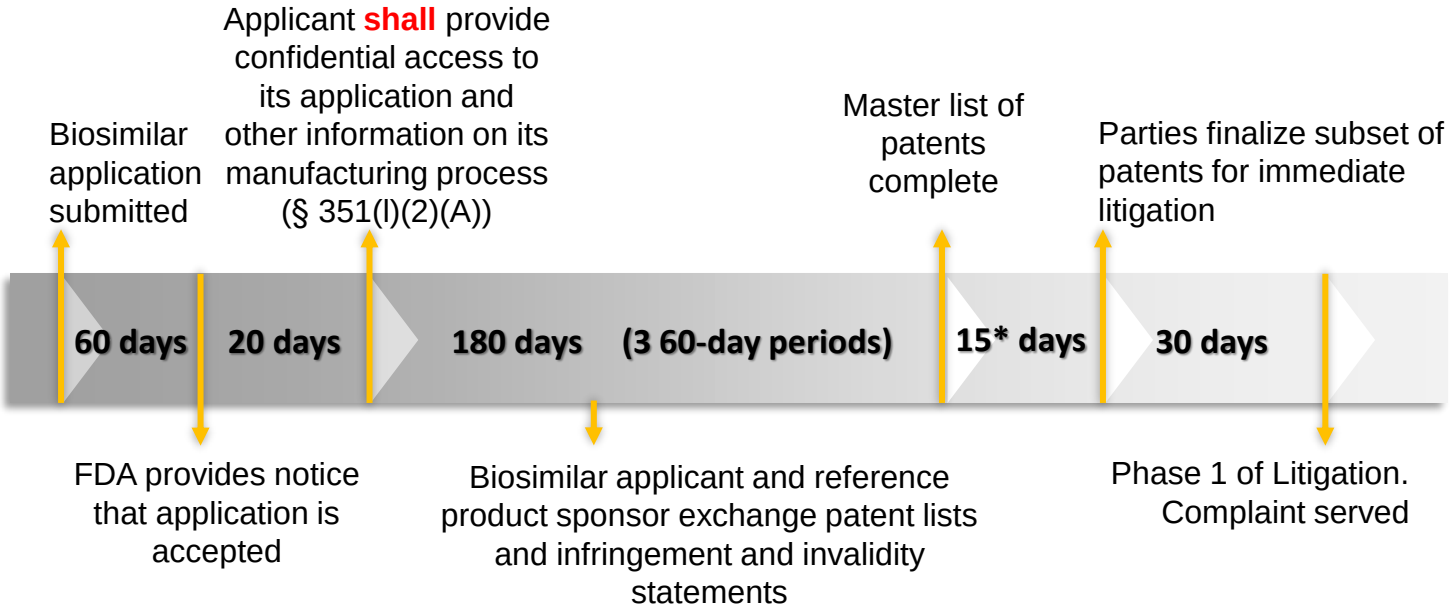
- Argument opposing umbrella exclusivity: The "shall not apply" language "language is clear and unambiguous," and "it evinces a clear Congressional repudiation of FDA's umbrella policy in the context of reference product exclusivity under the BPCIA."

Looking Forward

- Docket for comment on Biosimilars Action Plan closed in September 2018
- Biosimilars Action Plan states FDA is "prioritizing the development of guidance" including a final or revised draft version of the 2014 draft guidance on reference product exclusivity

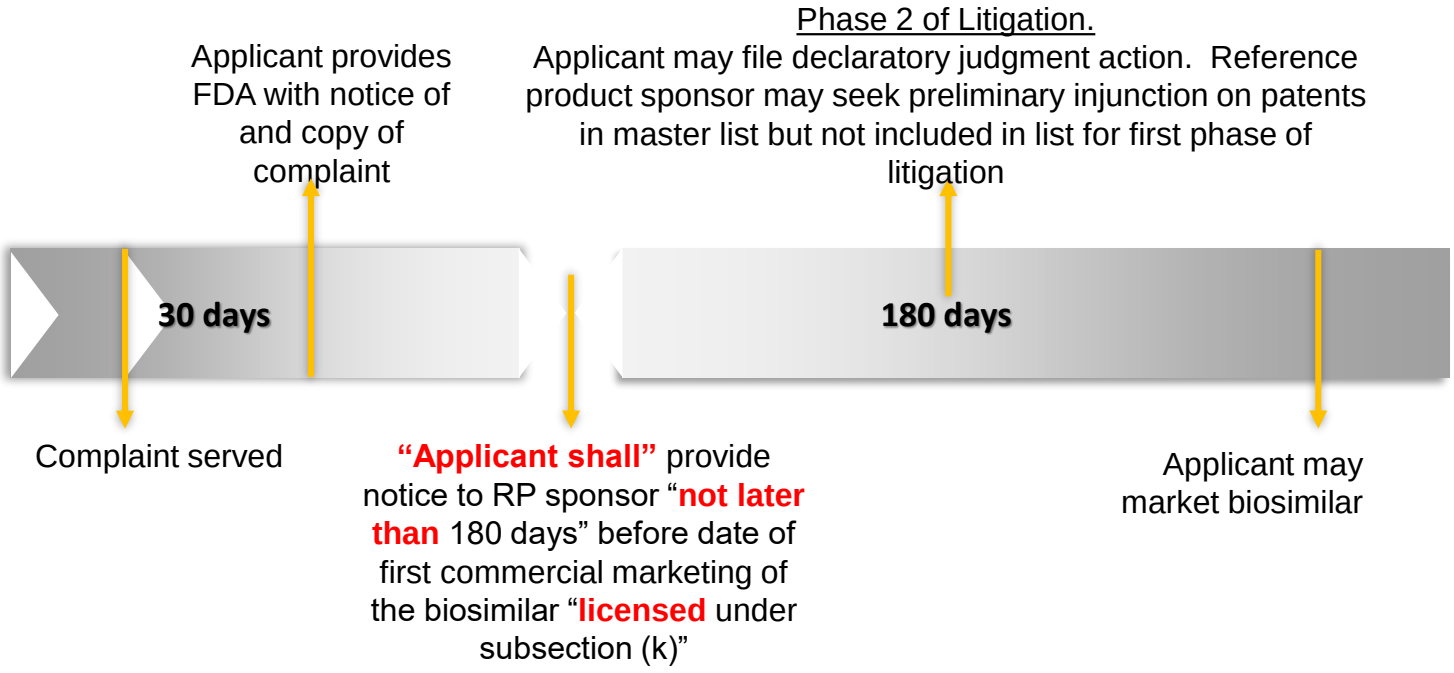
PATENT PROVISIONS

Patent Litigation Process Overview



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

Patent Litigation Process Overview



Limitations on Declaratory Judgment Actions

- Section 351(l)(9)(A): If applicant provides the application and information required under paragraph (2)(A), neither party may bring a DJ on patent validity, infringement, or enforceability until 180-day notice received
- Section 351(l)(9)(B): If applicant fails to complete specified actions (e.g., respond to RP sponsor list of patents), RP sponsor but not applicant can bring DJ regarding a patent in RP sponsor's initial list
- Section 351(l)(9)(C): "If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action . . . for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product"

Amgen v. Sandoz Underlying Facts

- Sandoz filed its biosimilar application referencing Amgen's Neupogen (filgrastim)
- Sandoz did not provide Amgen with the biosimilar application and manufacturing process information and asserted that Amgen was entitled to sue Sandoz under § 351(l)(9)(C)
- The parties did not engage in any patent exchanges
- Sandoz also provided notice of commercial marketing upon FDA acceptance of the biosimilar application

Amgen v. Sandoz (N.D. Cal. 2015)

- Amgen sued Sandoz for patent infringement, unfair competition, and conversion
- Amgen alleged that Sandoz violated the BPCIA by failing to provide confidential access to its application and process information and by giving a premature, ineffective notice of commercial marketing before licensure of the biosimilar
- Sandoz alleged patent dance is optional and 180-day notice was valid
- District court found for Sandoz on both issues

Federal Circuit's Decision

- A divided panel affirmed the district court's finding that the patent dance is optional
- "The 'shall' provision in [section 351(l)(2)(A)] cannot be read in isolation" and "BPCIA explicitly contemplates that a subsection (k) applicant might fail to disclose the required information by the statutory deadline"
- "[W]hen a [biosimilar] applicant fails the disclosure requirement, [section 351(l)(9)(C)] and 35 U.S.C. § 271(e) expressly provide the only remedies as those being based on the claim of patent infringement"

Federal Circuit's Decision (cont'd)

- A divided panel reversed the district court's 180-day notice holding
- Notice can only be given after FDA licenses biosimilar, "at which time the product, its therapeutic uses and its manufacturing processes are fixed"
- 180-day notice is mandatory, at least in cases where applicant fails to provide its application

Supreme Court's Decision

- Section 351(l)(2)(A) may not be enforced by an injunction under federal law
- Court focused on 351(l)(9)(C)
  - "The presence of [this provision], coupled with the absence of any other textually specified remedies, indicates that Congress did not intend sponsors to have access to injunctive relief, at least as a matter of federal law, to enforce the disclosure requirement"
  - The Federal Circuit must determine on remand if an injunction to enforce section 351(l)(2)(A) is available under state law

Supreme Court's Decision

- A biosimilar applicant may provide notice of commercial marketing before or after FDA approval of the biosimilar
- Section 351(l)(8)(A) states that the applicant "shall provide notice to the [RP sponsor] not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)"
- The Court interpreted the underlined phrase to modify "commercial marketing"—not "notice"—stating that "'commercial marketing' is the point in time by which the biosimilar must be 'licensed'"

Federal Circuit Decision on Remand

- Held: BPCIA preempts state law claims predicated on an applicant's failure to comply with section 351(l)(2)(A)
  - Field preemption: "The field here is biosimilar patent litigation," and "the federal government has fully occupied this field"
  - Conflict preemption:
    - "Amgen seeks through state law to impose penalties on Sandoz unavailable under the BPCIA"
    - Also stated that compliance with 50 state laws on torts and unfair competition might "'dramatically increase the burdens'" on biosimilar applicants

IPR

- Low institution rate for biologics compared to other technologies
- Article III standing issues to maintain appeal

Questions?

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