NEW, EMERGING, AND CONTINUALLY INTERESTING ISSUES

FDLI's Introduction to Biologics and Biosimilars Law and Regulation

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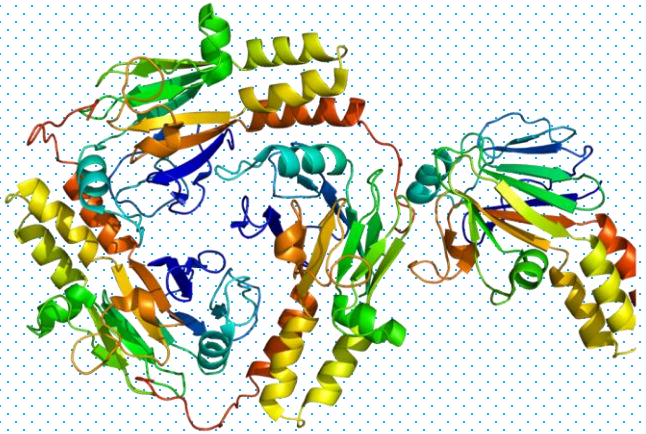
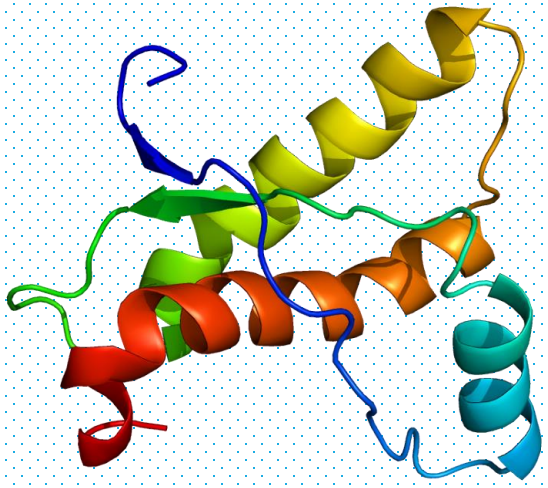
MARCH 10, 2021

Emerging Issues

- Protein Definition
- Strength Definition
- Labeling “Carve-Outs”
- “Unbranded Biologics”
- Purple Book Reforms
- Umbrella Policy for RP Exclusivity





Protein Definition

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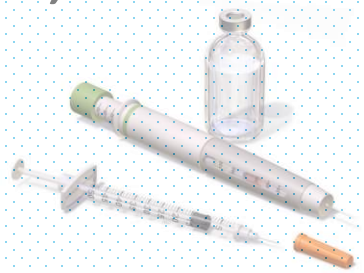
Transitional Biologics

- Historically, many proteins were regulated as drugs (e.g., insulin, human growth hormone, hyaluronidase)



- The Biologics Price Competition and Innovation Act (BPCIA) sought to require all proteins to be regulated as biologics within 10 years

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Transition Day Occurred Last Year

- March 23, 2020 Transition Date
- All approved New Drug Applications (NDAs), including 505(b)(2) applications, have now been "deemed" to be approved BLAs
- FDA issued a final list of transitioned proteins available at https://www.fda.gov/media/119229/download
- Most proteins on the list have been removed from the Orange Book and added to the Purple Book

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Random Quizzlet

A product **cannot** be a "protein" if it has this characteristic:

- Naturally sourced
- Over 100 amino acids in length
- No fixed sequence of amino acids
- 100% synthetic
- Previously approved under a New Drug Application (NDA)

FDA "Protein" Definition

- Final regulation issued February 21, 2020 (85 Fed. Reg. 10057)
- Protein defined as "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size" (21 C.F.R. 600.3(h)(6))
  - Counts all amino acids where two or more chains are "associated with each other in a manner that occurs in nature" (e.g., insulin)
- Intended to be a "bright line" rule to promote certainty
- FDA rejected suggestions to consider structural or functional attributes (e.g., folding, transports other molecules), which could engender more uncertainty (how much "folding" is enough)

Chemically Synthesized Polypeptides

Under the BPCIA, "chemically synthesized polypeptides" were excluded from the definition of protein and thus would continue to be regulated as "drugs" even after the transition

Congress revised the definition of "protein" on December 20, 2019 to DELETE the exclusion for chemically synthesized polypeptides

Now, chemically synthesized polypeptides are no longer excluded from the protein definition and can be subject to regulation as biologics after the transition if they otherwise meet the "protein" definition

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Effects of New Definition

- Reportedly, three "chemically synthesized polypeptides" will now be regulated as "proteins" and "biological products"
  - Acthrel (corticorelin ovine triflutate),
  - Adlyxin (lixisenatide), and
  - Egrifta(tesamorelin acetate)

- Unexpected loss of Hatch-Waxman exclusivity and patent protections for affected drugs
  - Adlyxin had NCE exclusivity until July 27, 2021
  - Adlyxin and Egrifta had listed patents expiring after March 23, 2020

- First lawsuit filed regarding transition provisions

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Copaxone Lawsuit

- Copaxone (glatiramer acetate) is a complex mixture of polypeptides made by chemical synthesis
- After Congress revised the definition of "protein," Teva requested that FDA transition the Copaxone NDA to a BLA on March 23, 2020, but FDA did not do so
- Teva filed a lawsuit on March 24, 2020 challenging FDA's failure to treat Copaxone as a "protein"
- Teva argued that Copaxone qualifies as a "protein" because:
  - It meets the protein size threshold of "greater than 40 amino acids"
  - It has a "specific, defined sequence," and
  - It is no longer excluded as a "chemically synthesized polypeptide"
- At a minimum, Teva argues that Copaxone qualifies as an "analogous product" because, *inter alia*, it is functionally and structurally similar to other proteins and to biological products generally
- FDA and intervenor-competitors argue that Copaxone is not a protein because it does not have a "specific, defined sequence"

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Court Decision on Copaxone

Teva has standing to bring suit based on state substitution laws

FDA's requirement that proteins must have a "specific, defined sequence" of amino acids was reasonable

- No "unambiguous scientific agreement" but not foreclosed by the statute either (Chevron Step One)
- FDA requirement supported by scientific "consensus" and thus reasonable (Chevron Step Two)
- "Specific, defined sequence" based on the way proteins are made in nature (DNA/RNA template) and is critical to their structure and function

FDA determination that Copaxone is not a protein is not "arbitrary and capricious"

- Vitrase and Creon examples are distinguishable
- FDA's "sameness" criteria for approving generic versions does not mean Copaxone has a "specific, defined sequence"

FDA's interpretation of "analogous" protein products is reasonable

- **FDA**: ***"it would not be appropriate to interpret the statutory term 'analogous product' (with reference to 'protein') in a way that would include amino acid polymers that are specifically excluded by the interpretation of the term 'protein'" adopted by FDA***
- Thus, products without a "specific, defined sequence" cannot be "analogous products"

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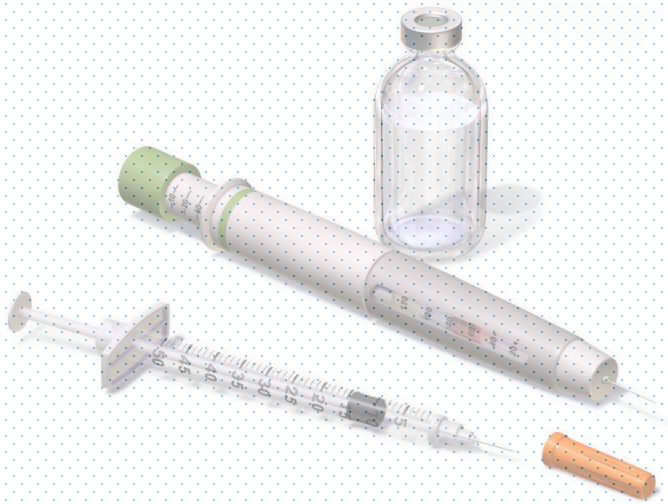
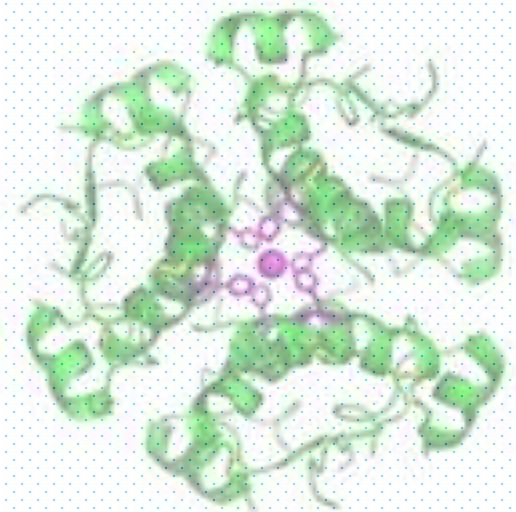
Strength Definition





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Random Quizzlet

Most biological products are available as parenteral solutions. How does FDA define the strength of parenteral solution biological products?

- Total content drug substance per container
- Concentration
- Total content of drug substance and concentration
- The same way it defines the strength the of dry powders intended for reconstitution
- None of the above

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BPCIA Strength Requirement

- Under the BPCIA, biosimilars and interchangeable biologics must have the same "strength" as the Reference Product (RP), 42 U.S.C. § 262(k)(2)(A)(i)(IV)
- The BPCIA does not define the terms "strength" or "same strength" but these terms appear to be borrowed from the Hatch-Waxman Act
- FDA Draft Guidance:
  - Strength of "injection" dosage forms (e.g., a solution) is based on both total drug content and concentration
  - Strength of "for injection" dosage forms (e.g., lyophilized powders) is based solely on total drug content, not concentration of constituted or reconstituted solution
  - New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (Dec. 2018)

Boehringer Ingelheim Petition

- Docket No. FDA-2020-P-2247 (filed December 2, 2020)
- Requests FDA to interpret "strength" in the BPCIA to mean "total drug content" in the relevant container without regard to concentration or volume
- Legal/Policy Justifications for Request:
  - Required by clear meaning of the BPCIA
  - Necessary to prevent abusive "evergreening" tactics
  - Maintains fair and consistent treatment of similarly situated biological products intended for injection

Boehringer's Legal Position

The BPCIA is clear and unambiguous and defines "strength" to mean "total drug content" (Chevron Step One)

Congress adopted the term "strength" from the Hatch-Waxman Act

At time of passage, strength was a term of art that meant total drug content, without regard to concentration

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Orange Book Definition (pre-2016)

"The strength of parenteral drug products is defined as the total drug content of the container."

- FDA changed the definition in 2016 in both the Orange Book and new regulations to reference both total drug content and concentration (81 Fed. Reg. 69580 (Oct. 6, 2016))

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Boehringer's Legal/Policy Positions

FDA's interpretation is unreasonable (Chevron Step Two)

- Promotes anti-competitive evergreening tactics
- "Blunt instrument" approach prevents licensure of products that meet statutory biosimilar and interchangeability requirements

FDA's interpretation is arbitrary and capricious (APA)

- Treats injectable solutions differently than similarly situated products
- E.g., the strength of lyophilized powders is defined as the total drug content of the container, without regard to concentration after reconstitution

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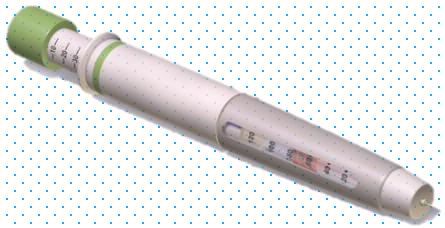
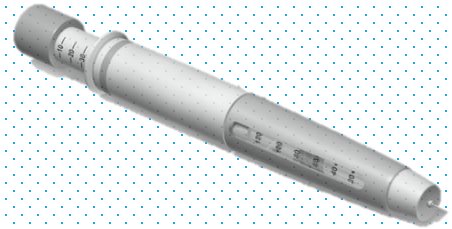
Protection of the Public Health

- Concentration is not always relevant for biosimilarity or interchangeability
  - E.g., entire content of unit administered, dosing devices (e.g., prefilled syringe), small volumes
- Where concentration is relevant, FDA has more calibrated mechanisms to assess and address it under the BPCIA
  - Assess whether concentration differences are "clinically meaningful"
  - Assess whether concentration differences preclude a finding of "same clinical result" in any given patient
  - FDA already uses these alternate (non-strength) assessments for lyophilized powders

Is there a meaningful difference?



- Single dose autoinjector
- 5 second injection time
- Thigh injection site
- Comparable directions for use
- 50 mg active ingredient
- 0.5 mL volume
- Entire content administered



- Single dose autoinjector
- 5 second injection time
- Thigh injection site
- Comparable directions for use
- 50 mg active ingredient
- 1 mL volume
- Entire content administered

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Labeling Carve-Outs

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Labeling Carve-Outs

- No “same labeling” requirement for biosimilars
- No legal provision limiting carve-outs to indications or other conditions of use protected by patents or exclusivity
- No “use codes” that would define the parameters of a carve-out
- BPCIA and FDA’s Biosimilars Labeling Guidance specifically allows a biosimilar applicant to seek licensure for fewer than all of the RP’s approved indications or conditions of use

FDA Guidance

- Draft Guidance on Licensure for Fewer Than All Conditions of Use for Which the RP Has Been Licensed issued in February 2020
- Carve-outs allowed for exclusivity (e.g., orphan), patents, or other reasons
- Carve-out standards still unclear
  - Deviations from RP labeling "should be carefully considered" to ensure conditions of use have been previously approved
  - Biosimilar applicants may submit information intended to "inform FDA's view of the draft labeling"
- Substantive revisions may be acceptable if modified labeling does not fall outside previously approved conditions of use
- FDA will target a 6-month review timeline (although 10-month BsUFA goal technically still applies)
- Applicants can request "Not Before" approval dates

GSK v. Teva Decision

- Recent patent infringement decision from Federal Circuit regarding small-molecule drugs
- Court found that Teva induced infringement based on:
  - FDA labeling that carved out the protected use; and
  - Company statements in catalogues and press releases that its generic drug was "therapeutically equivalent" to the RLD
- Serious concern that this decision could chill labeling carve-outs for generic drugs
- ***Will this decision affect labeling carve-outs for biosimilars and interchangeable biological products?***
- Federal Circuit recently granted rehearing and may revisit this decision

Repercussions for Biologics

Biosimilars

- Labeling may present heightened risk
- Required to state “biosimilar to [Brand]”
- Disclaimer regarding indications may or may not reduce this risk
- Risks associated with promotional claims of “biosimilarity”

Interchangeable Biologics

- Labeling likely presents heightened risk
- Required state “interchangeable to [Brand]”
- Disclaimer may or may not reduce this risk
- Interchangeability even less ambiguous than “AB-rated”
- Thus, there are heightened risks associated with promotional claims regarding “interchangeability”

Potential Effect on Promotion

Less willingness to carve-out indications protected by patents?

More hesitation to promote products as “biosimilar” or “interchangeable” without clear and comprehensive caveats?

Increased need to define clearly and comprehensively in all promotional pieces the licensed indications and the non-licensed indications?

Will promotion of biosimilars and, especially, interchangeable biologics be driven more by patent concerns than by FDA/FTC considerations?

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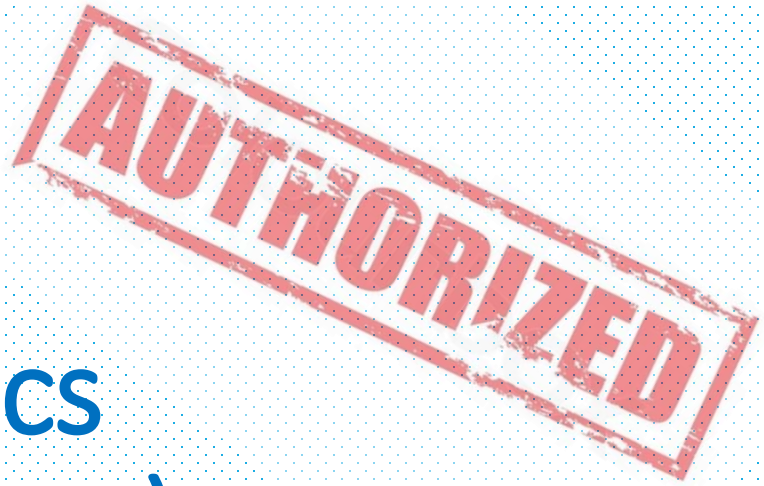

Unbranded Biologics (Authorized Biosimilars)

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"Authorized Biosimilars"

- Term first used by Lilly in its February 11, 2019 public comments to FDA's draft Q&A Guidance
- Discussed as: "A section 351(k) application submitted by the holder of a section 351(a) application that cites the sponsor's section 351(a) product as the reference product and proposes a modified or identical version of that reference product."
- Essentially asking FDA to allow the sponsor to maintain two applications (a full BLA and an aBLA) for the same product

Differs from "Authorized Generics"

- Authorized generics are genericized versions of the brand name marketed under a single application – the original NDA

- FDA is notified of the authorized generic through the annual report for the brand name drug, not a separate application

Biosimilar Industry Concerns

Creates New Disincentives	Current disincentives are significant (high development and patent litigation costs)	First-to-market status of authorized biologics will create a significant new disincentive
Fosters Evergreening Tactics	Much easier and quicker for authorized biosimilar to match formulation of other changes to RP	
Undercuts First Interchangeable Exclusivity	Likely no switching studies needed for authorized biologic	Can always be the first interchangeable

FDA Guidance

- FDA's "Deeming" Q&A Final Guidance issued March 2020
- FDA clarified that holders of standalone 351(a) BLAs may not use the 351(k) pathway to obtain approval of a biosimilar or interchangeable version of their own RP
- Instead, a 351(k) application must reference "another" RP, i.e., a different RP
- "Unbranded biologics" may still be marketed under the sponsor's 351(a) application
  - Just like "authorized generics"
  - Such unbranded biologics should be substitutable for the brand since they are the same product marketed under the same BLA
  - However, no formal interchangeability determination by FDA or listing as such in Purple Book

Purple Book Reforms

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Regulatory Reforms

- On February 24, 2020, FDA rolled out a searchable, online database version of the Purple Book
- Provides detailed information, including status as a Reference Product or biosimilar, proprietary and proper name, dosage form, strength, route of administration, product presentation, approval date, date of first licensure, and BLA number
- Makes is more usable like the Orange Book
- All CDER and CBER approved biologics are now listed in online database
- https://purplebooksearch.fda.gov/

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Legislative Reforms

- In December 2020, Congress passed Purple Book reforms as part of the Consolidated Appropriations Act of 2021
- Requires FDA to publish certain patent information in the Purple Book within 180 days (June/July 2021)
  - RP sponsor must provide FDA with list of patents (and expiration dates) identified during the patent dance (i.e., the (l)(3)(A) and (l)(7) lists)
  - List must be provided within 30 days after list provided to aBLA applicant (although there are no penalties for failure to provide patent list)
  - FDA must update Purple Book every 30 days with newly provided patent information
- Also requires FDA to post information about licensure status and marketing status (as available)

Umbrella Policy

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FDA's Umbrella Policy

- Applies in the Hatch-Waxman context
- Umbrella Policy: New products that share the same protected feature (*e.g.*, new chemical entity) will be protected by the remainder of the original product's exclusivity
- Example:
  - New chemical entity approved in immediate release tablet on January 1, 2015
  - Extended-release capsule version of NCE approved on January 25, 2017
  - Both immediate release and extended-release versions would be protected by original NCE exclusivity until January 1, 2020

Justifications for Umbrella Policy

Policy

- Encourages continued innovation
- Failure to protect new products would create disincentives to innovation

Legal

- FDA justifies umbrella policy by interpreting “drug” broadly in the bar clause (“no application may be submitted … which refers to the drug”)
- “Drug” means “active moiety”

Umbrella Policy for Biologics?

- FDA specifically asked for feedback in 2018 on whether an umbrella policy should apply to Reference Product (RP) exclusivity (Docket No. FDA-2018-N-2689)
- Exclusivity systems much different
  - Hatch-Waxman exclusivity periods are carefully calibrated ("Goldilocks system")
  - BPCIA provides a single 12-year exclusivity period
- Policy justifications arguably are the same for protecting innovation
- Legal justification more difficult in BPCIA context
  - Harder to define "reference product" as "active moiety"
  - Non-evergreening provisions explicitly state RP exclusivity does NOT apply to product enhancements
  - Potentially violates "single RP" requirement
  - Congress aware of brand "shenanigans" when it enacted BPCIA

Questions?

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Scott also is author of the Exclusivity Rules blog, which focuses on the written and unwritten rules governing FDA's exclusivity decisions. The blog is available at:

https://www.lassmanfdalaw.com/blog/