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The Pathway Cleared for Biosimilars? A Guide for the Road Ahead

Nate Beaver, Partner, Foley & Lardner
Jackie Wright-Bonilla, Partner, Foley & Lardner
Kristel Schorr, Senior Counsel, Foley & Lardner

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Background

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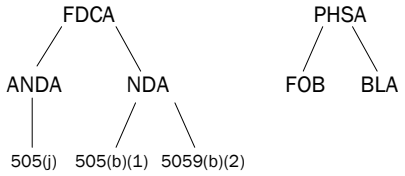
- Two main pathways for seeking drug approval from the FDA



NDA vs. BLA: Standard for Approval/Licensing

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- For NDA (FDCA):
  - "Substantial evidence" of effectiveness (in the form of "adequate and well-controlled studies"), and
  - Product is "safe for use under the conditions prescribed"
- For BLA (PHSA):
  - Product is "safe, pure, and potent," and
  - Manufacturing facility meets "standards designed to assure that the biological product continues to be safe, pure and potent"

NDA vs. BLA: Standard for Approval/Licensing *(con't)*

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- BLA standard reflects historical focus on manufacturing process and facilities
- Traditionally, lack of "substantial evidence" requirement for BLAs meant a more flexible standard on evidence of effectiveness
- However, the transfer of therapeutic biologics to CDER has lead to a more "NDA-like" standard in determining effectiveness, while providing some legal flexibility

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New Biosimilar Legislation

- Official title: "Biologics Price Competition & Innovation Act of 2009."
- The Act amended the Public Health Service Act (PHSA) to create a new pathway for the approval of biological products biosimilar to an approved reference product or biosimilar and interchangeable with an approved product.

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Definitions

- A "biosimilar" is (1) highly similar to the reference product notwithstanding minor differences in clinically inactive components and (2) no clinically meaningful differences in terms of safety, purity and potency.
- An "interchangeable" biosimilar is a biological product that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

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Effective Date

- Effective date is March 23, 2010 with full retroactivity
- Applies to already approved biologics
- Applies to biologics now under review

Scope of Biologics Covered

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- Anything for which a BLA is filed
  - "Biologics licensing application" ("**BLA**") is required for most complex biotech products:
    - "a virus, therapeutic serum, toxin, antitoxin, blood, or blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." PHSA § 351(i)
    - New legislation amends this definition to include "protein (except any chemically synthesized polypeptide)"

Basic Requirements for US Biosimilar Application

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(1) Analytical studies showing product is "highly similar" to a reference despite "differences in clinically inactive components;"

(2) animal studies (including the assessment of toxicity);

(3) Clinical study(ies) sufficient to demonstrate "safety, purity and potency in 1 or more appropriate conditions for use" that parallel an approved use of the reference product;

*note: FDA may determine that any of 1-3 is not required in a given case

Basic Requirements For US Biosimilar Application

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(4) Requires same mechanism of action as reference product (if known) for approved indication;

(5) Label for biosimilar must match approved indication of reference product;

(6) Route of administration, dosage form, and strength must match reference product;

(7) Must be approved manufacturing facility (safety, purity and potency).

Standard for Approval of Interchangeable Biosimilar

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- The FDA will label a biosimilar as "interchangeable" if:
  - (1) it is found to be "biosimilar" and
  - (2) expected to produce the "same clinical result as the reference product in any given patient"
  - (3) for a biological product that is administered more than once the risk of safety or diminished efficacy of switching between the reference product and interchangeable is not greater than using reference product without switch

There Are Scientific Issues to Address

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- Establishing sameness or similarity to the reference product.
- Issues related to immunogenicity
- Equivalence
  - Bioequivalence
  - Pharmaco-dynamic effects
  - Clinical equivalence
  - Interchangeability

Data Exclusivity For Reference Product

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- 12 years of market exclusivity for innovators, i.e., no biosimilar will be *approved* before expiration of 12 year period of the reference biologic product
- Runs from date of first approval for reference product
- First 4 years of data exclusivity from approval date, i.e., no biosimilar application will be *accepted* by FDA during that period

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6-Month Pediatric Exclusivity Possible

- Innovators may obtain an additional 6 month pediatric exclusivity based on similar provisions for small molecule drugs
- The 6 months is added to the 4 year filing period (no biosimilar application may be filed before 4 years and 6 months) and to the 12 year data exclusivity period (no biosimilar application may be approved before 12 years and 6 months)

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Strategic Consideration

- 12 year exclusivity does not apply to
  - (i) a supplement for the biological product that is the reference product or
  - (ii) subsequent app filed by same sponsor for (a) change resulting in new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or (b) structural modification that does not change safety, purity or potency.
- Therefore, need a structural modification that changes "safety, purity or potency" but not yet clear what FDA thinks is such a change

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NDA vs. BLA: Market Exclusivities

- NDA Market Exclusivities
  - NCE 5 year exclusivity for New Chemical Entity
  - 3 year Waxman-Hatch Exclusivity
  - Pediatric Exclusivity
  - 7 year Orphan Drug Designation and Exclusivity
- BLA Market Exclusivity
  - 12 year exclusivity for innovator
  - 6 month Pediatric Exclusivity
  - 7 year Orphan Drug Designation and Exclusivity

Exclusivity For 1st Approved Interchangeable Biosimilar

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1st "interchangeable" biosimilar eligible for additional exclusivity:

THE EARLIER OF:

(1) One year exclusivity from first marketing date of first approved interchangeable biosimilar;

(2) 18 months after final court decision or dismissal of action against applicant of the first approved interchangeable biosimilar;

(3) 42 months after approval of first interchangeable biosimilar if litigation is still pending; or

(4) 18 months after approval of first interchangeable biosimilar if no litigation is filed

Strategic Consideration

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- Innovator should consider keeping aspects of the manufacturing process a trade secret, thereby making it more difficult for the biosimilar applicant to replicate a product such that it could be deemed "interchangeable"

FDA's Past Position on Biosimilarity

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- Science will govern:
  - "As a science-based agency, the FDA will continue to integrate scientific advances and public health needs into its review of protein products." Woodcock, et al. The FDA's assessment of follow-on protein products: a historical perspective, in Nature (June 2007) at 442.
  - Woodcock testimony:
    - Although current technology, like peptide mapping, can determine amino acid sequence of a recombinant protein, more complex aspects of a protein's structure govern function, such as:
      - Folding of the protein's amino acid chain into highly organized structures;
      - Association of multiple protein molecules into aggregates; and
      - Modification of proteins through biochemical additions, such as glycosylation, acetylation, and phosphorylation

Establishment of User Fee Program for Biosimilars

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- Congress authorized use of User Fees
  - Effective Oct. 1, 2012
  - FDA responsible for evaluating costs of review during interim period
  - No user fees prior to 2012
  - However, FDA may accept and review applications

Establishment of Guidance Documents for Biosimilars

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- FDA may issue guidance (but is not required)
  - FDA must allow public comment on any guidance before issuing final guidance
  - If FDA issues product class-specific guidance must include a description of:
    - Criteria FDA will use to determine "highly similar"
    - Standards FDA will use to determine interchangability"
  - FDA may indicate in guidance that "science and experience, as of date of such guidance" with respect to a product or class does not allow approval of an application.
    - May subsequently modify or reverse such guidance document

Citizen Petition Process – 505(q)

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- Section 505(q) of the FDCA requires FDA to respond to Citizen Petitions which relate to 505(b)(2) and (j) applications within 180 days
- Requires certification by party submitting
- Section does not apply to biosimilar applications submitted under Section 351(k) of PHS
- Effect of Petitions?

Mechanism For Filing Suit Against Biosimilar Applicant

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- 20 days after FDA accepted biosimilar application, biosimilar applicant must provide BLA holder (1) copy of biosimilar application and (2) information describing manufacturing process for biosimilar.
- Therefore, BLA holder is given access to any confidential information of biosimilar applicant needed in its discretion to assess whether a claim of patent infringement may be made.

Mechanism For Filing Suit Against Biosimilar Applicant *(con't)*

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- Confidential info may ONLY be used for evaluating claim of infringement.
- Access to: one or more outside counsel designated by BLA holder and one in house counsel (not involved in prosecution of relevant or related patents), and owner of patent exclusively licensed if retained right to enforce patent or participate in litigation.

Mechanism For Filing Suit Against Biosimilar Applicant *(con't)*

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- 60 days after receiving copy of biosimilar application, BLA holder must send (1) a list of patents that may be infringed ("BLA list") and (2) indication of any of those patents in list (1) that are available for licensing

Mechanism For Filing Suit Against Biosimilar Applicant *(con't)*

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- Within 60 days after receiving BLA list, biosimilar applicant must respond and identify any patents in BLA list it believes may be infringed and for each one state why it is invalid / unenforceable / not infringed, or state that it will not begin marketing until expiration date
- Biosimilar applicant must also respond to BLA holder's offer to license patent
- Biosimilar applicant may also within this timeframe provide BLA holder with list that biosimilar applicant believes could be subject to infringement claim ("biosimilar list")

Mechanism For Filing Suit Against Biosimilar Applicant *(con't)*

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- Third 60 day period is for BLA holder to provide response to non-infringement/invalidity arguments from biosimilar applicant
- Thereafter, both parties engage in "good faith negotiations" to resolve disputes about which patents apply. No guidance in legislation re when negotiations to begin but presumably quickly
- When agreement is reached as to which patents apply, innovator has 30 days to file suit

Mechanism For Filing Suit Against Biosimilar Applicant *(con't)*

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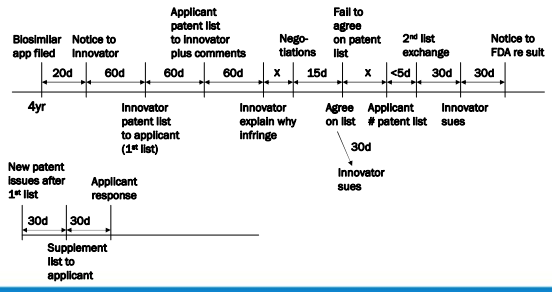
- If no agreement between parties within 15 days of starting negotiations, biosimilar applicant must notify BLA holder of the number of patents that it believes should be subject for an action for patent infringement and it will provide in a second list ("2nd biosimilar list").
- Within 5 days of notice, parties exchange list of patents each believes to be subject of infringement suit. Number of patents in 2nd BLA list cannot exceed number of patents in 2nd biosimilar list, but if 2nd biosimilar list does not list any patents, 2nd BLA list can list one patent.

Mechanism For Filing Suit Against Biosimilar Applicant *(con't)*

- BLA holder shall sue biosimilar applicant on each patent in second lists within 30 days of exchanging second lists.
- Biosimilar applicant provides notice to FDA within 30 days after complaint served, which will be published in the Federal Register.
- For new patents issued after initial list of patents is sent to biosimilar applicant, BLA holder must provide supplemental notice within 30 days. Legislation is not clear whether the other steps provided above are also followed with the newly issued patents.

Timeline for Filing Suit Against Biosimilar Applicant



Strategic Consideration

- Due to short time periods for providing patent lists to biosimilar applicant, diligence should be performed early:
  - Creating and maintaining lists of all patents owned and licensed, and products to which they relate is essential.
  - Assess relative strength of applicable patents so that litigation strategy is developed before biosimilar applicant files for approval.

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Preliminary Injunction

- Biosimilar applicant to provide notice to BLA holder 180 days before market entry
- Following 180 day notice, BLA holder may seek a preliminary injunction preventing manufacture or sale until a court decides patent validity, enforcement and infringement of the patents in the first BLA list or biosimilar list that are not subject to litigation based on the above process.

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Preliminary Injunction *(con't)*

- For example:

Innovator List No. 1	Biosimilar List No. 1	Innovator List No. 2	Biosimilar List No. 2	Patent Infringement Action	PI
A B C	E F	A B	E F	A B E F	C

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Strategic Consideration

- BLA holder cannot sue biosimilar applicant for infringement on a patent not included in first patent list BLA holder provides to biosimilar applicant and therefore, important to submit a comprehensive first BLA list.

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Declaratory Judgment

- BLA holder may bring action for declaratory judgment of infringement, validity or enforceability of any patent in first BLA list or supplemental new patent list if biosimilar applicant does not exchange list of patents and provide detailed statements on listed patents, or does not provide notice of commercial marketing, or notify Secretary of HHS of infringement complaint.

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Declaratory Judgment *(con't)*

- BLA holder may bring action for declaratory judgment of infringement, validity or enforceability of any patent claiming the biological product or use thereof if biosimilar applicant does not provide copy of the application and manufacturing information.

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Declaratory Judgment *(con't)*

- If biosimilar applicant complied with all requirements, neither BLA holder nor applicant can bring DJ action prior to 180 day marketing notice.

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Comparison With ANDA

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
Orange Book listing by NDA holder	No Orange Book equivalent
271(e)(2)(A), (B) Submitting ANDA= infringement: — with respect to patents listed in Orange Book	271(e)(2)(C) Submitting biosimilar application= infringement: — with respect to patents identified on BLA holder's first list, or — with respect to patents that could have been listed in BLA holder's first list, if biosimilar applicant fails to provide application and manufacturing information

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NDA vs. BLA: Patent Submissions *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
In Orange Book, NDA holder may only list patents relating to the chemical entity, formulation or methods of use, not methods of making Patents having only "methods of making" claims may not be subject to ANDA litigation	BLA holder assesses patent infringement and sues based on biosimilar application and information about methods of making Patents having "methods of making" claims may be subject to biosimilar litigation

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
Certification required	No certification required
ANDA applicant must certify regarding all patents listed in Orange Book for product: (I): patent not listed in Orange Book (II): patent has expired (III): Date patent will expire and generic will not market before then (IV): patent is invalid, unenforceable or not infringed	

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
Within 20 days after ANDA with P(IV) certification is accepted for filing, generic must provide NDA holder: (1) Notice ANDA has been accepted for filing and (2) Statement of factual and legal basis of opinion that patent(s) is invalid, unenforceable, or not infringed	Within 20 days after biosimilar application accepted for filing, applicant must provide BLA holder: (1) copy of application (2) other information describing processes used to manufacture product

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
(con't)	Within 120 days later, regarding submission in first BLA list, applicant must provide BLA holder statement of: (1) factual and legal basis for opinion that patent is invalid, unenforceable or not infringed or (2) it will not market before patent expires

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
In response to factual and legal basis by ANDA applicant: NDA holder not required to provide factual and legal basis regarding infringement, or provide response concerning validity and enforceability	In response to factual and legal basis by biosimilar applicant: BLA holder must provide factual and legal basis that patent is infringed, and response concerning validity and enforceability

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
Within 45 days of receiving notice ANDA accepted for filing: NDA holder may bring suit regarding P(IV) patents	Within 30 days of party agreement on first patent list or exchange of second lists: BLA holder can sue regarding agreed upon patents or second lists. If BLA holder does not bring suit within the 30 days: Exclusive remedy is reasonable royalties regarding those patents.

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
If NDA holder sues within 45 days, FDA will approve ANDA: After 30 month stay or when district court or appeals court decides patent is invalid or not infringed, whichever earlier	No 30 month stay FDA not required to stay approval based on pending litigation – applicants market "at risk"

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
ANDA applicant may file DJ action if ANDA has P(IV) certification and NDA holder has not sued within 45 days. NDA holder cannot file DJ action except as normally available after generic commercially markets	If biosimilar applicant provides application and manufacturing information to BLA holder, neither party may sue for DJ before applicant provides 180 day notice of marketing. If applicant fails to do required actions, BLA holder may bring DJ action for any patent listed in first BLA list (or supplemental first BLA list)

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Comparison with ANDA *(con't)*

ANDA-Hatch Waxman Act (1984)	New Biosimilar Legislation
271(e)(1) safe harbor applies	271(e)(1) safe harbor applies

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Strategic Considerations

- For M&A and in-licensing of biologics, new assumptions are needed to address potential for biosimilar competition and market erosion
- 12 year exclusivity provides one potential exclusivity scenario for valuation purposes
- Patent protection beyond 12 year exclusivity period may not exist for some biologics due to long FDA review
- However, patents may protect subject matter broader than approved biologic, and hence may still provide value in keeping competitors out

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Strategic Considerations

- Implications for portfolio management of 12 year data exclusivity
- Late stage patents may be more valuable if their terms extend beyond 12 year data exclusivity
- Because of 20 year from filing date term, patents filed out of Phase III results are more likely to have terms extending beyond data exclusivity

Thank You & Questions

Contact Information:

- Nathan Beaver: nbeaver@foley.com or (202) 295-4039
- Jackie Wright Bonilla: jwrightbonilla@foley.com or (202) 295-4792
- Kristel Schorr: kschorr@foley.com or (202) 672-5574