The Patient Protection and Affordable Care Act of 2010: The Meaning of "Related Entities"

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Question

". . . in light of the potential transfer of BLAs from one corporate entity to another and the complexities of corporate and business relationships, what factors should the agency consider in determining the types of ***related entities*** that may be ineligible for a period of 12-year exclusivity for a subsequent BLA?" *

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PPACA of 2010

- 42 U.S.C. §262(k)(7)
  - (A) EFFECTIVE DATE OF BIOSIMILAR APPLICATION APPROVAL. Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed . . . .
  - (B) FILING PERIOD. An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed . . . .
  - (C) FIRST LICENSURE. Subparagraphs (A) and (B) shall not apply to a license for or approval of: (i) a supplement for the biological product that is the reference product; or (ii) a subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) for (I) a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or (II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

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Intent: To grant Innovators 12 years market exclusivity against FOB applicant competition.

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Intent: To prevent FOB applicants from submitting drug applications to FDA for 4 years.

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Intent: To prevent a singular corporate entity, or related entity, from accumulating multiple 12/4 year exclusivity periods for "non-innovative" biologic derivatives lacking any measurable change in *"safety, purity, or potency."*

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Intent: To deny additional 12/4 exclusivity to any company for filing a "non-innovative" sBLA (e.g., new label indication, market a new dosage or strength of a drug, or change the way it manufactures a drug).

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Intent: To prevent evergreening by a single "related" entity. Any "related entity" filing multiple applications for a new indication, market a new dosage or strength of a drug, or change the way it manufactures a drug (i.e., sBLA) will not be rewarded with additional 12/4 exclusivity for such "non-innovative" changes.

Problem: Evergreening Loophole #1—If the same sponsor or any "related entity" makes any "structural" change, then additional 12/4 is possible.

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Intent: To deny additional 12/4 exclusivity to a single company or "related entity" who file multiple applications for "non-innovative" structurally tweaked biologics that fail to demonstrate a change in safety, purity or potency.

Problem: Evergreening Loophole #2—Any structural change will likely presuppose a change in safety and/or potency. If the same sponsor or any "related entity" makes any "structural" change, then additional 12/4 is possible.

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1. Most FOBs will be "biosimilar" and not "interchangeable" (but recent FDA approval of an ANDA for a pseudo-biologic like Lovenox™ may signal that interchangeable biologics are possible).

2. Most FOBs—even biologics with minor changes—will represent distinct biologic drugs with distinct structural, safety and potency issues.

3. "Structural" language is problematic and an obvious evergreening loophole.

4. "Related entity" language is problematic and an obvious evergreening loophole.

Preliminary Thoughts

How to strengthen the anti-evergreening clause and still encourage innovation

Before

(C) FIRST LICENSURE. Subparagraphs (A) and (B) shall not apply to a license for or approval of:

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Suggested

(C) FIRST LICENSURE. Subparagraphs (A) and (B) shall not apply to a license for or approval of:

(i) a supplement for the biological product that is the reference product; or

(ii) **any** subsequent application for **a biosimilar or interchangeable product filed by (I) the same sponsor, (II) any entity currently under the financial control of the same sponsor, (III) the same manufacturer, (IV) the same licensor or (V) any predecessor in interest** of the biological product that is the reference product.

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- The Related Entity Problem:
  " . . . application filed by the same sponsor . . . or other related entity . . ."

- Questions:
  1. What happens when a different sponsor, a different manufacturer, a licensee, a successor in interest or other unrelated entity files the application and that entity is subsequently acquired (or the marketing rights are licensed) by the reference product sponsor?

  2. What are the boundaries of "other related entity"?

What is an unrelated entity?

It is an entity which:

(1) does not directly or indirectly control,
(2) is not controlled by or
(3) is not under common control with another entity.

For the purposes of this law, an entity shall be regarded as in control of another entity if:

(a) it owns, directly or indirectly, more than 50% of the voting stock or other ownership interest of the other entity or
(b) it possesses, directly or indirectly, the power to
  (i) direct the management and policies of the other entity or
  (ii) elect or appoint more than 50% of the members of the governing body of the other entity.

Scenario 1

Time		Market Exclusivity Ends
Jan. 2011	Company A files BLA for mAb 1a	
↓		
Jan. 2015	BLA Approved; 12/4 years exclusivity granted; Becomes a blockbuster	Jan. 2027
Jan. 2017	Due to blockbuster status of mAb 1a, Company A files second BLA for mAb 1b	
↓		
Jan. 2021	BLA Approved; 12/4 years exclusivity granted	Jan. 2033

Scenario 2

Time		Market Exclusivity Ends
Jan. 2011	Company A files BLA for mAb 1a	
↓		
Jan. 2015	BLA Approved; 12/4 years exclusivity granted; Becomes a blockbuster	Jan. 2027
Jan. 2017	Due to blockbuster status of mAb 1a, ***Company B*** files BLA for mAb 1b	
↓		
Jan. 2021	BLA Approved; 12/4 years exclusivity granted	Jan. 2033

Company A **buys** Company B one month after Company B's BLA filing - OR -
Company A **licenses** Company B's mAb 1b - OR -
Company A **establishes** "unrelated entity" to develop mAb 1b and file a BLA.

Feb. 2017	A mAb 1a	+	B mAb 1b	=	A(B) mAb 1a/1b	Jan. 2033 (18 year exclusivity for mAb 1a/1b)

Benefits of Multiple 12/4 Year Exclusivity Periods

- **Patient Safety**—More products come into the marketplace. Patients will have more choices, so there is greater safety for the public. This technology is complicated and unpredictable: what is safe for one patient may not be safe for another.

- **Better Drug Products**—An incentive for all companies to develop and commercialize "biobetters."

- **Collaboration Among Drug Companies**—An incentive for large reference drug companies to help "unrelated entities" to develop "biobetters."

- **Fairness To All Drug Companies**—No loss of rightfully gained exclusivity rights during intellectual property licensing, business acquisitions, mergers or similar other transaction.

Thank You

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