Impact of NCE and 3-Year Exclusivities on 505(b)(2) NDAs and ANDAs

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Celebrating 40 Years: An In-Depth Examination of the FDA Orange Book –
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Learning Objectives

- Hatch-Waxman Amendments
- 5-Year Exclusivity for New Chemical Entities
- 3-Year Exclusivity for New Clinical Investigations
- Section 505(u): Not Hatch-Waxman
- Impact on 505(b)(2) NDAs and ANDAs
- CDER Exclusivity Board

Hatch-Waxman Amendments[1]

- Balance between two potentially competing policy interests
- Created the pathways for abbreviated applications
  - 505(b)(2) application
  - 505(j) application (ANDA)
- NDA holders could list patents in the Orange Book and qualify for NCE and 3-year exclusivities
  - Also 180-day exclusivity for ANDAs

1. Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417)

Hatch-Waxman Amendment - Exclusivity

- Available for any qualifying 505(b)(1) or 505(b)(2) NDA
- Does not affect the submission or approval of 505(b)(1) applications
- May affect submission/approval of 505(b)(2) NDAs or ANDAs
- Length and scope of protection depends on whether the drug contains a “new active moiety”
  - New chemical entity (NCE) (5 years)
  - Change to a drug containing no new active moiety (3 years)

5-Year Exclusivity for NCEs - Eligibility

- "… a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [505(b)] application …"[1]
  - *New Chemical Entity* - "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act."[2]
    - i.e., the drug substance must contain no previously approved active moiety

1. Sections 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act
2. 21 CFR 314.108(a)

5-Year Exclusivity for NCEs - Eligibility

- *Active Moiety*[1] –
  - The molecule or ion responsible for the physiological or pharmacological action of the drug substance (or active ingredient)
  - Excludes those appended portions that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as complex, chelate or clathrate)

1. 21 CFR 314.108(a)

Determining the Active Moiety

- FDA's interpretation of the NCE exclusivity provisions has consistently focused on the **chemical structure** of the drug under consideration
- FDA's definition of active moiety depends in part
  - Non-covalent vs. covalently bonded molecules
  - Covalently bonded molecules that are esters vs. covalently bonded molecules that are not esters

Determining the Active Moiety

- Look at the chemical structure and exclude:
  - Salt
  - Other noncovalent derivatives
  - Ester
  - You're left with the active moiety
- Prodrugs could be considered a previously unapproved active moiety, even if the molecule after metabolic conversion is previously approved

5-Year Exclusivity for NCEs - Eligibility

- Previous approvals include NDAs approved between 1938-62
- NCE exclusivity travels with the active moiety ("umbrella policy")
  - Subsequent drug product will be protected for the balance of the 5-year period

5-Year Exclusivity for NCEs - Eligibility

- ***Change in Policy for Fixed-Combination Drug Products***[1]
  - Prior to October 2014, a fixed-combination was ineligible for 5-year NCE exclusivity if it contained a *new* active moiety and a previously approved active moiety
  - FDA changed its policy in October 2014 to allow a fixed-combination to be eligible for 5-year NCE exclusivity if it contains a *new* active moiety

1. Guidance, New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products

5-Year Exclusivity for NCEs - Bar

- Bars the submission of 505(b)(2) NDAs and ANDAs for drugs containing the protected active moiety for 5 years
  - Can be submitted after 4 years if it contains a Paragraph IV certification for any listed patents

Patent and Exclusivity for: N211616

Product 001
BEMPEDOIC ACID (NEXLETOL) TABLET 180MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	7335799	12/03/2025	DS				03/06/2020
001	8497301	12/23/2023			U-2747		03/06/2020
001	9000041	12/23/2023			U-2747		03/06/2020
001	9624152	12/23/2023			U-2748		03/06/2020
001	10118881	12/23/2023			U-2747		03/06/2020

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NCE	02/21/2025

Patent and Exclusivity for: N211617

Product 001
BEMPEDOIC ACID; EZETIMIBE (NEXLIZET) TABLET 180MG;10MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	7335799	12/03/2025	DS				03/06/2020
001	8497301	12/23/2023			U-2746		03/06/2020
001	9000041	12/23/2023			U-2746		03/06/2020
001	9624152	12/23/2023			U-2749		03/06/2020
001	10118881	12/23/2023			U-2746		03/06/2020

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NP	02/26/2023
001	NCE	02/21/2025

3-Year Exclusivity - Eligibility

- Rewards innovation for NDAs containing previously approved active moiety(ies)
- Eligible for NDAs and supplements to NDAs
- NDA must contain:[1]
  - At least one new clinical investigation
  - Other than bioavailability studies
  - Essential to approval
  - Conducted or sponsored by the applicant

1. Definitions at 21 CFR 314.108

3-Year Exclusivity - Eligibility

- FDA has interpreted the statute so the exclusivity-protected conditions include:
  - Previously approved active moiety in new salt/ester/presentation
  - New indications
  - New dosage form
  - New dosing regimen
  - New route of administration
  - New extended release formulations
  - New conditions of use

3-Year Exclusivity - Bar

- Bars 505(b)(2) NDAs or ANDAs seeking approval for at least one "exclusivity-protected condition of approval"
- FDA consider the scope of exclusivity based on the clinical investigations essential to approval[1]
  - Look at the history of approvals for drugs containing the same active moiety
  - Innovative features of the product for which new clinical investigations were essential to approval
  - Relevant characteristics of the drug are clinically meaningful

1. *Braeburn Inc. v. FDA*, No. 19-cv-00982-BAH, ECF No. 53 (D.D.C. Nov. 7, 2019)

3-Year Exclusivity - Bar

- If the 505(b)(2) NDA or ANDA is not seeking approval of the exclusivity-protected conditions, then may be approved if
  - Omit or "carve out" uses protected by exclusivity (or patent) in the proposed labeling, and
  - Only if not rendered to be less safe or effective for all remaining, nonprotected conditions of use[1]
- E.g., RLD approved for Indications X and Y; Y protected by 3-year exclusivity and X is not protected by exclusivity
  - ANDA or 505(b)(2) NDA may be approved if it seeks approval for Indication X and carves out Indication Y

1. See e.g., 21 CFR 314.127(a)(7).

Patent and Exclusivity for: N208464

Product 001
TENOFOVIR ALAFENAMIDE FUMARATE (VEMLIDY) TABLET EQ 25MG BASE

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	7390791	04/17/2025	DS	DP			11/28/2016
001	7803788	02/02/2022			U-999		11/28/2016
001	8754065	08/15/2032	DS	DP	U-999		11/28/2016
001	9296769	08/15/2032	DS	DP	U-999		11/28/2016

Exclusivity Data

Product	Exclusivity Code	Exclusivity Expiration
001	NCE	11/05/2020
001	M-255	02/04/2023

INFORMATION ADDED TO THE LABELING TO DESCRIBE STUDY GS-US-320-4018 IN VIROLOGICALLY SUPPRESSED ADULTS W/ CHRONIC HEP B INFECTION WHO SWITCHED FROM TENOFOVIR DISOPROXIL FUMARATE TO TENOFOVIR ALAFENAMIDE

Exclusivity Codes are shorthand descriptions to describe the approval and are not meant to describe the scope of exclusivity.

Section 505(u): Not Hatch-Waxman

- Certain single enantiomer of a previously approved racemic mixture can qualify for NCE exclusivity
  - Must elect for this exclusivity
  - Must contain reports of new clinical investigations (excluding BA studies) essential to approval conducted or sponsored by applicant
  - Different therapeutic category compared to racemic mixture
  - May not rely on studies conducted for the racemic drug

CDER Exclusivity Board

- CDER staff from Office of Regulatory Policy, Office of Generic Drugs, Office of New Drugs, Office of Pharmaceutical Quality, and Office of Medical Policy
- Focus on NCE and 3-year exclusivities (reference product exclusivity for BLAs)
- Coordinate with other offices concerning other exclusivities (e.g., 180-day exclusivity, ODE, pediatric, GAIN)
- Do not review every exclusivity matter; most decisions resolved by Orange Book Staff
- Inquiries come from within CDER, applicants, and competitors
- Questions may be submitted to CDERExclusivityBoard@fda.hhs.gov or the Orange Book Staff at orangebook@fda.hhs.gov
- Exclusivity Board Website: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-exclusivity-board

Summary

- 5-year exclusivity protects new active moiety
  - Bars the submission of abbreviated applications seeking approval for that exclusivity-protected active moiety
- 3-year exclusivity protects innovation for which new clinical investigations (excluding BA studies) are essential
  - Bars the approval of abbreviated applications seeking approval for an exclusivity-protected condition of approval
  - May be able to carve out the exclusivity-protected condition as long as it does not affect the safe or effective use

Challenge Question #1

5-Year Exclusivity bars the _____ of 505(b)(2) and 505(j) applications for 5 years

A. Submission and Approval

B. Submission

C. Approval

Challenge Question #2

Which of the following statements is NOT true about 3-year exclusivity?

A. Bars the approval of 505(b)(1) NDAs

B. Always bars the approval of abbreviated applications

C. Bars the approval of abbreviated applications seeking approval of the exclusivity-protected conditions

D. Must be supported by new clinical investigations

E. A and B

Resources

- Section 505 of the FD&C Act (21 U.S.C. 355)
- 21 CFR 314.108 (exclusivity) and 21 CFR part 320 (BA/BE studies)
- Approved Drug Products with Therapeutic Equivalence Evaluations - Orange Book
- Guidance, New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products
- Guidance, Determining Whether to Submit an ANDA or a 505(b)(2) Application
- *Actavis Elizabeth L.L.C. v. FDA*, 625 F.3d 760 (D.C. Cir. 2010)
- *Veloxis Pharms, Inc. v. FDA*, 109 F. Supp. 3d 104 (D.D.C. 2015)
- *Braeburn Inc. v. FDA*, No. 19-cv-00982-BAH, ECF No. 53 (D.D.C. Nov. 7, 2019)

Closing Thought

Check **the Orange Book** before you submit your abbreviated application to determine if it may be blocked by another drug's exclusivity


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Definitions in 21 CFR 314.108

Clinical Investigation

- Any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

New Clinical Investigation

- An investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

Definitions in 21 CFR 314.108

Bioavailability Study

- A study to determine the bioavailability or the pharmacokinetics of a drug.
- See also 21 CFR part 320

Essential to Approval

- *Essential to approval* means, with regard to an investigation, that there are no other data available that could support approval of the NDA.

Definitions in 21 CFR 314.108

Conducted or sponsored by the applicant

- With regard to an investigation means that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. To demonstrate “substantial support,” an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.