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Back to the Well: FDA's Draft Guidance on New Clinical Investigation Exclusivity

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March 10, 2026, 11:39 AM
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I. Introduction

FDA recently published a new draft Guidance for Industry titled "New Clinical Investigation Exclusivity (3-Year Exclusivity) for Drug Products: Questions and Answers" (Mar. 2026) (the "Draft Guidance").[1] The Draft Guidance outlines the Agency's approach to determining new clinical investigation ("NCI") exclusivity.[2] The Draft Guidance also suggests some strategies for maximizing possible NCI exclusivity that could result from *in vivo* studies conducted by an applicant.[3]

NCI exclusivity lasts for three years, and can result from investigations submitted either with an original application or in a supplement to an approved application.[4] During that time, FDA is precluded from approving a 505(b)(2) or 505(j) drug that incorporates the changes that were supported by the new investigation.[5] NCI exclusivity is available to NDAs submitted under Section 505(b) of the Federal Food, Drug, and Cosmetics Act ("FDCA"), which makes it an attractive and relatively accessible route to obtain exclusivity for 505(b)(2) drug products.[6] To qualify for NCI exclusivity, an NDA or supplement must check three boxes: First, it must contain a new clinical investigation that is not a bioavailability study; Second, the clinical investigation

must have been conducted or sponsored by the applicant; Third, the clinical investigation must be "essential to the approval" of the application or supplement.[7]

II. **An FDA Guide to Spinoffs and Sequels**

FDA highlights some ways in which *in vivo* studies may be designed to maximize the opportunities for NCI exclusivity. To start, FDA notes that methods for a "bioavailability study" can vary from an *in vivo* assessment of pharmacokinetic endpoints to the "acute pharmacological effect of the active moiety" in patients.[8] Such studies may nevertheless qualify an NDA for NCI exclusivity if they also include information supporting the safety or effectiveness of the proposed drug.[9] This must go beyond routine safety monitoring and should be reflected in the study prospectively, including in "its endpoints, its design, and/or its role in the evidentiary package."[10] When an *in vivo* bioavailability study is required (for any reason), applicants can leverage the opportunity to maximize future exclusivities by thoughtfully designing bioavailability and bioequivalence studies to include aspects of safety and/or efficacy. Of note, the drug studied need not be the same as the approved drug, which (by virtue of its reliance on the study) qualifies for NCI exclusivity.[11]

The Draft Guidance goes on to explain that clinical investigations that were previously submitted to FDA may nonetheless be considered "new clinical investigations" for purposes of NCI exclusivity provided that (1) the results have not been previously relied on by FDA to establish effectiveness for any indication or safety in a new population; and (2) the results are not duplicative of another investigation on which FDA did rely.[12] Provided those conditions are met, the same study could give rise to multiple periods of NCI exclusivity (in the same or different drug products).[13]

FDA also outlines how studies may be prospectively designed to examine different cohorts or treatment arms such that a single trial can be used to obtain more than one period of NCI exclusivity.[14] Even if FDA previously relied on a particular study to approve an application or supplement, a cohort or treatment arm may qualify a drug for NCI exclusivity if it otherwise meets the requirements outlined above.[15] To make this determination, FDA considers a number of factors, including the scientific or medical reason for the separate cohort, whether the cohort evaluates different patient populations or drug products, and whether the cohort is prespecified in the protocol.[16]

III. **Takeaways for 505(j) and 505(b)(2) Applicants**

Applications submitted under both 505(j) and under 505(b)(2) rely on previously approved products or published studies to establish safety and effectiveness.[17] One of the main distinctions between the two pathways is that a 505(b)(2) application permits the submission of studies other than those needed to establish bioequivalence.[18] 505(b)(2) applications will thus frequently contain studies that could qualify for NCI exclusivities. Applicants should consider the potential for NCI exclusivity when evaluating FDA's approval requirements for a given drug product. For example, FDA will sometimes publish Product Specific Guidance suggesting a 505(j) applicant conduct *in vivo* studies to establish bioequivalence to a particular reference product.[19] In that case, applicants can consider whether such an *in vivo* study can

be efficiently designed to meet FDA's bioequivalence standards while also examining aspects of safety or efficacy. In some cases, a 505(b)(2) application may be attractive either as an alternative to a 505(j) or as an additional product pursued under the 505(b)(2) pathway. Through thoughtful consideration of the regulatory landscape and prospective design of *in vivo* studies, 505(j) and 505(b)(2) applicants may be able to leverage distinct parts of a single study to qualify for multiple periods of NCI exclusivity across one or several drug products.

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[1] Available at https://www.fda.gov/media/191368/download.

[2] *Id. See* 21 U.S.C. § 355(c)(3)(E)(iii)-(iv) and (j)(5)(F)(iii)-(iv).

[3] *Id.*

[4] *See id.* at 2 (Background).

[5] *See id.* at 1-2 (Background).

[6] *See id.*

[7] *See id.* at 2 (Background).

[8] *See id.* at 4-5 (QB.4).

[9] In support, the Draft Guidance cites *Liquidia Techs., Inc. v. FDA*, Civ. A. No. 24-2428, 2025 WL 637413, at *7 (D.D.C. Feb. 27, 2025) (finding that a study qualified as a clinical investigation notwithstanding the fact that it also assessed bioavailability).

[10] *Id.* at 5 (QB.5).

[11] *See id.* at 4 (QB.2).

[12] *Id.* at 5-6 (QB. 6).

[13] *See id.*

[14] *See id.* at 6-8 (QB.8).

[15] *See id.* at 7 (QB.8).

[16] *Id.*

[17] *See* Determining Whether to Submit an ANDA or a 505(b)(2) Application at 3-5 (May 2019), https://www.fda.gov/media/124848/download.

[18] *See id.*

[19] *See* Product-Specific Guidances for Generic Drug Development, FDA, https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

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