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Regulatory Implications of Clinical Immunogenicity Data

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ANDA v. 505(b)(2) NDA: Application Type Matters

According to FDA, clinical immunogenicity data precludes submission of a duplicate drug under the ANDA pathway:

"Based on the types of data permitted to be submitted in an ANDA (see section 505(j)(2)(A) of the FD&C Act) and current scientific considerations, FDA does not expect that an ANDA could include sufficient evidence (e.g., clinical investigations to assess potential immunogenicity) for approval of a proposed peptide of rDNA origin at this time. An applicant seeking approval of a proposed peptide of rDNA origin may file a 505(b)(2) application or a "stand-alone" NDA submitted under section 505(b)(1) of the FD&C Act."

"[I]t may not be possible to adequately address the larger variance"—i.e., a peptide-related impurity level higher than 0.5 percent—"through the ANDA process (e.g., the risk of immunogenicity requires a clinical investigation."

FDA Guidance, ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021).*

	ANDA	505(b)(2) NDA
Therapeutic Equivalence ("TE") Rating	All ANDAs (other than petitioned ANDAs)	Only required for 505(b)(2) NDAs "for which the sole difference" is a difference in non-exception excipients Otherwise, must submit a Citizen Petition with no timeline
Application Fees (FY26)	$ 358,247	Full: $ 4,682,003 (requiring clinical data) Half: $ 2,341,002 (not requiring clinical data)
180-Day Exclusivity	FTF eligibility	N/A

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See also FDA Guidance, Determining Whether to Submit an ANDA or a 505(b)(2) Application (2019) ("If a clinical investigation (i.e., any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects) is necessary to demonstrate the safety or effectiveness of a proposed drug product, generally this type of study goes beyond the scope of information that may be relied upon as necessary for approval in an ANDA.")

Biosimilars: Collection of Immunogenicity Data and Application Implications

- Original applications
  - User fee depends on whether a biosimilar application includes “clinical data (other than comparative bioavailability studies) with respect to safety or effectiveness” (21 U.S.C. § 379j-52(a)(2)(A))
  - FDA Guidance, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (2004) predates biosimilars and lacks clarity

- Supplements
  - CMC Supplements (4-month clock) may include pharmacokinetic comparability studies
  - If that pharmacokinetic study *also* collects descriptive immunogenicity data, FDA has taken a variety of approaches (ranging from a 4- to a 10-month clock across 351(a) and 351(k) BLAs)

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