

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Draft Guidance on Exenatide Synthetic**

**May 2022**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic exenatide synthetic.

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**Active Ingredient:** Exenatide synthetic

**Dosage Form; Route:** For suspension, extended release; subcutaneous

**Recommended Studies:** Two options: (1) one in vivo single-dose bioequivalence study with pharmacokinetic endpoints in healthy subjects or (2) one in vivo multiple-dose steady state bioequivalence study with pharmacokinetic endpoints in patients

The two options in this guidance are selective. An ANDA applicant may utilize either one of the two study designs based on considerations including but not limited to detection limit of bioanalytical method, data variability, study duration, and/or sample size.

**I. Option 1: One in vivo single-dose bioequivalence study with pharmacokinetic endpoints**

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
Design: Single-dose, randomized, parallel, in vivo  
Strength: 2 mg, 2 mg/vial  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: Subjects with personal or family history of medullary thyroid carcinoma should be excluded. Subjects should be appropriately monitored for hypoglycemia during the study, which may include a period of on-site monitoring. When the study subjects are not confined at the clinical site, they should be provided with a glucometer and instructed on its use.

**Analyte to measure:** Exenatide in plasma

**Bioequivalence based on (90% CI):** Exenatide

The 90% confidence intervals of the following pharmacokinetic parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ . Applicant should submit  $AUC_{Week\ 4\ to\ t}$  as supportive data.  $AUC_{0-t}$  is the area under the curve from 0 to the last sampling point,  $AUC_{0-\infty}$  is the area under the curve from 0 to infinity,  $C_{max}$  is the maximum plasma concentration, and  $AUC_{Week\ 4\ to\ t}$  is the area under the plasma concentration time curve from Week 4 to last sampling point.

**II. Option 2: One in vivo multiple-dose steady state bioequivalence study with pharmacokinetic endpoints**

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
Design: Multiple-dose, randomized, parallel, in vivo  
Strength: 2 mg, 2 mg/vial  
Subjects: Male and non-pregnant, non-lactating female patients with type II diabetes who are already receiving a stable regimen of exenatide extended release injectable suspension via subcutaneous route  
Additional comment: Implement safety monitoring as recommended in the drug labeling. PK data should be submitted to demonstrate that steady state of test and reference products has been reached for each individual.

**Analyte to measure:** Exenatide in plasma

**Bioequivalence based on (90% CI):** Exenatide

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be submitted for exenatide:

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels ( $C_{min\ ss}$ )

- Individual and mean peak levels ( $C_{\max ss}$ )
- Calculation of individual and mean steady-state  $AUC_{\tau}$  ( $AUC_{\tau}$  is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [ $=100 * (C_{\max ss} - C_{\min ss})/C_{\text{average ss}}$ ]
- Individual and mean time to peak concentration

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and  $C_{\max}$ ) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The trough concentration data should also be analyzed to verify that steady state was achieved prior to pharmacokinetic sampling.

**Waiver request of in vivo testing:** Not Applicable

**Dissolution test method and sampling times:**

The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Additional information:**

Device:

The reference listed drug (RLD) product is a drug-device combination product with two presentations: (1) a vial of drug for suspension and a prefilled syringe of diluent and (2) a single-dose, prefilled manual injection pen.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test device. In addition, test device design should take into consideration the following characteristics of the RLD devices:

1. For the vial with prefilled syringe (single-dose tray) presentation:
  - Syringe
  - Vial connector
  - Needle gauge and length
2. For the prefilled manual injection pen:
  - Single-dose, fixed-dose format of RLD device
  - Needle gauge and length

User Interface Assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA

guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.<sup>a</sup>

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<sup>a</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.