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Draft Guidance on Tirzepatide

August 2023

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Tirzepatide
Dosage Form:	Solution
Route:	Subcutaneous
Strengths:	2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Recommended Studies:	Comparative characterization studies to support active pharmaceutical ingredient (API) sameness and request for waiver of in vivo bioequivalence study requirements

Recommendations to support API Sameness and Impurity Assessment:

In addition to ensuring API sameness (i.e., same primary sequence and physicochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic tirzepatide and the reference listed drug (RLD) product on no less than three batches of the proposed drug product tested on or near release and at the end of the proposed shelf life and no less than three batches of the RLD aged prior to expiry, after aging under conditions consistent with the label storage conditions:

1. Secondary structure
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RLD
3. Biological activities[1]

[1] Applicant may provide justification for not conducting biological assays as part of the comparative analyses if there is evidence that the structure of the API peptide would not interfere with the functional activity.

4. API-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RLD and impurities found at a significantly higher level in the proposed generic drug product than in the RLD, should be identified. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be required.
5. Comparative study demonstrating comparable innate immune response risk of the proposed product and RLD

Waiver of in vivo bioequivalence study requirements:

In vivo bioequivalence study may be waived on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), for a generic tirzepatide injection product that is qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD.

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[4]

Additional information:

Device:
The RLD is presented in an autoinjector. The autoinjector is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test devices including:

- A single-use, single-dose format of the autoinjector device
- Needle gauge and length

User interface assessment:
An abbreviated new drug application 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*.[a]

[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference list drug product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference listed product.
[4] 21CFR 314.94(a)(9)(iii)

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.