

**Draft Guidance on Metformin Hydrochloride; Saxagliptin Hydrochloride**  
**August 2024**

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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.

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| <b>Active Ingredients:</b>  | Metformin hydrochloride; Saxagliptin hydrochloride                                                                                                                                                                                                                                                                                                                            |
| <b>Dosage Form:</b>         | Tablet, extended release                                                                                                                                                                                                                                                                                                                                                      |
| <b>Route:</b>               | Oral                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Strengths:</b>           | 500 mg; EQ 5 mg Base, 1 gm; EQ 2.5 mg Base, 1 gm; EQ 5 mg Base                                                                                                                                                                                                                                                                                                                |
| <b>Recommended Studies:</b> | Two in vivo bioequivalence studies with pharmacokinetic endpoints                                                                                                                                                                                                                                                                                                             |
| 1.                          | Type of study: Fasting<br>Design: Single-dose, two-treatment, two-period crossover in vivo<br>Strength: 1 gm; EQ 5 mg Base<br>Subjects: Healthy males and non-pregnant, non-lactating females<br>Additional comment: Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement an appropriate hypoglycemia management protocol. |
| 2.                          | Type of study: Fed<br>Design: Single-dose, two-treatment, two-period crossover in vivo<br>Strength: 1 gm; EQ 5 mg Base<br>Subjects: Healthy males and non-pregnant, non-lactating females<br>Additional comments: See comments above.                                                                                                                                         |
| <b>Analytes to measure:</b> | Metformin, saxagliptin, its metabolite 5-hydroxy saxagliptin (M2) in plasma                                                                                                                                                                                                                                                                                                   |

## **Bioequivalence based on (90% CI): Metformin and saxagliptin**

Bioequivalence acceptance criteria will be based on metformin and saxagliptin results. Provide the data for M2 as supportive evidence of comparable therapeutic outcome. For M2, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for area under the curve (AUC) and peak concentration ( $C_{max}$ ).

**Additional strengths:** Bioequivalence of the 500 mg; EQ 5 mg Base and 1 gm; EQ 2.5 mg Base strengths to the corresponding reference listed drug (RLD) strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.<sup>a</sup>

**Dissolution test method and sampling times:** For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and RLD products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and RLD products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

**Alcohol dose dumping studies:** Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 900 mL, 0.1N HCl, USP Apparatus 1(basket) at 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and RLD products accordingly, and provide data on individual unit, means, range and %CV.

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**Document History:** Recommended March 2012; Revised August 2024

**Unique Agency Identifier:** PSG\_200678

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