

Draft Guidance on Metformin Hydrochloride

May 2025

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Active Ingredient:	Metformin hydrochloride
Dosage Form:	Tablet, chewable ¹
Route:	Oral
Strengths:	500 mg, 850 mg, 1 gm
Recommended Studies:	Two options: (1) two in vivo bioequivalence studies with pharmacokinetic endpoints using the designated reference standard (RS) for metformin hydrochloride tablets, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints using the designated RS for metformin hydrochloride chewable tablets

I. Option 1: Two in vivo bioequivalence studies with pharmacokinetic endpoints using the designated RS for metformin hydrochloride tablets²

1. Type of study: Fasting
Design: Single-dose, three-treatment, three-period, crossover in vivo
Strength: 1 gm
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Conduct the study by testing one metformin hydrochloride chewable tablet of the test drug products, administered with and without water, compared to one metformin hydrochloride tablet of the RS. The chewable tablets should be chewed, then swallowed with or without water. Monitor blood glucose concentrations and signs

¹ New dosage form identified is the subject of an approved suitability petition (FDA-2011-P-0558).

² The currently designated RS is metformin hydrochloride tablets, 1 gm.

and symptoms of hypoglycemia during the study. Implement an appropriate hypoglycemia management protocol.

2. Type of study: Fed
Design: Single-dose, three-treatment, three-period, crossover in vivo
Strength: 1 gm
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints using the designated RS for metformin hydrochloride chewable tablet³

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1 gm
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Conduct the study by testing one metformin hydrochloride chewable tablet of the test drug product, administered without water compared to one metformin hydrochloride chewable tablet of the RS without water. The chewable tablets should be chewed, then swallowed without water. Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement an appropriate hypoglycemia management protocol.

Analyte to measure: Metformin in plasma

Bioequivalence based on (90% CI): Metformin

Waiver request of in vivo testing: 500 mg and 850 mg strengths based on (i) acceptable bioequivalence studies on the 1 gm strength, (ii) acceptable in vitro dissolution testing of all the strengths, and (iii) proportional similarity of the formulations across all strengths

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 for each of all strengths of the test product and the RS.⁴ Specifications will be determined upon review of the abbreviated new drug application.

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³ This option can be used when a petitioned ANDA for metformin hydrochloride chewable tablets is approved and designated as the RS.

⁴ If the RS is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.