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Draft – Not for Implementation

Draft Guidance on Metformin Hydrochloride

February 2026

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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 tablets[2]

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:
   - Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement an appropriate hypoglycemia management protocol.

[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.

- 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.

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

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints using the designated RS for metformin hydrochloride chewable tablet[3]

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:
    - Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement an appropriate hypoglycemia management protocol.
    - 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.

Analyte to measure: Metformin in plasma

Bioequivalence based on (90% CI): Metformin

Waiver request of in vivo testing of additional strengths: Justification based on (i) acceptable bioequivalence studies on the 1 gm strength, (ii) acceptable comparative in vitro dissolution studies between additional strengths and the 1 gm strength using 12 units per strength, and (iii) proportional similarity of the formulations across all strengths

Dissolution: Dissolution test(s) should be included for quality control and to support waiver request of in vivo testing of additional strengths.

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

Dissolution test method and sampling times: Provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[4] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

For drug products containing high solubility drug substances that meet the rapidly dissolving criteria, demonstration of discriminating ability may not be needed. For additional information, refer to the most recent version of the guidance for industry *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances.*[a]

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

[4] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm