Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Potassium Chloride

December 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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: Potassium chloride

Dosage Form: For suspension, extended release

Route: Oral

Strengths: 8 mEQ/packet,[1] 10 mEQ/packet,[1] 20 mEQ/packet

Recommended Studies: Two options: (1) one in vivo bioequivalence study with pharmacokinetic endpoints and one in vitro characterization study, or (2) alternative approach to establish bioequivalence

I. Option 1: One in vivo bioequivalence study with pharmacokinetic endpoints and one in vitro characterization study

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mEQ/packet at a dose of 40 mEQ (2 x 20 mEQ/packet)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The entire contents of two packets of 20 mEQ/packet should be slowly added to 180 mL of room temperature water and stirred for approximately 1 minute until slightly thickened. The potassium chloride suspension should be administered by mouth immediately and followed by 180 mL of room temperature water. Refer to the most recent version of the FDA product-specific guidance *potassium chloride extended release capsules* (NDA 018238)[a] for other specific recommendations regarding the bioequivalence study in fasting conditions.

[1] Strengths identified are the subject of an approved suitability petition (FDA-2020-P-2181).

Analyte to measure: Potassium in urine

Bioequivalence based on (90% CI): Baseline-corrected potassium for cumulative urinary excretion from 0 to 24 hours (Ae0-24h) and maximum rate of urinary excretion (Rmax)

2.	Type of study:	In vitro dissolution after exposure to soft food and liquid vehicles
	Strength:	20 mEQ/packet
	Apparatus:	United States Pharmacopeia (USP) Apparatus 2 at 75 rpm
	Testing vehicles:	One tablespoon (15 mL) of room temperature applesauce, 60 mL of orange juice, 60 mL of tomato juice, 60 mL of apple juice, and 60 mL of milk
	Media:	Three different dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer)
	Volume:	900 mL
	Temperature:	37°C
	Sampling times:	Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released. The applicant should use at least 12 dosage units for each of the test product and reference listed drug (RLD). The f2 metric should be used to compare dissolution profiles of the test product and RLD in each vehicle. Provide mass balance to account for drug substance present in the food and liquid vehicles after filtrating and washing and amount present in sample for dissolution.
	Reconstitution:	For testing in juice or milk, one 20 mEQ/packet should be slowly added to 60 mL of room temperature juice or milk and stirred for approximately one minute. For testing in applesauce, one 20 mEQ/packet should be sprinkled on to one tablespoon (15 mL) of room temperature applesauce.

For general procedures of in vitro methods for product quality assessments, refer to the most recent guidance for industry *Use of Liquids and/or Soft Food as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments*.[b]

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 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 of the test product and RLD.[2] Specifications will be determined upon review of the abbreviated new drug application (ANDA).

[2] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.

In addition to the method above, submit dissolution profiles on 12 dosage units for each of the test product and RLD 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.

II. Option 2: Alternative approach to establish bioequivalence

Option 2 can be used when the RLD is listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations' (the Orange Book) Discontinued Drug Product List (Discontinued Section) and there is no drug product listed in the Orange Book's Prescription Drug Product List (Active Section) that is, or can be, designated as a reference standard for the RLD. Applicants are recommended to discuss their development program with the FDA via the pre-abbreviated new drug application meeting pathway. For additional information, refer to the most recent versions of the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b] Conduct one in vivo study with pharmacokinetic endpoints using the reference standard potassium chloride extended release capsules at a dose of 40 mEQ (8 mEQ x 5 capsules).

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mEQ/packet at a dose of 40 mEQ (2 x 20 mEQ/packet)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The potassium chloride extended release capsules should be administered by mouth and immediately followed with 360 mL of room temperature water. Refer to additional comments in fasting study for Option 1 for reconstitution of the test for suspension product.

Analyte to measure: Potassium in urine

Bioequivalence based on (90% CI): Baseline-corrected potassium for Ae0-24h and Rmax

2. Type of study: In vitro dissolution after exposure to soft food and liquid vehicles
   Strength: 20 mEQ/packet

   See recommendations in Option 1 and conduct testing for test product only. In addition, conduct testing in 60 mL of room temperature water. Compare dissolution profiles of the test product mixed in water to the test product mixed in the listed vehicles. For reconstitution in water, one 20 mEQ/packet should be slowly added to 60 mL of room temperature water and stirred for approximately one minute, until slightly thickened.

Additional strengths: Bioequivalence of the 8 mEQ/packet and 10 mEQ/packet strengths to the corresponding RLD strengths may be demonstrated based on principles laid out in the most recent version of the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[b]

Dissolution test method and sampling times: Conduct for the test product only. Include both the discriminating dissolution and multi-pH dissolution tests referenced in Option 1.

Additional comments regarding Option 2 fasting study:

Applicants should refer to the published study that compares potassium chloride extended release capsules (C1) and the RLD potassium chloride extended release for suspension (R) conducted by the innovator (See Footnote below[3] for study details). Refer to the point estimate of the log-transformed geometric mean ratio ($\theta_{C1/R}$), along with the mean squared error ($MSE_{C1/R}$), and degrees of freedom ($df_{C1/R}$) from the table below. Calculate the point estimate of the log-transformed geometric mean ratio of T vs. R (θ_{T_R}) and the 90% CI of θ_{T_R} using 1) Table 1 results from the published study comparing C1 and R and 2) results from the Option 2 study comparing the reference standard potassium chloride extended release capsules (C2) to the proposed test product. Illustrative equations for statistical analysis using this alternative approach to establish bioequivalence are provided in the draft guidance for *trazodone hydrochloride extended release tablets* (NDA 022411).[a] The statistical analysis methodology and equations may require case-specific modifications.

Table 1. Statistical Analysis of Pharmacokinetic Parameters for Potassium Chloride Extended Release Capsule and RLD Potassium Chloride Extended Release for Suspension

Parameter	**GMR (90% CI)**	**CV%**	$\boldsymbol{\theta_{C1/R}}$ **(log-transformed)**	$\boldsymbol{MSE_{C1/R}}$	***n***	$\boldsymbol{df_{C1/R}}$
Baseline-corrected Ae0-24	78.99 (63.26, 98.63)	50.70	-0.23586	0.22876	27	26
Baseline-corrected Rmax	90.18 (78.11, 104.13)	32.39	-0.10332	0.09974	28	27

C1 = potassium chloride extended release capsules 8 mEQ x 5 capsules (40 mEQ); R = potassium chloride extended release for suspension for oral use 20 mEQ/packet x 2 packets (40 mEQ); Ae0-24 = cumulative urinary excretion from 0 to 24 hours ; CI = confidence interval; CV% = coefficient of variation as percent; GMR = geometric mean ratio; MSE = mean squared error; Rmax = maximum rate of urinary excretion

[3] Melikian AP et al. J Clin Pharmacol. 1988 Nov;28(11):1046-50. doi: 10.1002/j.1552-4604.1988.tb03128.x. PMID: 3243918.

Document History: Recommended December 2025

Unique Agency Identifier: PSG_019561

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

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