Guidance for Industry

Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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I. INTRODUCTION

This guidance is intended to provide information to sponsors of abbreviated new drug applications (ANDAs) on the design of bioequivalence studies for modified-release (MR) dosage forms of potassium chloride. FDA first issued a guidance on this topic on May 15, 1987, and we issued revised guidance on June 6, 1994. The 1987 guidance recommended a single-dose, three-way crossover study. This guidance provides recommendations for a two-way crossover design comparing the generic product to the reference listed drug (RLD). In addition, the Agency has determined that analysis of variance (ANOVA) with baseline correction is adequate for bioequivalence analysis of pharmacokinetic data obtained following oral administration of potassium chloride drug products. The in vitro dissolution testing and criteria for waivers of in vivo testing for lower strengths have also been revised to reflect the Agency thinking in the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consideration*.[2]

FDA's guidance documents, including this guidance, 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.

[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

II. BACKGROUND

The potassium ion is the principal intracellular cation of most body tissues. Potassium ions are crucial in a number of essential physiological processes, including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle, and the maintenance of normal renal function. The intracellular concentration of potassium is approximately 150 to 160 milliequivalents (mEq) per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane.

Potassium is a normal dietary constituent, and under steady state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50 to 100 mEq per day.

Potassium supplements are indicated for the treatment of patients with potassium depletion (hypokalemia) with or without metabolic alkalosis and in digitalis intoxication in patients with hypokalemic familial periodic paralysis. It is also indicated for the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop (e.g., patients receiving digitalis therapy or patients with significant cardiac arrhythmias).

Urinary potassium measurements are commonly used in studies of bioavailability and bioequivalence. Because of the homeostatic mechanisms that maintain serum potassium levels within a relatively narrow range, serum levels do not necessarily reflect intake.

The most common adverse reactions to oral potassium are nausea, vomiting, flatulence, abdominal pain and/or discomfort, and diarrhea. Patients are instructed to take each dose with a full glass of water or other liquid.

III. IN VIVO STUDY

A. Product Information

1. FDA Designated Reference Product

Potassium chloride for oral administration is marketed as various solid oral dosage forms. Applicants may consult FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) for the appropriate reference product.

2. Batch Size

The test batch or lot should be manufactured under production conditions and be of a size at least 10 percent that of the largest lot planned for production, or a minimum of 100,000 units, whichever is larger.

3. Potency

The assayed potency of the reference product should not differ from that of the test product by more than 5 percent.

B. Single-Dose Bioequivalence Study

1. Objective

The objective of a single-dose bioequivalence study is to compare the rate and extent of absorption of a generic potassium chloride formulation with that of a reference formulation.

2. Methodology

The recommended study design is a two-treatment, two-period, two-sequence crossover study. Each subject would receive a single oral dose of potassium chloride at 80 mEq of both the test and reference formulations. Extensive urine sampling for determination of urinary potassium excretion should be performed before and after each dose, with creatinine clearance determined to ensure that urine collection has been adequate.

3. Inclusion/Exclusion Criteria

It is recommended that the applicant include a sufficient number of subjects in the study to demonstrate bioequivalence. Subjects eligible for participation should be between the ages of 20 and 40 years and be within $\pm$ 10 percent of ideal body weight. Study subjects should be asked not to undertake vigorous physical exercise beginning 7 days before the start of the study period and continuing until discharge from the clinic. They should also be asked not to consume alcoholic beverages for a period beginning 48 hours before drug administration and ending after study completion.

Subjects with any of the following conditions would be excluded from the study:

- Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, or adrenopituitary disorders, as evidenced by medical examination, physical examination, and/or clinical laboratory tests
- Use of tobacco in any form, currently or within the 6 months before study initiation
- Use of any known enzyme inducers or inhibitors within 30 days before study entry
- History of drug or alcohol abuse

- History of hypersensitivity to the drug or similar compounds
- Use of any prescription or nonprescription (over-the-counter (OTC)) medication within 2 weeks before study entry
- Pregnancy, nursing, or failing to use a medically acceptable form of contraception by female subjects

4. Dietary and Housing Considerations

The subjects should be placed on a standardized diet, with known amounts of potassium, sodium, calories, and fluid-with-fluid intake. The fluid intake should be maintained at 3,000 to 5,000 milliliters (mL) per day to ensure an adequate rate of urine flow throughout the study period. This is higher than the normal fluid intake of 1,300 to 2,500 mL per day. Strict control and knowledge of the actual intakes of potassium, sodium, calories, and fluid are critical for study success. Detailed information regarding the composition of the diet should be included in the final report.

Study subjects should be placed in a climate-controlled environment, remaining in-house as much as possible. Physical activity should be restricted to avoid excessive sweating and thus potassium loss. Meals, snacks, and fluids should be given at standard times, and subjects strongly encouraged to ingest the recommended amounts while refraining from unnecessary physical activity. In addition, subjects should be queried regarding any prolonged episodes of diarrhea or excessive sweating, as these occurrences may invalidate or obscure the results. A test for fecal occult blood should be performed on each dosing day.

5. Collection of Urine and Blood Samples

The volume of each urine collection should be recorded. Aliquots of each urine collection should be stored frozen until assayed for potassium. After the aliquots are drawn, all remaining urine samples for each subject over a 24-hour period can be pooled for urine creatinine determination. A blood sample should be drawn at approximately the same time each day for serum creatinine determination. The usual time to collect blood samples for creatinine determination is at the mid-point of the urine collection.

6. Study Design

It is recommended that the study be conducted over a single period of residence in the clinic, the duration of which is 16 days and 17 nights. This time would be divided into two 8–day periods, with dose administration to take place on days 7 and 15. Recommended study procedures are identical for each of the 8-day periods (see Appendix). The recommended schedule for study periods 1 and 2 follows:

Diet Equilibration Days, Days 1-4 and 9-12

- Diets should be standardized to provide the following daily intake of potassium, sodium, and calories:

Potassium:	50-60 mEq
Sodium:	160-180 mEq
Calories:	2500-3500

- Fluids should be administered according to the following schedule:

  500 mL of room temperature water initially (at 07:00 hours)
  200 mL every hour afterwards for 12 hours
  Additional (known) amounts of fluid can be administered at the investigator's discretion from 19:00 hours until 07:00 hours the following day

- No urine is collected during the diet equilibration days

Baseline Days, Days 5-6 and 13-14

- The standard diet and fluid schedule should continue as described for the equilibration days.

- Urine should be collected each day to establish each subject's baseline level of potassium excretion.

- Urine collection intervals should be at hours 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16 and 16-24.

- Urine collection should begin at 07:00 hours. On days 5 and 13, subjects can dispose of this sample. On days 6 and 14, the urine collected at 07:00 hours completes the 16-24 hour sample.

- Blood samples for creatinine clearance determination should be collected on days 6 and 14.

Drug Dosing Days, Days 7 and 15

- After an 8-hour overnight fast, 80 mEq of either test or reference product should be given by mouth at 07:00 hours with 500-mL room temperature water.

- Subjects should remain upright (sitting upright, standing, or slowly walking) for at least 3 hours following dosing.

- The standard diet and fluid schedule should continue as described for the equilibration days.
- Urine collection times should be the same as on days 5, 6, 13, and 14.
- Blood samples should be collected for creatinine clearance determination.
- Fecal blood determinations should be made on each bowel movement.

Post-Drug Dosing Days, Days 8 and 16

- The standard diet and fluid schedule should continue as described for the equilibration days.

Discharge, Day 17

- Subjects can be discharged following the final urine collection at 07:00 hours.

7. Clinical Reports and Adverse Reactions

Patient medical histories, physical examination reports, and all incidents of possible adverse reactions should be reported.

IV. DATA ANALYSIS

Baseline excretion of potassium (obtained during the baseline days) should be subtracted from the amount obtained on the drug dosing day to yield the net effect of drug administration. The baseline data used should be the average of the two readings obtained on the two baseline days and be subject specific and period specific (e.g., for subject #12, his or her **period II** amount of baseline excretion would **only** be used to adjust his or her **period II** drug dosing day amount).

The following information on urine potassium concentration data should be recorded for each subject:

- Amount excreted in each collection interval (Ae)
- Cumulative urinary excretion from 0 to 24 hours (Ae0-24h)
- Cumulative urinary excretion from 0 to 48 hours (Ae0-48h)
- Maximal rate of urinary excretion (Rmax)
- Time of maximal urinary excretion (Tmax)
- Excretion rate in each collection interval (R)
- Midpoint of each collection interval (t)

All data should be calculated using baseline-adjusted and nonbaseline-adjusted data. Statistical analysis (p=0.05) should be done by ANOVA for baseline-adjusted parameters, and the 90 percent confidence intervals should be generated for natural log-transformed cumulative urinary excretion from 0 to 24 hours (Ae0-24h) and maximal rate of urinary excretion data (Rmax). The two one-sided tests procedure can be used to determine 90 percent confidence intervals.

V. IN VITRO TESTING

A. Dissolution Testing

Dissolution testing should be conducted on 12 individual dosage units from the batches of test and reference products used in the bioequivalence studies. Early sampling times of 1, 2, and 4 hours can be included in the sampling schedule to ensure against premature release of the drug (dose dumping) from the formulation. The recommended general dissolution conditions are shown below:

1. Apparatus:	USP Apparatus 1 (rotating basket) for capsules USP Apparatus 2 (paddle) for tablets
2. Rotation Speed:	100 rpm (basket) 50 rpm (paddle)
3. Temperature	37 ± 0.5^0 C
4. Units to be Tested	12
5. Dissolution Medium	900 mL of de-ionized water
6. Sampling Schedule	1, 2, and 4 hours, and every 2 hours thereafter, until 80 percent of the drug is released

Specifications for the dissolution procedure to ensure quality control will be determined upon review of the data.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in the latest edition of the *U.S. Pharmacopeia*.

VI. WAIVER OF IN VIVO TESTING FOR LOWER STRENGTHS

Waiver of in vivo bioequivalence study requirements for the lower strengths of a generic product can be granted (21 CFR 320.22(d)(2)) provided the following conditions are met:

- The in vivo study on the highest strength is acceptable and demonstrates that the test potassium chloride product is bioequivalent to the corresponding reference product.

- The lower strengths are proportionally similar in both active and inactive ingredients to the strengths tested in vivo, and have the same drug release mechanism.

- All strengths should be similar, based on the f2 test using the dissolution method described previously (see section V.A) and in three additional dissolution media (e.g., pH 1.2, 4.5, and 6.8).

REFERENCES

Physicians' Desk Reference, 58th Edition, 2004.

Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987;15:657-680.

Skelly JP, Amidon GL, Barr WK, et al. Workshop Report: In vitro and in vivo testing and correlation for oral controlled/modified-release dosage forms. *Pharmaceutical Research* 1990; 7:975-982.

Food and Drug Administration, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

APPENDIX – RECOMMENDED STUDY SCHEDULE

Bioequivalence Study Schedule for Potassium Chloride Modified-Release Tablets, Capsules																	
Activity	Day	Days								Days							
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Admission to Clinic	X																	
Diet Equilibration		X	X	X	X					X	X	X	X					
Baseline						X	X							X	X			
Drug Dosing								X								X		
Post-Drug Dosing									X								X	
Collect Urine Samples						X	X	X	X					X	X	X	X	
24 –hr Creatinine Clearance							X	X	X	X					X	X	X	X
Fecal Occult Blood								X								X		
Discharge																		X