This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Sodium zirconium cyclosilicate

Dosage Form; Route: For suspension; oral

Strength: 5 gm/packet; 10 gm/packet

Recommended Studies: Two in vitro studies

Recommendations for Demonstrating Active Pharmaceutical Ingredient (API) Sameness

The chemical formula of sodium zirconium cyclosilicate is Na$_{1.5}$H$_{0.5}$ZrSi$_3$O$_9$•2–3H$_2$O. API characterization should include, but not limited to, stoichiometric composition, crystalline structure, pore size, particle size distribution, Fourier-transform infrared spectroscopy (FTIR), density, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC) and potassium exchange capacity. Generic drug sponsors are advised to perform side-by-side comparative testing using at least three batches of the Test and three batches of Reference Standard (RS) products to assess API sameness.

Recommendations for Demonstrating Bioequivalence of Drug Product

1. Type of study: In vitro equilibrium binding study
   Design: At pH 1.2, 4.5 and 6.8 at 37°C
   Strength: 10 gm/packet
   Subjects: Not applicable (N/A)
   Additional comments: The equilibrium binding study is considered the pivotal bioequivalence (BE) study. This study should be conducted by incubating the Test and Reference products with at least eight different concentrations of potassium, at pH 1.2, 4.5, and 6.8 buffer. The potassium concentrations for each study condition should be appropriately selected to represent the adsorption isotherm including the maximum binding capacity (i.e., attainment of adsorption plateau) is clearly established. All incubations should be conducted at 37°C. Each binding study should be repeated at least 12 times, each replicate should be a separate sodium zirconium cyclosilicate sample

2 Selected media should minimize interference of other ions.
(packet). In addition, data should be provided demonstrating that the selected potassium incubation time ensures adsorption equilibrium conditions are met.


2. Type of study: In vitro kinetic binding study
   Design: At pH 1.2, 4.5 and 6.8 at 37°C
   Strength: 10 gm/packet
   Subjects: N/A
   Additional comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. Both the Test and Reference products should be incubated with at least three potassium concentrations: the lowest and highest concentrations used in the corresponding equilibrium binding study, and the mid concentration of approximately 50% of the highest concentration used. Furthermore, the study should be conducted at pH 1.2, 4.5, and 6.8. Potassium binding should be monitored as a function of time. At least eight different time points should be selected up to 24 hours that adequately illustrate the binding rate profile, including time in which binding equilibrium is achieved, under each condition. All incubations should be conducted at 37°C under constant gentle shaking, and each binding study should be repeated at least 12 times.

Analytes to measure (in appropriate biological fluid): Unbound potassium in filtrate (to calculate potassium bound to sodium zirconium cyclosilicate)

For the in vitro equilibrium binding study, the Langmuir binding constants k₁ and k₂ should be determined. The test/reference ratio should be calculated for k₁. The 90% confidence interval (CI) should be calculated for k₂ with the acceptance criteria of 80% to 125%.

For the in vitro kinetic binding study, the test/reference bound potassium ratios at various times should be compared but not subjected to the 90% CI criteria.

Bioequivalence based on (90% CI): The Langmuir binding constant k₂ from the equilibrium binding study.

Waiver request of in vitro equilibrium and kinetic binding studies: Waiver request of 5 gm/packet strength based on (i) acceptable in vitro equilibrium binding and kinetic binding studies on the 10 gm/packet strength. (ii) proportionally similar 5 gm/packet formulation to the 10 gm/packet strength.

Dissolution test method and sampling times: N/A