Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Sodium Zirconium Cyclosilicate

August 2021

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In June 2020, FDA issued a draft product-specific guidance for industry on generic sodium zirconium cyclosilicate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Sodium zirconium cyclosilicate

Dosage Form; Route: For suspension; oral

Recommended Studies: Two in vitro studies

Recommendations for Demonstrating Active Pharmaceutical Ingredient (API) Sameness

The chemical formula of sodium zirconium cyclosilicate is $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet 2–3H_2O$. API characterization should include, but not limited to, stoichiometric composition, crystalline structure, pore size,[1] particle size distribution, Fourier-transform infrared spectroscopy (FTIR),

[1] Cation selectivity studies may be used to support comparative pore size of Test and Reference products. Stavros, Fiona, et al. "Characterization of structure and function of ZS-9, a K+ selective ion trap." *PLoS ONE* 9.12 (2014): e114686.

density, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC) and potassium exchange capacity[2]. 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
   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 (packet). In addition, data should be provided demonstrating that the selected potassium incubation time ensures adsorption equilibrium conditions are met.

For general considerations on similar equilibrium binding study design, see FDA's product-specific *Guidance on Lanthanum Carbonate* tablet/oral and chewable tablets/oral and *Guidance on Sevelamer Hydrochloride* tablet/oral. Also see Swearingen, et al., "Determination of the Binding Parameter Constants for Renagel® Using the Langmuir Approximation at Various pH Values by Ion Chromatography," *J. Pharm. Biomedical Anal.* 29 (2002), pp. 195-201.

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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
   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.

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[2] Selected media should minimize interference of other ions.

Analyte to measure: Unbound potassium in filtrate (to calculate potassium bound to sodium zirconium cyclosilicate)

For the in vitro equilibrium binding study, the Langmuir binding constants k_1 and k_2 should be determined. The test/reference ratio should be calculated for k_1. The 90% confidence interval (CI) should be calculated for k_2 with the acceptance criteria of 80% to 120%.

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 k_2 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.

Revision History: Recommended June 2020; Revised August 2021

Unique Agency Identifier: PSG_207078