

Draft Guidance on Sodium phosphate dibasic anhydrous & sodium phosphate monobasic monohydrate

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Active ingredient: Sodium phosphate dibasic anhydrous & sodium phosphate monobasic monohydrate

Form/Route: Tablet; Oral

Recommended studies: 2 Options: *In Vitro* or *In Vivo* Studies

1. *In Vitro* Option

If your test product formulations are qualitatively (Q1, i.e., contains all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, then bioequivalence (BE) of all tablet strengths may be established based solely on the comparative dissolution testing. This means that (1) the amount of any excipient in the test product should not be more than $\pm 5\%$ different than the corresponding excipient in the RLD; and (2) the total weight of the test product tablet should not be more than $\pm 5\%$ different than the total weight of the RLD tablet.

For Q1 and Q2 the same formulations, the following comparative dissolution testing of 12 tablets each of test and reference products is recommended:

The following multi-media dissolution testing should be conducted on 12 tablets each of test and reference products.

Apparatus	USP Apparatus 2 (paddle)
Media	0.1N HCl, pH 4.5 buffer, and pH 6.8 buffer
Volume	900 mL
Rotation speed	50 rpm
Sampling times	10, 20, 30, 45, 60, 75, 90, 120 minutes

The use of phosphate in the buffers should be avoided. An f2 test should be performed using mean profiles to assure comparable test (T) and reference (R) product drug release under a range of pH conditions. The f2 test comparing T vs. R in each media should be 50 or greater. Note that the f2 test is not necessary when both T and R dissolve 85% or more in 15 minutes or less using all three media.

2. *In Vivo* and *In Vitro* Option

If your test product formulations are not Q1 and Q2 the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence should be established by conducting (a) the in vitro dissolution study described above; and (b) the following:

Type of study: Fasting

Design: Single-dose, two-way crossover *in-vivo*

Strength: 1.5 g “1.5 g x 20 tablets (30 g dose)”

Subjects: Normal healthy males and non-pregnancy females, general population.

Additional Comments:

- a) Because sodium phosphate treatment is associated with renal failure and transient electrolyte changes, please monitor subjects’ renal function and serum electrolytes, and perform 12-lead ECGs during the study. Please use the following exclusion criteria: (a) acute or chronic renal insufficiency; (b) uncontrolled congestive heart failure or unstable angina pectoris; (c) ascites; (d) percutaneous transluminal coronary angioplasty; (e) myocardial infarction or coronary artery bypass graft surgery; (f) electrolyte imbalance; (g) experiencing an acute exacerbation of chronic IBD; (h) chronic constipation; (i) ileus and/or acute obstruction; (j) ileostomy, colostomy, subtotal colectomy with ileosigmoidostomy, or 50% of colon removed; (k) hypomotility syndrome, megacolon, or idiopathic pseudo-obstruction. All subjects should demonstrate laboratory values within normal limits for inclusion in the study.
- b) Since phosphates may be obtained from various food sources, the subjects’ diets should be closely monitored from the beginning of the confinement period through the end of the blood sampling period. The type and amount of food/beverages as well as the time they are consumed should be recorded.
- c) Only inorganic phosphate should be measured in plasma.
- d) Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. The data should be analyzed using both uncorrected and corrected data.
- e) We recommend that you submit protocols for evaluation prior to initiating the pivotal bioequivalence study.

Waiver request of in-vivo testing: N/A.

Dissolution test method and sampling times:

Please note that a Dissolution Methods Database is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Regardless of which option is used to establish bioequivalence, please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.