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Draft - Not for Implementation

Draft Guidance on Sodium Phosphate, Dibasic, Anhydrous; Sodium Phosphate, Monobasic, Monohydrate

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Active Ingredients:	Sodium phosphate, dibasic, anhydrous; Sodium phosphate, monobasic, monohydrate
Dosage Form; Route:	Tablet; oral
Recommended Studies:	Two options: (1) in vitro bioequivalence studies (comparative dissolution) or (2) in vitro bioequivalence studies (comparative dissolution) and one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: In vitro bioequivalence studies (comparative dissolution)

If the test drug product formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD) with respect to inactive ingredients, bioequivalence should be established based on the following in vitro comparative multi-media dissolution testing on 12 tablets for each of the test and the reference products.

In addition to performing the inorganic phosphate dissolution testing for quality control, provide in vitro comparative dissolution data for the test and the reference products under the following conditions:

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

1. Strength: 0.398 g; 1.102 g
   Apparatus: U.S. Pharmacopeia (USP) Apparatus 2 (paddle)
   Rotational speed: 100 rpm
   Media: 0.1N HCl, pH 4.5 buffer, and pH 6.8 buffer
   Volume: 900 mL
   Sampling times: 10, 20, 30, 45, 60, 75, 90, and 120 minutes

Avoid the use of phosphate in the buffers. Use the f2 test to compare test and reference product drug release under a range of pH conditions. Note that it is not necessary to determine f2 when both test and reference products dissolve 85% or more in 15 minutes or less.

II. Option 2: In vitro bioequivalence studies (comparative dissolution) and one in vivo bioequivalence study with pharmacokinetic endpoints

If the test product formulations are not Q1/Q2 the same as the RLD with respect to inactive ingredients, bioequivalence should be established by conducting the in vitro comparative dissolution studies and one in vivo bioequivalence study with pharmacokinetic endpoints.

In vitro bioequivalence studies (comparative dissolution): The same studies as recommended under Option 1

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.398 g; 1.102 g at the dose of 30 g sodium phosphate
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects with abnormal laboratory values and electrocardiograms. Monitor subjects' renal function, electrolytes, and electrocardiograms during the study. Phosphates may be obtained from various food sources. Therefore, monitor the subjects' diets from the beginning of the confinement period through the end of the blood sampling period. Record the type and amount of food/beverages and the time they are consumed.

Analyte to measure: Inorganic phosphate in plasma

Multiple baseline concentrations should be measured from each individual subject in the time period before administration of the study drug and subtract the time-averaged baseline or time-matched baseline from post-dose concentrations for those subjects in an appropriate manner consistent with the pharmacokinetic properties of the drug.

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 pharmacokinetic and statistical analyses should be performed on both uncorrected and corrected data.

Bioequivalence based on (90% CI): Baseline-corrected inorganic phosphate

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

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