

Draft Guidance on Ruxolitinib Phosphate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; Oral

Recommended Studies: Two Options: BCS waiver or in vivo studies

I. Biopharmaceutics Classification System waiver option:

It may be possible to request a waiver of in vivo testing for all the strength of this product, provided that the appropriate documentation regarding high solubility, high permeability, and rapid dissolution as detailed in the Guidance for Industry: Waiver of In vivo Bioavailability and Bioequivalence for Immediate-Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System is submitted in the application. You may use information contained in the approved labeling of the reference product. Peer-reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon review of the data submitted in the application.

II. In vivo option:

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: EQ 25 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females, general population.
Additional Comments: None

2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: EQ 25 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females, general population.
Additional Comments: None

Analytes to measure (in appropriate biological fluid): Ruxolitinib in plasma

Bioequivalence based on (90% CI): Ruxolitinib

Waiver request of in vivo testing: EQ 5 mg Base, EQ 10 mg Base, EQ 15 mg Base, and EQ 20 mg Base strengths based on (i) acceptable bioequivalence studies on the EQ 25 mg Base strength, (ii) proportionally similar formulation across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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 abbreviated new drug application (ANDA).

In vitro Comparative Nasogastric Tube Studies:

Note: In vitro comparative nasogastric (NG) tube studies should be conducted for both aforementioned options.

The approved labeling for the reference product states that the product may be administered by an NG tube. As a result, conduct the following in vitro comparative testing using 8 French NG tube to compare the performance of the test product to that of the reference product to support NG tube administration.

Since the pH values for different types of water (e.g., distilled, sterile, and tap water) may vary between the range of 5.0 to 8.5, there is a concern that the process of administering a Ruxolitinib Tablet in water with different pH values via an NG tube might adversely impact the excipient solubility. NG tubes may be made with different materials (e.g., PVC, silicone, and polyurethane) and excipients in the suspension may interact with tubing material differently. Therefore, the applicant should consider the water pH (5.0 to 8.5) and material of various NG tubes that may be used for product administration and justify that the conditions used in the equivalence testing conducted below are sufficient for risk evaluation. Justification of testing conditions may be made on the basis of recovery studies (for testing procedure, see below). Studies should be performed demonstrating the recovery of the suspension through NG tubes and tested to determine the worst case scenario conditions (including, but not necessarily limited to, pH and tubing material) which will be used for the equivalence testing below.

1. Conduct the comparative recovery studies on a suspension of ruxolitinib tablet that is passed through a combination of oral syringe and 8 French NG tube, using at least 12 units of the test and the reference products. The Eq 5 mg Base and Eq 25 mg Base strength tablets should be tested for each product. Prepare the suspension by suspending one tablet in 40 mL of water with stirring for approximately 10 minutes. Connect a syringe to the NG tube and pass the suspension through the NG tube. The tube should be rinsed with approximately 75 mL of water. Please measure the initial pH of water and pH of the water after the suspension is delivered through NG tube.

Determine the percentage of ruxolitinib recovered at the NG tube exit relative to the initial amount for both the test and the reference products at 0 min and 6 hours after the

suspension preparation. The Test-to-Reference (T/R) recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated.

2. Submit standard operating procedures for recovery testing. Include details about the tube and syringe used (e.g., material, brand, size, etc.), holding positions of the tube, shaking method of the syringe, analytical site, testing dates, etc., for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (% CV) of the study in an Excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supply supporting photographs. Provide explanation if additional pressure is needed during the testing to ensure complete recovery. Also provide the pre-study validation report and all data generated during the said study. Conduct the above testing on fresh test and unexpired reference batches.