Draft Guidance on Mycophenolate Mofetil

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Route: Suspension; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 200 mg/mL × 5 mL (1000 mg dose)
   Subjects: Healthy adult males, general population
   Additional comments: None

2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 200 mg/mL × 5 mL (1000 mg dose)
   Subjects: Healthy adult males, general population
   Additional comments: None

Analytes to measure (in appropriate biological fluid): Mycophenolate mofetil, and the active metabolite, mycophenolic acid (MPA) in plasma.

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): Mycophenolate mofetil.

If mycophenolate mofetil plasma concentrations can be reliably measured and its pharmacokinetics accurately determined, please analyze the data for the parent compound using the confidence interval approach. The data for the active metabolite can be used as supportive evidence. However, if you can demonstrate that it is not possible to measure mycophenolate mofetil in plasma accurately and reliably, please analyze the metabolite using the confidence interval approach.

Waiver request of in vivo testing: Not applicable

Recommended Jun 2010; Revised Feb 2014, Oct 2017
**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: [http://www.accessdata.fda.gov/scripts/cder/dissolution/](http://www.accessdata.fda.gov/scripts/cder/dissolution/). Conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

**In Vitro Comparative Feeding Tube Studies:**

The approved labeling for the reference product states that the product may be administered through a nasogastric (NG) tube. Conduct the following in vitro comparative testing with NG tube (8 French, minimum 1.7 mm inner diameter) to compare the performance of the test product (T) to that of the reference product (R) to support NG tube administration.

Feeding tube preparation procedure: Prepare the NG tube studies using 12 units each of the test and the reference products at the 1500 mg by the following procedure:

(a) Following the procedure described in the drug label, prepare the mycophenolate mofetil oral suspension at 200 mg/ml x 7.5 mL (1500 mg).

(b) Connect an oral syringe to the feeding tube, transfer the drug granule suspension into the oral syringe, and pass the suspension through the NG tube into a collection container. After administration of the suspension using feeding tube, flush the NG tube with additional amount of water.

(c) Repeat the testing procedure described above with a fresh set of 12 units. However, after suspending the powder content in step (a), wait 15 minutes prior to injecting the contents into the NG tube.

1. **Comparative recovery testing:** conduct comparative recovery studies to determine what percentage of the initial dose passes through a combination of oral syringe and feeding tube. Follow the feeding tube preparation procedure outlined above. Determine the percentage of mycophenolate mofetil recovered at the tube exit relative to the initial dose for both the test and the reference products using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, the applicant may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.

2. **Risk assessment of administration conditions:** Feeding tubes (NG) may be made with different materials (e.g., PVC, silicone, and polyurethane) which can impact the inner tube diameter. Feeding tubes are also available with different designs (e.g. number of ports and/or eyes; open or closed distal end) which can impact the flow of material through the tube. The applicant should consider the design of the various feeding tubes that may be used for product administration, and test a representative selection (a minimum of 3) of tube designs to ensure complete delivery of the drug product. Note that for the inner diameter should be equal or greater than 1.7 mm as per the drug label. Evaluation of testing conditions may be
made on the basis of recovery study (testing procedure as above) and visual analysis and documented with photographs and videos.

3. **Standard operating procedure submission:** Submit standard operating procedures for the above in vitro feeding tube testing. Include details about the type of water, the pH of water, flush volume used in the studies, the tube and syringe used (e.g. material, brand, size, etc.), holding position of the tube, shaking method, analytical site and testing dates, etc. for each of the studies. Submit individual data, mean values, standard deviations, and coefficients of variation (CV %) in all the testing 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. For recovery studies, videos may be provided to document the testing process and associated observations. Provide explanation if additional pressure is needed to be applied during the testing to ensure complete recovery. Provide the pre-study and within-study assay validation report. Conduct all the above testing on unexpired test and reference batches.