Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Acyclovir

Dosage Form; Route: Buccal tablet; oral

Recommended Studies: Two options: in vitro study, or in vivo and in vitro study

1. **In vitro option:**

   Bioequivalence based on in vitro studies if the test formulation is qualitatively and quantitatively the same (Q1/Q2) as the reference listed drug (RLD). In addition, the test formulation should have inactive ingredients of comparable grade (compendial/technical grade) to that used in the RLD. Under this approach, bioequivalence can be demonstrated based on:

   - a) In vitro comparative dissolution study
   - b) In vitro comparative adhesion study

2. **In vivo and in vitro option:**

   Bioequivalence based on both in vivo and in vitro studies if the test product formulations are not Q1/Q2 the same as the RLD or if the inactive ingredients are not of comparable grade (compendial/technical grade) to that used in the RLD. Under this approach, bioequivalence can be demonstrated based on:

   - a) In vivo study with clinical endpoints in patients with herpes labialis (cold sores). We recommend that any sponsor choosing this option submit a protocol outlining and validating their method to conduct a proposed clinical endpoint study to OGD for review and concurrence prior to initiating the study.
   - b) In vitro comparative dissolution study
   - c) In vitro comparative adhesion study
Analytes to measure (in appropriate biological fluid): Not applicable (N/A)

Bioequivalence based on (90% CI): Clinical endpoint (in vivo option)

Waiver request of in vivo testing: N/A

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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information on in vitro comparative dissolution study:

- **Apparatus:** U.S. Pharmacopeia (USP) 2 (paddle)
- **Speed:** 100 rpm
- **Media:**
  - pH 6 (KH₂PO₄) phosphate buffer (0.2 M)
  - pH 4.0 (0.1 % NaCl solution, pH adjusted to pH 4.0)
  - pH 6.0 (0.05 M phosphate buffer solution)
  - pH 7.0 (0.1 % NaCl solution, pH adjusted to pH 7.0)
  - pH 6.8 simulated salivary fluid – phosphate buffer saline solution
- **Volume:** 1000 mL
- **Temperature:** 37°C
- **Sampling times:** 1, 2, 4, 6, 8, and 12 hours, or as needed for profile comparison

Additional comments: The applicant should use at least 12 dosage units per test. The f² metric will be used to compare dissolution profiles.

Additional information on in vitro comparative adhesion study:

The firm is recommended to optimize relevant in vitro adhesion test conditions, including but not limited to contact time, applied force for adhesion, and withdrawal speed of the probe. This is primarily because the aforementioned instrument variables can have a profound effect on the adhesion force (peak detachment force) and energy of adhesion (work of adhesion). This may need to be optimized considering both the test and reference formulations, since they may differ with respect to physical attributes such as hardness.

A tensiometry study is recommended to compare the peak detachment force for test and reference products. Water is recommended between the buccal tablets and the base plate of the tensiometer. The loading weight and length of time the loading weight is applied to press the buccal tablet into contact with the base plate should be specified. Following removal of the weight, the rate at which the buccal tablet is pulled away from the base plate should be specified. The peak detachment force should be measured as the force required to detach the buccal tablet from the base plate. The comparative adhesion test should be conducted using 12 individual units of the test and reference products.

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Prior to conducting studies for submission to the ANDA, the firm should determine appropriate loading weight, length of time the loading weight is applied to press the buccal tablet into contact with the base plate of the tensiometer, and the rate at which the buccal tablet is pulled away from the base plate. These studies should be conducted to ensure the appropriateness of the test conditions to the test and reference products.

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