Draft Guidance on Rifamycin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed release tablet; oral

Recommended Studies: Two studies

1.   Type of study: In vitro comparative dissolution study
      Strength: EQ 194 mg Rifamycin
      Apparatus: USP Apparatus 2 (paddle)
      Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm (500 mL)
      Evaluation Stage: Each of
                              (1) pH 4.5 Acetate buffer at 100 rpm
                              (2) pH 6.0 Phosphate buffer at 100 rpm
                              (3) pH 6.5 Phosphate buffer at 100 rpm
                              (4) pH 6.8 Phosphate buffer at 100 rpm
                              (5) pH 7.2 Phosphate buffer at 100 rpm
                              (6) pH 7.5 Phosphate buffer at 100 rpm

      Volume: 900 mL
      Temperature: 37°C
      Sampling times: 1, 2, 3, 4, 5, 6, and 8 hours or as needed for profile comparison
      Additional comments: Use at least 24 dosage units of the test product and at least 2 lots of the reference product (12 dosage units per lot) per test. The f2 metric will be used to compare dissolution profiles.

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2.   Type of study: In vivo study with clinical endpoints
      Design: Three-arm, randomized, double-blind, parallel, placebo-controlled in vivo study
      Strength: EQ 194 mg Rifamycin [Recommended dose: 2 x (EQ 194 mg Rifamycin) tablets orally twice daily for three days]
      Subjects: Male and nonpregnant/nonlactating females with naturally-acquired traveler's diarrhea (TD)

Additional comments regarding the bioequivalence study with clinical endpoints:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoints in the treatment of travelers' diarrhea. After three unformed stools are recorded

within the 24 hours immediately preceding randomization, subjects are to be randomized to receive two generic rifamycin delayed release tablets [i.e., 2 x (EQ 194 mg Rifamycin)], two tablets of reference listed drug (RLD) [2 x (EQ 194 mg Rifamycin)], or placebo two times daily for 3 days (i.e., on study Days 1, 2, and 3). The primary endpoint is clinical cure at the test of cure (TOC) visit on study Day 5.

2. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. Inclusion Criteria (the sponsor may add additional criteria)
    a. Adult male or nonpregnant and non-lactating female aged ≥ 18 years non-indigenous travelers (e.g., visiting students/faculty or international tourists) affected by naturally acquired acute diarrhea. Diarrhea is defined as the passage of at least three unformed stools in a 24-hour period. Stools are classified as formed (retains shape), soft (assumes shape of container), or watery (can be poured). When using this classification, both soft and watery stools are unformed and abnormal.
    b. At least three unformed stools recorded within the 24 hours immediately preceding randomization.
    c. At least one of the following signs and symptoms of enteric infection:
        • abdominal pain or cramps
        • nausea
        • vomiting
        • fecal urgency
        • excessive gas/flatulence
        • tenesmus
    d. Women of child-bearing potential with a negative pregnancy test prior to beginning therapy and who agree to use effective contraceptive methods during the study.

4. Exclusion Criteria (the sponsor may add additional criteria)
    a. Pregnant, breast-feeding, or planning a pregnancy.
    b. Immediately prior to randomization, acute diarrhea for > 72 hours.
    c. Presence of:
        • fever (≥ 100 °F or ≥ 37.8 °C), or
        • hematochezia (blood in stool), or
        • clinical findings suggesting moderate or severe dehydration
    d. Active, uncontrolled, or clinically significant diseases or disorders of the heart, lung, kidney, GI tract (other than infectious diarrhea in travelers), or central nervous system.
    e. Administration of any of the following:
        • any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization
        • more than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents within 8 hours preceding randomization

f. Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding. Acetaminophen (Tylenol) or paracetamol is acceptable.
g. If required during the study antimalarial prophylactic treatment, including doxycycline, is permitted prior to and during the study.

5. Stools at subject screening (Day 0) and end of study (Day 5) should be cultured for pathogenic organisms, but microbiological cure rates will be considered as supportive of the similarity of populations in each arm of the study and not considered as evidence of bioequivalence.

6. Possible patient subgroups with travelers' diarrhea that should be considered in planning for the populations size required for this study include:
    - inflammatory/invasive pathogens
    - diarrheagenic *E. coli* without evidence of inflammatory/invasive pathogens
    - other agents without evidence of inflammatory/invasive pathogens

7. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
    a. Prescription and over-the-counter (OTC) anti-diarrheal drug product other than study product.
    b. Opioid analgesics.

8. The recommended primary endpoint is clinical cure at the TOC visit (study Day 5). Clinical cure is defined as either:
    a. No stools or only formed stools within a 48 hour period and no fever, with or without other enteric symptoms, OR
    b. No watery stools or no more than two soft stools passed within a 24 hour period with no fever and no other enteric symptoms except for mild excess gas/flatulence.

9. In addition, clinical deterioration by study Day 5 or failure to achieve formed stool in ≤ 3 days is a clinical failure.

10. The recommended secondary endpoint is Time to Last Unformed Stool (TLUS) defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed.

11. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race

h. Name of Actual Treatment (exposure): test product, RLD, placebo control
i. Duration of Treatment (total exposure in days)
j. Completed the study (yes/no)
k. Protocol Violations (yes/no)
l. Reason for premature discontinuation of subject
m. Subject required additional treatment for diarrhea due to unsatisfactory treatment response (yes/no
n. Per Protocol (PP) population inclusion (yes/no)
o. Reason for exclusion from PP population
p. Modified Intent to Treat (mITT) population inclusion (yes/no)
q. Reason for exclusion from mITT population
r. Safety population inclusion (yes/no)
s. Reason for exclusion from Safety population
t. Number of unformed bowel movements during 24 hours immediately prior to randomization
u. Number of formed bowel movements during 24 hours immediately prior to randomization
v. Number of unformed bowel movements during study Day 1
w. Number of formed bowel movements during study Day 1
x. Number of unformed bowel movements during study Day 2
y. Number of formed bowel movements during study Day 2
z. Number of unformed bowel movements during study Day 3
aa. Number of formed bowel movements during study Day 3
bb. Number of unformed bowel movements during study Day 4
cc. Number of formed bowel movements during study Day 4
dd. Number of unformed bowel movements during study Day 5
ee. Number of formed bowel movements during 2 study Day 5
ff. After randomization, no stools or only formed stools within a 48 hour period (yes/no)
gg. After randomization, no watery stools or no more than two soft stools passed within a 24 hour period (yes/no)
hh. After randomization, clinical deterioration (yes/no)
ii. Achieved formed stool in ≤ 3 days after randomization (yes/no)
jj. At TOC visit, any enteric symptom except for mild excess gas/flatulence (yes/no)
kk. Clinical cure at TOC visit (yes/no)
ll. Time to Last Unformed Stool (hours)
mm. Treatment compliance: number of missed doses per subject
nn. Concomitant medication (yes/no)
oo. Adverse event(s) reported (yes/no)

12. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis time point, using the following headings, if applicable:
    1. Study identifier
    2. Subject identifier
    3. Name of Actual Treatment (exposure): test product, RLD, placebo control

4. Visit number
5. Visit date
6. Study day; i.e., day of randomization is study day 1
7. Fever (yes/no)
8. Moderate or severe dehydration (yes/no)
9. Hematochezia (blood in stool) (yes/no)
10. Abdominal pain or cramps (yes/no)
11. Nausea (yes/no)
12. Vomiting (yes/no)
13. Fecal urgency (yes/no)
14. Excessive gas/flatulence (yes/no)
15. Tenesmus (yes/no)
16. Use of anti-diarrheal drug product, other than study product, or opioid analgesic reported during this visit (yes/no)
17. If reported during this visit, provide date(s) of use of anti-diarrheal drug product, other than   study product, or opioid analgesic.
18. Concomitant medication reported during this visit (yes/no)
19. Adverse event reported during this visit (yes/no)
20. Laboratory testing during this visit (yes/no)

13. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

14. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[1]

Dissolution test method and sampling times (for product specification)**:** For modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at http://www.accessdata.fda.gov/scripts/cder/dissolution/), provided that Applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed for the modified release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.
Due to concerns of dose dumping from this drug product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

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[1] Study Data Standards for Submission to CDER and CBER available at:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 100 rpm, with or without alcohol;

> Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.
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> Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.
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> Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.
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> Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and reference listed drug products should be tested accordingly and data should be provided on individual unit, means, range and %CV.