Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Rifaximin

November 2022

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Rifaximin

Dosage Form; Route: Tablet; oral

Recommended Studies: Two options: (1) four pharmacokinetic bioequivalence studies and in vitro bioequivalence studies (comparative dissolution) or (2) four pharmacokinetic bioequivalence studies, in vitro bioequivalence studies (comparative dissolution), and two clinical endpoint bioequivalence studies

I. Option 1: Four in vivo bioequivalence studies with pharmacokinetic endpoints and in vitro bioequivalence studies (comparative dissolution)

If the test product formulations are qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD) with respect to inactive ingredients, bioequivalence may be established by conducting both in vivo bioequivalence studies with pharmacokinetic endpoints and in vitro bioequivalence studies (comparative dissolution).

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 200 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Applicants may consider using a reference-scaled average bioequivalence approach. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*[a] for additional information regarding the reference-scaled average bioequivalence approach.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 200 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

3. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 550 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

4. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 550 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

Analyte to measure: Rifaximin in plasma

Bioequivalence based on (90% CI): Rifaximin

Waiver request of in vivo testing: Not applicable

In vitro bioequivalence studies (comparative dissolution):

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

1.

Strength:	200 mg
Apparatus:	U.S. Pharmacopeia (USP) Apparatus 2 (paddle)
Media:	pH 4.5, 0.125% and 0.375% sodium dodecyl sulfate (SDS) pH 6.8, 0.125% and 0.375% SDS
Volume:	1000 mL
Temperature:	37°C
Rotation speed:	75 rpm
Sampling times:	10, 20, 30, 45, 60, 90, and 120 minutes Use f_2 metric to compare dissolution profiles.

2.	Strength:	550 mg
	Apparatus:	USP Apparatus 2 (paddle)
	Media:	pH 4.5, 0.25% and 0.5% SDS
		pH 6.8, 0.25% and 0.5% SDS
	Volume:	1000 mL
	Temperature:	37°C
	Rotation speed:	75 rpm
	Sampling times:	10, 20, 30, 45, 60, 90, and 120 minutes
		Use f_2 metric to compare dissolution profiles.

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 each of both strengths of the test and reference products. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

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

In vivo bioequivalence studies with pharmacokinetic endpoints: The same studies as recommended under Option 1

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

Two in vivo bioequivalence studies with clinical endpoints:

A. Type of study: Bioequivalence study with clinical endpoints
Design: Three-arm, randomized, double blind, parallel, placebo controlled in vivo
Strength: 200 mg (dosed as three times daily for 3 days)
Subjects: Male and non-pregnant, non-lactating female patients with travelers' diarrhea
Additional comments: See specific recommendations below.

Additional comments regarding the in vivo bioequivalence study with clinical endpoints (200 mg):

1. FDA recommends conducting a bioequivalence study with clinical endpoints in the treatment of travelers' diarrhea. After at least three unformed stools are recorded within the 24 hours immediately preceding randomization, patients should be randomized to receive a test product of rifaximin 200 mg oral tablet, RLD 200 mg oral tablet, or placebo three times daily for three 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. Inclusion Criteria (the applicant may add additional criteria as needed):
    a. Males and non-pregnant, non-lactating females aged ≥18 years who are 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

3. Exclusion Criteria (the applicant may add additional criteria as needed):
    a. Pregnant, breast feeding, or planning a pregnancy
    b. Immediately prior to randomization, acute diarrhea for >72 hours
    c. Presence of any of the following:
        - Fever (≥100°F or ≥37.8°C)
        - Hematochezia (blood in stool)
        - Clinical findings suggesting moderate or severe dehydration
    d. Active, uncontrolled, or clinically significant diseases or disorders of the heart, lung, kidney, gastrointestinal (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 drugs such as, aspirin or ibuprofen, which can cause GI bleeding. Acetaminophen is acceptable.

g. If required during the study, antimalarial prophylactic treatment including doxycycline is permitted prior to and during the study.

4. Stools at patient 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.

5. Possible patient subgroups with travelers' diarrhea that should be considered in planning for the populations size required for this study include:
    a. Inflammatory/invasive pathogens
    b. Diarrheagenic *E. coli* without evidence of inflammatory/invasive pathogens
    c. Other agents without evidence of inflammatory/invasive pathogens

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

7. 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.

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

9. 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.

10. Provide Subject-Level Analysis Dataset (ADSL), one record per patient, using the following headings, if applicable:
    a. Study identifier
    b. Unique patient identifier
    c. Patient identifier for the study
    d. Study site identifier
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment

k. Safety population flag (yes/no)
l. Reason for exclusion from Safety population
m. Modified Intent to Treat (mITT) population flag (yes/no)
n. Reason for exclusion from mITT population
o. Per Protocol (PP) population flag (yes/no)
p. Reason for exclusion from PP population
q. Completers flag (yes/no)
r. Randomization population flag (yes/no)
s. Date of randomization
t. Date of enrollment
u. Date/time of first exposure to treatment
v. Date/time of last exposure to treatment
w. Reason for premature discontinuation of patient
x. Patient required additional treatment for diarrhea due to unsatisfactory response (yes/no)
y. Date/time of additional treatment
z. Number of unformed bowel movements during 24 hours immediately prior to randomization
aa. Number of formed bowel movements during 24 hours immediately prior to randomization
bb. Number of unformed bowel movements during study Day 1
cc. Number of formed bowel movements during study Day 1
dd. Number of unformed bowel movements during study Day 2
ee. Number of formed bowel movements during study Day 2
ff. Number of unformed bowel movements during study Day 3
gg. Number of formed bowel movements during study Day 3
hh. Number of unformed bowel movements during study Day 4
ii. Number of formed bowel movements during study Day 4
jj. Number of unformed bowel movements during study Day 5
kk. Number of formed bowel movements during study Day 5
ll. After randomization, no stools or only formed stools within a 48-hour period (yes/no)
mm. After randomization, no watery stools or no more than two soft stools passed within a 24-hour period (yes/no)
nn. After randomization, clinical deterioration (yes/no)
oo. Achieved formed stool in ≤3 days after randomization (yes/no)
pp. At TOC visit, any enteric symptom except for mild excess gas/flatulence (yes/no)
qq. Clinical cure at TOC visit (yes/no)
rr. Time to Last Unformed Stool (hours)
ss. Compliance rate (%)
tt. Concomitant medication (yes/no)
uu. Adverse event(s) reported (yes/no)

11. Provide the basic data structure (BDS) dataset with records per patient, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier

b. Unique patient identifier
c. Patient identifier for the study
d. Study site identifier (if applicable)
e. Name of planned treatment
f. Name of actual treatment
g. Safety population flag (yes/no)
h. Modified ITT population flag (yes/no)
i. PP population flag (yes/no)
j. Completers population flag (yes/no)
k. Analysis date
l. Analysis visit
m. Study visit within designated window (yes/no)
n. Fever (yes/no)
o. Moderate or severe dehydration (yes/no)
p. Hematochezia (blood in stool) (yes/no)
q. Abdominal pain or cramps (yes/no)
r. Nausea (yes/no)
s. Vomiting (yes/no)
t. Fecal urgency (yes/no)
u. Excessive gas/flatulence (yes/no)
v. Tenesmus (yes/no)
w. Use of antidiarrheal drug product, other than study product, or opioid analgesic reported during this visit (yes/no)
x. If reported during this visit, provide date(s) of use of antidiarrheal drug product, other than study product, or opioid analgesic
y. Concomitant medication reported during this visit (yes/no)
z. Adverse event reported during this visit (yes/no)
aa. Laboratory testing during this visit (yes/no)

12. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for in vivo bioequivalence studies with clinical endpoints.

13. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

B. Type of study: Bioequivalence study with clinical endpoints
Design: Three-arm, randomized, double blind, parallel, placebo-controlled in vivo
Strength: 550 mg (dosed as three times a day for 14 days)
Subjects: Male and non-pregnant, non-lactating female patients with irritable bowel syndrome with diarrhea (IBS-D)
Additional comments: See specific recommendations.

Additional comments regarding the in vivo bioequivalence study with clinical endpoints (550 mg):

1. FDA recommends conducting a bioequivalence study with clinical endpoints in the treatment of IBS-D. After a 1 to 2 week screening period, patients should be randomized to receive a test product of rifaximin 550 mg oral tablet, the RLD 550 mg oral tablet, or placebo tablet three times a day for 14 days. Patients should be followed for an additional 4 weeks. Rifaximin may be taken with or without food.

2. Inclusion Criteria (the applicant may add additional criteria as needed):
    a. Males and non-pregnant, non-lactating females aged ≥18 years with a clinical diagnosis of IBS-D confirmed by the Rome III diagnostic criteria should be enrolled. At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain associated with two or more of the following:
        - Relieved with defecation
        - Onset associated with a change in frequency of stool
        - Onset associated with a change in form (appearance) of stool
    b. Abdominal Pain Intensity: weekly average of worst daily (in past 24 hours) abdominal pain score of >3 on a 0 to 10 point scale, and
    Stool Consistency: at least one stool with a consistency of Type 6 or Type 7 Bristol Stool Score on at least 2 days per week.
    c. Patient has undergone a colonoscopy within the last 2 years as part of an evaluation for IBS or IBS symptoms (which excluded inflammatory or neoplastic disease). The patient has a colonoscopy scheduled and completed within 30 days of signing the informed consent.
    d. Patient required to maintain a stable diet for the duration of the study.
    e. Patient on stable treatment with a daily dietary fiber supplementation or bulking agents may be enrolled provided that the administration schedule is intended to be maintained throughout the study and the patient has been on therapy for at least 30 days prior to signing the informed consent.

3. Exclusion Criteria (the applicant may add additional criteria as needed):
    a. Patients presenting with the following symptoms of constipation IBS (during the diary eligibility phase of ≥7 days immediately prior to the first dose of study drug):
        - Less than 3 bowel movements a week
        - Hard or lumpy stools
        - Straining during a bowel movement
    b. Patient fails to record at least 7 days of daily diary assessments during the screening phase.
    c. Patient has current evidence of duodenal ulcer, gastric ulcer, diverticulitis, gastroesophageal reflux disease (GERD), or infectious gastroenteritis. Note: Patients with GERD controlled by stable doses of medication or diet are eligible to participate in the study.

d. Patient has a history of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and celiac disease), GI malignancy, GI obstruction, gastroparesis, carcinoid syndrome, pancreatitis, amyloidosis, ileus, or cholelithiasis. Patients may participate if they have a cholecystectomy.
e. Patient has diabetes (Type 1 or Type 2).
f. Patient is a candidate for GI surgery or has a history of GI surgery (exceptions appendectomy, cholecystectomy, benign polypectomy, and inguinal hernia).
g. Patient has lactose intolerance not controlled by a lactose-free diet.
h. Patient had a positive stool test for Yersinia enterocolitica, Campylobacter jejuni, Salmonella, Shigella, ovum and parasites, and/or Clostridium difficile. (Note: Stool sample was not required if a negative test was obtained within 14 days of randomization).
i. Patient has psychiatric disorder not controlled with current therapy.
j. Patient has current or recent (within 12 months) history of drug or alcohol abuse.
k. Patient is pregnant, breast feeding, or planning a pregnancy.
l. Patient has a history of human immunodeficiency virus (HIV), hepatitis (B or C), abnormal thyroid function not controlled by medication, hepatic disease manifested by twice the upper limit of normal (ULN) for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase or total bilirubin (except an isolated elevation of unconjugated bilirubin).
m. Patient has renal disease manifested by 1.5 times the ULN of serum creatinine or blood urea nitrogen concentrations.
n. Patient has unstable cardiovascular or pulmonary disease, categorized by a worsening in the disease condition that requires a change in treatment or medical care within one month of randomization.
o. Patient has any condition or circumstance that could cause noncompliance with treatment or visits.
p. Patient has known allergy to rifaximin or rifampin or excipients.
q. Patient has had an active malignancy except for basal cell carcinoma or in situ cervical carcinoma that has been excised within the last 5 years.
r. Patient has participated in an investigational drug or device study within the 30 days prior to signing the informed consent.
s. Patient has taken rifaximin within 60 days of signing the informed consent form (ICF).
t. Patient has taken any experimental drugs within 30 days of signing the ICF and patients who have taken probiotics after initiation of the diary eligibility phase (yogurt and standard food products are allowed).
u. Patient has taken any antibiotics within 14 days prior to signing the ICF.
v. Patient has taken antipsychotic drugs, antispasmodics, antidiarrheals (e.g., loperamide, lubiprostone, and bismuth subsalicylate), narcotics, prokinetic drugs, drugs indicated for IBS (e.g., alosetron), or warfarin after the initiation of the diary eligibility phase.

4. The protocol should include a list of the prescription and OTC drug products, procedures, and activities that are prohibited during the study. This may include prescription and OTC antidiarrheal drug products or a significant change in diet.

5. The study should include a 1 to 2 week screening period. The 1 to 2 week screening period can be used to establish the presence and persistence of trial entry criteria and train patients in the mode of data collection selected for the trial. The screening period can also be used to select patients with specified levels of severity of signs and symptoms. Refer to the most recent version of the FDA guidance for industry on *Irritable Bowel Syndrome Clinical Evaluation of Drugs for Treatment*.[a] Baseline should be defined from the diary data collected during seven days immediately preceding the beginning of the treatment period.

6. The recommended primary endpoint is responder rate at week 6 and should measure the effect of treatment on two major IBS signs and symptoms (i.e., abnormal defecation and abdominal pain). A patient should be categorized as an overall responder if the patient is weekly responder for at least two weeks during the four-week follow-up period. A patient is categorized as a weekly responder if the patient achieves the following improvement in both pain intensity and stool consistency for a week as described below:
    a. ≥30% improvement from the baseline in the weekly average abdominal pain score based on the daily question: "In regard to your specific IBS symptoms of abdominal pain, on a scale of 0 to 10, what was your worst IBS-related abdominal pain over the last 24 hours? 'Zero' means you have no pain at all; 'ten' means the worst possible pain you can imagine"
    b. At least a 50% reduction in the number of days in a week with a daily stool consistency of Bristol Stool Scale type 6 or 7 compared with the baseline where 6=fluffy pieces with ragged edges, a mushy stool; 7=watery stool, no solid pieces, entirely liquid

7. Applicant should choose a format for daily sign or symptom assessment (e.g., interactive voice response or personal digital assistant) so that patients can evaluate IBS signs or symptoms on a daily basis throughout the trial. Daily questionnaire should be answered at approximately same time each day. Appropriate questions to evaluate IBS signs and symptoms include (applicant may add additional as needed):
    a. How many bowel movements did you have in the last 24 hours?
    b. On a scale of 1 to 7, what was the score of your least formed bowel movement in the last 24 hours (Bristol Stool Scale)?
        1=Separate hard lumps, like nuts (hard to pass)
        2=Sausage-shaped but lumpy
        3=Like a sausage but with cracks on its surface
        4=Like a sausage or snake, smooth and soft
        5=Soft blobs with clear cut edges (passed easily)
        6=Fluffy pieces with ragged edges, a mushy stool
        7=Watery stool, no solid pieces, entirely liquid
    c. Have you felt or experienced a sense of urgency in the last 24 hours with any of your bowel movements? (yes/no)
    d. In regard to your specific IBS symptom of abdominal pain, on a scale of 0 to 10, what was your worst IBS-related abdominal pain over the last 24 hours? 'Zero'

means you have no pain at all; 'Ten' means the worst possible pain you can imagine.

e. In regard to your specific IBS symptom of bloating, on a scale of 0 to 6, how bothersome was your IBS-related bloating in the last 24 hours?
   0=not at all
   1=hardly
   2=somewhat
   3=moderately
   4=a good deal
   5=a great deal
   6=a very great deal
f. In regard to all your symptoms of IBS, on a scale of 0 to 6, how bothersome were your symptoms of IBS in the last 24 hours?
   0=not at all
   1=hardly
   2=somewhat
   3=moderately
   4=a good deal
   5=a great deal
   6=a very great deal

8. Provide the ADSL, one record per patient, using the following headings, if applicable:
   a. Study identifier
   b. Unique patient identifier
   c. Patient identifier for the study
   d. Study site identifier
   e. Age
   f. Age units (years)
   g. Sex
   h. Race
   i. Name of planned treatment
   j. Name of actual treatment
   k. PP population inclusion (yes/no)
   l. Reason for exclusion from PP population
   m. mITT population inclusion (yes/no)
   n. Reason for exclusion from mITT population
   o. Safety population inclusion (yes/no)
   p. Reason for exclusion from safety population
   q. Completers population flag (yes/no)
   r. Randomized population flag (yes/no)
   s. Date of randomization
   t. Date of enrollment
   u. Date/time of first exposure to treatment
   v. Date/time of last exposure to treatment
   w. Reason for premature discontinuation of patient

x. Patient required additional treatment for diarrhea due to unsatisfactory response (yes/no)
y. Mean abdominal pain score at baseline
z. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 at baseline
aa. Mean abdominal pain score at Week 1
bb. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 1
cc. Mean abdominal pain score at Week 2
dd. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 2
ee. Mean abdominal pain score at Week 3
ff. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 3
gg. Mean abdominal pain score at Week 4
hh. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 4
ii. Mean abdominal pain score at Week 5
jj. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 5
kk. Mean abdominal pain score at week 6
ll. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 6
mm. Weekly responder in abdominal pain intensity for Week 3 (yes/no)
nn. Weekly responder in stool consistency for Week 3 (yes/no)
oo. Weekly responder for Week 3 (yes/no)
pp. Weekly responder in abdominal pain intensity for Week 4 (yes/no)
qq. Weekly responder in stool consistency for Week 4 (yes/no)
rr. Weekly responder for Week 4 (yes/no)
ss. Weekly responder in abdominal pain intensity for Week 5 (yes/no)
tt. Weekly responder in stool consistency for Week 5 (yes/no)
uu. Weekly responder for Week 5 (yes/no)
vv. Weekly responder in abdominal pain intensity for Week 6 (yes/no)
ww. Weekly responder in stool consistency for Week 6 (yes/no)
xx. Weekly responder for Week 6 (yes/no)
yy. Overall responder (yes/no)
zz. Compliance rate (%)
aaa. Concomitant medication (yes/no)
bbb. Adverse event(s) reported (yes/no)

9. Provide the BDS dataset with records per patient, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique patient identifier
    c. Patient identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. Modified ITT population flag (yes/no)
    i. PP population flag (yes/no)
    j. Completers population flag (yes/no)
    k. Analysis date
    l. Analysis visit
    m. Study visit within designated window (yes/no)
    n. Date/time of answer to daily IBS sign and symptom questionnaire
    o. Number of days since treatment start date
    p. Worst abdominal pain score on a scale of 0 to10 in the past 24 hours
    q. Bristol Stool Scale score of the least formed bowel movement in the past 24 hours
    r. Rescue medication (e.g., antidiarrheal) use reported during the past 24 hours (yes/no)
    s. Concomitant medication reported during this visit (yes/no)
    t. Adverse event reported during this visit (yes/no)
    u. Laboratory testing during this visit (yes/no)

10. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for in vivo bioequivalence studies with clinical endpoints.

11. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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 each of both strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

Revision History: Recommended November 2011; Revised March 2017, November 2022

Unique Agency Identifier: PSG_021361

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.