Guidance for Industry

Helicobacter pylori-Associated Duodenal Ulcer Disease in Adults: Developing Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2009
Clinical Antimicrobial

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in clinical drug development for the treatment of adults with duodenal ulcers caused by *Helicobacter pylori* (*H. pylori*) for the reduction of duodenal ulcer recurrence.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs to support antimicrobial-containing *H. pylori* treatment regimens. This guidance intends to serve as a focus for continued discussions among the Division of Special Pathogen and Transplant Products, pharmaceutical sponsors, the academic community, and the public.[3] As the science of this indication evolves, this guidance may be revised as new information accumulates.

This guidance pertains to development of drugs for the treatment of adults with duodenal ulcers. It does not address treatment of children, or those with other conditions also associated with *H. pylori*, including gastric ulcers and non-ulcer dyspepsia. If sponsors are interested in pursuing an indication for the treatment of patients with other conditions associated with *H. pylori* infection or other endpoints not mentioned in this guidance, they are encouraged to discuss their proposals with the division. Sponsors desiring to pursue an indication for ulcers caused by clarithromycin-resistant organisms should discuss the types of data needed to support such a claim with the division early in drug development.

[1] This guidance has been prepared by the Division of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated by CDER unless otherwise specified.

[3] In addition to consulting guidance documents, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs intended to treat *H. pylori*.

This guidance, when finalized, will supersede advice given in the draft guidance for industry *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products*, published in 1997, which contains section V, regarding indication 25 *Helicobacter pylori*. With regard to the development of drugs to treat *H. pylori*-associated duodenal ulcer disease in adults, this guidance also supersedes more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development and Labeling of Anti-Infective Drug Products*,[4] as well as the joint FDA/Infectious Disease Society of America's *Guidelines for the Evaluation of Anti-Infective Drug Products*).[5]

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials*, *E9 Statistical Principles for Clinical Trials*, and *E10 Choice of Control Group and Related Issues in Clinical Trials*. This guidance focuses on specific drug development and trial design issues that are unique to the study of duodenal ulcers caused by *H. pylori*. For general information related to clinical trials of antimicrobial drugs, see the draft guidance for industry *Developing Antimicrobial Drugs — General Considerations for Clinical Trials*.[6]

FDA's guidance documents, including this guidance, 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.

II. BACKGROUND

H. pylori infection can be found in up to 95 percent of patients with peptic ulcer disease. Following bacterial eradication, ulcer recurrence rates have been shown to be significantly and reproducibly reduced compared to long-term acid suppressive therapy. In 1994, a National Institutes of Health consensus panel recommended that "Since cure of *H. pylori* decreases ulcer recurrence and facilitates healing, antibiotic therapy is definitely indicated for all *H. pylori*-infected ulcer patients." The panel further concluded that "ulcer patients with *H. pylori* infection

[4] See the following PDFs, respectively:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM133315.pdf;
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070975.pdf.

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clinical Infectious Diseases, Nov.15, Supplement 1:S5-32.

[6] When final, this guidance will represent the FDA's current thinking on this topic.
For the most recent version of a guidance, check the FDA Drugs guidance Web page at
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation with the illness or on recurrence."[7]

On October 26, 1995, a joint Anti-Infective and Gastrointestinal Drugs Advisory Committee met to consider issues in clinical trial design for drugs being developed to treat duodenal ulcers caused by *H. pylori* infection.[8] The committee recommended that *H. pylori* eradication at greater than 28 days from the end of therapy should be used as the primary endpoint for determining outcome in studies evaluating active duodenal ulcer treatment. This eradication endpoint was considered a valid (and validated) surrogate endpoint for duodenal ulcer recurrence, based on published studies demonstrating that *H. pylori* eradication in patients with an active ulcer significantly reduced future ulcer recurrence. Therefore, clinical trials did not need to include evaluation of ulcer recurrence to be approved for the indication below.

On December 13, 1995, the same joint advisory committee reconvened and recommended the following two-sentence statement for the Indications and Usage section of the package insert for drugs developed to treat *H. pylori* infection:[9]

> *Drug [X] is "indicated for the treatment of patients with an active duodenal ulcer associated with H. pylori infection. The eradication of H. pylori has been demonstrated to reduce the risk of duodenal ulcer recurrence."*

Subsequently, with the accumulation of additional clinical data, the division has broadened the indication to include *H. pylori*-infected patients with a recent history (within 5 years) of ulcer disease in addition to patients with an active duodenal ulcer:

> *Drug [X] is "indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence."*

III. DEVELOPMENT PROGRAM

A. General Considerations

Sponsors should conduct at least two adequate and well-controlled trials for the purposes of establishing the safety and efficacy of antimicrobial-containing regimens to treat *H. pylori*-associated duodenal ulcer disease. The primary efficacy parameter should be a microbiological outcome at the test-of-cure visit (i.e., the proportion of *H. pylori*-infected ulcer patients who are cured of their infection).

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[7] NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease, 1994, *Helicobacter pylori* in Peptic Ulcer Disease, JAMA, 272:65-9.

[8] A transcript of the October 26, 1995, meeting can be found at: http://www.fda.gov/ohrms/dockets/ac/95mt.htm.

[9] A transcript of the December 13, 1995, meeting can be found at http://www.fda.gov/ohrms/dockets/ac/95mt.htm.

At least one of the trials should be conducted in the United States and/or Canada, because of known differences in *H. pylori* response rates and susceptibility patterns in various parts of the world.[10] These trials should be conducted by multiple investigators from geographically diverse areas to ensure a broad range of patients and *H. pylori* strains are studied.

B. Specific Efficacy Trial Considerations

1. Study Design

All currently approved regimens are multidrug regimens consisting of antimicrobials plus anti-ulcer medications because use of either drug type alone is unable to eradicate *H. pylori*. Previous studies have shown eradication rates of 0 percent for placebo,[11] less than 5 percent for monotherapy with a proton pump inhibitor (3 to 4 percent with omeprazole,[12] 2 percent with lansoprazole[13]), and 0 percent for amoxicillin alone.[14]

Sponsors may wish to consider one of the following three possible study designs for new drugs or regimens to treat *H. pylori*: 1) substitution of a new drug for one component of an approved regimen; 2) addition of a new drug to an approved regimen; and 3) development of a new regimen not studied previously. The appropriate study design depends upon the drug or regimen under development.

Depending on the design chosen, proof of efficacy may be determined based on a determination of superiority of the new drug containing regimen over the active-controlled drug containing regimen, or placebo containing regimen. Alternatively, proof of efficacy can be based on the determination of noninferiority of the new drug containing regimen to the active-controlled drug containing regimen. Note that the use of noninferiority studies relies on adequate historical information regarding the effect of the active control in the current regimen. If adequate historical information is not available, noninferiority studies should not be considered.

In any of these situations, sponsors may wish to develop fixed-dose combination or co-packaged drug products. Fixed-dose combination drug products are subject to 21 CFR 300.50, and the

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[10] Fischbach, L, K Goodman, M Feldman, et al., 2002, Sources of Variation of *Helicobacter pylori* Treatment Success in Adults Worldwide: A Meta-Analysis, Int J Epidemiol, 31:128-39.

[11] Peterson, WL, AA Ciociola, DL Sykes, et al., 1996, Ranitidine Bismuth Citrate Plus Clarithromycin Is Effective for Healing Duodenal Ulcers, Eradicating *H. pylori* and Reducing Ulcer Recurrences, RBC *H. pylori* Study Group, Aliment Pharmacol Ther, 10:251-61.

[12] Laine, L, E Johnson, L Suchower, et al., 1998, US Double-blind, Controlled Trials of Omeprazole and Amoxicillin for Treatment of *Helicobacter pylori*, Aliment Pharmacol Ther, 12:377-82.

[13] Schwartz, H, R Krause, B Sahba, et al., 1998, Triple Versus Dual Therapy for Eradicating *Helicobacter pylori* and Preventing Ulcer Recurrence: A Randomized, Double-blind, Multicenter Study of Lansoprazole, Clarithromycin, and/or Amoxicillin in Different Dosing Regimens, Am J Gastroenterol, 93:584-90.

[14] Harford, W, F Lanza, A Arora, et al., 1996, Double-blind, Multicenter Evaluation of Lansoprazole and Amoxicillin Dual Therapy for the Cure of *Helicobacter pylori* Infection, Helicobacter, 1:243-50.

FDA has generally applied the principles outlined in 21 CFR 300.50 to co-packaged drug products.

a. Substitution of a new drug for one component of an approved regimen

The component of the approved regimen that the new drug is replacing is considered the active control in this situation. The remaining drugs are the background regimen and should be similar between the two arms. Because each of the components of approved multidrug regimens for *H. pylori* appears to contribute to the observed treatment effect, it may be possible to perform noninferiority trials testing the new drug against an approved regimen. When this approach is chosen, the noninferiority margin selected should be justified in the protocol, supported by evidence from past studies (21 CFR 314.126(b)(2)(iv)), and provided to the division for review. Sponsors also should provide data from the literature or earlier studies showing that each component of the new drug regimen is contributing to the efficacy of the regimen.

Sponsors should consult ICH E9 and ICH E10 for information on how to design a noninferiority trial and noninferiority margin.

b. Addition of a new drug to an approved regimen

When an investigational drug is added to a previously approved regimen, the study design should be placebo-controlled; patients should be randomized to the approved regimen plus investigational drug versus the approved regimen plus placebo. The goal should be to demonstrate superiority of the approved regimen plus investigational drug over the approved regimen plus placebo. When considering an add-on study design, sponsors also should provide a discussion concerning the risks and benefits of a multidrug regimen.

c. Development of a new regimen not studied previously

When developing a new multidrug regimen, sponsors should demonstrate the contribution of each component to the overall effect. This can be done by conducting a trial with a factorial design. In factorial design trials, the primary analysis should evaluate the contribution of each component. In addition, we recommend that an FDA-approved regimen be included as a positive control arm to interpret studies with unexpectedly low cure rates. Given the high rates of efficacy with approved regimens, new regimens with lower than expected cure rates would be reflected in labeling in the description of clinical studies.

2. Study Population

The population targeted for enrollment into clinical trials should consist of adult patients with *H. pylori* infection and an active duodenal ulcer or a documented history of duodenal ulcer disease within the past 5 years.

3. Entry Criteria

a. Inclusion criteria

The following inclusion criteria should be used for patient enrollment in studies conducted for the treatment of *H. pylori*-associated duodenal ulcer disease.

- Endoscopically or radiographically documented presence of an active duodenal ulcer with a diameter between 3 mm and 25 mm, or a history of duodenal ulcer (confirmed by endoscopy or radiography) within the previous 5 years before enrollment.[15]

- Confirmed *H. pylori* infection based on biopsy specimens collected during upper endoscopy performed in all patients at baseline for inclusion into the study. Prerandomization evaluability, based on endoscopic diagnostic testing, is defined in Table 1 in the Appendix.

- Confirmed *H. pylori* infection based on an FDA-approved urea breath test (UBT) performed in all patients before randomization for inclusion into the study, if this test is used to determine patient outcome at the test-of-cure visit. The UBT can be performed as a screening test before or following endoscopy.

b. Exclusion criteria

The following exclusion criteria should be used for patient enrollment in studies conducted for the treatment of *H. pylori*-associated duodenal ulcer disease.

- Presence of ulcer smaller than 3 mm or larger than 25 mm.
- History of any previous esophageal or gastric surgery, except for simple closure of perforated ulcer.
- Gastric outlet obstruction.
- Hypersecretory states, such as Zollinger-Ellison Syndrome.
- History of gastric cancer or gastric biopsy positive for cancer on baseline endoscopy.
- Presence of both active gastric and duodenal ulcers, or presence of three or more active ulcers. Multiple ulcers are believed to potentially signify disease of other etiology (e.g., undiagnosed Zollinger-Ellison Syndrome).
- Treatment with proton pump inhibitors or full therapeutic doses of histamine H2-receptor antagonists within 14 days before diagnostic testing at screening.
- Treatment with systemic antibiotics known to have in vivo efficacy against *H. pylori* or bismuth-containing compounds within 28 days before diagnostic testing at screening.

[15] An active ulcer is defined as endoscopic evidence of a break in the gastrointestinal mucosa that penetrates the muscularis mucosa and has a fibrinous surface.

4. Blinding

A double-dummy trial design should be used to maintain blinding in comparative trials. Appropriate blinding procedures should be discussed with the division before beginning the trial. All participants involved in the trial including patients should be blinded to treatment. The following additional recommendations apply to blinding:

- The investigator and the endoscopist should be blinded to treatment
- The microbiologist should be blinded to treatment, clinical information, endoscopic information, and all *H. pylori* endoscopic tests other than culture
- The pathologist should be blinded to treatment, clinical information, endoscopic information, and results of all *H. pylori* diagnostic information other than histology
- The investigator that performs other diagnostic tests (e.g., UBT) should be blinded to treatment and all other *H. pylori* diagnostic information

5. Efficacy Endpoints

The primary efficacy endpoint should be eradication of *H. pylori* measured at least 28 days, but no more than 56 days from the end of the treatment (see section III.B.7.c., Test-of-cure (post-treatment) visit). A patient should be considered as a failure of therapy in the primary analysis if there was no determination of whether his or her *H. pylori* infection was eradicated. See section III.B.8.b., Missing data, for a discussion of missing data.

Outcomes for patients should be defined as follows:

- Success. Eradication of *H. pylori* infection is documented at the test-of-cure visit, occurring between 28 and 56 days from the end of treatment. Eradication should be defined by a single negative UBT result at the test-of-cure visit. If an endoscopy is used in place of a UBT at the test-of-cure visit, eradication should be defined as described in Table 2 in the Appendix.
- Failure. Does not meet the criteria for success and can include the following:
  - Persistence of *H. pylori* infection is documented by UBT or endoscopy anytime after treatment (see Table 2 in the Appendix).
  - A test-of-cure visit less than 28 days or more than 56 days from the end of treatment (for an analysis of the modified intent-to-treat (MITT) population, see below).
  - A test-of-cure visit at least 28 days from the end of treatment and an outcome reported as not determined, not assessable, or missing (see Table 2 in the Appendix) (for an analysis of the MITT population, see below).
  - No test-of-cure visit (for an analysis of the MITT population, see below).

6. Analysis Populations for Efficacy Analyses

Sponsors should perform efficacy analyses on two specific populations: MITT and per-protocol, as described below. In addition, a third population, the intent-to-treat (ITT) population, which can also be called the safety population, should be defined as all patients who took at least one dose of trial medication, regardless of baseline infection status. Sponsors should analyze the ITT population for safety outcomes.

The specific definitions and outcomes of the MITT and per-protocol populations should be as follows:

MITT population

A patient should be included in the MITT population if all of the following occur:

- *H. pylori* infection is documented by UBT or endoscopy before treatment (see Table 1 in the Appendix)
- At least one dose of trial medication is taken
- An active duodenal ulcer with a diameter between 3 mm and 25 mm is documented at the baseline endoscopy **or** a history of duodenal ulcer within the previous 5 years is documented (by endoscopy or radiograph) before enrollment

Per-protocol population

A patient should be included in the per-protocol population if all of the following occur:

- The patient is included in the MITT population
- The test-of-cure visit occurs between 28 and 56 days from the end of treatment with documented diagnostic testing by UBT or endoscopy (see Table 2 in the Appendix), unless the patient has documented persistence of *H. pylori* infection at any time after the end of treatment
- At least 75 percent of each medication was taken and/or less than 20 percent of consecutive doses of each medication were missed, unless caused by treatment failure
- An antimicrobial known to be effective against *H. pylori* before (within 7 days), during, or following treatment was not taken, unless given for treatment failure
- A proton pump inhibitor or high dose H2-receptor antagonist was not taken within 14 days of the baseline and/or follow-up endoscopy (if applicable) or during treatment, unless given for treatment failure

  Patients can use *non-ulcer healing* doses of H2-receptor antagonists following treatment, as indicated below, and still be included in the per-protocol population:
  - ranitidine less than 300 mg/day
  - cimetidine less than or equal to 400 mg/day
  - famotidine less than 40 mg/day
  - nizatidine less than 300 mg/day

7. Study Procedures and Timing of Assessments

The timing of key study visits and associated procedures is discussed below.

a. Entry visit

The pretreatment (entry) visit should occur within 1 week of beginning trial treatment and may require two separate visits. Investigators should perform an upper endoscopy and obtain biopsy specimens for *H. pylori* diagnostic testing (see Table 1 in the Appendix) in all patients upon entry. Investigators should document (e.g., photograph) any ulcers at the time of the procedure. Randomization to treatment can occur at a separate visit that occurs within 4 days of the

diagnosis of *H. pylori*, which is based upon the results of diagnostic testing (as shown in Table 1). Effort should be made to ensure that results are available from all three endoscopic tests (i.e., culture, histology, and rapid urease test) because missing data from one or more tests can result in exclusion of patients from the efficacy populations.

Investigators can perform the UBT as a screening test before or following endoscopy, depending on the clinical presentation of the patients. If the UBT also will be used as the primary endpoint, a positive UBT result should be documented before the patient is randomized to treatment, so the test can be used to determine patient outcome at the test-of-cure visit.

For patients with a history of ulcer disease, investigators should procure an official radiographic or endoscopic report documenting a prior ulcer.

Investigators should obtain the patient's history, a physical examination, vital signs, a pregnancy test (when appropriate), serum chemistry, and hematology before randomization.

Investigators should evaluate whether patients meet the inclusion and exclusion criteria and obtain their informed consent.

b. End-of-treatment visit

The end-of-treatment visit should include a physical examination, laboratory determinations, assessment of adverse events and concomitant medications, symptom assessment, and a medication compliance assessment.

The end-of-treatment visit should not replace the test-of-cure visit.

c. Test-of-cure (post-treatment) visit

The post-treatment visit should occur at least 28 days but not more than 56 days after the last dose of the study treatment and is considered the test-of-cure visit. The test-of-cure visit should occur at the same time point for all treatment arms, regardless of the duration of treatment. Sponsors should determine the timing of the test-of-cure visit based upon the treatment arm with the longest duration of treatment.

At this visit, investigators should evaluate the primary endpoint. If a UBT is used to determine patient outcome (i.e., *H. pylori* eradication or persistence), a repeat upper endoscopy should not be needed for all patients. However, investigators should repeat an upper endoscopy and obtain biopsies for culture and antimicrobial susceptibility testing in patients with a positive UBT result, indicating persistence of *H. pylori* infection.

Alternatively, sponsors can choose to use endoscopy at the post-treatment visit in place of a UBT to determine patient outcome. If endoscopy is used, investigators should obtain biopsies in all patients for histology, rapid urease test, and culture with antimicrobial susceptibility testing.

The choice of post-treatment diagnostic test (UBT or endoscopy) should be prespecified and consistent across all study arms in a given trial.

Investigators should obtain serum chemistry and hematology profiles and assess patients for adverse events.

d. Discontinuations

Patients discontinuing study therapy prematurely should have post-treatment procedures performed at the time of termination. In addition, if appropriate, patients also should be evaluated at the time of the test-of-cure visit (at least 28 days but not more than 56 days after the last dose of the study treatment). The reason for early discontinuation from the study treatment and/or the trial should be documented in the case report form.

e. Safety evaluations

The protocol should clearly specify the methods to be used to obtain safety data during the course of the study. Both adverse event information and safety laboratory data should be collected during the study. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations also may be needed because of the preclinical and clinical profile of the specific drug under study (e.g., additional electrocardiogram measurements). Longer-term assessment of adverse events after discontinuation or completion of the antimicrobial also can be considered depending on the specific drug being studied.

All patients should be evaluated for safety at the time of each study visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on study would otherwise have been completed. For specific safety reporting recommendations during clinical trials, see the ICH guidance for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

8. Statistical Considerations

a. Primary efficacy analysis

The primary efficacy analysis should be a comparison of the percent of successes in the MITT population, as described above. Note that patients with missing data will be automatically counted as *failures* in this analysis. The method for analysis should be clearly stated in the protocol. Specific details can be provided in a separate document (i.e., data analysis plan).

b. Missing data

All efforts should be made to obtain data from the test-of-cure visit for each patient enrolled in clinical trials. Given that some missing data will occur, however, we recommend that the sponsor define prospectively the method for handling missing data and perform secondary

analyses in which data are analyzed in several different ways to assess the effect on interpretation and conclusions in the MITT analysis.

The following three methods are examples of ways to handle missing data in *H. pylori* clinical trials; however, other methods can be used.

1. Calculating eradication rates by treatment in patients with observed data, and assuming eradication rates are the same in patients with unobserved (missing) data.

2. Assuming all active-controlled patients with missing data are eradicated while all patients treated with the investigational regimen are not eradicated. This method is used only to give an upper bound on the upper limit of the confidence interval for the difference in eradication rates because such a scenario would be unlikely to actually occur.

3. Assuming all patients with missing data are successes.

c. Noninferiority trial design considerations

As mentioned earlier, for some *H. pylori*-associated duodenal ulcer trials, it may be possible to use a noninferiority trial design if adequate historical information exists that allows for the determination of a valid noninferiority margin. In those cases, the active-controlled arm of the trial should be treated with an approved regimen consisting of an active control of interest plus a specified background regimen. The test arm of the trial should be treated with the new regimen consisting of the new test drug, replacing the active control of the approved regimen, but keeping the same background regimen of the approved regimen of the control arm. The noninferiority trial will compare the test regimen arm with the active-controlled regimen arm. The purpose of such a comparison would be to show that the treatment difference C – T (i.e., the difference between the response rate of the active-controlled regimen *minus* that for the test regimen) is smaller than some prespecified noninferiority margin.

The following should be noted when designing noninferiority trials:

- **Assay sensitivity of the current noninferiority trial.** This is a critical property of a noninferiority trial. A noninferiority trial that lacks assay sensitivity may conclude that an ineffective treatment is noninferior to a control and can lead to an erroneous conclusion of efficacy. Before initiating a noninferiority trial, sponsors should evaluate and determine the treatment effect of the active control with background regimen over placebo with background regimen from adequate historical trials. This treatment effect is referred to as M1. A discounted M1 should be chosen as a conservative estimate of the treatment effect caused by uncertainties in the estimate of the treatment effect.

- **The constancy assumption.** The current noninferiority trial should be sufficiently similar to past historical trials with respect to all design and conduct features that can influence the estimation of M1. These design features include the characteristics of the patient population, important concomitant treatments (besides the fixed background

regimen), definition and ascertainments of study endpoints, dose of active control and background regimen, entry criteria, and analytic methods.

- **The quality of the current noninferiority trial.** Undesirable conduct features of the trial would tend to minimize the difference, C – T, causing bias toward the null. These undesirable features include imprecise or poorly implemented entry criteria, poor compliance, the use of concomitant treatments whose effects may overlap with the test drug under study, inadequate measurement techniques, or errors in treatment assignments.

9. Clinical Pharmacology Consideration

CYP450 enzymes and efflux/uptake transporters are involved in the absorption and hepatic clearance of certain antimicrobials and proton pump inhibitors, which are components of many approved regimens. These enzymes and transporters may alter the overall systemic exposure (oral bioavailability) of these drugs. Therefore, sponsors should consider determining the association between drug exposure and enzymes or transporters to assess clinical efficacy and safety of the regimen in various subpopulations. For additional information on submission of genomic data, see the draft guidance for industry *Pharmacogenomic Data Submissions — Companion Guidance*.[16]

10. Microbiology Considerations

Special attention should be given to reliable methods for obtaining, culturing, and determining the in vitro susceptibility of *H. pylori* because most clinical laboratories do not routinely perform these procedures. Sponsors should provide details as part of each protocol for the following microbiological procedures used in the trial: collection and transport of biopsy specimens, isolation of *H. pylori* from biopsy specimens, identification of *H. pylori*, antimicrobial susceptibility testing, and quality control.

Investigators should collect at least one antral and one corpus biopsy specimen during endoscopy from all randomized patients for culture and subsequent antimicrobial susceptibility testing pretreatment and at the test-of-cure visit. In trials where sponsors use the UBT to determine patient outcome at the test-of-cure visit, a repeat endoscopy with biopsies collected for culture and subsequent antimicrobial susceptibility testing should be performed in patients with a positive UBT result. In trials where sponsors use endoscopy to determine patient outcome at the test-of-cure visit, all patients should have a repeat endoscopy with biopsies collected for culture and subsequent antimicrobial susceptibility testing.

Investigators should also collect at least two antral and two corpus biopsy specimens during endoscopy from all randomized patients for histopathologic examination pretreatment and at the test-of-cure visit, in all patients in trials where endoscopy is used to determine outcome at the test-of-cure visit.

[16] When final, this guidance will represent the FDA's current thinking on this topic.
For the most recent version of a guidance, check the FDA Drugs guidance Web page at
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Agar dilution minimum inhibitory concentration (MIC) methodology is the reference method for antimicrobial susceptibility testing and has been standardized for testing certain antimicrobials against *H. pylori* by the Clinical Laboratory Standards Institute (CLSI). If sponsors use a method other than that recommended by the CLSI, we strongly recommend that they contact the division before study initiation. If an experimental assay is used for any microbiologic measurement, then the performance characteristics of the assay should be provided for review.

Sponsors should present complete microbiology data, including individual MIC values for all tested antimicrobials. Sponsors should also calculate MIC_{50} and MIC_{90} values for the pretreatment isolates. Where applicable, sponsors should analyze the data to determine the percentage of patients with pretreatment antimicrobial resistance, the bacteriologic efficacy among patients with antimicrobial resistant strains pretreatment, and the emergence of antimicrobial resistance on therapy.

Sponsors should include information on the mechanism of action of the therapeutic agents against *H. pylori*, if known.

Sponsors should also include information on the mechanism of antimicrobial resistance for *H. pylori*, if known. If the antimicrobial resistance mechanism of resistance is not known, sponsors should make an effort to assess the mechanism to better understand the spread of resistance and clinical failure.

In general, a four-fold or greater increase in MIC suggests a change in antimicrobial susceptibility. Sponsors should record such changes, even if the shift in endpoint does not represent a change in the proposed interpretive category. Newer microbiological methods may allow detection of drug resistance by genotyping to identify mutants, and may also differentiate between new infection and relapse. If any of these methods are used in a clinical trial, the details of these methods and performance characteristics of the assay should be included for review.

C. Labeling Considerations

In addition to the statistical outcome regarding efficacy of study drug therapy in the clinical trials (as described in section III.B.8., Statistical Considerations), approvability and product labeling depends on the assessment of multiple factors, including safety, tolerability, and emerging antimicrobial resistance as a result of drug therapy. In general, product labeling will reflect the manner in which the drugs were used in clinical trials. For example, use in combination with specific other drugs, as well as the dose and duration studied.

APPENDIX: TABLES

Table 1. Prerandomization Evaluability Based on Three Endoscopic *H. pylori* Tests[1]

H. pylori Tests Obtained Prerandomization[2]			Patient Evaluability[3]
Culture	Histology	Rapid Urease Test	
Three Tests Available			
+	+	+	Included
+	+	-	Included
+	-	+	Included
+	-	-	Included
-	+	+	Included
-	-	+	Excluded
-	+	-	Excluded
-	-	-	Excluded
Two Tests Available			
+	+	N/A	Included
+	-	N/A	Included
-	+	N/A	Excluded
-	-	N/A	Excluded
+	N/A	+	Included
+	N/A	-	Included
-	N/A	+	Excluded
-	N/A	-	Excluded
N/A	+	+	Included
N/A	+	-	Excluded
N/A	-	+	Excluded
N/A	-	-	Excluded
One Test Available			
+	N/A	N/A	Included
-	N/A	N/A	Excluded
N/A	N/A	+	Excluded
N/A	N/A	-	Excluded
N/A	+	N/A	Excluded
N/A	-	N/A	Excluded

[1] All patients should have a positive UBT result, in addition to endoscopic diagnostic testing, if the UBT is used to determine patient outcome at the test-of-cure visit.

[2] N/A indicates not available or missing result.

[3] This column relates to whether or not patients are considered *Included* or *Excluded* in the efficacy populations and is not necessarily used as criteria for inclusion into or exclusion from the trial. When incongruent test results preclude an accurate *H. pylori* diagnosis, patients should be considered *Excluded* and should not be included in either the MITT analysis or per-protocol populations.

Table 2. Test-of-Cure Evaluability Based on Three Endoscopic *H. pylori* Tests[1]

H. pylori Tests Obtained at Test-of-Cure Visit[2]			Patient Outcome[3]
Culture	Histology	Rapid Urease Test	
Three Tests Available			
+	+	+	Persistence
+	+	-	Persistence
+	-	+	Persistence
+	-	-	Persistence
-	+	+	Persistence
-	-	+	Persistence
-	+	-	Persistence
-	-	-	Eradicated
Two Tests Available			
+	+	N/A	Persistence
+	-	N/A	Persistence
-	+	N/A	Persistence
-	-	N/A	Eradicated
+	N/A	+	Persistence
+	N/A	-	Persistence
-	N/A	+	Persistence
-	N/A	-	Eradicated
N/A	+	+	Persistence
N/A	+	-	Persistence
N/A	-	+	Persistence
N/A	-	-	Eradicated
One Test Available			
+	N/A	N/A	Persistence
-	N/A	N/A	Indeterminate
N/A	N/A	+	Persistence
N/A	N/A	-	Indeterminate
N/A	+	N/A	Persistence
N/A	-	N/A	Indeterminate

[1] A UBT that is FDA-approved for monitoring the effectiveness of treatment can be used at the test-of-cure visit (at least 28 days following the end of treatment) in place of endoscopy. If this test is negative, no further testing is needed.

[2] N/A indicates not available or missing result.

[3] An *Indeterminate* assessment at test-of-cure visit indicates that the patient should be considered to have *Persistence* for the MITT analysis and be *Excluded* for the per-protocol analysis. Persistence should be considered synonymous with infected.