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See Attached Distribution List

I would like to acknowledge your time and efforts in reviewing the draft document "Points to Consider when reviewing Therapeutic regimens for Eradication of *Helicobacter pylori* in GI diseases" (PTC). Comments received have been considered and this assessment is available upon request. The revised document is now referred to as "Guidance when Developing Therapeutic Regimens for the Eradication of Helicobacter Pylori in GI Diseases".

Several comments received suggested that the document is too restrictive, while others recommended that some sections need to be expanded. Please note that while many of the comments provided are accurate when treating patients in the clinic, additional rigor is required to ensure that clinical trials are as robust and reliable as possible. It is also important to reiterate the intent of the document. The document presents issues to be resolved when designing clinical trials aimed at the eradication of *Hp* in GI diseases. Special consideration has been given to clinical trials in duodenal ulcer patients. Additional guidelines and/or recommendations in the field should be consulted. References to FDA guidance for Industry (draft, Indication #25), European Working Group in Hp, and published articles dealing with specific issues are provided as references in the bibliography of the document. In addition, the guidance document provides the basis for evaluating such submissions by TPP in a consistent manner.

As a result of the comments received the text of the "Points to Consider" document has been edited and has incorporated footnotes to clarify some of the issues. Please refer to the enclosed guidance document.

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This guidance document will shortly be posted on the Therapeutic Products Programme (TPP) Website (http://www.hc-sc.gc.ca/hpb-dgps/therapeut).

Dann M. Michols
Director General

Attachments

Therapeutic Products Programme
GUIDANCE DOCUMENT[1]

Guidance when Developing Therapeutic Regimens for the Eradication of *Helicobacter pylori* in GI diseases

1. INTRODUCTION

1.1 PURPOSE

The purpose of this document is to suggest elements for consideration when designing clinical trials dealing with eradication of *H. pylori* in GI diseases and to outline elements to be reviewed in the submissions. It expands on the design of clinical trials when patients with active duodenal ulcers are included as subjects in clinical trials. For other *Hp* associated GI diseases, the guide provides elements to be considered in the study design. The document is not intended to be exhaustive but to ensure that the studies and their subsequent review are carried out in a consistent manner.

Basic clinical trial design should comply with current ICH Good Clinical Practice: Consolidated Guidelines[2] (GCP). Specific considerations in relation to methodology, study end-points, definition of outcome, definition of infection and selection of subjects are presented here.

Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. Submission sponsors are encouraged to discuss, in advance, alternate approaches with the aim to prevent the withdrawal or rejection of a submission.

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1 Guidance documents are developed to provide advice on selected issues relating to the development and evaluation of therapeutic products. Guidance documents, typically serve as a means of documenting acceptable approaches to regulatory requirements in areas where rapid and ongoing change preclude the development of formal guidance documents. They are intended to be revised in accordance with scientific advances.

This and other Guidance Documents are available on the Therapeutic Products Programme (TPP) Website (**http://www.hc-sc.gc.ca/hpb-dgps/therapeut**). Guidelines listed on the Directorate's *Guidelines Order Form* are available in printed form only, through the Canadian Government Publishing Centre (CGPC). The *Order Form* is available on the TPP Website under "Forms" or from the CGPC (Tel: 819-956-4800; Fax: 819-994-1498; Internet: http://publications.pwgsc.gc.ca).

2 Website: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/guide-ich.html# EFFICACY/.
The file name of the document is "goodclin_e.zip".

1.2 BACKGROUND

H. pylori was first found in gastric biopsy specimens in association with gastritis in 1980. While the association between *H. pylori* and peptic ulcer disease is now recognized, the involvement of *H pylori* in other GI diseases is still under investigation: e.g. non-ulcer dyspepsia, NSAID-induced ulcers with *H. pylori* positive status, gastric cancer (gastric adenocarcinoma, mucosa-associated lymphoid tissue, and non-Hodgkin's lymphoma).

It has been generally accepted that eradication of *H. pylori*, assessed at least 4 weeks after completion of therapy, may be used as a surrogate when investigating the reduction of peptic ulcer recurrence. The healing of duodenal ulcers is determined at least 4 weeks following the end of treatment; follow-up to demonstrate decrease in recurrence of duodenal and gastric ulcers is not required. There is insufficient scientific/medical information (in the literature) to accept eradication of *H. pylori* as surrogate for prevention of recurrence in other GI diseases; therefore, at the present time, follow-up studies should be carried out.

Treatment of *H. pylori* infection may require use of dual, triple or quadruple therapies. Triple therapies refer to a combination of three medications including, generally, antisecretory drugs (PPI or H2 antagonist) plus antimicrobials. These therapies have shown eradication rates of 80% or larger after a relatively short treatment period. However, there is still room for improvement. Not all possible triple drug combinations have been subjected to clinical trials; nor do we know the place of possible quadruple therapies. Finally, more and better drug regimens may be developed in the future to eradicate *H. pylori*.

1.3 SCOPE

This guide addresses specifically issues on clinical trial design for the demonstration of eradication of *H. pylori* in patients with duodenal ulcers. Other elements address aspects of such submissions relevant to regulatory requirements.

The following is noted: (1) Clinical trials of an infectious disease such as *H.pylori* should have measurable clinical endpoints. (2) The document does not cover every conceivable disease; it also addresses briefly the history of duodenal/gastric ulcers and functional dyspepsia (non-ulcer dyspepsia). (3) Different decisions on study design are acceptable pending convincing documentation.

Finally, TPP understands that when treating patients in the clinic two diagnostic tests are redundant. However, additional rigor may be desirable to ensure that clinical trials are as robust and reliable as possible, thus justifying additional procedures.

2. GASTRODUODENAL DISEASES AND HELICOBACTER PYLORI

General Comments on *H. pylori* status: It is preferred that the presence of *H. pylori* be diagnosed with at least two distinct testing methodologies (Hopkins et al., 1996; Megraud 1997). Until now, no single technique has been considered to be ideal for the detection of *H. pylori*. The combination of at least two tests is encouraged: in spite of high specificity, a sensitivity of 90% has been considered not high enough to allow one test alone to be used as diagnostic test after treatment, while a combination of two tests gave a sensitivity of 99% (Megraud 1997). In addition, the sensitivity and specificity of a test do not take into consideration the inherent variability in determining the value of many laboratory tests nor the intra- and inter-rater reliability.

Endoscopically based tests are desirable as experience is abundant (culture, histology with specific staining for *H pylori*, rapid urease test [CLOtest]). Culture is considered the "gold standard" test[3] and if positive, this test alone may suffice i.e., confirmation with another test is not necessary. If UBT is selected, the second test should be either culture or histology (using the Genta or Giemsa or Warthin-Starry stain). It is desirable that the selected tests (at least two) base their results on different assay methodologies. The rapid urease test and UBT both measure urease activity in the stomach; the rapid urease test is a local test while the UBT is a global test. The specificity of the urease tests when other urease-producing organisms are colonizing the gastric mucosa needs further clarification/considerations.
Concordance between tests (sensitivity and specificity of one test with respect to the other) at the pre-entry and post treatment phase should be presented in the submission, analysed and commented on.

Although the CLOtest was the first rapid urease test to be developed, other rapid urease tests are commercially available in Canada. The rapid urease tests have been recommended not to be used as the post-treatment test because of relatively low sensitivity, especially in patients treated with urease inhibitors, such as PPIs. In fact, it does not provide useful information and jeopardizes blinded testing with regard to *Hp* status. Please note that this recommendation on the rapid urease test relates to studies investigating eradication of *H. pylori*. In cases where *Hp* infection is used as a prognostic factor in other diseases, or in epidemiological studies, the rapid urease test may be used unless serious problems are revealed later. The test selected should be supported by the sponsor on a scientific basis.

TPP has approved various C^{13}-UBT and rapid urease tests; therefore validation of these tests in each testing site may be dispensed with. However, adherence to GCP and Acceptable Methods guidelines is expected and evidence should be available when required. A testing site is considered the site where the test is implemented (from samples taken to final results). Multicenter trials most probably have a central laboratory where the analysis is conducted; this is considered the core of the validation, however, the protocol for sample collection and delivery to the central facility from each trial site should be clearly defined and available when requested.

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3 Culture is still considered the "gold standard", because has maximum specificity and *Hp*-susceptibility to antibiotics can be tested. A positive result with culture indicates the presence of the bacteria but a negative result does not indicate absence of the bacteria. Therefore if the culture is negative the *Hp* status is unevaluable.

Serology based tests are considered acceptable for epidemiological studies or screening purposes prior to eradication therapy but not for evaluation of infection status in clinical trials. *H. pylori*-saliva based tests have been developed but they are not currently accepted.

An alternative to the two tests for assessing *H. pylori* status at post-treatment may be acceptable when the eradication regimen under investigation had proven to be highly effective (MITT≥80%). The UBT can be used twice with an 8 week time interval. This could be considered as two tests (Working Party of the European *Helicobacter pylori* Study Group, 1997). Other alternatives may be acceptable when scientific justification is provided.

2.1 Minimum clinical trial requirements for Duodenal Ulcer Disease: active duodenal ulcer.

Study Design: Pivotal study(ies) should be multi-centre, double blind, concurrently controlled and randomized, and if necessary stratified according to ulcer size. The choice of the most appropriate control for any new regimen is difficult to define *a priori*. An antisecretory drug may be used alone or a combination therapy already approved in Canada may be considered. We discourage the use of control regimens known to potentially result in the emergence of resistant strains as a result of their low eradication efficacy. However, the study design should attempt to demonstrate the need for the particular combination under investigation. Consultation with the regulatory agency is encouraged.

Study Objective: The primary objective of the study should be the eradication of *H. pylori* assessed at least 4 weeks after the end of treatment. The secondary objectives are the healing of duodenal ulcer at least 4 weeks after the end of treatment and the disappearance of symptoms.

Inclusion Criteria: Patients to be included in the study should have active duodenal ulcers and be *H. pylori* positive. However, when patients with a recent history of duodenal ulcers are also included, the trial analysis should stratify patients into active duodenal ulcer and history of duodenal ulcer (up to 2 years of history).

Exclusion Criteria: In addition to the usual exclusion criteria in these studies, the following should also be considered:

- Patients with previous exposure to drugs capable of interfering with their *H. pylori* status (antibiotics, H2 antagonists, bismuth, PPI etc.). Such patients could be included, however, if an appropriate washout period is allowed to elapse (minimum 2 weeks; four weeks are preferred. Deviations should be discussed and justified).
- Allergy to any drug of the multiple therapy.
- Previous gastric surgery.
- Patients previously treated with anti-*H. pylori* therapy, unless at least 4 weeks from the end of the previous eradication therapy are allowed to elapse.

Definition of Ulcer: a lesion in the gastroduodenal mucosa that penetrates the muscularis

mucosae and of ≥ 5 mm in diameter. Ulcers should be confirmed by endoscopy. Because of the difficulty in assessing the depth of the ulcer by endoscopy (the difficulty increases with smaller ulcers), TPP has selected the 5 mm lesion as the most reliable definition on which the efficacy analysis is to be based. The manufacturer may wish to consider a secondary analysis for smaller lesions: > 3 mm to <5 mm.

Definition of Healing: a complete re-epithelisation of the ulcer, with or without erythema, with re-establishment of continuity of the mucosa.

Definition of Ulcer relapse: a reappearance of lesion of at least 5 mm with depth, as defined above.

Definition of *H pylori* Status:

Pre-treatment: **if two tests** give positive results, the status is classified as "infected" and therefore evaluable, otherwise " negative" or unevaluable. Presently, only results from the culture test are given more weight than results from other tests. If the culture test is positive and the other test is unevaluable or negative, the status is classified as "infected".

Post-treatment: **if two endoscopic or UBT tests** give negative results and no test gives a positive result, the status is classified as "eradicated" in both the "Modified Intent to Treat" (MITT) and "Per Protocol " (PP) analysis. If one positive test is found either alone or with other tests with negative or missing results, the status is classified as "persistent" [4]. If one test is negative and the other is missing or unevaluable, the status is classified as "unevaluable" and excluded from the PP analysis but included as "failure" in the MITT analysis. The diagnostic status should be clearly described.

Endoscopic examinations: all DU-patients should be endoscoped at pre and post treatment to obtain biopsies and to document the presence, size and location of duodenal ulcer(s) and other lesions.

Biopsies: Appropriate number of biopsies from antrum and corpus should be taken for assessment of infected status and for microbial sensitivity testing (if the antibiotic regimen contains an antibiotic to which *H pylori* may be resistant) at the very least in those patients who fail therapy. The number and site of biopsies should be indicated in the submission. Currently at least 2 biopsies from both antrum and corpus may be adequate for the DU studies.

Withdrawal of patient: Reasons for withdrawal of patients from the study should be clearly indicated. Patients withdrawn due to adverse reactions related to the study medication or to progression of disease should **be included as "failures" in the PP analysis**.

Protocol Violation should be specified. A violation is considered major when patients:
- received less than 80% of study medication.
- received treatment for less than 80% of the treatment time sought.

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4 "Persistent" refers to infected or not eradicated.

Figures between 70-80% may be acceptable after thorough review of the file: lack of compliance due to drug adverse events, potential of the regimen to develop microbial resistance, and efficacy of the eradication regimen, etc.

Populations: Intent to Treat population (ITT): all patients randomized to one of the treatment groups regardless of the *H. pylori* status, with documented duodenal ulcer.

Modified ITT population (MITT): A **subset** of the ITT population: those patients who are *H. pylori* positive at prestudy and have duodenal ulcer.[5]

Evaluable or Per Protocol population (PP): a subset of MITT who adhere to the protocol throughout the study.

On Data Analysis:

Primary efficacy analyses :

- *H. pylori* eradication rate is the % of patients with a negative *H. pylori* status at ≥ 4 weeks following the end of treatment among those patients in the MITT or PP population.

For the MITT analysis, failure is defined as those patients who have a positive *H. pylori* status (infected) at ≥ 4 week following end of treatment, those who were prematurely withdrawn, those who dropout from the study, and those who had a follow-up visit < 4 weeks following the end of treatment. These patients are included in the MITT analysis as failures. The MITT analysis provides the worse case scenario.

For the PP analysis, failure is defined as those patients who have a positive *H. pylori* status (infected) at ≥ 4 week following end of treatment, those who drop out due to the study medication or progression of the disease, and those who had a follow-up visit <4 weeks following the end of treatment with a positive *H. pylori* status. These patients are included in the PP analysis as failures. A positive test under 4 week after the end of treatment is an indication of persistent infection and the patients should be included in the PP analysis as failures. Conversely, if the test is negative at < 4 week from end of treatment, the status is considered unevaluable and the patient should be withdrawn from the PP analysis. Similarly, the status of an "unreliable" test due to intake of antibiotics or proton pump inhibitors during treatment (in addition or aside of those prescribed) or during follow-up, is considered unevaluable and the patient is excluded from PP analysis.

A clear description of the patients included and excluded from analysis is at the discretion of the investigator(s), but must be presented in the submission.

Secondary efficacy analyses:

- Duodenal Ulcer healing rate is the % of patients with healed ulcers at or after 4 weeks

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5 The term MITT is used in duodenal ulcer trials if the patients with identified duodenal ulcer(s) are randomized to the different study groups and *H.pylori* status is confirmed after randomization. Care should be placed when prevalence of *Hp* is lower than in the DU diseases as the groups may became unbalanced. ITT refers to those patients randomized to treatment groups. However, any denomination could be used if clear definition is provided.

following the end of treatment among the MITT and PP population, based on endoscopic evaluation.

- GI symptoms: the disappearance of symptoms or significant improvement of symptoms after treatment assessed using a validated symptom score questionnaire should be documented.

Special considerations should be given to associated mucosal pathological findings in the GI-*Hp* diseases. The status of gastritis, mucosal atrophy and/or intestinal metaplasia changes should be reported[6]. At the present time, whenever possible, the presence of reflux esophagitis at any time during the trial should be documented.

Sensitivity to the antibiotic coprescribed: At the very least this should be determined in patients who fail therapy (remained *H. pylori* positive). For microbiological considerations the FDA Guidelines should be consulted (Feb 1997, pages 81-85).

2.2 Clinical Trials with other objectives:

- **History of peptic ulcer:** patients with Inactive (healed) Peptic Ulcer, who had not been treated with eradication therapies, represent a heterogenous population in term of risk of ulcer recurrence. Patients whose ulcers have been recently healed (up to 1 to 2 years) are at higher risk of ulcer recurrence as compared to those who have their ulcers healed for a longer period of time. It is, then, recommended that patients with history of peptic ulcer (gastric or duodenal) be stratified according to the length of time the ulcers have been inactive. Other methods of validated analysis may be acceptable with proper justification.

For patients diagnosed as having ulcer history it must be established whether the ulcer diagnosis was based on symptoms only, or on upper GI series or endoscopy. At the present time, there is limited evidence that the eradication of *Hp* in patients with history of peptic ulcers, who had not been treated with eradication therapies, is associated with decrease in ulcer recurrence.

It is important that the study design include endoscopy at pre- and post- treatment to assess both *H. pylori* and ulcer status in addition to *Hp*- associated histological gastritis, as described for active duodenal ulcer clinical trials (two tests, one of which is endoscopy based).
When using an approved therapeutic regimen for eradication of *H. pylori*, placebo or H2-antagonist or PPI may be used as the control group to which the study therapy can be compared to. These patients should not required maintenance antisecretory therapies during the follow-up phase.

The follow-up period should be 6 months or more following completion of *Hp* eradication therapy. During the follow-up no antisecretory therapies are prescribed.

Inclusion of patients who are on maintenance antisecretory therapy because of high risk of serious GI events (eg., elderly patients using NSAID and with a history of GI events, such as ulcer perforation or bleeding) is problematic because discontinuation of the maintenance therapy is not ethical, for safety reasons.

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6 It is preferred that the definition of gastric atrophy be standardized, for example see Genta 1998.

- **Non-ulcer dyspepsia (NUD) or functional dyspepsia** refers to a chronic or recurrent condition defined as pain or discomfort centred in the upper abdomen. Symptoms are usually present for at least 3 months and oesophageal-gastro-duodenal endoscopy has excluded peptic ulceration, reflux oesophagitis and malignancy. This group includes patients with histological gastritis associated with *H. pylori* infection in the absence of ulcers or erosions. The presence or absence of gallbladder disease documented by ultrasound is optional. However, as NUD is diagnosed by excluding other known organic diseases that give rise to similar upper abdominal symptoms, the exclusion criteria for other diseases (including irritable bowel syndrome) should be presented and documented in the submission. It is assumed that a long term follow-up after end of treatment might mitigate concerns.

Patients with Gastroesophageal Reflux Disease (GERD) are not considered to have non ulcer dyspepsia (even if they do not have endoscopic oesophagitis). When dyspeptic patients have predominantly symptoms such as heartburn or reflux, they are considered to be suffering from GERD. Patients with non-ulcer dyspepsia may have heartburn or regurgitation as well as a number of other symptoms, and it is only when heartburn and reflux are predominant that the dyspepsia should be considered as being due to gastroesophageal reflux disease.

The study design for nonulcer dyspepsia should be double blind, placebo controlled and randomized. Symptom relief is the principal end point of the study. *H. pylori* infection at pre- and post-treatment should be assessed by two tests as discussed before. However, when an approved[7] treatment is used, post-treatment evaluation of eradication may be performed with one test only, in particular the UBT which is carried out twice with a two month interval. Once eradication has been confirmed, only one UBT could be acceptable in the follow-up phase. The follow-up period should be long enough (6-12 months) to demonstrate continuous lack of symptoms.

Methods or instruments for measuring symptoms should be validated (see Talley 1994). Reviews on clinical trial design on NUP could be consulted, see V. van Zanten et al., 1996, 1997.

Finally, it is important to consider including in some studies assessment of quality of life. This, however, is not an absolute requirement.

3. Other issues

Bioequivalence : When various drugs are to be combined for treatment purposes (co-

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7 An approved treatment refers to a treatment that is available in Canada, has an eradication efficacy of >80% and has a known potential for microbial resistance development.

therapy), it is desirable that each of the drugs be an approved Canadian formulation. When the studies are conducted in other countries, are multinational and the drugs used are not the Canadian formulation then, the sponsor should provide assurance that all non-Canadian drug products are as safe and effective as the Canadian reference product (s). Conducting comparative bioavailability studies is one way to provide this assurance. However, TPP is prepared to review indirect demonstration of equivalence based on data from the public domain. The use of published clinical trials to justify the exchange of formulations/products is acceptable if the sponsor shows that the outcome (i.e., the response rates as recorded) from the different studies are within the same range. The published clinical trials should qualify as Level 1 evidence[8] and have the same study design; only the formulation is different.

When direct bioequivalence studies are considered, input from the Division of Bioequivalence should be sought. Manufacturers are encouraged to consult TPP before deciding on the type of evidence they intend to provide for demonstrating the bioequivalence of the drugs.

Doses: It is desirable that the doses proposed for co-therapies should not exceed the dose recommended in the Product Monograph of each individual drug. Higher doses introduce new complexities concerning the safety of the product (s). This is particularly important with co-therapies when drugs are metabolized by the same enzyme system. Manufacturers should address these issues when developing regimens to eradicate *H. pylori.*

A particular dilemma is posed when marketed strengths differ from those used in pivotal trials (e.g. metronidazole 400 mg vs 500 mg tablets). The validity of these trials is doubtful unless the manufacturer shows, directly or indirectly (by published data that qualify as Level 1 evidence and have the same study design), that such exchange has no impact on the safety (and/or efficacy) of the regimen proposed.

Length of Treatment: The proposed treatment period should be fully supported by the pivotal clinical trials.

There is a tendency to shorten the eradication treatment period from 2 weeks to 1 week and recently to 3 days or even one day therapy. *A priori,* there is no reason why a clinical trial in which a short term therapy is sought, should not be carried out. However, for short term therapies (<1 week) , there is the risk of infection recrudescence and/or the development of secondary antimicrobial resistance. Patients enrolled in short term trials should be followed up (eradication tests and endoscopy) for at least 12 weeks following discontinuation of drugs.

There are no clear data on whether patients who fail one regimen may be less responsive to another regimen: this issue require further elucidation.

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8 In general, Level 1 evidence is considered when results derived from randomized, double-blinded and controlled clinical trials. For *H. pylori* studies the design should also follow the minimal recommendation proposed in this guide (such as: at least two tests to assess *H. pylori* status, a well defined patient population, proper quantitative clinical endpoints).

Drug Interaction Studies: Bioavailability studies should be conducted for each of the medicines of the multiple therapy alone and in the proposed dosage combination.

Study drug bioavailability should be conducted in the presence and absence of the coprescribed medicines (antibacterials). For dual therapies, the antisecretory drug (ASD) with and without an antibacterial should be compared. Ideally, for triple therapy (ASD plus 2 antibacterials): ASD bioavailability should be compared to ASD bioavailability in the presence of the two antibacterials.

Similarly, for each antibacterial, the corresponding bioavailability should be compared with that found in the presence of the other two medicines (antisecretory plus antibacterial). Studies should use the doses proposed in the therapeutic trials.

4. REFERENCES

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