Bowel Cleansing for Colonoscopy: Efficacy and Safety Considerations for Developing New Products

Guidance for Industry

DRAFT GUIDANCE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)

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I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of products[2] for bowel cleansing in preparation for a colonoscopy[3]. Specifically, this guidance describes the Food and Drug Administration's (FDA's) current thinking about the necessary attributes of clinical trials for drugs being developed under Section 505 of the Food, Drug, and Cosmetic Act (21 U.S.C §355) and 21 CFR Parts 312 and 314 for use as bowel cleansing agents before colonoscopy, including trial population, trial designs, efficacy considerations, and safety assessments.[4]

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[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration.

[2] For the purposes of this guidance, *product* refers to either a new drug with a single active pharmaceutical ingredient, or a fixed-dose combination drug product.

[3] This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). When finalized, it will represent FDA's current thinking on this topic.

[4] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during the development of products.

II. BACKGROUND

Colorectal cancer is a leading cause of cancer death in U.S. adults (Siegel et al. 2017). A colonoscopy is recommended as the preferred modality for colorectal cancer screening (Rex et al. 2017).

The success of a colonoscopy is closely linked to the adequacy of preprocedure bowel cleansing, and up to 25 percent of all colonoscopies are reported to have inadequate bowel preparation. Inadequate bowel preparation results in lower adenoma detection rate, longer procedural time, lower cecal intubation rate, increased electrocautery risk, and shorter intervals between examinations (Johnson et al. 2014). Adequate bowel preparation is also important for diagnosing, surveilling, and treating other gastrointestinal conditions.

The goal of bowel cleansing is to remove fecal matter and fluids from the colon to permit adequate visualization of colonic mucosa (Wexner et al. 2006; Mamula et al. 2009). An optimal bowel cleansing product is safe, efficacious, and well tolerated, and results in high rates of patient compliance with the prescribed regimen.

III. DEVELOPMENT PROGRAM

A. Trial Population

Sponsors developing products for bowel cleansing for colonoscopy should consider the following:

- Include patients undergoing routine colonoscopy either for screening or diagnostic purposes.

- Enroll a population that is sufficiently broad and inclusive to assess safety and efficacy across all relevant subgroups likely to use the product. For example, enroll adequate numbers of patients older than 65 years of age, as well as adequate representation of ethnic and racial minorities.

- Include patients with stable chronic kidney disease when available nonclinical and clinical data indicate that exposing patients with reduced kidney function to a bowel-cleansing product would not place patients at unreasonable risk and/or adequate steps can be taken to mitigate potential risks. Sponsors should provide adequate justification for including/excluding patients with different levels of kidney function based on the stage of product development, safety profile of the product, and understanding of the effect of kidney function on elimination of the product, if absorbed.

B. Trial Design

Sponsors developing products for bowel cleansing for colonoscopy should consider the following:

- We recommend a randomized, investigator/colonoscopist-blinded, parallel group trial design.

- Typically, trials to demonstrate efficacy of new bowel-cleansing products are designed as noninferiority trials with comparison to one or more approved bowel-cleansing products.

- Sponsors should select an appropriate active comparator that demonstrates an efficacy profile that is relevant to the current standard of care. The active comparator should be agreed upon with the Division before trial initiation.

  – An appropriate comparator is a U.S.-approved product, is widely used in U.S. clinical practice at the time of the trial, and has demonstrated efficacy using split-dose administration. Choice of active control is further discussed in the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).[5]

  – In general, we recommend that both the active comparator and the new product be administered in a split-dose administration schedule, consistent with current recommendations to optimize efficacy. Sponsors intending to study the new product as a single-day dose should discuss the plan and justification (e.g., safety in a specific subpopulation, etc.) with the Division before trial initiation.

  – We recommend that a different active comparator be used across the two phase 3 trials (e.g., large volume versus low volume, or two products with different active ingredients) to best characterize the efficacy and safety profile of the new product.

C. Efficacy Considerations

1. Efficacy Assessments

Sponsors developing products for bowel cleansing for colonoscopy should consider the following:

- Efficacy should be assessed during insertion of the colonoscope (i.e., before washing and suctioning) to ensure that the effect measured is attributable to the bowel-cleansing product, not to intraprocedural cleansing efforts of the colonoscopist.[6]

- All colonoscopy readings should be video recorded.

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] For studies that were initiated before publication of this guidance and are assessing efficacy during withdrawal of the colonoscope, sponsors should discuss with the Division the additional analyses that will be requested to support the efficacy assessment (e.g., volume of water used to clean, time spent washing, etc.).

- We recommend that each endoscopy video be reviewed and scored by at least one independent central reader who is blinded to treatment assignment. However, alternative proposals (e.g., adjudicating a random subset for quality control) may be discussed with the Division.

- The quality of the bowel preparation on insertion should be assessed primarily using air insufflation, and colonoscopists should be instructed to minimize use of water flushing to permit assessment of the effects of the bowel-cleansing product.

- We recommend the following regarding selection of a bowel cleansing scale to assess efficacy:

  – Efficacy scales used to define the categories of *excellent*, *good*, *fair*, and *poor* should be based on nonoverlapping criteria. Previously used scales[7] have some limitations (such as overlapping criteria between grades) but may be modified to improve clarity of definition or criteria. A recommended four-point scale that could be used is shown in Table 1 (see Appendix). Sponsors wishing to develop an alternative scale should meet with the Division early in development to ensure agreement is reached on the adequacy of the proposed scale.

  – Each colon segment should be scored individually.[8]

- We recommend the following primary endpoint:

  – Proportion of patients achieving successful bowel cleansing (defined as a score of excellent or good in every colon segment).

  – Because adequate visualization of the entire colon is important, particularly in screening colonoscopy to avoid missed lesions, a score of fair or poor in any segment will result in the patient being considered a failure for the primary efficacy analysis.

- We recommend the following secondary endpoints:

  – Cecal/ileal intubation rate
  – Proportion of patients achieving excellent grade in all segments
  – Time to reach cecum
  – Adenoma detection rate
  – Nonpolypoid adenoma detection rate[9]

[7] Examples of scales used in the past include Aronchick, Boston, and Harefield cleansing scales.

[8] Colon segments should be defined as follows: right colon (to include cecum and ascending colon); transverse colon (to include splenic flexure, transverse colon, and hepatic flexure); and left colon (to include descending colon, sigmoid colon, and rectum).

[9] Defined as the proportion of subjects with at least one nonpolypoid adenoma detected.

2. Statistical Considerations

Sponsors developing products for bowel cleansing for colonoscopy should consider the following:

- Sponsors should prespecify a primary estimand of interest for each endpoint and justify that it is meaningful and that it can be estimated with minimal and plausible assumptions with the proposed analysis.[10]

- Sponsors should conduct the primary efficacy analysis in the population of all randomized patients who received at least a partial dose (initiated the first dose), excluding patients who did not undergo a colonoscopy for reasons other than safety or lack of efficacy (e.g., procedure cancelled for scheduling reason, study colonoscopist unavailable because of emergency). The reason should be clearly documented. Excluding a large number of patients for these types of reasons would be evidence of poor study conduct and may raise a review issue.

- Sponsors should prespecify methods to handle missing values for the primary and secondary endpoints in the statistical analyses and should align them with the targeted estimand of interest.

- Patients unable to complete preparation because of adverse events or patients whose physician opted not to conduct the colonoscopy because of inadequate preparation should be considered nonresponders.

  – Supplementary analyses should evaluate the probability of successful bowel cleansing in the subset of patients who completed the full dose of study medication.

- Strategies for handling other types of missing data, including missing segmental data, should be discussed with the Division and clearly specified in the SAP.

- The noninferiority (NI) margin should be prespecified and informed by the maximal degree of inferiority of the test product to the active control that can be considered acceptable to support approval.[11] Sponsors should submit a detailed justification of the proposed NI margin to FDA and reach agreement with FDA on this margin before initiating a trial.

[10] For additional recommendations, see the International Council for Harmonisation harmonized guideline *E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical Principles for Clinical Trials*, available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

[11] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.

- The choice of active comparator should be justified and relevant to current practice standards to avoid biocreep[12] (refer to section III. B., Trial Design).

D. Safety Considerations

Sponsors developing products for bowel cleansing for colonoscopy should consider the following:

- In-person study visits should occur at randomization, day of colonoscopy (before procedure), and 48 to 72 hours after colonoscopy for all patients to assess vital signs and blood chemistry.

- For patients with clinically significant abnormal laboratory tests at 48 to 72 hours post-colonoscopy, sponsors should conduct an additional study site visit for laboratory testing 7 days post-colonoscopy.

  – Thresholds to define clinically significant abnormal laboratory parameters that would mandate repeat visits, even in the absence of symptoms, should be specified in the protocol and agreed upon with FDA before trial initiation.

- Patients with ongoing adverse events should be followed until resolution or stabilization of symptoms. If the adverse event was a laboratory test abnormality, sponsors should conduct repeat testing to document return to baseline or, if not resolving, until stable.

- Sponsors should prospectively plan for safety analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, rate ratio, or hazard ratio) along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison. Sponsors should stratify by study any analyses of integrated data from multiple studies.

- We recommend the following laboratory shift analyses:

  – Proportion of patients with a normal baseline laboratory value who had a post-baseline value outside the normal limit at the 48 to 72 hours post-colonoscopy visit.

    ▪ Sponsors should further summarize these results by severity grade of the electrolyte abnormality, using a standard rating scale such as the Common Terminology Criteria for Adverse Events.

  – Proportion of patients with possible acute kidney injury, defined as those patients who experienced an increase in serum creatinine from baseline of more than 0.3 mg/dL within 48 to 72 hours.

[12] Biocreep phenomenon may occur when an investigational treatment is noninferior but slightly worse compared with its active control; later on, the same treatment is used as an active control for another NI trial. If this pattern repeats several times in a sequence of NI trials, then it may result in a suboptimal standard for achieving efficacy and allow inferior treatments to be marketed.

- Sponsors should summarize additional details on the clinical course of these patients in the submission, with documentation of outcome as resolved, resolving or persistent increase above baseline.

- Sponsors should also conduct this analysis separately in the subgroup of patients with abnormal baseline renal function to determine whether patients with preexisting renal impairment are more susceptible to acute kidney injury.

E. Additional Considerations

If the proposed study product contains two or more active ingredients, it would most likely be considered a fixed-dose combination product as defined in 21 CFR 300.50. Sponsors should meet with the Division regarding fixed-dose combination considerations early in the development process.

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Guidances[1]

Guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016)

International Council for Harmonisation harmonized guideline *E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical Principles for Clinical Trials* (November 2019)[2]

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[2] Available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

APPENDIX

An acceptable four-point efficacy scale (see Table 1) that could be used to define the categories of excellent, good, fair, and poor is shown below.

Table 1 Elements That Should Be Included in the Grading Criteria of the Bowel Cleansing Assessment Scale

Grading	Criteria
Excellent	No more than small bits of fecal residue or fluid that requires no washing and no/minimal suctioning, resulting in clear visualization of the entire colonic mucosa.
Good	Small amounts of fecal residue or fluid that can be easily washed and suctioned but still results in clear visualization of the entire colonic mucosa.
Fair	Enough feces to require extensive washing and suctioning, which may prevent clear visualization of the entire colonic mucosa.
Poor	Large amount of fecal residue; clear visualization of entire colonic mucosa is not possible.