Guidance for Industry

Irritable Bowel Syndrome — Clinical Evaluation of Products for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Guidance for Industry

Irritable Bowel Syndrome — Clinical Evaluation of Products for Treatment

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I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators who are conducting new product development for the treatment of irritable bowel syndrome (IBS). IBS diagnosis and status depends mainly on an assessment of IBS signs and symptoms. However, capturing all of the clinically important signs and symptoms associated with IBS for measuring treatment benefit in clinical trials can be challenging. This guidance addresses three main topics regarding IBS sign and symptom assessment: (1) the evolution of primary endpoints for IBS clinical trials; (2) interim recommendations for IBS clinical trial design and endpoints; and (3) the future development of patient-reported outcome (PRO) instruments for use in IBS clinical trials. These interim recommendations are provided in this guidance until properly developed and validated PRO instruments become available for incorporation in clinical trials.

This guidance applies to the IBS indications for IBS with diarrhea (IBS-D) and IBS with constipation (IBS-C). Sponsors should contact the Division of Gastroenterology Products for recommendations regarding trial design for other types of IBS populations not discussed in this guidance (i.e., mixed irritable bowel syndrome, unsubtyped irritable bowel syndrome, and alternating irritable bowel syndrome).

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.

[1] This guidance has been prepared by the Division of Gastroenterology Products and the Study Endpoints and Labeling Development Team in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

II. BACKGROUND

IBS is a complex condition with variable symptomatology and involves a broad range of physiologic and psychologic alterations that may affect brain-gut dysregulation, gut function, visceral perception, and mucosal integrity and function. Despite advances in our understanding of basic neuroenteric mechanisms and the role of effectors and transmitters in the brain-gut axis, a reliable biologic marker of IBS has yet to be indentified.[2] This has made development of optimal endpoints and trial design for evaluation of efficacy of IBS drugs a challenge.

III. EVOLUTION OF PRO MEASURES IN IBS CLINICAL TRIALS

An adequate measure of treatment benefit should capture the most significant signs and symptoms of IBS. The primary challenge in designing clinical trials to evaluate the efficacy of products for this condition has been not only effectively defining the critical signs and symptoms that are most relevant to patients, but then selecting or developing adequate assessment tools that measure all of the clinically relevant domains or subconcepts of those same signs and symptoms.

In the past, IBS clinical trials commonly used a single-item patient-reported rating of overall change in condition as the primary efficacy endpoint.[3] Specific IBS signs and symptoms were included as separate secondary endpoints. Examples of single-item patient-reported ratings of change included questions posed to patients about *adequate relief* or *satisfactory relief* and the single item *Subject Global Assessment of Relief (SGA) of IBS symptoms*. Usually, the patient-reported ratings of change required patients to average either specific symptoms (e.g., abdominal pain or discomfort) or all symptoms of IBS over a week's time, and then compare this average to a period in the past, typically before trial entry. Table 1 describes primary endpoints that have been used to support efficacy in IBS clinical trials.

[2] See reference numbers 1-8 in the References section at the end of the guidance.

[3] See reference numbers 9-23 in the References section at the end of the guidance.

Table 1. Primary Endpoints Used in IBS Clinical Trials

Product and Specific Indication	Primary Endpoint	Questions Used to Assess Endpoint	Response
Alosetron — IBS-D[1]	Adequate relief	*In the past 7 days, have you had adequate relief of your IBS pain or discomfort?*	Binary endpoint (Yes/No)
Tegaserod — IBS-C[2]	Satisfactory relief	*Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS?* *Did you have satisfactory relief of your overall IBS symptoms during the last week?* *Did you have satisfactory relief of your abdominal discomfort or pain during the last week?*	Binary endpoint (Yes/No)
	Subject Global Assessment of Relief (SGA)	*Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit.*	5-Point Likert scale: worse, not at all relieved, somewhat relieved, considerably relieved, completely relieved
Lubiprostone — IBS-C[3]	Modified version of the SGA	*How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the study?*	7-Point Likert scale: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, substantially improved

[1] See reference numbers 9-14 in the References section at the end of the guidance.
[2] See reference numbers 15-22 in the References section at the end of the guidance.
[3] See reference number 23 in the References section at the end of the guidance.

The guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (PRO guidance), published in December 2009, defines *treatment benefit* as an improvement in how a patient survives, feels, or functions demonstrated by either an effectiveness or safety advantage.[4] PRO instruments define and capture the patient's perspective with respect to the disease or condition of interest and can be appropriate for measuring the effect of treatment in a clinical trial. Consistent with FDA regulations for medical product approval, the effectiveness of a treatment must be based on substantial evidence including evidence that all assessments of treatment benefit are well-defined and reliable (21 CFR 314.125(b)(5) and 314.126(b)(6)). In the case of treatment benefit claims based on PRO measures, the PRO guidance recommends and provides the FDA's review principles for determining whether assessments are well-developed and adequately validated to measure what they are intended to measure.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

To effectively capture the patient's experience, it is important to interview patients with the underlying disorder through qualitative research and generate an assessment tool based upon this input. Before publication of the PRO guidance, the development of many PRO measures (including patient-reported ratings of change) were not based upon sufficient qualitative research with the target population to support conclusions that they capture treatment benefit in a *well-defined and reliable* way. The specific symptoms that are clinically important to patients were never established based upon patient input, and how to measure these symptoms using patient-appropriate terminology was never defined.

In light of the PRO guidance, the type of PRO instruments that the FDA now finds appropriate for data collection to support labeling claims has evolved from what it found appropriate in the past. For example, we no longer recommend general items asking patients to rate overall change in their IBS symptoms as primary endpoints to support efficacy claims. We consider patient-reported ratings of change, whether describing a general or single-focused concept, to be inappropriate for the following reasons.

- As a single general item, a patient-reported rating of change cannot adequately delineate whether benefit is achieved in all of the important subconcepts (i.e., signs and symptoms) that comprise the composite concept of IBS. For example, a single-item response that queries a patient about his or her overall symptoms won't capture whether a patient's stool frequency has improved, but abdominal pain or discomfort has not. In contrast, evaluation of a treatment benefit in only a single domain, such as abdominal pain or bowel function alone, would not establish benefit for the entire experience of IBS, since benefit in one sign or symptom does not necessarily mean improvement is also experienced in the other signs and symptoms of the composite concept of IBS.

- A patient-reported rating of change does not describe the patient's current symptom experience. Instead, it merely describes a summary comparison of the current state to a previous point in time. As such, the patient-reported rating of change does not quantify the intensity of the current symptoms (e.g., mild, moderate, or severe) or describe absence of symptoms.

- Comparisons of current symptoms to a previous time point, such as before the trial began, are problematic because they necessitate that patients recall their status over a period of weeks or months.

- Patient-reported ratings of change may not be uniformly understood or describe the full range of possible treatment effects. For example, IBS clinical trials have typically included patient-reported ratings of change that use a question concerning *adequate or satisfactory relief* of symptoms. The response options are usually binary (yes/no). General terms such as *adequate*, *satisfactory*, and *relief* are unlikely to be interpreted consistently among patients. In addition, the binary response options do not allow patients to record worsening symptoms or to quantify the treatment effect (e.g., minimal improvement versus complete resolution).

In recognition of the limitations of using a single-item patient-reported rating of change as a primary endpoint and based on the principles explained in the PRO guidance, we now recommend the development of a multi-item PRO instrument that captures all of the clinically important signs and symptoms of IBS. Prospectively defined changes in the scores measured by this PRO instrument between treatment arms should be used as the primary endpoint in IBS clinical trials. The instrument should be population specific (i.e., developed for use in IBS-C or for use in IBS-D). The instrument should have evidence of content validity.

Content validity is defined as evidence, based upon qualitative research in the target population of patients, that the scores produced by the items and domains of a PRO instrument fully represent and capture the intended measurement concept and are meaningful, appropriate, and interpretable relative to the intended measurement concept(s), population, and use. Although input from experts in the field and literature reviews are an important and necessary first component in drafting the items and domains of an instrument, patient input is essential for finalizing the instrument and supporting that content validity has been achieved.

The content validity of an IBS instrument should be verified by protocol-driven qualitative research that aims to understand the concept of interest. Open-ended, one-on-one interviews or focus groups should include IBS patients with characteristics similar to the population that will enroll in the IBS clinical trials, and should represent a diverse group (e.g., both sexes, varying degrees of IBS intensity, and broad age range). Open-ended probing questions to patients about the concept of interest, in this case the signs and symptoms of IBS, can be used to discover the specific terminology used by patients to describe the important signs and symptoms. This terminology should be used to construct the questionnaire. Open-ended patient interviews should continue until saturation is reached. Saturation is the point when no new relevant information emerges and it becomes clear that additional data do not add to the understanding of how IBS patients perceive their disorder. Summarized responses to these broad questions should be analyzed so that subconcepts and items can be identified, grouped, and ultimately formatted into a framework that forms the backbone of the instrument.

After the instrument has been developed, additional qualitative interviews can be useful for discovering any problems with the questionnaire and to confirm that the instructions, items, and response options are appropriate and understandable. An appropriate recall period for the PRO instrument is an essential part of establishing content validity. For frequently occurring signs and symptoms, such as bowel habits, a daily diary is generally advised.

IV. INTERIM ENDPOINTS AND TRIAL DESIGN FOR IBS CLINICAL TRIALS

A content-valid PRO instrument that measures the clinically important signs and symptoms associated with each IBS subtype is the ideal primary efficacy assessment tool in clinical trials used to support labeling claims. However, at this time, an adequate instrument is not available. We recognize that it will take some time to develop adequate instruments and that in the meantime, there is a great need to develop effective therapies for patients with IBS. Therefore, until the appropriate PRO instruments have been developed, we recommend sponsors consider the following strategies when designing IBS clinical trials for IBS-C and IBS-D.

A summary of the main IBS-C and IBS-D trial design recommendations, including the entry criteria, co-primary endpoints, and responder definitions, is provided in Table 2. More detailed information is provided in the subsections that follow.

Table 2. Summary of Recommended IBS Trial Designs by IBS Subtype

IBS Subtype	Co-Primary Endpoints	Entry Criteria	Responder Definition
IBS-C	Pain Intensity AND Stool Frequency	**Pain Intensity** Weekly average of *worst abdominal pain in past 24 hours* score of ≥ 3.0 in a 0 to 10 point scale AND **Stool Frequency** < 3 complete spontaneous bowel movements (CSBM) per week	**Pain Intensity** Decrease in weekly average of *worst abdominal pain in past 24 hours* score of ≥ 30% compared with baseline AND **Stool Frequency** Increase of 1 or more CSBM per week compared with baseline
IBS-D	Pain Intensity AND Stool Consistency	**Pain Intensity** Weekly average of *worst abdominal pain in past 24 hours* score of ≥ 3.0 in a 0 to 10 point scale AND **Stool Consistency** Weekly average ≥ Type 6 Bristol stool score (BSS) (see Figure 1 for details)[1]	**Pain Intensity** Decrease in weekly average of *worst abdominal pain in past 24 hours* score of ≥ 30% compared with baseline AND **Stool Consistency** Weekly average of ≤ Type 5 BSS (≤ Type 2 BSS can be considered an adverse event)

[1] See reference number 24 in the References section at the end of the guidance.

1. Trial Design

Because the clinical signs and symptoms associated with IBS-C and IBS-D can be significantly different, the two conditions optimally should be studied in separate clinical trials.

A randomized, placebo-controlled trial design should include a 1- to 2-week screening period, 8- to 12-week treatment period, and 2-week post-treatment period. The 1- to 2-week screening period can be used to establish trial entry criteria and train patients in the mode of PRO data collection selected for the trial.

Sponsors should consider stratification, particularly for IBS-D trials, based upon the presence or absence of fecal incontinence.

2. Trial Endpoints

Because IBS is defined as abdominal pain or discomfort that is improved with defecation,[5] we recommend evaluation of a co-primary endpoint that includes the two major IBS symptoms: abdominal pain and defecation (constipation measured as stool frequency for IBS-C and diarrhea measured as stool consistency for IBS-D).

For IBS-C, the defecation component of the proposed co-primary endpoint can be evaluated by assessing stool frequency. Stool frequency is readily defined, has been useful in defining a treatment response in chronic constipation clinical trials, and is probably more clinically relevant for IBS-C patients.

For IBS-D, the defecation component of the proposed co-primary endpoint can be evaluated by assessing stool consistency. When patients participating in the alosetron clinical trials were asked to select the single symptom that *bothers you the most*, *urgency* ranked second only to *abdominal pain* as the most bothersome symptom (from a list of five symptoms).[6] Unfortunately, there are currently significant limitations for using the term urgency as a key endpoint. It is not clear how patients define or describe urgency and what terminology will appropriately capture this symptom from the patient's perspective. Adequate qualitative data that establish the content validity of the symptom urgency for the IBS population are not available.

Because urgency cannot be readily measured at present, we recommend that either stool frequency or consistency be the defecation component co-primary endpoint in IBS-D. However, based upon input from experts in the IBS field, including input that was solicited during the April 2009 Rome Endpoints and Outcomes Conference,[7] we conclude that stool consistency is more likely to affect the urgency experienced by patients than stool frequency. For this reason, we recommend that stool consistency be the defecation component co-primary endpoint for IBS-D trials. The Bristol Stool Form Scale, which is reproduced in Figure 1, provides a pictorial and verbal description of stool consistency and form and is an appropriate instrument for capturing stool consistency in IBS trials.[8]

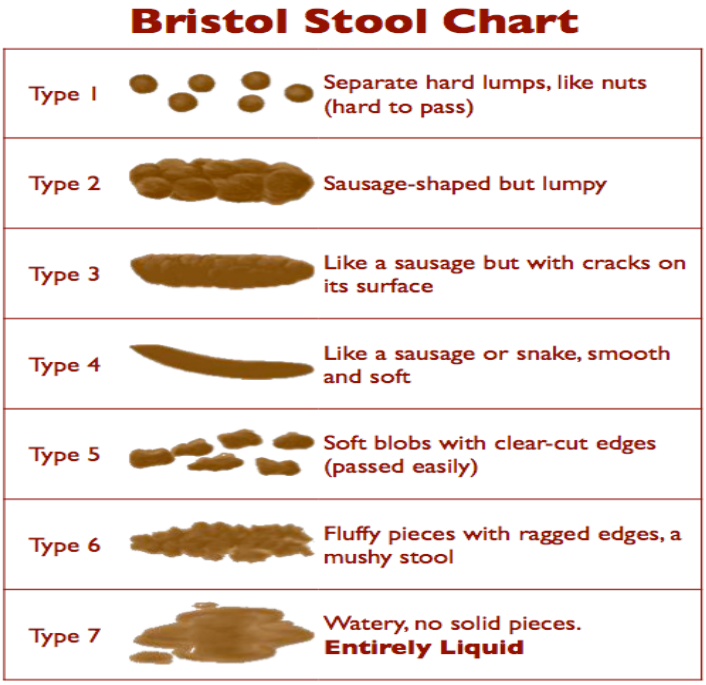
[5] See reference number 25 in the References section at the end of the guidance.

[6] See reference number 29 in the References section at the end of the guidance.

[7] See reference numbers 30 and 31 in the References section at the end of the guidance.

[8] See reference number 24 in the References section at the end of the guidance.

Figure 1. Bristol Stool Form Scale



The second symptom component of the co-primary endpoint in both IBS-C and IBS-D is abdominal pain. Although previous IBS clinical trials have used an item that assesses abdominal *pain or discomfort*, it is unclear if the abdominal pain and abdominal discomfort experienced by patients with IBS are synonymous or different symptoms. Although adequate qualitative studies have not fully addressed these questions, clinical data submitted to and reviewed by the FDA suggest that abdominal pain and discomfort may be different symptoms that should, therefore, be assessed by different questions. Because frank pain seems to be a symptom that is experienced with more significant intensity than discomfort and because the chronic pain literature suggests that pain intensity may be a more clinically relevant assessment than pain frequency,[9] we recommend abdominal pain intensity as the primary pain assessment in IBS trials. Abdominal discomfort can be evaluated as a secondary endpoint.

We recommend evaluating abdominal pain intensity by using an 11-point (i.e., 0 to 10) numeric rating scale that asks patients daily to rate their *worst abdominal pain over the past 24-hours*.[10] This type of pain assessment has been used to assess pain in somatic, visceral, and neuropathic chronic pain conditions.[11]

IBS clinical trials should also incorporate clinically relevant secondary and exploratory endpoints. Since urgency is believed to be a key symptom in IBS-D, clinical trials in this population should include an exploratory endpoint that captures this symptom using less

[9] See reference number 26 in the References section at the end of the guidance.

[10] See reference numbers 26 and 27 in the References section at the end of the guidance.

[11] See reference number 28 in the References section at the end of the guidance.

ambiguous terminology (e.g., do you have to hurry to the bathroom to have a bowel movement?). If satisfactory patient language can be identified, a measure of days without such episodes can be a useful efficacy assessment. Fecal incontinence is another important symptom to capture in IBS-D trials. Again, language that is readily understood by patients should be used in assessing fecal incontinence.

Until an adequate and comprehensive PRO measure of the clinically important symptoms associated with each subtype of IBS is available, we encourage inclusion of an exploratory open-ended question that asks patients to list on a weekly basis any additional bothersome IBS symptoms.

3. Trial Populations

Based upon the evolution of the IBS diagnostic criteria, prospective IBS clinical trials should enroll patients who meet the subtype-specific Rome III IBS diagnostic criteria.[12] In addition, to demonstrate clinical benefit, patients who enter the trial should have the clinical manifestations of IBS that will be assessed in the trial to define treatment response, and the manifestations should have sufficient magnitude of intensity to make demonstration of a clinically meaningful improvement possible. In light of the components of the co-primary endpoints for IBS-C and IBS-D previously described, we recommend trial entry criteria include the following:

IBS-C

- **Pain Intensity:** weekly average of *worst abdominal pain in past 24 hours* score of $\geq$ 3.0 on a 0 to 10 point scale

- **Stool Frequency:** < 3 CSBMs per week

IBS-D

- **Pain Intensity:** weekly average of *worst abdominal pain in past 24 hours* score of $\geq$ 3.0 on a 0 to 10 point scale

- **Stool Consistency:** weekly average of $\geq$ Type 6 BSS

4. Efficacy Measures

Sponsors should choose a format for daily symptom assessment (e.g., interactive voice response, personal digital assistant, or paper diaries) so that patients can evaluate their IBS symptoms on a daily basis throughout the trial. The weekly average of 7 daily assessments can be used to calculate a weekly response to treatment. Because significant missing data may result in concerns regarding the validity of efficacy conclusions, it is important that patients provide a predetermined minimum number of entries per week to be considered in the weekly responder analysis.

[12] See reference number 25 in the References section at the end of the guidance.

5. Definition of a Responder

A definition of a responder for use in an analysis of proportions for evaluation of the co-primary endpoints should be prospectively described in the protocol and statistical analysis plan. Statistical power calculations should be based on a predefined difference in proportions. The predefined difference that would be considered clinically meaningful should be discussed during protocol development with the review division.

We recommend the following responder definitions for IBS-C and IBS-D:

IBS-C

A patient is categorized as a weekly responder if the patient is a weekly responder in **both** pain intensity **and** stool frequency.

- A Pain Intensity Responder for IBS-C is defined as a patient who experiences a decrease in weekly average of *worst abdominal pain in past 24 hours* score of equal to or greater than 30 percent compared with baseline.

- A Stool Frequency Responder is defined as a patient who experiences an increase of at least one CSBM per week from baseline.

IBS-D

A patient is categorized as a weekly responder if the patient is a weekly responder in **both** pain intensity **and** stool consistency.

- A Pain Intensity Responder is a patient who experiences a 30 percent or greater decrease in weekly average of *worst abdominal pain in past 24 hours* compared with baseline.

- A Stool Consistency Responder is a patient who has equal to or less than Type 5 in their weekly average BSS. (Note: During the trial, if a patient reports having equal to or less than Type 2 in weekly average BSS, the event can be considered an adverse event.)

Overall, classification as a responder involves achieving a prespecified improvement in symptoms for at least 50 percent of the time. This is consistent with the recommendations for evaluation of medicinal products for the treatment of IBS by the European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use.[13] Response should be observed at several points throughout the trial to establish sustained improvement.

V. FUTURE DEVELOPMENT OF IBS PRO INSTRUMENTS

A public and private partnership or PRO Consortium was formed in 2008 as a means to expedite development of adequate PRO measures that effectively capture the patient's experience and support labeling claims. The PRO Consortium is conducted under the FDA's Critical Path

[13] See reference number 32 in the References section at the end of the guidance.

Initiative and is charged with the task of efficiently and collaboratively developing reliable, interpretable instruments that will be available in the public domain for all sponsors to use in medical product clinical trials. The collaboration is administered by the Critical Path Institute and includes members from the FDA, industry, academia, professional organizations, patient advocacy groups, and other governmental agencies. The development of subtype-specific IBS PRO instruments has been identified by the PRO Consortium Coordinating Committee as one of its first areas of focus. Additional information about the PRO Consortium can be found at http://www.c-path.org.

The PRO Consortium is just one resource for the development of effective PRO instruments. We will continue to review the adequacy of PRO instruments developed outside the PRO Consortium process if they will be used to support labeling claims.

VI. CONCLUSION

The trial design and endpoint recommendations in this guidance, which move the field forward from the traditionally used global assessment paradigm, are provided as a path forward for IBS product developers to continue their efforts to develop treatments to address the needs of patients with IBS, while the important work in developing validated PRO instruments continues to completion. We recommend the use of a well-defined and validated IBS PRO instrument to help capture clinically important signs and symptoms associated with IBS. The instrument should represent a meaningful, appropriate, comprehensive, and interpretable assessment of the clinically important signs and symptoms of each subconcept of IBS to be used as the single primary endpoint in IBS clinical efficacy trials.

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