Interstitial Cystitis/Bladder Pain Syndrome: Establishing Drug Development Programs for Treatment 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DRAFT GUIDANCE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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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance provides recommendations for clinical drug development for drugs intended to treat patients with interstitial cystitis/bladder pain syndrome (IC/BPS). This guidance incorporates advice FDA received at a December 2017 advisory committee meeting[2] on appropriate patient selection criteria and trial design features, including enrollment criteria and acceptable efficacy endpoints for drugs intended to treat IC/BPS.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents means that something is suggested or recommended, but not required.

Although this guidance discusses the selection of endpoints for clinical trials, it does not address detailed design considerations for patient-reported outcome (PRO) instruments. Those issues are addressed in the FDA guidance for industry *Patient-Reported Outcome Measures: Use in*

[1] This guidance has been prepared by the Division of Urology, Obstetrics, and Gynecology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Information on the meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee is available at https://public4.pagefreezer.com/browse/FDA/01-03-2022T00:42/https:/www.fda.gov/advisory-committees/bone-reproductive-and-urologic-drugs-advisory-committee-formerly-reproductive-health-drugs-advisory/2017-meeting-materials-bone-reproductive-and-urologic-drugs-advisory-committee-formerly-advisory.

Medical Product Development to Support Labeling Claims (December 2009)[3] and the FDA Patient-Focused Drug Development (PFDD) guidance series.[4]

II. BACKGROUND

IC/BPS is a complex, poorly understood heterogeneous syndrome of unknown etiology.

Interstitial cystitis (IC) was first characterized over 100 years ago in patients as a symptom complex with these two factors:

- Bladder pain related to bladder filling
- Historical pathognomonic cystoscopic finding of Hunner's lesion[5] in the bladder

In the intervening years, beginning in the 1970s and 1980s, there began a gradual acknowledgment that IC might encompass more diverse forms of the disorder than solely identifying patients with Hunner's lesions (mucosal lesions or ulcerations seen with or without hydrodistention of the bladder). The disorder definition was expanded to include patients with very similar symptoms but not necessarily requiring the presence of Hunner's lesions on cystoscopic examination.

Clinical IC management has evolved and expanded to include patients with symptoms of pain or discomfort and accompanying urinary symptoms, and with or without obvious bladder inflammation, which encompasses a very heterogeneous patient population, hereafter referred to as IC/BPS.

Currently, there are no FDA-authorized diagnostic laboratory tests or biomarkers to establish IC/BPS presence or response to therapy. There is wide variability in IC/BPS diagnostic criteria, which results in patient population heterogeneity, complicating development of drugs for widespread use among all patient subpopulations.

In general, current IC/BPS clinical diagnosis requires the following:

- Chronic pain or discomfort localized to the bladder with the following variabilities:
  - Can be related to bladder filling and/or voiding
  - Can be constant, of variable intensity, or intermittent in nature

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] These guidances are part of FDA's PFDD efforts in accordance with the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act of 2017 Title I. When final, the PFDD guidance series will replace the 2009 final PRO guidance.

[5] Hunner G., 1918, A Rare Type of Bladder Ulcer: Further Notes, with a Report of Eighteen Cases, JAMA, 70(4):203–212.

- Accompanying lower urinary tract symptoms such as urinary frequency, urgency, or nocturia

- Exclusion of other disorders or conditions that can have similar presentations, such as malignancy, any surgically diagnosed endometriosis, chronic prostatitis, and bladder outlet obstruction

- Cystoscopy may show bladder inflammation, including Hunner's lesions or other nonspecific pathology, but also can be normal.

III. EARLY DRUG DEVELOPMENT PROGRAM FEATURES–KEY CONSIDERATIONS

Current IC/BPS clinical diagnosis criteria encompasses a very heterogeneous patient population who present with a common symptom: pain or discomfort localized to the bladder. Historically, this has resulted in difficulty developing drug products intended for use in a heterogenous patient population. Early clinical trials during drug development should focus on well-defined IC/BPS populations with similar clinical features in addition to pain or discomfort localized to the bladder. This approach may better inform the selection of clinically meaningful efficacy endpoints and outcomes for future studies.

Sponsors are encouraged to assess dosing strategies, including dose-finding. In addition, drug programs should explore multiple efficacy endpoints, and collect safety information during early drug development to inform design strategy and selection of clinically meaningful endpoints for later studies.

Patients' experience with IC/BPS symptoms may vary (e.g., symptom type, severity, and duration). It is important to incorporate the patient's voice during early drug development. Obtaining information from patients can better define the appropriate target population (e.g., IC/BPS patient subpopulations) and identify what matters most to patients regarding their condition to inform endpoint selection. Sponsors should specify and define concepts (e.g., symptoms, functional impacts) early in development that are both relevant and important to patients with IC/BPS. These concepts are more likely to lead to demonstration of clinically meaningful and interpretable changes in later planned clinical trials. Identification of concepts should come from patient input (e.g., conducting patient interviews, identifying literature related to previously conducted patient qualitative studies). The Agency refers sponsors to the following guidances for industry, FDA staff, and other stakeholders for more details about the collection of evidence to inform the patient experience and obtain information from patients, caregivers, and other relevant stakeholders:

- *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)[6]

- *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (February 2022)

Once concepts from patient input are identified, sponsors should select and prioritize fit-for-purpose patient-reported outcome (PRO) assessments and related endpoints to assess the targeted concepts in their phase 2 clinical trials.[7] The Agency encourages collaboration among patient groups, medical product developers, PRO developers, and other stakeholders with the goal of generating publicly available fit-for-purpose[8] PRO instruments for use in IC/BPS across multiple medical product development programs.[9]

In general, FDA recommends that early targeted IC/BPS studies assess the following concepts related to the patient experience, at a minimum:

- Most bothersome pain or discomfort symptom(s)

- Accompanying urinary symptom(s) not captured by the pain or discomfort outcome (e.g. urinary frequency, urgency, or nocturia)

- Symptom intensity/severity scoring or measurement, where applicable

- Symptom changes, including worsening of symptoms

- Functional impacts (e.g., interference with daily activities)

Sponsors may refine their IC/BPS indication during the drug development program based on earlier study results to include the following:

- Findings in the targeted patient subpopulations
- Focused inclusion/exclusion criteria

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for Purpose Clinical Outcome Assessments* (June 2022) and the draft guidance for industry *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making* (April 2023). When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] For purposes of this guidance, *fit-for-purpose* is defined as a conclusion that the level of validation associated with a tool is sufficient to support its context of use. See the BEST (Biomarkers, Endpoints, and other Tools) Resource, available at https://www.ncbi.nlm.nih.gov/books/NBK326791/?report=reader.

[9] See the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020).

- Diagnostic procedures follow-up or serial diagnostic procedures for confirmation of effect(s)

IV. CLINICAL TRIAL DESIGN FEATURES–KEY CONSIDERATIONS

A. Enrollment Criteria

Sponsors of investigational drugs intended to treat IC/BPS should consider including the following for subject enrollment criteria in clinical trials:

- Subjects should report bladder pain and/or bladder discomfort and lower urinary tract symptoms:
  - Subjects should have at least 6 months' duration of bladder pain and/or discomfort symptom(s) before enrollment to exclude other disorders with similar presentations that have a shorter time course.
  - Subjects should have at least 6 months' duration of one or more accompanying lower urinary tract symptom(s), such as urinary frequency, urgency, or nocturia. This may be intermittent or persistent.
- The reported symptoms (bladder pain and/or bladder discomfort and lower urinary tract symptoms) should be of sufficient severity (intensity or frequency) at baseline to allow for measurement of a clinically meaningful improvement with the drug (i.e., a score greater than the prespecified threshold or range of thresholds for clinically meaningful within-patient change). Refer to section E, Selecting Potential PRO and Secondary Endpoints for IC/BPS Clinical Trials, later in this guidance.
- Subjects should have a cystoscopy at screening (if not obtained within the preceding 6 months) to exclude other conditions (e.g., transitional cell carcinoma and endometriosis, etc.).
- Subjects may have received prior treatment(s) for IC/BPS, including surgical procedures such as fulguration. In general, FDA recommends including these subjects in the trials to improve the generalizability of the results unless a compelling effectiveness or safety reason exists for excluding them. During the protocol trial design phase, sponsors should discuss with the Agency the extent to which such subjects should be included in the trials.
- Subjects should undergo standard medical evaluation to exclude other conditions or diseases that can cause similar symptoms, using information from medical history, physical and pelvic examination findings, laboratory studies (e.g., negative urine bacterial culture), and other previously performed procedures (e.g., gynecologic or prostate examination, urodynamics, cystoscopy, laparoscopy, radiological studies).

B. Clinical Trials Efficacy Endpoints

When developing efficacy endpoints for clinical trials, sponsors of investigational drugs intended to treat IC/BPS should include both of the following as co-primary endpoints:

- Improvement in bladder pain and/or bladder discomfort
- Improvement in accompanying lower urinary tract symptom(s)

Sponsors are reminded that statistical improvement in these symptoms is not sufficient. Sponsors should demonstrate that the changes reported are clinically meaningful to establish effectiveness (refer to section E for more details about interpretation of PRO results).

If a drug is not expected to improve lower urinary tract symptoms[10] based on the mechanism of action specific for IC/BPS, a single primary effectiveness endpoint related to symptoms of bladder pain and/or bladder discomfort may be considered, but clinical meaningfulness should still be demonstrated. However, lower urinary tract symptoms should still be captured as a secondary endpoint as these symptoms should not be worsened by the drug.

Sponsors should discuss with the Agency early in the development program the endpoints, analyses, and anchors[11] to ensure that study results are both clinically meaningful and interpretable.

C. Other Considerations

Sponsors of investigational drugs intended to treat IC/BPS should also consider the following for trial design:

- Treatment duration should be at least 6 months to adequately assess persistence of benefit and capture intermittent symptomatic disease flares. For example, studies can be designed with two treatment phases:
  - Randomized, double-blind, placebo-controlled treatment phase of a minimum of 3 months or longer
  - Extension treatment phase of a minimum of 3 months or longer following the initial randomized, double-blind, placebo-controlled phase. This extension phase could be open-label, crossover, or active control.

[10] See section II, Background, "lower urinary tract symptoms such as urinary frequency, urgency, or nocturia."

[11] For general recommendations regarding PRO instruments and documents to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making, available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

- Other randomized, double-blind, placebo-controlled study design approaches for a dedicated 6-month-or-longer trial may be appropriate depending on the drug under development. Sponsors should discuss their approach with the Agency before initiating the trials.

- Sponsors should clearly prespecify in the protocol and statistical analysis plan how:

  - Bladder pain or discomfort will be defined, documented, and treated during clinical trials, including localization to bladder (i.e., physical findings, patient-derived diagrams, etc.)

  - Pain flares will be defined, documented, and treated during clinical trials

  - Types and doses of rescue medications and accompanying sensitivity analysis will be used and documented during clinical trials

The following should be discussed with the Agency in advance of clinical trial initiation:

- How sponsors will include targeted subgroups in their drug development program (e.g., patients with Hunner's lesion(s)).

- How sponsors will ensure that there is a sufficient representative proportion of males and females in the clinical trials for a general IC/BPS indication. Sponsors should take into consideration the underlying proportion of males and females in the IC/BPS population or subpopulation targeted by the drug. We encourage sponsors to collect information on race, age, and other demographics to assist enrichment of their patient population. If the product is studied only in a specific subpopulation, the labelled indication would be limited to that subpopulation.

D. Hunner's Lesions Subpopulation

Patients with Hunner's lesions have been described in the literature as a "classic" IC patient population, distinguishable from other IC/BPS populations. Hunner's lesions have been described as distinctive inflammatory bladder wall areas, found only at cystoscopy.[12] Patients with Hunner's lesions may be a subgroup of IC/BPS patients, and alternative endpoints, such as healed lesion and regression of bladder inflammation, may be considered in designing clinical trials in this subgroup.[13]

FDA recommends that sponsors specify criteria for diagnosis and treatment benefits if patients with documented Hunner's lesions are included in studies. Sponsors may study patients with

[12] Fall, M, Y Logadottir, and R Peeker, 2014, Interstitial Cystitis Is Bladder Pain Syndrome With Hunner's Lesion, Int J Urology, 21(Suppl 1): 79–82.

[13] Peeker, R, F. Aldenborg, and M Fall, 2000, Complete Transurethral Resection of Ulcers in Classic Interstitial Cystitis, Int Urogynecol J, 11:290–295.

Hunner's lesions alone or include this group as a subpopulation in individual trials. Detailed design features should be discussed with the Division in advance.

If studies are restricted to patients with documented Hunner's lesions, sponsors should ensure that the diagnostic tools used to diagnose Hunner's lesions are available for use by the intended provider community in the United States. If sponsors determine that they would like to develop a companion diagnostic, refer to section IV.E.

- Sponsors should consider the following if they will recruit participants with Hunner's lesions for their trial(s):
  - Baseline appearance of bladder pathology should be documented in a standardized fashion during screening and at follow-up after treatment. For this purpose, sponsors can opt to use a standard representative bladder diagram, photographic imagery, or videography.
  - Resolution of Hunner's lesions should correlate with improvement in a clinical outcome in the IC/BPS population.
- Sponsors that choose to adopt Hunner's lesions as an inclusion criterion for trial entry should discuss their approach in advance with the Agency. Sponsors that select patients with Hunner's lesions for their trials should provide specific guidance to clinicians about how these lesions were identified to ensure that providers who are not familiar with identification of these lesions will be able to select appropriate patients for treatment.

E. Selecting Potential PRO and Other Secondary Endpoints for IC/BPS Clinical Trials

IC/BPS is a symptomatic condition, so use of a PRO assessment is the most appropriate clinical outcome assessment for evaluating changes in symptoms. A separate PRO assessment can also be used to evaluate the impacts of IC/BPS symptoms on activities of daily living (e.g., functioning). Then these PRO assessments can be used to better assess impacts of the investigational drugs on IC/BPS symptoms. It is critical that sponsors use fit-for-purpose PRO instruments to assess IC/BPS symptoms (including lower urinary tract symptoms).[14] FDA encourages sponsors to seek Agency input as early as possible and at important milestones throughout the drug development process to ensure the inclusion of fit-for-purpose PRO instruments in phase 3 trials.

[14] For general recommendations regarding PRO instruments and documents to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making, available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

- Considerations for selecting assessments of bladder pain and/or bladder discomfort in patients with IC/BPS include:

  – Patient input to understand how to describe and qualify pain and/or discomfort (with bladder empty or full, relief or not relief with voiding) that is consistent with reported symptom changes

  – Inclusion of pain and/or discomfort type in the question stem (e.g., localization of pain, localization of discomfort)

  – Inclusion of pictorial diagram identifying the area where bladder pain and/or bladder discomfort may present

  – Assessments with a recall period[15] (including patient diaries, if appropriate) that is suitable for how bladder pain and/or bladder discomfort presents in the target population (e.g., variability, duration (chronic versus episodic), frequency, and/or intensity)

- Considerations for selecting assessments of functioning in study participants with IC/BPS include:

  – Assess bladder pain and/or bladder discomfort in relation to how it interferes with a patient's ability to perform activities of daily living to provide direct evidence of whether there is an impact on a patient's function.

  – Provide detailed evidence (i.e., qualitative and quantitative data) that the instrument is fit-for-purpose for the context of their drug development program. The Agency is open to evaluating existing or modified PRO instruments for use in the IC/BPS population.

Piloting the proposed PRO instruments in phase 2 trials provides opportunities to evaluate the instruments' measurement properties (reliability, validity, and ability to detect change), to develop and propose an appropriate scoring algorithm, to document evidence to support a definition of clinically meaningful within-patient change in scores, and to confirm the endpoint definition before use in phase 3 trials.

- To interpret PRO endpoint results, FDA has the following recommendations:

[15] For general recommendations regarding PRO instruments and documents to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making, available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

342 – Propose an appropriate range of within-patient score change that patients consider to
343 be clinically meaningful using anchor-based methods supplemented with anchor-
344 based empirical cumulative distribution function curves.
345
346 – Anchor each pain or discomfort assessment and functioning assessment. The sponsor
347 should generate an anchor scale specific to bladder pain and/or bladder discomfort
348 and an anchor scale specific to functioning to provide the most direct evidence for
349 evaluating clinically meaningful patient-level improvement.
350
351 – Develop anchor scales to assess at baseline (where applicable) and at the same time
352 points as the target PRO–derived endpoint(s). These anchors should be clearly stated
353 in the protocol and statistical analysis plan. At a minimum, the following anchor
354 scales should be used to generate a threshold for clinically meaningful within-patient
355 change:
356
357 ▪ Static current state patient global impression rating of severity/status scale
358 ▪ Patient global impression of change scale
359
360 Secondary Endpoints:
361
362 Sponsors may choose to capture other exploratory or diagnostic endpoint(s) in their drug
363 development program. The following points can be considered:
364
365 • No specific biomarkers or other laboratory tests have been associated with change in the
366 diagnosis or changes in symptomatology in patients with IC/BPS to date. The Agency
367 will consider new biomarkers and laboratory assessments relevant to the development of
368 therapeutic products seeking to treat IC/BPS.
369
370 • For sponsors considering developing a therapeutic product for an IC/BPS indication with
371 a companion diagnostic device, FDA recommends that they request a meeting with the
372 relevant device and therapeutic product review divisions to ensure that the development
373 plan will provide sufficient data to establish the safety and effectiveness of both the
374 companion diagnostic device and the therapeutic product.[16]
375

[16] See the draft guidance for industry and FDA staff *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product* (July 2016). When final, this guidance will represent the FDA's current thinking on this topic.