

FDA Briefing Document

Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC)

December 7, 2017

Agenda: The committee will discuss appropriate patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. The committee will also discuss whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions.

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF BONE, REPRODUCTIVE, AND UROLOGIC PRODUCTS**

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the topic of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to BRUDAC to gain the panel members' insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by BRUDAC. The FDA will not issue a final determination on the issues at hand until input from BRUDAC has been considered. The final determination may be affected by issues not discussed at the BRUDAC meeting.

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**Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic
Products, Office of New Drugs**

Introductory Memorandum

A

Introductory Memorandum

To: Bone, Reproductive, and Urologic Drugs Advisory Committee
(BRUDAC) Members

From: Audrey Gassman, MD
Deputy Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

RE: Overview of topics to be discussed at the December 7, 2017, Bone, Reproductive
and Urologic Drugs Advisory Committee (BRUDAC) meeting

The FDA is convening this BRUDAC meeting to discuss appropriate patient selection and clinical trial design features, including acceptable endpoints for demonstrating clinical benefit, for drugs intended to treat interstitial cystitis and bladder pain syndrome.

This meeting will not be discussing the benefit/risk assessment of a particular drug or the safety profiles of individual drugs or classes of drugs.

The FDA briefing document presents our clinical perspective on the issues, an overview of clinical outcome assessments, and draft points for the BRUDAC members to consider.

On the day of the BRUDAC meeting, there will be several presentations to provide the BRUDAC members with the necessary background information for their deliberations. There will be two pharmaceutical companies Aquinox Pharmaceuticals and Urigen Pharmaceuticals, Inc. that will provide their perspectives on the appropriate patient population and clinical trial design features. Next, the FDA will present its views on these topics. The day will end with BRUDAC deliberation, discussion, and voting.

We look forward to the BRUDAC's input and thank the members in advance for their contributions to public health.

Draft Points to Consider:

1. Discuss the key inclusion and exclusion criteria, including diagnostic procedures, for trials evaluating drugs intended to treat interstitial cystitis.
2. Discuss the key inclusion and exclusion criteria, including diagnostic procedures, for trials evaluating drugs intended to treat bladder pain syndrome.
3. For drugs intended to treat patients with interstitial cystitis, discuss:
 - a. How the key symptoms and signs should be defined and assessed
 - b. Acceptable endpoints for demonstrating clinical benefit
 - c. Other key trial design features that should be considered
4. For drugs intended to treat patients with bladder pain syndrome, discuss:
 - a. How the key symptoms and signs be defined and assessed
 - b. Acceptable endpoints for demonstrating clinical benefit
 - c. Other key trial design features that should be considered
5. When assessing efficacy for drugs intended to treat patients with interstitial cystitis and bladder pain syndrome, should clinical trials use:
 - a. One set of patient reported outcome (PRO) instruments for patients with interstitial cystitis and a different set of PRO instruments for those with bladder pain syndrome?
 - b. One set of PRO instruments used both for patients with interstitial cystitis and those with bladder pain syndrome?
6. When assessing drugs intended to treat interstitial cystitis and bladder pain syndrome, discuss:
 - a. The advantages of enrolling patients with interstitial cystitis and bladder pain syndrome in the same trial

- b. The disadvantages of enrolling patients with interstitial cystitis and bladder pain syndrome in the same trial

- 7. Should patients with interstitial cystitis and those with bladder pain syndrome be combined in clinical trials?



**Center for Drug Evaluation and Research
Division of Bone, Reproductive and Urologic Products
Office of New Drugs**

Clinical Perspective

B

I. INTRODUCTION

The purpose of this Advisory Committee (AC) meeting is to help the Food and Drug Administration (FDA) assist Sponsors in developing drugs for the treatment of interstitial cystitis and bladder pain syndrome (hereafter referred to as IC/BPS), a syndrome associated with pain and of unknown etiology, generally defined as pain perceived or attributed to the bladder with associated urinary symptoms. The FDA would like to move the field forward for drugs to become available to these patients. This briefing document summarizes the FDA’s current thinking regarding the overall clinical development program to support an indication for the treatment of these conditions, including some of the associated challenges.

We are seeking insight from this AC on the appropriate patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for these drugs. This AC meeting is intended to serve as a focus for continued discussions among the Division of Bone, Reproductive, and Urologic Products (DBRUP), pharmaceutical companies (Sponsors), the academic community, and the public.

II. BACKGROUND

A. *First Descriptions of IC*

AJ Skene described interstitial cystitis (IC) over 130 years ago in 1887 in patients with a chronic bladder disorder involving inflammation of the bladder wall.¹ Dr. Guy Hunner, an English physician, further described IC in 1918 as a symptom complex of bladder pain related to bladder filling and a pathognomonic cystoscopic finding of a bladder lesion, later termed a Hunner’s lesion² after his original description.³ Urologists diagnosed “classical IC” over the next half-century with these two factors:

- 1) Symptom complex of bladder pain related to bladder filling
- 2) A provoked cystoscopic finding of Hunner’s lesion

A Hunner’s lesion is a recognizable bladder mucosal reaction that appears on cystoscopy after hydrodistension of the bladder, and is integral to the diagnosis of “classical IC”.

¹ Skene AJC. *Diseases of Bladder and Urethra in Women*. Wm Wood, New York, 1887; 167 p.

² Hunner’s ulcer and Hunner’s lesion are interchangeable terms for the same bladder findings. Hunner’s lesion will be used in this document.

³ Hunner GL. Elusive ulcer of the bladder: further notes on a rare type of bladder ulcer with report of 25 cases. *Am. J. Obstet.* 1918; **78**: 374–95.

Worldwide, many urology centers still routinely perform cystoscopy with hydrodistension on IC/BPS patients for diagnosis. Multiple publications and clinical sites have published very similar standardized methods for cystoscopy and hydrodistension under anesthesia for diagnosis of Hunner's lesions. Briefly, these standardized methods^{4,5 6} are described as:

- 1) Fill bladder under gravity to 80 cmH₂O for 2-3 minutes
- 2) Establish total bladder capacity
- 3) Repeat filling of bladder with one or two additional milder hydrodistensions to 20-50% bladder capacity to incite the notable "waterfall" bleeding of the lesion and atypical edema after dilatation.

B. Evolution of Classical IC to IC by NIDDK Criteria

Beginning in the 1970s, there began a gradual acknowledgment that IC might encompass more diverse forms of the disorder than only patients with Hunner's lesions and could include patients with very similar symptoms but no Hunner's lesions.

In 1988, the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) developed research criteria for IC based on expert opinion from a consensus committee. These criteria became widely accepted for research and are often referenced as "the NIDDK criteria" or "the 1988 NIDDK IC criteria". The NIDDK criteria not only included the original classical IC patients with Hunner's lesions, but also included other patients with similar symptoms which expanded this patient population.

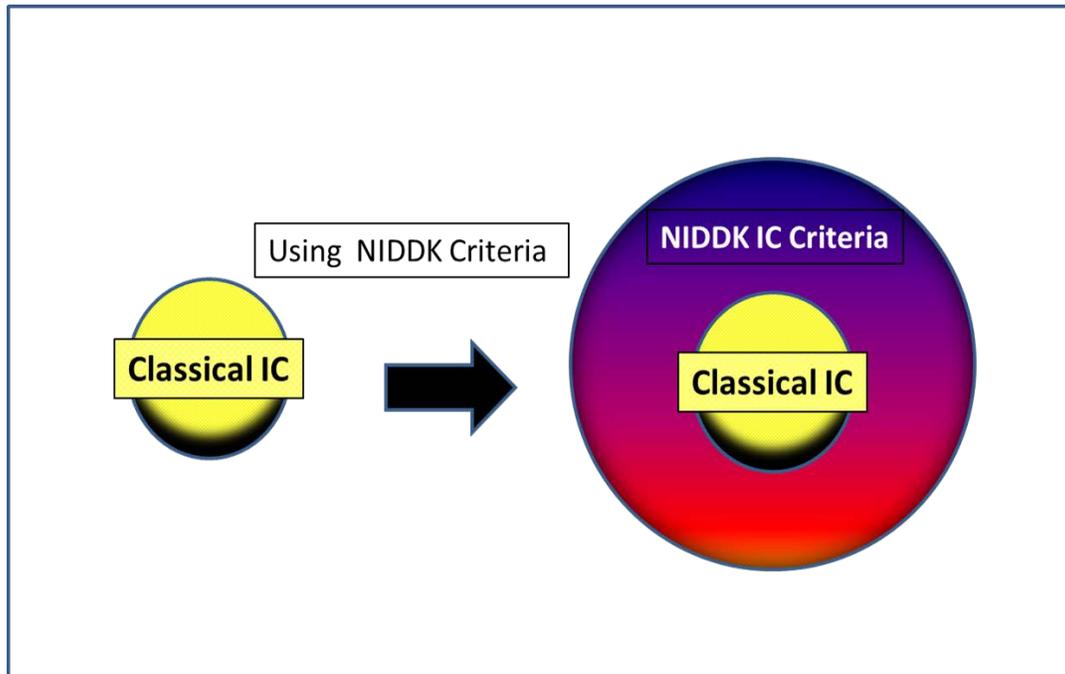
Figure 1 illustrates the expansion of the IC patient population using the NIDDK criteria into a more heterogeneous patient population:

⁴ Fall M, Logadottir Y, Peeker R. Interstitial cystitis is bladder pain syndrome with Hunner's lesion. *Int J Urology* (2014) 21 (Suppl 1), 79-82.

⁵ Nordling J, Anjum FH, Bade JJ, et.al. Primary evaluation of patients suspected of having interstitial cystitis (IC). *European Urology* 2004, 45:662-669

⁶ Campbell-Walsh Urology Tenth Edition, Ed. Wein AJ, Kavoussi LR, Novick AC, Partin AW and Peters CA. Saunders, 2011; 10th revised edition; 382.

Figure 1: Illustration of IC Patient Population Expansion using NIDDK Criteria



Patients were classified as meeting the NIDDK criteria if they had Hunner’s lesions - or if they met two out of four other “positive factors” – these factors are summarized below.⁷ In addition, patients could not meet any of the listed exclusion criteria to be considered IC patients by NIDDK criteria. Classical IC patients (i.e., those who had Hunner’s lesions) were encompassed within the greater NIDDK criteria patient population. Of note, the NIDDK criteria standardized the cystoscopy and hydrodistension method as: “*Bladder distension is defined arbitrarily as 80 cm. water pressure for 1 minute*” which is similar to current worldwide practices for cystoscopy and hydrodistension. The 1988 NIDDK criteria for IC are summarized below:

⁷ Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Work- shop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28–29, 1987. J Urol 1988; 140:203–6.

1988 NIDDK IC Research Criteria “NIDDK Criteria”

Automatic inclusion:

Hunner’s lesion

Positive factors (patients without Hunner’s lesion must meet at least 2 of the following four “positive factors” for inclusion):

- 1) Pain on bladder filling relieved by emptying
- 2) Pain (suprapubic, pelvic, urethral, vaginal or perineal)
- 3) Glomerulations (petechial bladder mucosal hemorrhages) on endoscopy
- 4) Decreased bladder compliance on urodynamics (office procedure to measure bladder pressures and capacity during filling and emptying)

Automatic exclusions:

- 1) <18 yrs. old
- 2) Benign or malignant bladder tumors; Radiation cystitis
- 3) Tuberculous cystitis, Bacterial cystitis, Vaginitis
- 4) Cyclophosphamide cystitis
- 5) Symptomatic urethral diverticulum
- 6) Uterine, cervical, vaginal, or urethral carcinoma
- 7) Active herpes infection
- 8) Bladder or lower ureteral calculi
- 9) Waking urinary frequency < 5 times in 12 hours
- 10) Nocturia < 2 times
- 11) Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (for example phenazopyridine hydrochloride)
- 12) Duration < 12 months
- 13) On urodynamics, having involuntary bladder contractions, bladder capacity > 400 cc, or absence of sensory urgency

The NIDDK criteria were intended to define a homogeneous and consistent IC population for research purposes. Although not the original intent, the NIDDK criteria also became widely accepted as criteria for clinical treatment of IC patients.

The NIDDK criteria expanded the IC patient population from only patients with classical IC with Hunner's lesion, to include patients without Hunner's lesion but who had similar symptoms and glomerulations or decreased bladder compliance by urodynamics. At the same time, the NIDDK criteria contained many automatic exclusions which emphasized that IC is a complex pain syndrome of unknown etiology and requires exclusion of patients who may have co-existing diseases or conditions that could account for the symptoms and signs. Furthermore, the European Society for the Study of Interstitial Cystitis (ESSIC) has suggested that Hunner's lesion is not a bladder mucosal ulcer but a distinctive inflammatory lesion provoked with hydrodistension which is not readily visible with simple cystoscopy.

C. Further Expansion of the IC Patient Population

After the 1988 NIDDK criteria were published, studies using these criteria found that even this expansion did not account for some patients with similar symptoms thus, it became apparent that up to 60% of patients who had bladder pain syndromes were not being identified or treated.⁸ Furthermore, researchers have since demonstrated that some of the NIDDK criteria are not specific for IC such as bladder glomerulations, which can be found in other bladder inflammatory disorders.

In the intervening years since the release of the NIDDK criteria, clinical IC management has evolved and expanded to include patients with and without obvious bladder inflammation, encompassing a very heterogeneous patient population, hereafter referred to as IC/BPS. Concurrently, cystoscopy and other diagnostic procedures are considered clinically unnecessary in many U.S. clinical practices as bladder lesions are no longer an absolute criterion to establish a clinical bladder pain syndrome diagnosis for beginning treatment. Patient comfort, burden, and controlling medical care costs became important considerations.

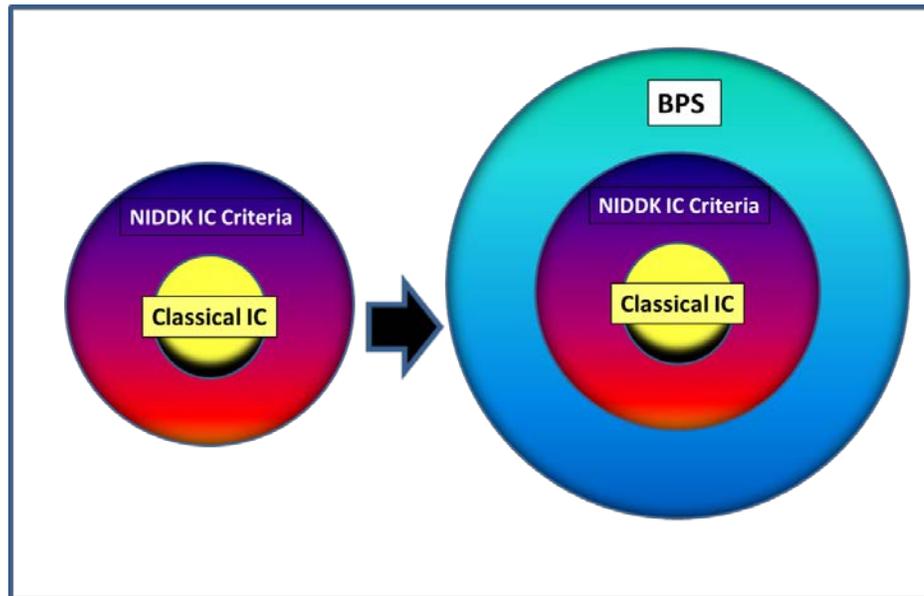
Because of this widening concept of bladder pain syndrome, IC clinical diagnosis evolved and Hunner's lesions or other bladder inflammatory lesions were no longer required for patients to be included in this expanded clinical IC/BPS patient population.

But, the converse remained true in that Hunner's lesions remain a distinct, identifiable, pathognomonic finding for classical IC, so these patients continue to be an important subset of this expanded IC/BPS patient population. The expanded patient population now includes the original classical IC patients with Hunner's lesions, NIDDK criteria patients, and other patients who do not

⁸ Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L, the diagnosis of interstitial cystitis revisited: Lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999, Feb; 161(2):553-7.

fulfill any of the criteria but have similar symptoms. The following Figure 2 schematically illustrates the expanded and inclusive patient population that comprises bladder pain syndrome (BPS).

Figure 2: Expansion of the NIDDK IC Patient Population into IC/Bladder Pain Syndrome (IC/BPS)



D. Continued Relevance of the Classical IC Patient Population in Clinical Practice and Clinical Trials

Since the first description in 1918, Hunner’s lesions have been widely accepted as diagnostic for IC. It is a pathognomonic finding which defines “classical IC” along with bladder symptoms and may comprise a more homogeneous group of patients. Multiple studies have demonstrated that clinical symptoms alone without cystoscopy and hydrodistension cannot distinguish patients with Hunner’s lesions from patients without lesions. Additionally, no studies have confirmed that patients without Hunner’s lesions progress into patients with Hunner’s lesions which supports a separate and distinct patient population for classical IC.

Classical IC patients with Hunner’s lesion are reported to be older, have smaller bladder capacities when measured under anesthesia, have biopsies with mast cells across all layers of the bladder wall, and have higher rates of bladder frequency symptoms when compared to patients without bladder lesions. It has been suggested that IC patients with Hunner’s lesions may also have a greater severity of disease and may have higher rates of fibrotic bladder wall present at diagnosis. Although the rates of females to males with IC is disproportionately high (at least 5 – 10 females: 1 male), men who are diagnosed with IC have higher rates of Hunner’s lesions than women.

Importantly, treatment of Hunner's lesions with fulguration or transurethral resection is reported to be more successful than in other forms of IC/BPS without Hunner's lesions. Clinicians have reported up to 90% relief of symptoms in 50% of patients for up to three years.^{9,10, 11} . Thus, the classical IC patient population may be a distinctly identifiable patient population who, without proper diagnosis, may not have optimal and timely therapy.

E. Worldwide Classical IC rates

Interestingly, Hunner's lesion rates differ considerably across different regions of the world but there is consensus that the finding of a Hunner's lesion is pathognomonic of IC. The Interstitial Cystitis Data Base (ICDB) found that 10.5% of IC/BPS patients who had cystoscopy with hydrodistension had Hunner's patches (lesions)¹². Recent authors have estimated Hunner's lesions at 3-20% of IC/bladder pain syndrome cases in the U.S.¹³ Anecdotally, some U.S. clinicians have stated publicly that they doubt that Hunner's lesions exist, having never seen lesions in clinical practice.

Contrary to U.S. clinicians, European and Asian (Japan and Taiwan) clinicians publish Hunner's lesions rates of 30% - 50% of their bladder pain patients.¹⁴ There has been no clear reason why there are such different rates of Hunner's lesions across the world and U.S. researchers have postulated a genetic difference as many of these studies were in patient populations with more homogeneous genetic backgrounds than the diverse U.S. population or different tertiary medical referral systems where one hospital or clinic receives the most severe cases of IC. However, cystoscopy with hydrodistension under anesthesia and accompanying bladder biopsies is still widely practiced in the studies in Europe and Asia, potentially increasing the likelihood of identifying Hunner's lesions.

The questions of whether there are different patient populations within the IC/BPS population and/or whether increased instrumentation results in the differences between the U.S. and other regions in identifying lesions have yet to be determined.

⁹ Fall M. Conservative management of chronic interstitial cystitis: transcutaneous electrical nerve stimulation and transurethral resection. *J Urol*. 1985; 133:774–8.

¹⁰ Peeker R, Aldenborg F, Fall M. Complete transurethral resection of ulcers in classic interstitial cystitis. *Int Urogynecol J*. 2000; 11:290–5.

¹¹ Chennamsetty A, Khourdaji I, Goike J, Killinger K, Girdler B, Peters KM. Electrosurgical Management of Hunner Ulcers in a Referral Center's Interstitial Cystitis Population *Urology*, Volume 85, Issue 1, 2015, pp. 74-78

¹² Simon LJ, Landis, JR, Erickson DR, Nyberg LM, The interstitial Cystitis Data Base Study: Concepts and Preliminary Baseline Descriptive Statistics, *UROLOGY* 49 (Supplement 5A), May 1997.

¹³ Koziol JA, Adams HP, Frutos A. Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. *J Urol* 1996; 155:87–90.

¹⁴ Fall, M., Logadottir, Y. and Peeker, R. (2014), Interstitial cystitis is bladder pain syndrome with Hunner's lesion. *Int J Urol*, 21: 79–82.

F. Current IC/BPS Definitions

Worldwide harmonization for IC/BPS has coalesced around similar clinical definitions from multiple groups with some notable differences. The following tenants are generally in the current American and European definitions. These same tenants were included in the NIDDK criteria:

- Chronic pain or discomfort related to the bladder
- Accompanying urinary symptoms
- Exclusion of other diseases or disorders with similar presentations

In 2008, the European Society for the Study of Bladder Pain Syndrome (ESSIC) developed a definition for IC which later expanded to BPS and included all the above tenants:

*“Chronic pelvic pain (> 6 months duration), pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of symptoms must be excluded.”*¹⁵

The 2014 American Urological Association (AUA) guidelines use a similar definition but designate other urinary symptoms as lower urinary tract symptoms without mentioning specific symptoms such as persistent urge to void or frequency.¹⁶ The AUA guidelines notably differ from other definitions in specifying pain duration for a shorter time of > 6 weeks rather than 6 months as in the ESSIC definition:

“An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes.”

Of note, the American and European definitions are silent on objective bladder findings for inclusion into the IC/BPS population.

The East Asian Guidelines (2011/ 2016) differ significantly from the American and European definitions by including only patients with bladder findings of either Hunner’s lesions or bladder glomerulations after hydrodistension. Other differences in the East Asian Guidelines are that bladder pain is not necessary for inclusion in the definition of IC/BPS and overactive bladder syndrome is included within the definition of IC/BPS.¹⁷

¹⁵ van de Merwe JP, Nordling J, Bouchelouche P *Et al.* Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur. Urol.* 2008; **53**: 60–7.

¹⁶ American Urological Association (AUA) Clinical Guidelines: Diagnosis and Treatment Interstitial Cystitis/ Bladder Pain Syndrome Published 2011: Amended 2014; available at: [http://www.auanet.org/guidelines/interstitial-cystitis/bladder-pain-syndrome-\(2011-amended-2014\)](http://www.auanet.org/guidelines/interstitial-cystitis/bladder-pain-syndrome-(2011-amended-2014))

¹⁷ Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH *et al.* Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. *Int J Urol* 2009; 16(7):597–615.

In summary, the current clinical definitions for IC/BPS in the U.S. and Europe are aligned and include pain or discomfort related to the bladder, accompanying urinary symptoms such as frequency, nocturia, and other lower urinary tract symptoms and excludes other diseases or conditions that may explain the findings such as endometriosis, urinary tract carcinoma, overactive bladder, ongoing urinary tract infection, and other chronic pain syndromes etc.

Currently, IC/BPS encompasses a very heterogeneous population. The National Institutes of Health (NIH) has not published updated criteria since the 1988 NIDDK criteria although the field has expanded to include many more patients with similar clinical presentations. To date, there are no established sensitive or specific biomarkers to distinguish different phenotypes; thus, IC and BPS remain a complex pain syndrome of unclear cause.

III. Considerations Regarding Development Programs for IC/BPS

A. Nonclinical Pharmacology

There is no established animal model of IC/BPS. Investigational drugs and biologics proposed for this indication are often tested in early development in animal models of chronic inflammation and chronic neuropathic pain. In addition, studies of bladder inflammation and bladder function in animals are commonly submitted. Although mechanistic studies of these types may prove useful for initial dose setting or in hazard assessment, no evidence is available to indicate that any one nonclinical model is a superior predictor of efficacy.

B. General Clinical Considerations

Early clinical development generally includes dose-finding in the target population to ensure that the most appropriate dosing regimen(s) are selected for further study. We recommend that Sponsors take at least two of the most promising doses into Phase 3 testing. See the following for additional information regarding dose response:

- The Fit-for-Purpose Initiative dose-finding tool MCP-MOD (Multiple Comparison Procedure-modeling), a statistical methodology for dose response¹⁸
- The Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

¹⁸ See the Drug Development Tools: Fit-for-Purpose Initiative Web page at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm>. See also Bretz F, Pinheiro JC, and Branson M, 2005, Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies, *Biometrics*, 61(3), 738-748.

- The Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- The International Conference on Harmonization (ICH) Guidance for Industry: E4 Dose-Response Information to Support Drug Registration

If the investigational drug contains two or more drug components, the combination drug rule is generally addressed by demonstrating that: (1) each component makes a contribution to the claimed effects; and (2) the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for the intended patient population.¹⁹

Exploration of new patient reported outcome (PRO) instruments or novel diagnostic measures in early development may allow correlation of results obtained from these modalities with dose-response findings. It is important for Sponsors to have early and regular discussions with the FDA regarding trial design to help ensure the use of adequate and interpretable assessments of treatment benefit. More information on the development of PRO instruments is discussed in the Clinical Outcome Assessment (COA) section of this briefing document.

C. Specific Considerations for IC/BPS Efficacy Trials

Generally, evidence from two adequate and well-controlled trials is recommended to establish efficacy. Randomized and placebo-controlled trials are considered optimal designs for IC/BPS trials, but trials in this area do not need to be identical in design. Depending on the mechanism of action of a drug, 24 weeks of blinded treatment appears to be optimal to allow demonstration of effect onset and persistence of treatment given that the symptoms appear to fluctuate over time. Timing of effect is especially critical for drugs intended for “as needed” use by patients to ensure that the efficacy is captured during the period when the drug is expected to have activity.

It is possible that future therapies could involve a novel companion diagnostic procedure or device. For those development programs, contemporaneous development of the drug and the diagnostic is preferable such that the clinical performance of the diagnostic can be established using data from the drug development program.

¹⁹ 21 CFR 300.50(a)

D. Considerations on Trial Population(s)

1. Appropriate Target Population(s)

It is important that clinical trials in this area focus on a well-defined patient population. This is particularly relevant for IC/ BPS patients, where there appears to be a heterogeneous patient population that is impacted by how extensively other confounding conditions or diseases are excluded. Given the heterogeneity, one approach could be to evaluate subjects using standardized, provoked cystoscopy with hydrodistension and bladder biopsies using specialized bladder pathology laboratories to separate the population with classical IC from ones without Hunner's lesions or any bladder lesions. In addition, trials could have inclusion and exclusion criteria that rigorously exclude confounding conditions or diseases. Hunner's lesions are best captured by pictures or other video equipment. These images could be used to support consistency of diagnosis across sites.

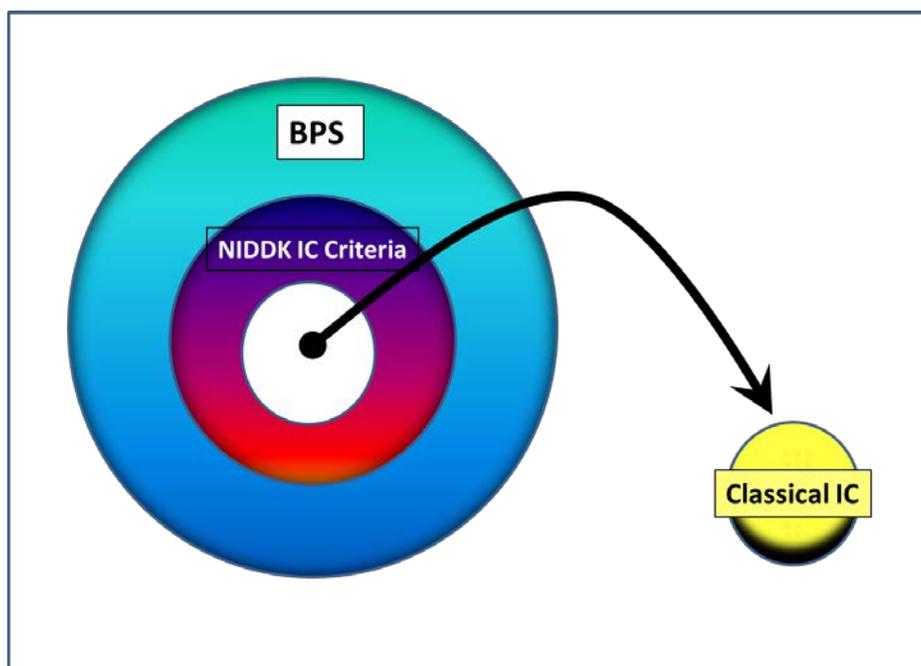
Clearly, studying patients only with classical IC would reflect a well-defined population as these patients have pathognomonic findings. The advantage of studying only classical IC is that the homogenous population will reduce variability and make it more likely to detect a treatment effect, if one exists. However, this approach will narrow the target population and could potentially exclude other patients who could also benefit from treatment.

Alternatively, Sponsors could include the classical IC patient population in general IC/BPS clinical trials if the investigational drug is expected to have beneficial effects on the classical IC as well as BPS populations. The presence or absence of classical IC by hydrodistension should be documented in enrolled patients so that subgroup analyses can evaluate treatment effects among those with classical IC and those without classical IC.

If patients with classical IC are included in the trials, Sponsors should consider how currently available treatments such as fulguration by electrocautery and laser will be incorporated when designing the trials.

Figure 3 schematically illustrates the separation of the classical IC patient population who have currently available treatment options from the expanded IC/BPS patient population.

Figure 3: Schematic Illustration of Separation of IC/ BPS Target Population:



For the purposes of establishing efficacy in the IC/BPS population, it is important to evaluate a population that reflects the demographic characteristics of the US population. Significant differences in the diagnosis, practice of medicine, rates of classical IC, and expectation of treatment effects in different geographical regions are well recognized. These differences likely will affect the generalizability of efficacy data from patients outside the United States to the U.S. population. Therefore, we recommend that the efficacy trials be conducted primarily in the U.S. and Canada. If the development program includes trials conducted in other geographical regions, those data at a minimum, can be used to support safety.

2. Eligibility Considerations

IC/ BPS remains a diagnosis of exclusion. The study protocol should specify the inclusion and exclusion criteria for participants across study sites. It is important to rigorously capture baseline history, physical exams, laboratory studies, and other procedures as needed such as urodynamics, office cystoscopy, laparoscopy, and radiological studies to rule-out other diseases and disorders. Documentation from procedures such as cystoscopy with hydrodistension and bladder biopsies is important.

The development program could evaluate men and women in separate trials or within the same trial. If studied in the same trial, randomization of subjects stratified by sex would be an important consideration to ensure that the treatment groups are reasonably balanced with regard to the

number of men and women. This is potentially important as there may be differences in etiologies and treatment responses between men and women, which could in turn affect the benefit/risk assessment. Note that across all drug development programs, the FDA routinely requires subgroup analyses based on age and race.²⁰

Clinical trials for IC/BPS should enroll patients with clinically significant symptoms at baseline (e.g. minimum severity of bladder pain symptoms with accompanying urinary symptoms) so that there is the potential for clinically meaningful improvement. We also recommend the patients have an adequate duration of symptoms (e.g. > 6 months of pain) prior to enrollment to ensure that patients do not have other confounding diseases or disorders with similar presentations.

Eligibility criteria do not need to be identical in all trials and different clinical trial designs can be considered.

E. Clinical Outcome Assessment Instruments

Clinical outcome assessment instruments are discussed in the COA section of this briefing document and are appropriate for symptomatic conditions such as IC/BPS.

F. Trial Endpoints

Efficacy assessments from adequate and well-controlled trials provide a basis for determining whether there is substantial evidence to support the claims of effectiveness for a new drug.²¹ Endpoint selection needs to reflect the primary symptoms experienced by patients (e.g., bladder pain on filling which is relieved by emptying, pain perceived to be related to the bladder, and lower urinary tract symptoms such as frequency, nocturia, etc.).

1. Considerations on Efficacy Endpoints

Efficacy analyses need to focus on establishing a meaningful treatment benefit that is both clinically and statistically significant. Key to the analyses is selecting a clinically meaningful change for each of the measures used in the trials with supportive justification of the selected clinically meaningful threshold to define treatment success. In clinical programs for drugs intended to treat IC/ BPS, one possible approach could be to demonstrate a change from baseline for a bladder pain symptom (e.g., pain perceived to be from the bladder, bladder pain which increases with bladder filling and relieved by emptying, etc.) as the primary endpoint. A key secondary endpoint could assess changes in other urinary tract symptoms such as urinary frequency. Another possible approach is to have bladder pain and a key urinary tract symptom (e.g., frequency, nocturia, etc.) as co-primary endpoints with other lower urinary tract symptoms as key secondary endpoints.

²⁰ 21 CFR 314.50(d)(5)(v)

²¹ 21 CFR 314.126

As it is likely that the pivotal trials will include a pain endpoint, and rescue medication will confound this assessment, it will be important to prespecify in the protocols and statistical analysis plan as to how the frequency and type(s) of rescue medication will be handled.

Finally, there are concerns with use of generalized abdominal pain or lower abdominal pain for this population as the primary efficacy endpoint. A generalized pain endpoint is likely insufficient to be a sole endpoint to distinguish pain from other overlapping diseases/disorders of the lower abdomen including vulvodynia, chronic pelvic pain, and endometriosis. In addition, use of pain as the primary endpoint without key secondary endpoints may miss worsening of other symptoms important to the IC/BPS patient population, such as increased voiding. Finally, as this disorder has pain flares, it is necessary to capture sufficient treatment duration (e.g. 24 weeks) to ensure that relief is sustained.

A responder analysis demonstrating improvement in IC/BPS symptoms could be considered. Responder definitions need to be prospectively described and justified before initiation of the trial and be based on data that establish that the identified change is clinically important. Responder definitions can be derived using anchor-based methods.

G. Safety Considerations

1. Safety Evaluation for IC/BPS subjects

Patients with IC and/or BPS are likely to use a drug product on a chronic basis (defined as continuous or intermittent use for at least 6 months during a lifetime). For this reason, the International Conference on Harmonization (ICH) Guideline: *E1-The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* is a useful starting point in initial estimation of the size of the overall safety database. Larger exposures may be needed to assess specific safety concerns identified during drug development.

Additional studies to address specific characteristics of the drug, such as its pharmacology, safety signals that emerge during drug development, or the intended route of administration may be necessary. For example, a new molecular entity would need an assessment of cardiac repolarization potential.²²

²² See the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.

2. Pharmacokinetic/Pharmacodynamic Considerations

If feasible, pharmacokinetic assessment of blood samples collected during clinical trials will be helpful in correlating efficacy or safety findings with systemic exposure.



**Center for Drug Evaluation and Research
Clinical Outcome Assessments Staff
Office of New Drugs**

A Regulatory Approach to Clinical Outcome Assessment Review for Drug Development

C

1. Introduction and Background

The patient perspective is an important part of the medical product development process. FDA values the use of patient input to help foster the development and availability of safe and effective drugs. One way to include patient input is in the selection of clinical outcomes. Including clinical outcomes that are meaningful to patients can profoundly influence medical product development by ensuring the patient voice is captured. Patient input also helps to ensure the appropriateness of assessments used to collect trial data and helps to measure how patients feel and function as a result of their disease and its treatment in a valid and reliable manner. As a result, information on clinical benefit can be included in labeling²³ in a way that is accurate and not misleading.

This section of the briefing document provides an overview of how FDA reviews clinical outcome assessments for their adequacy to support labeling claims. General principles related to outcome measurement in clinical trials for regulatory use are described herein, while more detailed principles related to evaluation of patient-reported outcome assessments can be found in the *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, which is included in the Appendix and is herein referred to as the FDA Patient-Reported Outcome Guidance. Although this specific guidance was developed for patient-reported outcome assessments, many of the principles are appropriate to apply to any clinical outcome assessment type. It is important to note that FDA exercises flexibility where appropriate and feasible within the context of instrument development and its application in medical product development. Early planning and discussion with FDA is critical to ensure clinical trial assessments are fit-for-purpose and measure what is most important to patients.

2. Measurement of Clinical Benefit with Clinical Outcome Assessments

An important aspect of a drug's development is the demonstration of clinical benefit and how that benefit is measured. Clinical benefit is a positive, clinically meaningful effect of an intervention on how an individual feels, functions, or survives. The FDA utilizes outcome assessments to determine whether or not a drug has been shown to provide clinical benefit to patients. When clinical benefit is demonstrated in registration trials, a description of that benefit can be provided in labeling in terms of the concept or outcome measured (i.e., the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture).

²³ Labeling, as used in this document, refers to the information about an FDA-approved medical product intended for the health care provider to use in treating patients. See 21 CFR 201.56 and 201.57 for regulations pertaining to prescription drug (including biological drug) labeling. Section 201.56 specifically describes the need for labeling that is not false or misleading.

An overview of the clinical outcome assessment types are shown in Table 1.²⁴

Table 1. Overview of Clinical Outcome Assessment Types

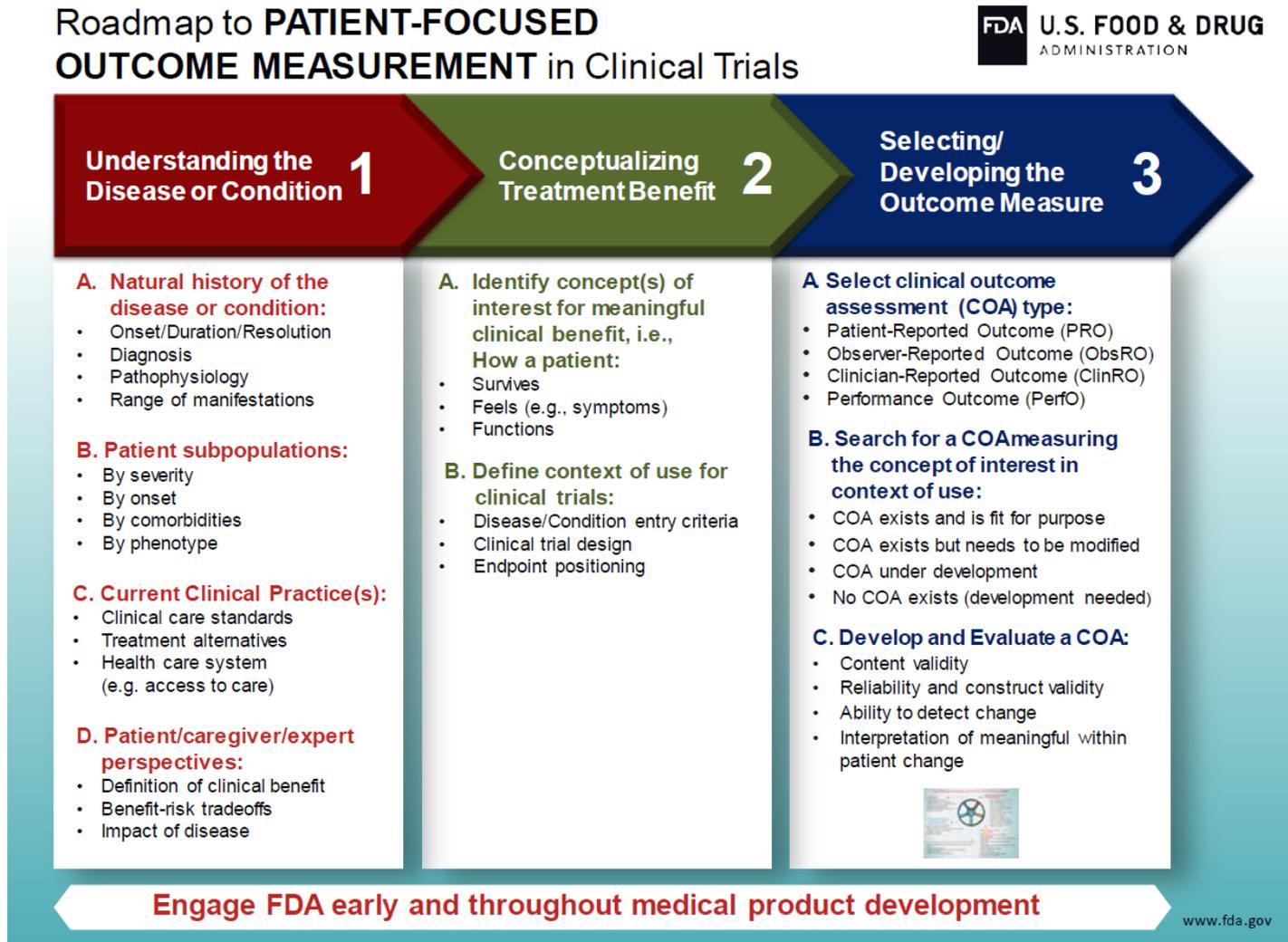
Clinical Outcome Assessment Type	Definition	Example
Clinician-reported outcome	A measurement based on a report that comes from a trained health care professional after observation of a patient’s health condition.	<ul style="list-style-type: none"> • Psoriasis Area and Severity Index (PASI) • Hamilton Depression Rating Scale (HAM-D)
Patient-reported outcome	A measurement based on a report that comes directly from the patient about the status of the patient’s health condition without interpretation of the patient’s response by a clinician or anyone else.	<ul style="list-style-type: none"> • Pain Numeric Rating Scale • Minnesota Living with Heart Failure Questionnaire
Observer-reported outcome	A measurement based on a report of observable signs, events, or behaviors related to a patient’s health condition by someone other than the patient or a health care professional.	<ul style="list-style-type: none"> • Acute Otitis Media Severity of Symptoms Scale (AOM-SOS) • Face, Legs, Activity, Cry, Consolability scale (FLACC)
Performance outcome	A measurement based on a standardized task performed by a patient, administered and evaluated by an appropriately trained individual or independently completed and intended to assess or infer patient capabilities relevant to their day-to-day functioning.	<ul style="list-style-type: none"> • Measures of gait speed (e.g., timed 25 foot walk test) • Measures of memory (e.g., word recall test)

²⁴ Definitions of clinical outcome assessment types were retrieved from the BEST (Biomarkers, Endpoints, and other Tools) Resource Glossary Website: <http://www.ncbi.nlm.nih.gov/books/NBK338448/>

3. Patient-Focused Outcome Measurement in Clinical Trials

In approaching selection or development of a clinical outcome assessment, it is important to have an adequate understanding of the disease under investigation and conceptualization of clinical benefit from the targeted treatment effect. Figure 4 outlines the general approach to patient-focused outcome measurement.

Figure 4. Roadmap to Patient-Focused Outcome Measurement in Clinical Trials



3.1. Understanding the Disease

While disease understanding is critical to drug discovery and development research, it is also critical to clinical outcome assessment selection and development. There are multiple elements to consider when exploring a disease area, which include but are not limited to, the natural history of the disease, patient subpopulations, current clinical practice, and patient/caregiver perspectives.

Knowledge of the natural history of a disease enables researchers to identify opportunities for measurement of clinical outcomes. There may be different stages of a disease with features that might be more measurable using a clinical outcome assessment. Because the spectrum of disease can include asymptomatic and symptomatic stages, identifying patients within an appropriate stage (e.g., patient subpopulations) is another key element for consideration of a clinical outcome assessment. It is also important to consider any expected variations in experiences of patients across different subpopulations when selecting or developing clinical outcome assessments.

In addition to understanding the natural course of a disease and patient subpopulations, there should be awareness of how the disease is currently treated in clinical practice, as this may influence clinical trial entry criteria, design, and outcome measurement.

Lastly, the literature and other data sources, expert input, and patient/caregiver input should also be evaluated when considering a clinical outcome assessment. Gathering input from these multiple streams can provide comprehensive insight on aspects of the disease (e.g., symptom burden, disease impacts on daily functioning) that are important to patients and clinicians and capable of demonstrating change with treatment.

3.2. Conceptualizing Clinical Benefit

As stated in Section 2, clinical benefit is a positive, clinically meaningful effect of an intervention on how an individual feels, functions, or survives. As such, clinical outcome assessments are often used to measure how a patient feels or functions.

To be able to select or develop an appropriate clinical outcome assessment, the trial outcome concepts must be known or hypothesized based on scientific evidence. Clinically important outcomes of an intervention may include core signs, symptoms, or aspects of functioning (e.g., physical function, such as activities of daily living) that define the disease in the targeted population.

In addition to recognizing the concepts of interest, the context of use (e.g., type of COA proposed, target clinical trial patient eligibility criteria, clinical trial design, placement of the COA in the endpoint testing hierarchy) should be clearly defined in order to select or develop an appropriate clinical outcome assessment.

Once the concept of interest and context of use is known and trial objectives have been established, it is important to consider how the clinical outcome assessment will be incorporated into the planned trial endpoint(s) and its endpoint hierarchy. An endpoint is a precisely defined variable (e.g., clinical outcome assessment score) intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other information, as applicable, such as how multiple assessments within an individual are to be combined.²⁵

3.3. Selection or Development of a Clinical Outcome Assessment

The process of selecting, modifying, or developing a clinical outcome assessment for a clinical trial depends on having a concept of interest that represents clinical benefit in the target population. Sponsors should plan early in medical product development whether they plan to use clinical outcome assessments in their clinical trials, as well as engage the FDA in a discussion about their clinical outcome assessment measurement strategy.

Determining the type of clinical outcome assessment is dependent on the concept of interest, context of use, and planned trial endpoint(s). The detectability of a concept (e.g., unobservable vs. observable) is a key determinant in selection of clinical outcome assessment type. Unobservable concepts are generally subjective feelings and sensations (i.e., symptoms). Because only the affected individuals can directly report on their feelings and sensations, a patient-reported outcome assessment would be the most appropriate tool to measure unobservable concepts.

Observable concepts could be signs, events, behaviors, or verbal expressions by the patient. If self-report of signs and/or symptoms is not feasible, such as in infants, young children, and the cognitively impaired, an observer-reported outcome assessment could be a tool of choice. In the case that clinical judgment is required to interpret an observation, a clinician-reported outcome assessment is the most appropriate tool. It is important to note that a proxy (a person reporting as if they were the patient) is not sufficient and the use of proxy-reports is discouraged. When it would be useful to observe an actual demonstration of defined tasks demonstrating functional performance in the clinical and/or simulated setting, a performance outcome assessment may be the selected tool.

For symptomatic conditions or conditions associated with functional impairment, patient-reported outcome assessments are generally used as they provide direct evidence of how patients feel and function. However, when patients cannot self-report, reports based on observation of signs, events and/or behaviors that are reflective of how the patient feel or functions are often useful.

²⁵ Definition of an endpoint was retrieved from the BEST (Biomarkers, Endpoints, and other Tools) Resource Glossary Website: <http://www.ncbi.nlm.nih.gov/books/NBK338448/>

Sponsors may consider leveraging and building upon existing clinical outcome assessments, literature, and data to fit the specific needs of the research question(s) when planning to use a clinical outcome assessment for a clinical trial. Sponsors should consider working with the FDA to determine the adequacy of existing clinical outcome assessment(s) to measure the concepts of interest.

Whether an existing tool is used or a tool is newly developed, FDA reviews the tool's measurement properties. Refer to Section 4 for more information on what measurement properties are evaluated by FDA.

4. Good Measurement Principles

FDA aims to provide a systematic way to ensure that patients are represented and patient perspectives are considered in the selection/development and use of clinical outcome assessments to collect the patient experience in medical product development. Some general principles to determine whether the clinical outcome assessment tool is fit-for-purpose include the following:

- The clinical outcome assessment tool is appropriate for its intended use (e.g., study design, patient population)
- The clinical outcome assessment tool validly and reliably measures concepts that are clinically relevant and important to patients
- The clinical outcome assessment data can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., well-defined)²⁶

There are also evidentiary standards to document clinical benefit and labeling. Within these standards, there are regulations for clinical outcome assessments that require methods of assessment of subjects' response to be well-defined and reliable in an effort to avoid labeling statements that may be potentially false or misleading.²⁷ When FDA evaluates clinical outcome assessments, it looks for tool characteristics that are consistent with the regulations.

The FDA Patient-Reported Outcome Guidance describes good measurement principles when evaluating whether an assessment is fit-for-purpose.²⁸ Although this guidance was developed for

²⁶ If the clinical outcome assessment is appropriately applied in medical product development.

²⁷ See 21 CFR 314.126 for regulations pertaining to assessment of subjects' responses. See 21 CFR 201.56 and 201.57 for regulations pertaining to prescription drug (including biological drug) labeling. Section 201.56 specifically describes the need for labeling that is not false or misleading.

²⁸ See the following FDA Web site:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf>

patient-reported outcome assessments, many of the principles are appropriate to apply to any clinical outcome assessment type. This guidance provides an optimal approach to patient-reported outcome assessment development, but it is understood that flexibility and judgment are needed in order to meet both regulatory standards as well as the practical demands of medical product development.

FDA looks at the following important measurement properties of a clinical outcome assessment:

- The assessment should directly/indirectly measure the most important concepts to the patient for that disease.
- The assessment's content/concepts should be well-defined.
- The assessment should generate consistent and reproducible data (reliability).
- The assessment should measure what it purports to measure (validity).
- The assessment should be sensitive to detect change whether it is improvement or deterioration (ability to detect change); and
- The assessment's score change should be interpretable and reflect meaningful changes.

Refer to the FDA Patient-Reported Outcome Guidance for more details on the measurement properties of a tool.

5. Considerations When Using Clinical Outcome Assessments in Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)

For clinical trials in patients with IC/BPS, it will be important to talk to patients who are similar to the clinical trial population (i.e., similar inclusion and exclusion criteria) to ensure the instrument is fit for purpose. Patient engagement will also allow a better understanding of how patients describe their disease symptoms and impacts in their own words, as well as which attributes of the concepts are most meaningful (e.g., intensity versus frequency). Understanding the trial population will confirm whether the questions in the instrument will capture meaningful information and help describe clinical benefit. Another key consideration is measuring concepts that are cross-culturally relevant if the clinical outcome assessment tools will be used multinationally.

5.1. Considerations When Selecting Clinical Outcome Assessment Trial Endpoints for IC/BPS

Based on the Clinical Perspective portion of this briefing document, endpoints that should be considered for this condition are related to the symptoms of IC/BPS. Consider evaluating the core symptoms that define the disease in the targeted population and are most important and bothersome to the patient, for which the treatment is expected to have an effect. The clinical trials should include patients who have sufficiently severe symptoms at baseline so that there is the potential for clinically meaningful improvement.

Another potential endpoint for consideration may be related to physical functioning or patients' abilities to carry out important and meaningful day-to-day activities that require physical effort (e.g., interference with self-care, domestic activities). However, the aspects of functioning measured would need to be related to the disease and amenable to a treatment effect. The measurements of functioning should generally be limited to the core aspects of functioning that can be attributed to the disease in the targeted population, and there should be a sufficient level of functional impairment to observe a meaningful clinical response.

5.2. Considerations for Assessment of Pain in IC/BPS

Factors to consider when using clinical outcome assessments to assess pain in IC/BPS:

- Pain type and location
 - Obtain patient input to understand how to describe and qualify pain to select or develop items (i.e., questions) for assessment.
 - Inclusion of the key pain characteristics (e.g., localization of pain in the item stem) to ensure patients are reporting on the pain intended for treatment.
 - Inclusion of pictures with location of pain circled to help focus the patient and increase consistency across patient responses.

- Recall period/Frequency and timing of assessment
 - Select a recall period that is suitable for how pain presents in the target population (e.g., variability, duration (chronic vs. episodic), frequency, and/or intensity).
 - The frequency of PRO assessment should correspond with the specific research questions being addressed, length of recall asked by the instrument's response options, demonstrated instrument measurement properties, the disease or condition's natural history (e.g., symptom flare-ups), the treatment's nature, and planned data analysis.

- Analgesic use
 - Capture patients' concomitant analgesic use (including analgesic type) at baseline and during the trial, and ensure that the prespecified analyses take into account rescue medication use, which can confound the results.

6. Summary on Clinical Outcomes Assessments for IC/BPS Patients

Patient input in combination with knowledge of disease and conceptualization of clinical benefit informs selection or development of a clinical outcome assessment. The clinical outcome assessments and “reporters” (i.e., patients, observers, clinicians) used in a clinical trial should be appropriate to the particular context of use. Furthermore, the assessment should be fit-for-purpose and measure the most important concepts to patients for the disease under investigation. Input from patients and scientific experts combined with examination of scientific evidence (e.g., natural history of disease and knowledge of the medical product) ultimately help determine what should be measured to provide evidence of clinical benefit, how best to measure concepts in a clinical trial, and the magnitude of change that will reflect meaningful improvement.

It is highly encouraged that Sponsors interested in developing clinical outcome assessments for IC/BPS patients have early interactions with FDA to obtain feedback on their clinical outcome assessment measurement strategy. Although there are evidentiary standards that are used to

determine whether a clinical outcome assessment is adequate for use in clinical trials, FDA maintains flexibility in our evaluation of evidence and takes into account feasibility and practicality.