



Regulatory Perspective: Clinical Trials for Interstitial Cystitis

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DISCLAIMER

- The opinions in this presentation are my own and do not represent the views of the FDA or of the Division of Bone, Reproductive, and Urologic Products

IND Content



IND Needs to Include the following:

- Protocol(s)
- Chemistry, Manufacturing and Control Information
- Pharmacology and Toxicology Information
- Previous Human Experience with the Investigational Drug

Complete requirements contained in: [21 CFR 312.22](#) and [21 CFR 312.23](#)

Initial IND- 30-Day Safety Review

- FDA receives > 1000 initial INDs per year
- Sponsors must wait 30 days before initiating the clinical study.
- FDA reviews the following issues:
 - 1) Are the risks to the clinical participants in the trial acceptable?
 - 2) Is there adequate safety monitoring?
 - 3) Has the sponsor submitted sufficient supporting data to establish relative safety of the proposed clinical dose?
 - 4) Is the trial design adequate to meet its intended objective(s)?

NDA Review Process

- A Sponsor submits an NDA for permission to market a drug in the US for a specific indication.
- Multi-Disciplinary Review
- Submission can be > 10,000 pages for a single drug
- Stringent criteria for assessing efficacy based on 21 CFR 314.126
- Safety review integrates information from nonclinical studies, early clinical studies, and phase 2 and phase 3 clinical trials.

NDA Safety Review

- 300-600 patients exposed for three to six months at clinical use dosage level to detect AE frequency of 0.5 to 5.0%
- Approximately 100 patients exposed for one year
- Total number of patients treated with investigational drug anticipated to be about 1500.
- These are minimum exposures for drugs that treat chronic, non-life-threatening conditions and depending on circumstances larger exposures may be needed

ICH E-1

Why Do Phase III Trials Fail?

Between 2000 and 2012, FDA approved 50% of the 302 new molecular entity applications during the first submission. Remaining had deficiencies.

Efficacy deficiencies alone **31.8%**

Safety deficiencies alone **25.8%**

Safety and efficacy **27.2%**

Chemistry, manufacturing, and controls (CMC) and/or labeling **15.2%**

For details, see Sacks LV, Shamsuddin HH, Yasinskaya YI, et al. *Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012*, JAMA. 2014;311(4):378-384. doi:10.1001/jama.2013.282542, available at:

<http://jama.jamanetwork.com/article.aspx?articleid=1817795>. Accessed,

November 2, 2015.

NIDDK 1987

- **Interstitial cystitis is a syndrome characterized by urinary frequency, nocturia, urgency, suprapubic pressure and pain with bladder filling relieved by emptying.**
- **Urine cultures and cytologies are negative.**
- **There is no precise definition for interstitial cystitis.**
- **The etiology and pathogenesis of the disease are unknown.**
- **Evidence based definitions of the disease are lacking.**
- **Our understanding of this condition relies largely on expert opinion.**

NIDDK Criteria for Diagnosing Interstitial Cystitis

J. Urol 161:553

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or classic Hunner's ulcer, and they must have either pain associated with the bladder or urinary urgency.

Interstitial Cystitis Trial NIDDK Inclusion Criteria

Must have:

- **Glomerulations or Hunner's ulcer**
- **Either pain associated with the bladder or urinary urgency for at least 9 months**
- **On cystometrics: Intense urge to void within 150cc, no involuntary bladder contractions, maximum capacity <350 cc**
- **Daytime frequency >8 for at least 9 months**
- **Nocturia for at least 9 months**

J Urol 1988;140 203-206

NIDDK INTERSTITIAL CYSTITIS EXCLUSION CRITERIA

- **Bladder capacity >350cc on awake cystometry**
- **Absence of intense urge to void at 150 water volume**
- **Phasic involuntary bladder contractions**
- **Symptom duration < 9 months**
- **Absence of nocturia**
- **Urinary Frequency <8 times a day**

Prevalence of IC Symptoms

- Prevalence of IC or conditions suggestive of IC-
0.01-2.3%
- [Int J Urol 23, 542-549](#)

Regulatory Patient Study Population Goal

- **To define a homogenous Interstitial Cystitis patient population suitable for enrollment in clinical Interstitial Cystitis trials.**

Measurable Symptoms of Interstitial Cystitis

- **Pain**
- **Urinary Frequency**
- **Nocturia**
- **Urgency**
- **Flares**

ELMIRON NDA 020193

- Approved September 26, 1996
- Orphan drug designation
- Endpoints used for approval
improvement in measures of pain
- Classified as orphan drug

Patient Reported Outcomes (PROs)

- **PROs may allow capture of disease aspects not felt to be previously quantifiable or discernible**
- **PROs are measurements that come directly from patients**
- **At current time PROs not used to diagnose IC or as IC efficacy endpoints as none have been shown to be accurate and reliable.**

Protocol Design Considerations



- **Two Double-Blind Placebo Controlled Studies**
- **Specify what baseline or maintenance therapy is acceptable**
- **Define Flares, criteria of severity and indication for Rescue Therapy**
- **Pre-Specify any Rescue Medication Regimens**

Going Forward: WHAT IS NEEDED?



- **Non-Invasive diagnostic methods for IC trial inclusion (Cystoscopy/cystometrics are invasive) such as biomarkers etc.**
- **A well defined and reliable measure of urgency**
- **A Patient Reported Symptom Outcome measure to capture aspects of disease important to patients**
- **Electronic Source Data in Clinical Investigations**

END

BACK UP SLIDES

Expedited Review Categories

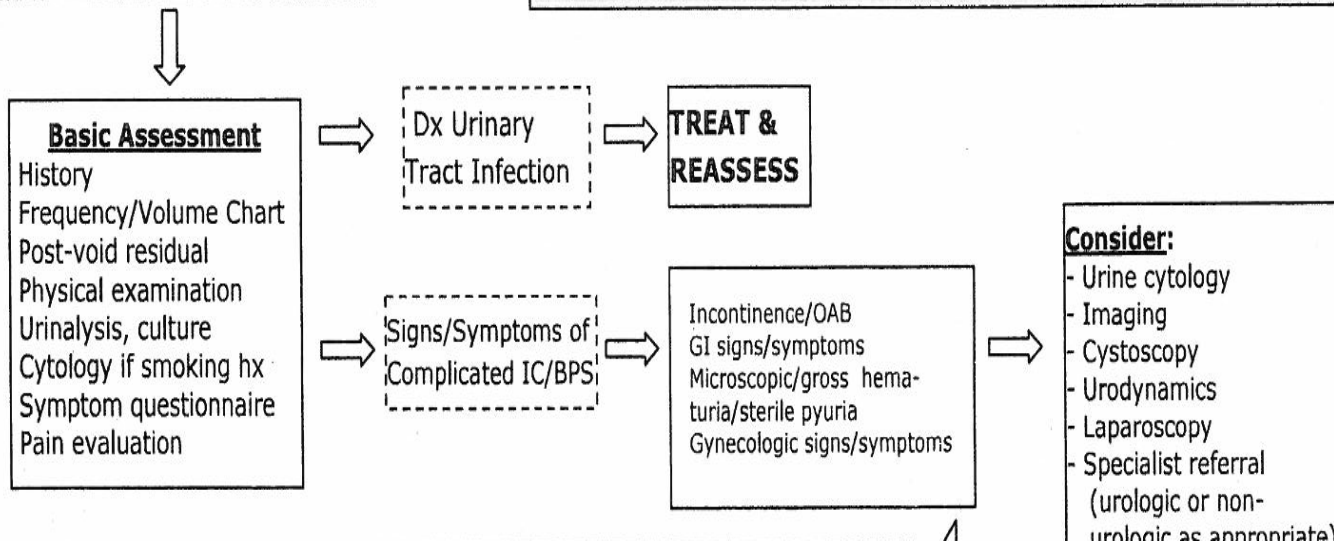
- **Breakthrough Therapy: Substantial improvement over available therapy**
- **Accelerated Approval: surrogate endpoint: Phase 4 confirmatory trials: FDA can withdraw approval if results do not confirm efficacy**
- **Fast Track: Unmet need: Potential Superior efficacy or safety: Rolling review: Frequent communication: Company request and can initiate anytime. Can lead to earlier approval and patient availability**
- **Priority Review: Action taken within 6 -8months: Significant improvement of safety or effectiveness(deceased rxn, increased compliance): Scientific standards not altered for efficacy or safety.**

<https://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm>

AUA Treatment Algorithm 2010

IC/BPS: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes

The evidence supporting the use of Neuromodulation, Cyclosporine A, and BTX for IC/BPS is limited by many factors including study quality, small sample sizes, and lack of durable follow up. None of these therapies have been approved by the U.S. Food and Drug Administration for this indication. The panel believes that none of these interventions can be recommended for generalized use for this disorder, but rather should be limited to practitioners with experience managing this syndrome and willingness to provide long term care of these patients post intervention.



DISEASES CAUSING BLADDER SYMPTOMS

- Bladder diseases: OAB, neurogenic bladder, bladder cancer, bladder calculus, chemical cystitis
- Prostate: BPH, CAP
- Urethra: cancer, stricture, diverticulum
- GU infections: bacterial cystitis, urethritis, prostatitis
- Gyn: malignancies, endometriosis, uterine myoma, climacteric disturbance
- Other: polyuria, urinary stones

Drug/ Biologic Product Development

- Phase 1 Trial(s)
 - Initial introduction of a new drug into humans
 - Estimation of initial safety and tolerability
 - Preliminary studies of potential therapeutic benefit
 - Pharmacokinetics, Pharmacodynamics, Drug metabolism, Mechanism of action
 - Small number of participants receive a limited number of doses

Drug/ Biologic Product Development



- Phase 2 Trial(s)
 - Controlled clinical trial
 - Preliminary efficacy in affected individuals with the disease or condition
 - Identify the doses for phase 3 testing
 - Identify common short-term side effects

Drug/ Biologic Product Development

- Phase 3 Trial(s)
 - Larger, inclusive, randomized controlled clinical trial(s)
 - Performed after proof-of-concept preliminary efficacy trial
 - Gather more information about efficacy, safety, dosing
 - Provide most of the basis for marketing and physician labeling
 - Range of number of enrolled individuals-
 - less than one hundred to several thousand depending upon the indication

Why Are Phase 3 Trials Necessary?



- Recent publication from FDA
- Case examples of divergent results from trials.

ORPHAN DRUGS

- Legislation 1983 (<200,000 US Patients)
- Years of Orphan Drug Exclusivity
- Grants Program
- Tax Credits for Clinical Research
- Assistance Trial Design
- Application Fee Wavers