

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Draft Guidance on Pentosan Polysulfate Sodium**

**May 2021**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In July 2014, FDA issued a draft product-specific guidance for industry on generic pentosan polysulfate sodium. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

**Active ingredient:** Pentosan polysulfate sodium

**Dosage Form; Route:** Capsule; oral

**Strength:** 100 mg

### **Recommendations for Demonstrating Active Pharmaceutical Ingredient Sameness:**

For a comprehensive characterization and demonstration of sameness between the test active pharmaceutical ingredient (API) and the API extracted from the reference listed drug (RLD) (reference), OGD recommends that the potential applicants develop and use properly validated orthogonal analytical methods to perform side-by-side comparative testing of the test API and the reference API. A minimum of three batches of the test API and three batches of the reference API should be characterized to assess API sameness. The API sameness can be established by evaluating the equivalence in the following:

1. Source of naturally-occurring starting material – The starting material used to manufacture the proposed pentosan polysulfate sodium (PPS) should be the same as that used to manufacture the drug substance for the RLD.

The following two criteria should be assessed to ensure botanical raw material (BRM) identity:

- a. The same plant species: the BRM (beechwood) used to manufacture the proposed PPS should be collected from the same plant species, *Fagus sylvatica* L. The species *F. sylvatica* should be correctly identified and authenticated using appropriate analytical methods (e.g. macroscopic/microscopic and/or DNA bar-coding methods). Due to the many cultivars within this species, identification and authentication of plant species should be conducted at the cultivar(s) level if potential cultivar(s) will be used as a natural source of the BRM.
  - b. BRM assessment: the plant parts (heartwood, sapwood, or outer bark etc.) used as the BRM should be defined. The BRM should be collected following established good agricultural and collection practices (GACP) procedures to minimize variations in BRM and eventually ensure the batch-to-batch consistency of the API. Refer to the Guidance for Industry: *Botanical Drug Development* for the Agency's current thinking on BRM quality control.
2. Physicochemical properties – The molecular weight distribution between the proposed PPS and the drug substance in the RLD should be comparable. Moreover, the overall structural properties or characteristic fingerprints of the proposed PPS, including (but not limited to) the degree of sulfation, sodium content, Raman and IR spectra, should be equivalent to that of the drug substance in the RLD.
  3. The monosaccharide building block composition and chain branching of the proposed PPS should be equivalent to the drug substance in the RLD, with respect to the molecular properties, including (but not limited to) xylose units, sulfation pattern, glucuronic acid groups, linkages, and anomeric configurations.

In addition, potential applicants should conduct a comprehensive characterization of impurity profile of the proposed drug product and the RLD.

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### **Recommendations for Demonstrating Bioequivalence:**

**Recommended Studies:** Two options: Option 1 or Option 2

#### **I. Option 1: Biopharmaceutics Classification System (BCS) Class 3 based biowaiver**

A waiver from submitting an in vivo bioequivalence study for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid

dissolution,<sup>1</sup> and the test product formulation is qualitatively the same and quantitatively very similar as detailed in the Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence for Immediate Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System* is submitted in the application. A decision regarding the acceptability of the waiver request will be made upon assessing the data submitted in the application.

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## II. Option 2: In vivo bioequivalence study with clinical endpoint

Type of study: Bioequivalence study with a clinical endpoint

Design: Randomized, double blind, parallel, placebo-controlled

Strength: 100 mg

Subjects: Male and female patients with bladder pain associated with interstitial cystitis.

Additional comments: See below.

1. OGD considers a bioequivalence study with a clinical endpoint conducted to demonstrate the bioequivalence of PPS to have a high risk of failure because of the limited number of patients who will be naïve to the drug product, the limited number of non-naïve patients who will be willing to undergo a wash-out of the drug product, the difficulty of enrolling sufficient patients who meet all of the Inclusion and Exclusion Criteria, the variable and sometimes limited efficacy results reported in the literature, and the need to differentiate both active drug products from placebo.
2. OGD recommends a parallel design bioequivalence study with a clinical endpoint comparing the PPS test product versus the RLD and placebo control, with each subject receiving one 100 mg capsule three times daily for 3 months and the primary endpoint evaluation occurring after 3 months of treatment (i.e., at the month 3 visit).
3. The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population identified as “treatment success” occurring after 3 months of treatment (i.e., at the Month 3 visit). A “treatment success” is defined as: 1) subject evaluating their degree of overall improvement as > 25% from baseline to study endpoint, AND 2) bladder pain improvement from baseline to study endpoint of > 25% per subject completed questionnaire, e.g.;
4. Compared to when you started the study, how would you rate the overall change in your interstitial cystitis?
  - a. Worse
  - b. No better (0% improvement)
  - c. Slightly improved (25% improvement)
  - d. Moderately improved (50% improvement)

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<sup>1</sup> Refer to Guidance for Industry: *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances*. Applicants may submit comparative dissolution data between test and reference products and proposed test product formulations to FDA via a controlled correspondence to obtain feedback on the applicability of a BCS-based biowaiver request.

- e. Greatly improved (75% improvement)
  - f. Symptoms gone (100% improvement)
5. Compared to when you started the study, how would you rate the overall change in your bladder pain?
- a. Worse
  - b. No better (0% improvement)
  - c. Slightly improved (25% improvement)
  - d. Moderately improved (50% improvement)
  - e. Greatly improved (75% improvement)
  - f. Bladder pain gone (100% improvement)
6. Inclusion Criteria:
- a. Males and females aged  $\geq 18$  years with moderate to severe interstitial cystitis defined as:
    - Bladder Pain: at least moderate on a scale of 0 to 5 (0=none, 1=mild, 3=moderate, 5=severe), AND
    - Urgency: at least moderate on a scale of 0 to 5 (0=none, 1=mild, 3=moderate, 5=severe), AND
    - Frequency: average  $\geq 10$  voids per day (as determined by  $\geq 30$  voids over 3 consecutive days, documented in the urinary frequency diary) and  $\geq 1$  nocturnal voids (as determined by  $\geq 3$  nocturnal voids over 3 consecutive days, documented in the urinary frequency diary).
  - b. Subject has experienced bladder pain, urinary urgency and urinary frequency, each not related to a urinary tract infection, for at least the previous 6 months prior to entry into the study.
  - c. An average voided bladder volume of 50 to 200 mL (as determined over 3 consecutive days documented in the urinary frequency diary).
  - d. Urine culture negative for clinically significant urinary tract infection (at baseline or within 2 weeks prior to baseline visit).
  - e. Urine cytology negative for neoplastic cells (at baseline or within 2 months prior to baseline visit).
  - f. Cystoscopic examination under anesthesia by the investigator showing petechial hemorrhages or ulcers following one or two distentions of the bladder at 80 cm of water pressure for one minute performed within 6 months prior to baseline visit and at least 6 weeks prior to baseline visit. Subjects that enter remission after their cystoscopic examination should not be scheduled for their baseline visit until the symptoms reappear.
  - g. Subjects currently being treated with PPS may be enrolled in the study if PPS treatment is stopped at least for 4 weeks (wash-out period) prior to baseline visit.
7. Stratify treatment groups by previous exposure to PPS (i.e., naïve versus non- naïve) to ensure similar proportions of naïve and non- naïve women in each of the three treatment groups. Enrollment in the non- naïve arm to not exceed a maximum of 50% of study subjects.

8. Exclusion Criteria:

- a. More than 25 voids per day (as determined by  $\geq 75$  voids over 3 consecutive days documented in the urinary frequency diary).
- b. Bladder capacity of more than 350 mL during awake exam (at baseline or within 6 months prior to baseline visit).
- c. Subject is planning to use intravesical therapy for interstitial cystitis, e.g., bladder distention or dimethyl sulfoxide, during the study period or has used any intravesical therapies within one month prior to baseline visit.
- d. Subject planning to use medical treatment for interstitial cystitis, e.g., antidepressants, antihistamines, antispasmodics, anticholinergics, or has used medical treatment for interstitial cystitis within one month prior to baseline visit.
- e. Subject taking any anticoagulant, e.g., warfarin sodium or heparin, or thrombolytic agent, e.g., tissue plasminogen activator or streptokinase.
- f. Subject with known aneurysm, thrombocytopenia, hemorrhagic disease, hemophilia, or gastrointestinal ulceration (e.g., active bleeding peptic ulcer disease), polyps, or diverticula.
- g. Exclude subjects with retinal pigment changes, a family history of hereditary pattern dystrophy, or other pre-existing ophthalmologic conditions.
- h. Subject with known hypersensitivity to PPS, including excipients (microcrystalline cellulose and magnesium stearate), or heparin.
- i. Subject who has a history of, or currently has, any of the following:
  - Neurogenic bladder or diabetic cystopathy.
  - Pelvic irradiation or chemical cystitis, including that due to cyclophosphamide.
  - Presence of urethral, pelvic, or rectal carcinoma.
  - Benign or malignant bladder tumors.
  - Tuberculous cystitis.
  - Urinary schistosomiasis.
  - Bladder or ureteral calculi.
  - Active genital herpes within 3 months prior to study entry.
  - Urethral and/or bladder obstruction.
  - Augmentation cystoplasty, cystectomy, cystolysis, neurectomy (i.e. hypogastric nerve plexus ablation) or implanted peripheral nerve stimulator that has affected bladder function.
- j. Subject has microscopic hematuria as defined as  $> 5$  RBC/high power field at baseline visit without a negative workup within the last year.
- k. Subject has current chronic pain condition, e.g., neuropathic pain, osteoarthritis pain, or chronic back pain (spasm) or is a chronic user of narcotics.
- l. Subject has clinically significant hepatic disease or clinically significant abnormal liver function tests.
- m. Gender specific exclusion criteria:
 

Male:

  - Subject has a post-void residual volume of  $>150$  cc by ultrasound.
  - Subject had a Trans Urethral Resection of Prostate (TURP), Trans Urethral Incision of Prostate (TUIP), Trans Urethral Incision of Bladder Neck (TUIBN), Trans Urethral Microwave Thermotherapy (TUMT), Trans Urethral Needle Ablation (TUNA), balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy.

- Subject has a history of prostate cancer.
- Subject is currently being treated for chronic bacterial prostatitis.

Female:

- Subject has a positive pregnancy test at the baseline visit, is pregnant or lactating, or is planning to become pregnant during the study period.
- Subject has a history of uterine, cervical or vaginal cancer during the past 3 years.
- Subject has clinically significant vaginitis at baseline visit.

9. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
  - a. Intravesical treatments for interstitial cystitis, e.g., bladder distention or dimethyl sulfoxide.
  - b. Medical treatments for interstitial cystitis, e.g., antidepressants, antihistamines, antispasmodics, anticholinergics.
  - c. Anticoagulant, e.g., warfarin sodium or heparin, or thrombolytic agent, e.g., tissue plasminogen activator or streptokinase.
  - d. Chronic use of narcotics.
  
10. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
  - a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Age
  - e. Age units (years)
  - f. Sex
  - g. Race
  - h. Name of planned treatment
  - i. Name of actual treatment (exposure): test product, RLD, placebo
  - j. Date/time first exposure to treatment
  - k. Date/time last exposure to treatment
  - l. Duration of Treatment (total exposure in days)
  - m. Completed the study (yes/no)
  - n. End of study date
  - o. End of study status
  - p. Reason for premature discontinuation of subject
  - q. Prior treatment with PPS (yes/no)
  - r. Subject required additional treatment for interstitial cystitis due to unsatisfactory treatment response (yes/no)
  - s. Per Protocol (PP) population flag (yes/no)
  - t. Reason for exclusion from PP population
  - u. Intent to Treat (ITT) population flag (yes/no)
  - v. Reason for exclusion from ITT population
  - w. Safety population flag (yes/no)
  - x. Reason for exclusion from Safety population
  - y. Randomized population flag (yes/no)

- z. Overall Improvement of >25% from baseline to study endpoint per subject (yes/no)
- aa. Bladder Pain score (from scale) at Baseline
- bb. Bladder Pain score (from scale) at Month 3
- cc. Bladder Pain Improvement from baseline to study endpoint of > 25% (yes/no)
- dd. Urgency score (from scale) at Baseline
- ee. Number of average voids per day (over 3 consecutive days documented in the urinary frequency diary) at Baseline
- ff. Number of average nocturnal voids per day (over 3 consecutive days documented in the urinary frequency diary) at Baseline
- gg. Average voided bladder volume (as determined over 3 consecutive days documented in the urinary frequency diary) at Baseline
- hh. Negative Urine Culture at Baseline or within 2 weeks prior to baseline visit (yes/no)
- ii. Negative Urine Cytology at Baseline or within 2 months prior to baseline visit (yes/no)
- jj. Compliance rate (%)
- kk. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
- ll. Concomitant medication (yes/no)
- mm. Adverse event(s) reported (yes/no)

11. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headers, if applicable:

- a. Study identifier
- b. Unique subject identifier
- c. Subject identifier for the study
- d. Study site identifier (if applicable)
- e. Name of planned treatment
- f. Name of actual treatment (exposure): test product, RLD, placebo control
- g. Safety population flag (yes/no)
- h. Modified ITT population flag (yes/no)
- i. Per-protocol population flag (yes/no)
- j. Analysis date
- k. Analysis visit
- l. Study visit within the designated window (yes/no)
- m. Number of days since baseline visit
- n. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
- o. Bladder Pain score (from scale)
- p. Overall Improvement from baseline per subject
- q. Concomitant medication reported during this visit (yes/no)
- r. Adverse event reported during this visit (yes/no)
- s. Laboratory testing during this visit (yes/no)

12. Refer to the product specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled Guidance on Adapalene; Benzoyl Peroxide for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

13. Study data should be submitted in a standardized format. Refer to the study data standards published at [www.fda.gov](http://www.fda.gov).<sup>2</sup>

**Analytes to measure:** Not applicable

**Bioequivalence based on (90% CI):** Clinical endpoint

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Revision History:** Recommended September 2012; Revised July 2014, May 2021

**Unique Agency Identifier:** PSG\_020193

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<sup>2</sup> Study Data Standards for Submission to CDER and CBER available at: <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>