Contains Nonbinding Recommendations

Draft Guidance on Pentosan Polysulfate Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Pentosan Polysulfate Sodium

Form/Route: Capsule/Oral

Recommended studies: 1 study

1. Type of study: Bioequivalence (BE) Study with Clinical Endpoint
   Design: Randomized, double blind, parallel, placebo-controlled in vivo
   Strength: 100 mg
   Subjects: Male and female patients with bladder pain associated with interstitial cystitis.
   Additional comments: See specific recommendations below.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Please note that a Dissolution Method Database is available to the public at the Office of Generic Drug (OGD) website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please 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 application.

Additional comments regarding the BE study with a clinical endpoint:

1) Before commencing in vivo studies, OGD recommends that potential applicants submit a CMC meeting request to OGD with characterization data on the proposed active ingredient that supports that the proposed product is pharmaceutically equivalent to the reference-listed drug.

   For characterization studies, based on our current understanding of this drug, OGD recommends potential applicants focus on evaluation of the following aspects and attributes, and demonstrate their equivalence to the RLD.

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

- 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.
- Equivalence of 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.

For a comprehensive characterization and demonstration of sameness between the PPS drug substances in the proposed drug product and the RLD, OGD recommends that, given the complexity associated with PPS, the potential applicants develop and use orthogonal analytical methods, corresponding to each attribute as listed above. These analytical methods should be properly validated. For example, it is important to demonstrate that the analytical methods used during drug development are specific to key structural attribute(s) and sensitive to their changes. OGD also recommends that multiple batches of the proposed PPS drug substance be analyzed and used for qualitative and quantitative sameness evaluation of drug substances in the proposed drug product and the RLD.

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

2) OGD is recommending a BE study with a clinical endpoint because FDA currently is not aware of an existing bioanalytical method that is sufficiently sensitive to measure the active ingredient (or surrogate) in an appropriate biological fluid. FDA will consider alternative methods for establishing bioequivalence and encourages sponsors to submit comments if they are aware of such alternative approaches and methods.

3) The OGD Clinical Team considers a BE study with a clinical endpoint conducted to demonstrate the bioequivalence of pentosan polysulfate sodium (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. [**NOTE**: PPS was designated an orphan drug product for the treatment of interstitial cystitis on 8/7/85.]

4) The OGD recommends a parallel design BE study with a clinical endpoint comparing the PPS test product versus the reference listed drug (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).

5) 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.;

   1. 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)
      e) Greatly improved (75% improvement)
      f) Symptoms gone (100% improvement)

   2. 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)
      b) Slightly improved (25% improvement)
      c) Moderately improved (50% improvement)
      d) Greatly improved (75% improvement)
      e) Bladder pain gone (100% improvement)

6) Inclusion Criteria:
   a. Males and females aged ≥ 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 ≥ 10 voids per day (as determined by ≥ 30 voids over 3 consecutive days documented in the urinary frequency diary) and ≥ 1 nocturnal voids (as determined by ≥ 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 ≥ 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. Subject with known hypersensitivity to PPS, including excipients (microcrystalline cellulose and magnesium stearate), or heparin.
   h. 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.

i. Subject has microscopic hematuria as defined as > 5 RBC/high power field at baseline visit without a negative workup within the last year.
j. Subject has current chronic pain condition, e.g., neuropathic pain, osteoarthritis pain, or chronic back pain (spasm) or is a chronic user of narcotics.
k. Subject has clinically significant hepatic disease or clinically significant abnormal liver function tests.
l. 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) The protocol should clearly define the per-protocol (PP), intent-to-treat (ITT) and safety populations:
a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, dosed a prespecified proportion of the scheduled administrations (e.g., 75% to 125%) of the assigned product for the specified duration of the study and completed the evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
b. The ITT population includes all randomized subjects who met all inclusion/exclusion criteria, administered at least one dose of assigned product and returned for at least one post-baseline evaluation visit.
c. The safety population includes all randomized subjects who received study product.

11) Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of interstitial cystitis during the treatment phase of the study should be discontinued, included in the PP population analysis using Last Observation Carried Forward (LOCF), and provided with effective treatment. Subjects discontinued early for any other reasons should be excluded from the PP population, but included in the ITT population, using LOCF.

12) The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

13) All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

14) If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.

15) The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

16) Provide a detailed description of the blinding procedure in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

17) Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly

selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

18) It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

19) To establish bioequivalence, the 90% confidence interval of the difference in the "treatment success" rate between the test product and RLD treatment groups occurring after 3 months of treatment (at the Month 3 visit) must be within [-0.20, +0.20] for the dichotomous primary endpoint, using the PP study population. Perform a secondary subgroup efficacy analysis comparing PPS naïve and PPS non-naïve subjects.

20) As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p<0.05$) with regard to the "treatment success" rate occurring after 3 months of treatment (at the Month 3 visit), using the intent-to-treat (ITT) study population and Last Observation Carried Forward (LOCF).

21) The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$

versus

H_A: $-.20 \leq p_T - p_R \leq .20$

where p_T = success rate of test treatment p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment group

$c\,n_T$ = number of subjects with success in test treatment group

n_R = sample size of reference treatment group

$c\,n_R$ = number of subjects with success in reference treatment group

$\hat{p}_T = c\,n_T / n_T$, $\hat{p}_R = c\,n_R / n_R$,

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$

$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$

We reject H_0 if $L \geq -.20$ and $U \leq .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

22) Study data should be submitted to the OGD in electronic format.
   a. A list of file names, with a simple description of the content of each file, should be included.
   b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
   c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
   d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
   e. Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline Bishop Score, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

23) Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
   a. Study identifier
   b. Subject identifier
   c. Site identifier: study center
   d. Age
   e. Age units (years)
   f. Sex
   g. Race
   h. Name of Actual Treatment (exposure): test product, RLD, placebo
   i. Duration of Treatment (total exposure in days)
   j. Completed the study (yes/no)

k. Reason for premature discontinuation of subject
l. Prior treatment with PPS (yes/no)
m. Subject required additional treatment for interstitial cystitis due to unsatisfactory treatment response (yes/no)
n. Per Protocol (PP) population inclusion (yes/no)
o. Reason for exclusion from PP population
p. Intent to Treat (ITT) population inclusion (yes/no)
q. Reason for exclusion from ITT population
r. Safety population inclusion (yes/no)
s. Reason for exclusion from Safety population
t. Overall Improvement of >25% from baseline to study endpoint per subject (yes/no)
u. Bladder Pain score (from scale) at Baseline
v. Bladder Pain score (from scale) at Month 3
w. Bladder Pain Improvement from baseline to study endpoint of > 25% (yes/no)
x. Urgency score (from scale) at Baseline
y. Number of average voids per day (over 3 consecutive days documented in the urinary frequency diary) at Baseline
z. Number of average nocturnal voids per day (over 3 consecutive days documented in the urinary frequency diary) at Baseline
aa. Average voided bladder volume (as determined over 3 consecutive days documented in the urinary frequency diary) at Baseline
bb. Negative Urine Culture at Baseline or within 2 weeks prior to baseline visit (yes/no)
cc. Negative Urine Cytology at Baseline or within 2 months prior to baseline visit (yes/no)
dd. Treatment compliance: number of missed doses per subject
ee. Concomitant medication (yes/no)
ff. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	pri_trt	add_trt	pp	pp_rs	itt	itt_rs
101	001	01	40	YEARS	F	1	A	90	Y		N	N	Y		Y	
101	002	01	35	YEARS	F	1	B	90	Y		Y	N	Y		Y	

safety	safe_rs	oimpr_25	pain_b	pain_3m	pimpr_25	urgency	void_day	void_noc	void_vol	ur_cult	ur_cyto	complian	CM	AE
Y		N	3	2	N	3	15	1	100	Y	Y	Y	Y	N
Y		N	4	3	N	4	12	1	75	Y	Y	Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=placebo
EXDUR:	Duration of Treatment (total exposure in days)
completd:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
pri_trt:	Prior treatment with PPS, e.g., Y=Yes, N=No
add_trt:	Subject required additional treatment for constipation due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=insert fell out prior to 12 hours after insertion, C=noncompliant, etc.
itt:	Intent to Treat (ITT) population inclusion, e.g., Y=Yes, N=No
itt_rs:	Reason for exclusion from ITT population, e.g., A=never treated etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
oimpr_25:	Overall Improvement of >25% from baseline to study endpoint per subject, e.g., Y=Yes, N=No
pain_b:	Bladder Pain score (from scale) at Baseline
pain_3m:	Bladder Pain score (from scale) at Month 3
pimpr_25:	Bladder pain Improvement from baseline to study endpoint of > 25%, e.g., Y=Yes, N=No
urgency:	Urgency score (from scale) at Baseline

void_day: Number of average voids per day (over 3 consecutive days documented in the urinary frequency diary) at Baseline
void_noc: Number of average nocturnal voids per day (over 3 consecutive days documented in the urinary frequency diary) at Baseline
void_vol: Average voided bladder volume (as determined over 3 consecutive days documented in the urinary frequency diary) at Baseline
ur_cult: Negative Urine Culture at Baseline or within 2 weeks prior to baseline visit, e.g., Y=Yes, N=No
ur_cyto: Negative Urine Cytology at Baseline or within 2 months prior to baseline visit, e.g., Y=Yes, N=No
complian: Treatment compliance, e.g., number of missed doses per subject
CM: Concomitant medication, e.g., Y=Yes, N=No
AE: Adverse event(s) reported, e.g., Y=Yes, N=No

24) Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Bladder Pain score (from scale)
    h. Overall Improvement from baseline per subject
    i. Concomitant medication reported during this visit (yes/no)
    j. Adverse event reported during this visit (yes/no)
    k. Laboratory testing during this visit (yes/no)

    Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	pain	oimpr	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	1	4		Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study

EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
pain:	Bladder Pain score (from scale)
oimpr:	Overall Improvement from baseline per subject
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

25) These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of pentosan polysulfate sodium.