DE NOVO CLASSIFICATION REQUEST FOR BRACHYGEL VAGINAL HYDROGEL PACKING SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Vaginal hydrogel packing system**. A vaginal hydrogel packing system is a non-powered positioning device composed of a flexible container filled with a hydrogel. The device is intended to reduce the radiation dose delivered to adjacent pelvic organs by temporarily displacing the vaginal wall and adjacent pelvic tissues during radiation therapy treatment planning and delivery.

NEW REGULATION NUMBER: 21 CFR 892.5735

CLASSIFICATION: Class II

PRODUCT CODE: QXR

BACKGROUND

DEVICE NAME: BrachyGel Vaginal Hydrogel Packing System

SUBMISSION NUMBER: DEN220052

DATE DE NOVO RECEIVED: August 26, 2022

SPONSOR INFORMATION:

BrachyFoam, Inc. d/b/a Advaray
722 Preston Ave. Suite 108
Charlottesville, VA 22093

INDICATIONS FOR USE

The BrachyGel Vaginal Hydrogel Packing System is indicated as follows:

> The BrachyGel Vaginal Hydrogel Packing System is a single-use, non-sterile, disposable, non-powered positioning device that delivers self-expanding hydrogel that forms and expands within the vaginal cavity. The purpose of this device is to displace the vaginal wall and adjacent pelvic tissues during radiation therapy planning and delivery, to reduce dose to adjacent tissues by attenuation of radiation dose, and to stabilize radiation treatment equipment during radiation therapy planning and delivery. The placement of the hydrogel device requires a physician or physician directed healthcare professional, and is performed as a separate procedure outside of brachytherapy applicator insertion, computed tomography and/or magnetic resonance imaging exam, radiation treatment

planning and radiation treatment delivery. This device is not intended to be inserted into the uterine cavity or rectum. This device is intended to be in place temporarily and removed after less than 24 hours.

LIMITATIONS

The sale, distribution, and use of the BrachyGel Vaginal Hydrogel Packing System are restricted to prescription use in accordance with 21 CFR 801.109.

The device is intended only for use in the vaginal cavity; it is not intended to be inserted into the uterine cavity or rectum.

The device is intended to be in place temporarily and removed within 24 hours.

The device is non-sterile, single-use, and cannot be reprocessed.

The clinical study was unblinded; therefore, clinicians and patients participating in the study would know when the device or standard of care packing was used.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The device, BrachyGel Vaginal Hydrogel Packing System (BVHPS), is intended for patients receiving brachytherapy for gynecological cancers. The BVHPS works by displacing the rectum and bladder, providing radiation attenuation and stabilizing the brachytherapy applicator. The device contains components for the preparation of a polyethylene glycol (PEG) based polymer hydrogel and hydrogel delivery system (Figure 1). After the bag is placed into the vaginal space, the hydrogel precursors are injected into the therapy bag and the hydrogel forms *in situ,* causing the bag to expand and displace nearby tissue and stabilize the brachytherapy applicator. The bag containing the hydrogel is later removed after the brachytherapy treatment delivery is complete. The physician may instill saline via the device's saline port to soften the hydrogel for easier extraction of the therapy bag. The hydrogel is not bioresorbable.

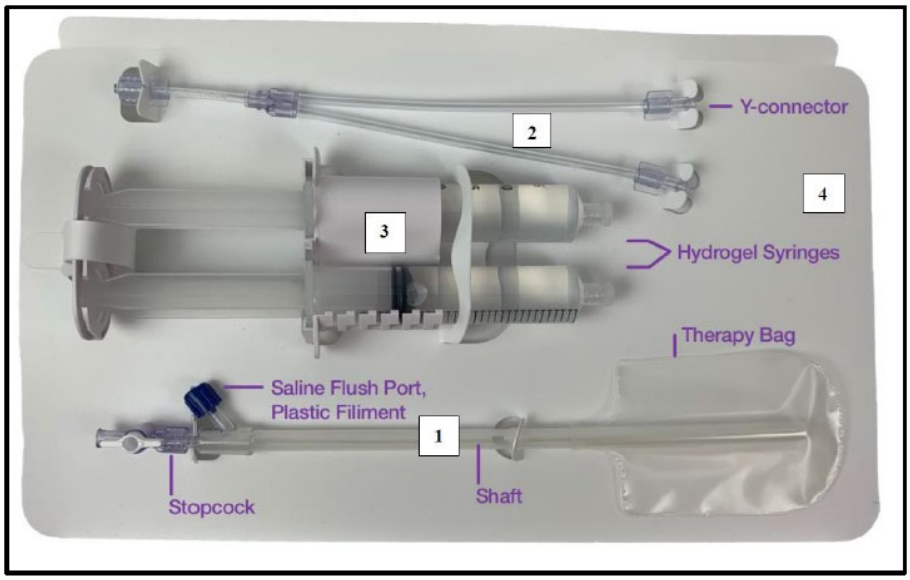

Figure 1. BrachyGel Vaginal Hydrogel Packing System with components identified (1: Dual Lumen Catheter Assembly, 2: Flexible Y Connector, 3: Dual Syringe Assembly, 4: Package Card)

Device Components and Specifications

Each BVHPS includes the following components:

- Prefilled THIOCURE Syringe (Syringe 1)
  - Contains a solution of THIOCURE ETTMP 1300, water, and sodium bicarbonate.
- Prefilled PEDGA Syringe (Syringe 2)
  - Contains a solution of Poly(ethylene glycol) diacrylate (PEDGA) average M_n 700 and water.
- Dual Syringe Holder
- Dual Syringe Clip
- Flexible Y Connector
- Catheter Assembly with Therapy Bag
  - The therapy bag is 2.2 MIL in thickness and 4.585 in x 2.75 in (LxW). The intended fill volume is 50ml.

Principle of Operation

The BVHPS is deployed in three steps: insertion, delivery of hydrogel, and removal. During insertion, the BVHPS is placed to the desired depth within the vagina, anterior or posterior to the brachytherapy treatment applicators. If desired, a second device may be inserted to the desired depth anterior or posterior to the brachytherapy treatment applicators. The Y connector tubing is attached to the device shaft, and the hydrogel reagents are injected continually. The chemical reaction between the polymer solutions occurs within the reaction bag itself**.** The maximum time between injection of the polymer solutions and gelation is one minute. The expansion of the bag upon filling displaces adjacent tissue, providing radiation attenuation, and stabilizing the brachytherapy applicator during a brachytherapy treatment fraction. Gel delivery can be performed sequentially if two BVPHs are placed.

Once radiation treatment is complete, the physician may instill saline solution through the saline port in order to soften the hydrogel for easier removal. Each BVHPS is then removed from the vagina.

In the event that the hydrogel reaction does not occur as intended, the physician should be able to detect the event by noticing the lack of expansion to fit the vaginal cavity and stabilize the applicator, or by identifying suboptimal packing on treatment planning CT or MRI images obtained after insertion of the BVHPS. If a device fails, the physician should remove the BVHPS and repeat the packing placement procedure with another BVHPS kit or alternative form of packing.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

Biocompatibility testing was conducted on the final, finished device. The test article consisted of the therapy bag and solidified hydrogel material. Biocompatibility was evaluated according to ISO 10993-1:2009 and the FDA Guidance, "*Use of International Standard ISO 10993, Biological Evaluation of Medical Devices – Part 1: Evaluation Testing*". The results showed that the device met acceptance criteria according to ISO 10993. A summary of the results is below.

The following biocompatibility endpoints were evaluated with testing:

- Cytotoxicity
- Sensitization
- Irritation
- Acute systemic toxicity
- Materials mediated pyrogenicity

The results of these evaluations support the biocompatibility of the BVHPS.

SHELF LIFE/STERILITY

The device is provided non-sterile and is single-use only.

Bioburden Testing
Bioburden testing was performed on the patient-contacting component (therapy bag) of the device as per USP <61>, USP <62>, and USP <1111>. The tests passed the pre-determined acceptance criteria and were found acceptable.

Shelf Life
The BVHPS is a non-sterile, single use device. The shelf-life has been established at 6 months. To support the 6-month shelf life, package testing and functional testing were performed. Package testing consisted of the following:

- Visual Inspection (ASTM F1886/F1886M-16, Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection)
- Seal strength (ASTM F88/F88M-21, Standard Test Method for Seal Strength of Flexible Barrier Materials)
- Simulated distribution testing in accordance with ASTM D4169-16.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The device is composed of materials that are electrically nonconductive, nonmetallic, and nonmagnetic. The device is considered MR Safe.

PERFORMANCE TESTING - BENCH

Bench testing was conducted to demonstrate that the BVHPS performs as expected under the anticipated conditions of use. The following bench testing was conducted to demonstrate the device performance characteristics:

Table 1. Performance testing completed for BrachyGel Vaginal Hydrogel Packing System

Test	Purpose	Method	Performance Metrics and Acceptance Criteria	Results
Hydrogel Raw Material Characterization Before and After Irradiation	To determine if the hydrogel materials maintained their chemical and physical properties after irradiation	(b) (4)	(b) (4)	Pass. There is no evidence to show that the gel's rheological properties are different before and after irradiation.
Material Characterization of the hydrogels at storage timepoints of (b) (4)	To determine storage conditions of the gel precursors	Samples were aged at 2 - 8°C, and then tested for gel time. Samples were stored for (b) (4)		At all timepoints, all samples stored at 2 – 8°C passed. The labeling states that the device should be stored at conditions 2 – 8°C.
Exothermic Testing of Hydrogel Reaction	To ensure that the device does not cause adverse reactions from increased heat by the hydrogel reaction	(b) (4)		The acceptance criteria were observational, so there were no specific pass/fail criteria. The results indicated the average temperature increase was less than 5°C and did not

		(b) (4)	(b) (4)	(b) (4) This is acceptable.
Radiation Attenuation	To determine the radiation dose attenuation properties of the device materials			Pass. (b) (4) (b) (4)
Computed Tomography (CT) Imaging	To determine if the device is visible on a CT image			Pass. (b) (4) (b) (4)
Stability of the Applicator	To determine the ability of the device to stabilize the applicator			Pass. (b) (4) (b) (4)
Bag Integrity – Leak Test	To demonstrate that there is no leaching of the hydrogel out of the vaginal fill bag			Pass. (b) (4) (b) (4)
Bag Burst Strength – Burst Volume	To determine maximum fill volume of the bag			Pass. (b) (4) (b) (4)

Mechanical and Dimensional Testing of Connectors	To ensure that the device joints and connectors function adequately	(b) (4)	(b) (4)	Pass. (b) (4) (b) (4)

SUMMARY OF CLINICAL INFORMATION

The study aimed to determine whether the device is non-inferior to standard vaginal packing (gauze) in dosimetric results for the rectum and bladder, as well as to determine the differences in participant discomfort, CT imaging clarity of packing, physician/physicist use experience, and impact of the device on complication rates and adverse events. The study evaluated the clinical performance of the device during high dose rate (HDR) brachytherapy for cervical cancer.

Table 2. Summary of Clinical Study Objectives and Endpoints

Clinical Study Title	A Randomized, Non-Inferiority Study of a Hydrogel Packing System Compared to Standard of Care Packing During Image-Guided High-Dose Rate Brachytherapy Boost for Cervical Cancer	
Objectives and Endpoints	Primary objective: To determine if BVHPS is non-inferior to standard method vaginal packing (standard) in dose thresholds for the rectum and the bladder.	Primary Endpoint: The dose to the hottest 2 cc (D2cc) (in Gy) for the rectum and the bladder in periods 1 and 2 (e.g., fractions 2 and 3).
	Secondary Objectives: 1) To estimate the difference in the safety profile of BVHPS compared to standard vaginal packing.	Secondary Endpoints: 1) Frequency, intensity, and duration of adverse events in periods 1 through 4 (e.g., fractions 2 through 5).

	2) To estimate period effects in dosimetry thresholds (D0.1cc, D1cc, D2cc) between BrachyGel and standard vaginal packing for the rectum and the bladder.	2) The dose to the hottest 0.1 cc (D0.1cc), 1cc (D1cc), and 2cc (D2cc) (in Gy) for the rectum and the bladder in periods 1 through 4 (e.g., fractions 2 through 5)
	Exploratory Objectives: 1) To estimate the difference in participant-reported discomfort between BVHPS and standard vaginal packing 2) To estimate the difference in physician/physicist evaluation of imaging clarity of the packing and completeness of packing between BVHPS and standard vaginal packing. 3) To estimate the difference in physician-scored use experience between BVHPS and standard vaginal packing	Exploratory Endpoints: 1) Participant-reported discomfort from packing scored on a 4-point scale for periods 2 through 4 (e.g. fractions 2 through 5). 2) Physician/physicist evaluation of imaging clarity and packing and completeness of packing scored on a 4-point scale for periods 1 through 4 (e.g., fractions 2 through 5). 3) Physician-scored use experience scored on a 4-point scale for periods 1 through 4 (e.g., fractions 2 through 5).

Study Design

Randomization was performed to determine the sequence of alternating BVHPS versus gauze packing for comparison, and to reduce the impact of timing on patient experience of the packing and on the impact of tumor response (Figure 2).

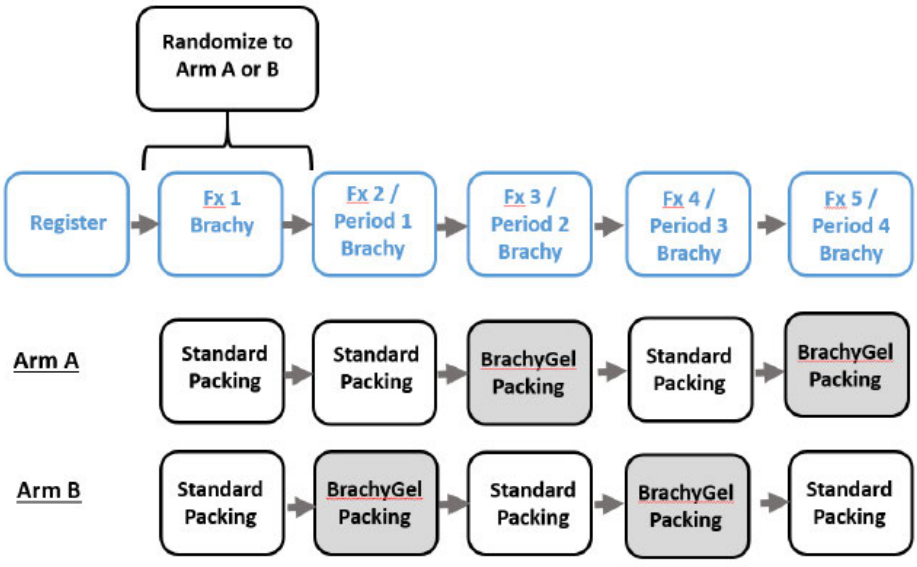

Figure 2. Study Schema

A CT scan was obtained with each fraction of brachytherapy after placement of the applicators and vaginal packing for brachytherapy planning. There were no additional imaging studies or re-packing prior to treatment.

All subjects enrolled in both arms of the study remained in the study for a maximum of thirty (30) days, or until they were discontinued or withdrew from the study.

Sample Size

The actual sample size did not achieve the pre-specified sample size calculated through power analysis. The study accrued a total of twenty (20) evaluable patients out of a planned enrollment of forty (40) evaluable patients at a single site.

Patients

Eligible participants were adult women (≥ 18 years old) with FIGO Stages IB2-IVA cervical cancer receiving definitive chemo-radiation with HDR brachytherapy boost with intra-cavitary +/- interstitial applicators. Twenty-one (21) patients were enrolled, and twenty (20) subjects were evaluated as the per protocol population, with one patient not treated due to disease progression. Exclusion criteria included: prior abdominal radiation therapy, prior a hysterectomy and/or contraindications to brachytherapy.

Table 3. Patient Demographics

	BVHPS (*n* = 20)
Age, mean years (range)	52 (34 – 71)
Gender, # (%)	
Female	20 (100.0%)
Male	0
ECOG Status, # (%)	
0	14 (70.0%)
1	6 (30.0%)
FIGO Stage, # (%)	
IB1	1 (5.0%)
IB2	1 (5.0%)
IIA	1 (5.0%)
IIB	7 (35.0%)
IIIA	0
IIIB	0
IIIC	7 (35.0%)
IVA	3 (15.0%)
IVB	0
Histology, # (%)	
Squamous cell carcinoma	14 (70.0%)
Adenocarcinoma	5 (25.6%)
Sarcomatoid carcinoma, HPV+	1 (5.0%)
Race, # (%)	
Asian	1 (5.0%)
White	17 (85.0%)
Other (Hispanic / Latino)	2 (10.0%)

Ethnicity, # (%)	
Hispanic or Latino Non-Hispanic	2 (10.0%) 18 (90.0%)
# Fractions, # (%)	
4 5	2 (10.0%) 18 (90.0%)
Treatment Duration (mean days)	
Arm A Arm B	10.8 ± 2.2 15.0 ± 7.8

Results

A total of 5 physicians at the University of Virginia performed BVHPS insertion and removal during the clinical trial. One or two therapy bags were utilized for each case, depending on the patient anatomy and brachytherapy applicator placement daily. The longest duration of use for a single fraction was five hours. Dose summation reports were provided, showing that the patients received the intended doses to the target volumes (high risk clinical target volume (HR-CTV)).

Primary Endpoint Analysis

The dosimetry results for the D2cc bladder and rectum and the HR-CTV for Fractions 2 and 3 are shown in the tables below. There was no evidence to show that the D2cc for bladder or rectum is different between the subject device and standard gauze packing, with high variability of dosimetric results, as may be expected given the clinical context and the sample size.

Table 4. Bladder Dosimetry for Fractions 2 and 3*

	Gauze Packing		BVHPS		
Subject number	**Prescribed dose per fraction (Gy)****	**D2cc**	**Prescribed dose per fraction (Gy)****	**D2cc**	**D2cc Difference (Gauze Packing - BVHPS)**
01-002	6.63	4.19	5.03	3.36	0.83
01-003	6.49	2.77	6.96	4.14	-1.37
01-004	6.23	2.21	5.53	3.2	-0.99
01-005	5.9	3.73	5.9	3.79	-0.06
01-006	5.13	3.75	5.74	3.42	0.33
01-007***					
01-008	6.04	2.25	8.41	2.48	-0.23
01-009	5.04	3.39	6.16	2.41	0.98
01-010	6.54	3.8	6.37	3.23	0.57
01-011	5.86	4.71	6.99	4.32	0.39
01-012	5.49	4.58	6.89	2.17	2.41
01-013	8.66	3.49	5.1	4.28	-0.79
01-014	7.56	2.94	5.92	3.28	-0.34
01-015	6.01	4.46	4.51	3.54	0.92
01-016	7.03	3.19	6.58	3.03	0.16

01-017	5.85	3.22	6.54	3.99	-0.77
01-018	9.24	3.66	6.4	3.22	0.44
01-019	6.76	4.12	6.32	4.81	-0.69
01-020	5.81	3.93	6.31	3.46	0.47
01-021	7.57	2.81	7.97	3.78	-0.97
Mean	6.52	3.54	6.30	3.47	**0.07**
Standard Deviation	1.11	0.73	0.95	0.68	**0.91**

*D2cc: Dose to the hottest 2 cc of the organ at risk, bladder, Gy: Gray
** HRCTV D90
*** Patient 01-007 was not considered in the Per Protocol population for the primary endpoint because a not per protocol standard packing was utilized for fraction #2 in place of the per protocol BVHPS.

Table 5. Rectal dosimetry for Fractions 2 and 3*

	Gauze Packing		**BVHPS**		
Subject number	**Prescribed dose per fraction (Gy)****	**D2cc (Gy)**	**Prescribed dose per fraction (Gy)****	**D2cc (Gy)**	**D2cc Difference (Gauze Packing - BVHPS)**
01-002	6.63	2.87	5.03	3.24	-0.37
01-003	6.49	2.94	6.96	3.15	-0.21
01-004	6.23	3.79	5.53	4.24	-0.45
01-005	5.9	3.45	5.9	3.42	0.03
01-006	5.13	3.19	5.74	3.54	-0.35
01-007***					
01-008	6.04	2.8	8.41	3.56	-0.76
01-009	5.04	2.35	6.16	3.16	-0.81
01-010	6.54	3.08	6.37	2.39	0.69
01-011	5.86	3.38	6.99	2.76	0.62
01-012	5.49	3.41	6.89	4.06	-0.65
01-013	8.66	4.36	5.1	3.47	0.89
01-014	7.56	2.52	5.92	3.01	-0.49
01-015	6.01	2.73	4.51	2.57	0.16
01-016	7.03	3.06	6.58	3.06	0.00
01-017	5.85	1.82	6.54	2.19	-0.37
01-018	9.24	3.28	6.4	3.44	-0.16
01-019	6.76	2.34	6.32	3.43	-1.09
01-020	5.81	3.29	6.31	2.8	0.49
01-021	7.57	3.39	7.97	3.85	-0.46
Mean	6.52	3.06	6.30	3.23	**-0.17**
Standard Deviation	1.11	0.57	0.95	0.55	**0.54**

*D2cc: Dose to the hottest 2 cc of the organ at risk, rectum, Gy: Gray
** HRCTV D90

*** Patient 01-007 was not considered in the Per Protocol population for the primary endpoint because a not per protocol standard packing was utilized for fraction #2 in place of the per protocol BVHPS.

Additionally, the proportion of prescribed dose, defined as dose to structure/prescribed dose to HR-CTV D90, was calculated for each patient, and the results showed that there were no clinically meaningful differences between the packing mechanisms. See Tables 6 and 7 below.

Table 6. Bladder D2cc comparison for Fractions 2 and 3 (Percentage of HR-CTV D90)

	Percentage of HR-CTV D90 (Gauze Packing) (%)	Percentage of HR-CTV D90 (BVHPS) (%)	Difference in Percentages (Gauze - BVHPS) (%)
Mean	55.96	56.53	-0.57
Standard Deviation	16.0	14.5	20.8

Table 7. Rectum D2cc comparison for Fractions 2 and 3 (Percentage of HR-CTV D90)

	Percentage of HR-CTV D90 (Gauze Packing) (%)	Percentage of HR-CTV D90 (BVHPS) (%)	Difference in Percentages (Gauze - BVHPS) (%)
Mean	47.50	51.74	-4.90
Standard Deviation	9.9	11.0	11.9

Secondary Endpoint Analysis – Adverse Events

Table 8: All Adverse Events

Subject	Arm	CTC AE v5 Description	AE Times	Toxicity Grade	Relation to Brachytherapy	Relation to BVHPS
01-001		NONE				
01-002	B	Vaginal inflammation	Between fraction 2 and 3	1	Unrelated	Definite
01-002	B	Vaginal Hemorrhage	Between fraction 5 and 30 day follow-up	1	Unrelated	Unrelated
01-003	B	Dysuria	Between fraction 2 and 3	1	Unrelated	Unrelated
01-003	B	Dizziness	Between fraction 3 and 4	2	Unlikely	Unrelated
01-003	B	Fatigue	Between fraction 3 and 4	2	Probable	Unrelated
01-003	B	Nausea	Between fraction 3 and 4	2	Probable	Unrelated
01-003	B	Vomiting	Between fraction 3 and 4	2	Probable	Unrelated
01-003	B	Vaginal pain	Fraction 4	2	Definite	Definite
01-004	B	Diarrhea	Fraction 1	1	Probable	Unrelated
01-004	B	Vaginal hemorrhage	Fraction 2	1	Definite	Definite
01-004	B	Bloating	Fraction 2	1	Unrelated	Unrelated
01-004	B	Vaginal dryness	Fraction 2	1	Probable	Unrelated
01-004	B	Fatigue	Between fraction 5 and follow up	1	Possible	Unrelated
01-004	B	Dysuria	Between fraction 5 and 30 day follow up	1	Unrelated	Unrelated
01-004	B	Pelvic pain	Between fraction 5 and follow up	1	Unrelated	Unrelated
01-004	B	Pelvic pain	Between fraction 5 and follow up	3	Unrelated	Unrelated
01-005	A	Dysuria	Fraction 5	2	Unrelated	Unrelated

01-005	A	Vaginal pain	Fraction 5	2	Definite	Definite
01-005	A	Fatigue	Between fraction 5 and follow up	1	Definite	Unrelated
01-006	A	Pelvic pain	Between fraction 5 and follow up	1	Unrelated	Unrelated
01-006	A	Fatigue	Between fraction 5 and follow up	1	Possible	Unrelated
01-006	A	Urinary urgency	Between fraction 5 and follow up	1	Possible	Unrelated
01-006	A	Diarrhea	Between fraction 5 and follow up	1	Possible	Unrelated
01-007	B	Pelvic pain	Between fraction 1 and 2	2	Possible	Unlikely
01-008	A	Constipation	Between fraction 5 and 30 day follow up	1	Unrelated	Unrelated
01-009		NONE				
01-010	B	Pelvic pain	Fraction 3	2	Probable	Unrelated
01-010	B	Vaginal pain	Fraction 4	1	Probable	Unrelated
01-010	B	Vaginal hemorrhage	Fraction 5	1	Unlikely	Unrelated
01-010	B	Vaginal discharge	Between fraction 5 and 30 day follow up	1	Possible	Unrelated
01-010	B	Vaginal pain	Between fraction 5 and 30 day follow up	1	Possible	Unrelated
01-011	A	Infections and infestations	Baseline	3	Unrelated	Unrelated
01-011	A	Vaginal pain	Fraction 2	1	Definite	Unrelated
01-011	A	Dermatitis radiation	Between fraction 2 and 3	2	Unrelated	Unrelated
01-011	A	Facial pain	Between fraction 5 and follow-up	1	Unrelated	Unrelated
01-011	A	Urinary tract infection	Between fraction 5 and follow-up	2	Possible	Unlikely
01-013	B	Dyspareunia	Between fraction 4 and 30 day follow up	1	Possible	Unlikely
01-014		NONE				
01-015	B	Vaginal inflammation	Fraction 2	2	Probable	Unrelated
01-015	B	Vaginal pain	Fraction 2	2	Probable	Unrelated
01-015	B	Vaginal hemorrhage	Fraction 3	1	Unlikely	Possible
01-015	B	Vaginal inflammation	Fraction 4	1	Probable	Unrelated
01-015	B	Vaginal infection	Fraction 4 or between fraction 3 and 4	1	Unrelated	Unrelated
01-016		NONE				
01-017		NONE				
01-018	A	Vaginal pain	Fraction 2	2	Definite	Unrelated
01-019	B	Pelvic pain	Fraction 3	2	Unlikely	Unrelated
01-020		NONE				
01-021	A	Anemia	Fraction 4	3	Unlikely	Unrelated
01-021	A	Dermatitis radiation	Between fraction 4 and 30 day follow up	2	Probable	Unrelated
01-021	A	Anorexia	Between fraction 4 and follow up	1	Possible	Unrelated

All BVHPS subject adverse events were reviewed for relationship to the investigational device. There were three events which did or may have occurred in relationship to the investigational device and are summarized in the table below.

Table 9: Relationship to BVHPS		
Event Type	**Relationship**	**Description**
Grade 2 Vaginal Pain	**Definitely**	Recovered/resolved without sequelae
Grade 1 Vaginal Hemorrhage	**Definitely**	Spotting; Recovered/resolved without sequelae
Grade 2 Vaginal Pain	**Definitely**	Recovered/resolved without sequelae

Secondary Endpoint Analysis – Dose to D0.1cc, D1cc, and D2cc in periods 1 through 4 (e.g., fractions 2 through 5)

The results suggest no clinically meaningful differences in bladder and rectal dosimetry values between the two packing mechanisms.

Exploratory Endpoints - Surveys

The exploratory objectives of the study involved clinician and patient surveys. These objectives included (1) an estimation in the participant-reported discomfort between BVHPS and standard vaginal packing; (2) an estimation of the difference in physician/physicist evaluation of imaging properties and completeness of packing between BVHPS and standard packing (as evaluated by physical exam and CT imaging); and (3) an estimation of the difference in physician-scored use experience between BVHPS and standard vaginal packing. See a summary of the results of the assessment surveys in the table below.

Table 10: Clinician and Patient Surveys		
	Standard Packing n (%)	BVHPS n (%)
Patient		
Discomfort during the entire brachytherapy treatment (n = 57)*		
• none • mild • moderate • severe	1 (3.7%) 11 (40.7%) 14 (51.9%) 1 (3.7%)	2 (6.7%) 14 (46.7%) 10 (33.3%) 4 (3.3%)
Discomfort during vaginal packing placement and removal (n = 57)*		
• none • mild • moderate • severe	2 (7.4%) 12 (44.4%) 8 (29.6%) 5 (18.5%)	7 (23.3%) 11 (36.7%) 10 (33.3%) 2 (6.7%)
Physician		
Completeness of the packing (n = 77)		
• excellent • good • fair • poor	3 (7.7%) 19 (48.7%) 14 (35.9%) 3 (7.7%)	5 (13.1%) 25 (65.8%) 7 (18.4%) 1 (2.6%)
Imaging clarity of the packing (n = 77)		
• very clear • clear	9 (23.1%) 17 (43.6%)	0 23 (60.5%)

• poor • no distinction	13 (33.3%) 0	15 (39.5%) 0
Ease of packing placement and removal (n = 62) **		
• extremely easy • somewhat easy • somewhat difficult • extremely difficult	0 21 (72.4%) 8 (27.6%) 0	7 (21.1%) 22 (66.7%) 2 (6.1%) 2 (6.1%)
Physicist		
Completeness of the packing (n = 77)		
• excellent • good • fair • poor	10 (25.6%) 21 (53.9%) 6 (15.4%) 2 (5.1%)	17 (44.7%) 16 (42.1%) 5 (13.2%) 0
Imaging clarity of the packing (n = 77)		
• very clear • clear • poor • no distinction	15 (38.5%) 20 (51.3%) 4 (10.3%) 0	12 (31.6%) 21 (55.3%) 3 (7.9%) 2 (5.3%)
* Surveys were not completed by patients who underwent anesthesia as the patient was not awake and unable to assess the procedure. ** One physician did not have surveys performed due to a conflict of interest and involvement with the device manufacturer.		

The participant surveys were administered to patients within one hour of the brachytherapy procedure for any procedure that was not administered under anesthesia (i.e., the participant was awake and able to assess the experience).

The clinician surveys were completed by the physician and physicist performing the brachytherapy procedures. Clinician assessment of packing completeness was based on physical examination and CT imaging. The results of the physician surveys showed that the BVHPS device received a larger proportion of favorable ease-of-use scores than gauze. Investigator observations from the clinical trial included that the BVHPS device remained solid, and in appropriate position, throughout the treatment planning and delivery process.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

Conclusions

The results of the clinical study support that there are no clinically meaningful differences in the D2cc in the rectum and bladder for BVHPS vs. standard gauze packing. As the trial did not meet the powered accrual number, non-inferiority could not be statistically determined. However patient accrual was sufficient to judge comparability of D2cc between the two methods. Additionally, the use of BVHPS on patients receiving intracavitary brachytherapy for cervical cancer was not associated with an increase in serious adverse events compared to the standard packing control group.

The patient survey results suggested less patient discomfort due to BVHPS placement and removal when compared to gauze. The clinician and physicist surveys also support favorable ease of use and completeness of packing. Variable results were observed for clarity on imaging, with fewer physicians describing BVHPS as "very clear" on CT imaging compared to gauze.

LABELING

The labeling consists of Instructions for Use and an exterior device label.

The Instructions for Use include a device description, Indications for Use, Contraindications, Warnings, Instructions on insertion, installation, and removal, the functional use life of the device, expiration date, a summary of the clinical results including adverse events, and an example CT image of the device in a patient.

The device label includes the expiration date.

The labeling meets the requirements of 21 CFR 801.109 for prescription devices.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a vaginal hydrogel packing system and the measures necessary to mitigate the risks.

Risks to Health	**Mitigation Measures**
Unintended irradiation of healthy tissue and/or underdosing of the target	Clinical performance data Performance testing Labeling
Tissue damage from device instability, failure, or removal	Clinical performance data Non-clinical performance testing Labeling
Infection	Sterilization validation Non-clinical performance testing Labeling Shelf life testing
Adverse tissue reaction	Biocompatibility evaluation
Prolonged or delayed procedure due to delays caused by device deployment, instability, or failure	Clinical performance data Labeling
Patient discomfort	Clinical performance data Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the vaginal hydrogel packing system is subject to the following special controls:

(1) Clinical performance data must demonstrate the device performs as intended under anticipated conditions of use and evaluate the following:
    (i) Radiation dose to adjacent organs at risk;
    (ii) Device stability;
    (iii) Ability to deploy, expand, and remove the device; and
    (iv) Patient comfort.
(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must include:
    (i) Testing to evaluate the effect of therapeutic radiation levels on device integrity;
    (ii) Bioburden testing to demonstrate the device does not pose an infection risk, if the device is not provided sterile; and
    (iii) Structural integrity testing of the container, including tensile strength, container leakage, and burst strength.
(3) Performance testing must demonstrate space creation and maintenance for the duration of a radiation treatment fraction.
(4) The patient-contacting components of the device must be demonstrated to be biocompatible.
(5) Performance data must demonstrate the sterility of patient-contacting components of the device that are provided sterile.
(6) Performance data must support the shelf life of the device by demonstrating package integrity and device functionality over the labeled shelf life
(7) Labeling must include:
    (i) Warnings that:
        (A) A 3-dimensional (3D) imaging method is needed to ensure the device is placed correctly; and
        (B) Failure to perform the standard imaging position verification protocol may cause the device to not perform as intended.
    (ii) Instructions on how to proceed if the device fails to perform as intended;
    (iii) A summary of clinical data relevant to the device, including device-related complications; and
    (iv) An expiration date or shelf life.

BENEFIT-RISK DETERMINATION

The probable risks are based on nonclinical laboratory data and data collected from the clinical study described above. The probable risks include: 1) Unintended irradiation of healthy tissue and/or underdosing of the target, 2) Tissue damage from applicator instability, failure, or removal, 3) Infection, 4) Adverse tissue reaction, 5) Prolonged or delayed procedure due to delays caused by device deployment, instability, or failure, 6) Patient discomfort.

The probable benefits of the device are also based on nonclinical laboratory data and data collected from the clinical study described above. The probable benefit of the device compared to the standard is that the gel is easier to remove and more comfortable for the patient. The current standard of care is gauze packing which may be more cumbersome and time-consuming, and it may cause more discomfort to the patient during removal. The sponsor demonstrated that there was no clinically meaningful difference in dose to organs at risk (OARs) and the tumor

when comparing standard gauze packing to the subject device in a clinical study. The sponsor also provided questionnaires that indicated that the physicians favored the device over standard gauze based on ease of placement and removal and packing assessment, and patient surveys indicated that they had less discomfort with the device compared to standard gauze.

Patient Perspectives

This submission included patient surveys which evaluated discomfort during the brachytherapy treatment and during the vaginal packing placement and removal. See results of the surveys above in the section "Summary of Clinical Information" > "Results" > "Exploratory Endpoints – Surveys"

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The BrachyGel Vaginal Hydrogel Packing System is a single-use, non-sterile, disposable, non-powered positioning device that delivers self-expanding hydrogel that forms and expands within the vaginal cavity. The purpose of this device is to displace the vaginal wall and adjacent pelvic tissues during radiation therapy planning and delivery, to reduce dose to adjacent tissues by attenuation of radiation dose, and to stabilize radiation treatment equipment during radiation therapy planning and delivery. The placement of the hydrogel device requires a physician or physician directed healthcare professional, and is performed as a separate procedure outside of brachytherapy applicator insertion, computed tomography and/or magnetic resonance imaging exam, radiation treatment planning and radiation treatment delivery. This device is not intended to be inserted into the uterine cavity or rectum. This device is intended to be in place temporarily and removed after less than 24 hours.

Though the probable risks are unintended radiation to healthy tissue and underdosing of the target, as well as adverse effects to the healthy tissue and patient, the probable benefit of the device is that it is easier to remove and more comfortable for the patient than the standard of care. The probable benefits outweigh the probable risks for the BrachyGel Vaginal Hydrogel Packing System. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the BrachyGel Vaginal Hydrogel Packing System is granted and the device is classified as follows:

> Product Code: QXR
> Device Type: Vaginal hydrogel packing system
> Regulation Number: 21 CFR 892.5735
> Class: II