510K LETTER

Palette Life Sciences
% David Goodnough
Regulatory Affairs Manager
27 East Cota Street, Suite 402
Santa Barbara, California 93101

Re: K220641
Trade/Device Name: Barrigel Injectable Gel
Regulation Number: 21 CFR 892.5725
Regulation Name: Absorbable Perirectal Spacer
Regulatory Class: Class II
Product Code: OVB
Dated: March 4, 2022
Received: March 4, 2022

Dear David Goodnough:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Palette Life Sciences
% David Goodnough
Regulatory Affairs Manager
27 East Cota Street, Suite 402
Santa Barbara, California 93101

May 26, 2022

Re: K220641
Trade/Device Name: Barrigel Injectable Gel
Regulation Number: 21 CFR 892.5725
Regulation Name: Absorbable Perirectal Spacer
Regulatory Class: Class II
Product Code: OVB
Dated: March 4, 2022
Received: March 4, 2022

Dear David Goodnough:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Julie Sullivan -S

Julie Sullivan, Ph.D.
Assistant Director
DHT8C: Division of Radiological Imaging
and Radiation Therapy
OHT8: Office of Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K220641

Device Name
Barrigel Injectable Gel

Indications for Use *(Describe)*
Barrigel is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space, it is the intent of Barrigel to reduce the radiation dose delivered to the anterior rectum. Barrigel is composed of biodegradable material and maintains space for the entire course of prostate radiotherapy treatment and is intended to be absorbed by the patient's body over time.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Section 5. 510(k) Summary for Barrigel® Injectable Gel

This 510(k) Summary for Barrigel Injectable Gel has been generated in accordance with 21 CFR §807.92 *Content and format of a 510(k) summary*. In response to the Safe Medical Devices Act of 1990, the following summarizes the information upon which substantial equivalence is based.

5.1 Sponsor

Palette Life Sciences, Inc.
27 East Cota Street, Suite 402
Santa Barbara, CA 93101

5.2 Contact

David Goodnough
Regulatory Affairs Manager
Palette Life Sciences
Phone: 805-869-7087
Email: dgoodnough@palettelifesciences.com

5.3 Date of 510(k) Summary Preparation

5 May, 2022

5.4 Proposed Device

Trade Name: Barrigel Injectable Gel
Common/Usual Name: Barrigel
Regulation Number: 892.5725
Classification Name: Absorbable Perirectal Spacer
Classification: Class II (Special Controls)
Product Code: OVB
Review Panel: Radiology

5.5 Predicate Device

Trade Name: SpaceOAR Hydrogel System, Model Number: SO-2101
Common/Usual Name: Hydrogel Spacer
Regulation Number: 892.5725
Classification Name: Absorbable Perirectal Spacer
Classification: Class II
Product Code: OVB
Identification of Predicate Device: SpaceOAR Hydrogel System, K202224

5.6 Device Description

Barrigel Injectable Gel is a sterile, transparent, biodegradable gel of stabilized hyaluronic acid (HA) at a concentration of 20 mg/mL in phosphate buffered saline.

The HA, formulated utilizing Q-Med's patented NASHA™ technology, is produced from non-animal hyaluronic acid by fermentation of *Streptococcus* species of bacteria. The HA gel is cross-linked with 1,4-butanediol diglycidyl ether (BDDE) under alkaline conditions, thereby creating ether bonds between the HA chains, resulting in a three-dimensional network. The gel is insoluble in water and organic solvents.

Barrigel is supplied in a single-use glass syringe, containing 3 mL of product. Each syringe is terminally sterilized by moist heat in a heat-sealed pouch of PET/Tyvek® and packaged in a cardboard carton. Barrigel is intended for use by health-care professionals only and should be stored up to 25° C (77° F). Barrigel is manufactured for Palette Life Sciences by Q-Med AB, a subsidiary of Galderma AB.

The Barrigel needle is a sterile 18G stainless-steel needle, 20 cm in length, provided with an optional stylet and protected by a polyester sheath which is removed prior to use. The needle is sterilized by radiation and two (2) needles are provided in each heat-sealed pouch of PET/Tyvek®, packaged in a cardboard carton. The Barrigel needle is identical to the needle used during the Barrigel IDE study and is manufactured for Palette Life Sciences by R.K. Manufacturing.

5.7 Indications for Use

Barrigel is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and, in creating this space, it is the intent of Barrigel to reduce the radiation dose delivered to the anterior rectum. Barrigel is composed of biodegradable material and maintains the space

for the entire course of prostate radiotherapy treatment and is intended to be absorbed by the body over time.

5.8 Technological Characteristics Compared to the Predicate

The intended use and principles of operation of the proposed Barrigel device and the predicate device are identical and meet the regulatory definition for Absorbable Rectal Spacers outlined in 21 CFR 892.75. Both devices are systems that facilitate implantation of biodegradable materials between the anterior rectal wall and the prostate prior to radiotherapy for prostate cancer, mechanically creating space between the anterior rectal wall and the prostate. Both devices maintain the separation between the prostate and the anterior rectal wall during the entire course of treatment and are absorbed by the body over time. The target population of both devices is adult human males being treated for prostate cancer. Both devices are single-use and are provided sterile to licensed medical professionals (only) and utilize Transrectal Ultrasound (TRUS) to provide safe and accurate placement of the device.

The shelf-life of 24 months for Barrigel and 24 months for SpaceOAR; intended volume of treatment of 9-12 ml for Barrigel and 10 ml for SpaceOAR; and 18G needles (20 cm length for Barrigel and 15 cm length for SpaceOAR) are considered to represent technological characteristics of the devices that are similar and support the claim of substantial equivalence between the subject and predicate devices.

The differences between the subject and predicate device materials, syringes, treatment process, and absorption rates of the devices are as follows:

- Material:
    - **Barrigel Injectable Gel** is comprised of non-animal hyaluronic acid (NASHA) sourced from the fermentation of *Streptococcus* species of bacteria and produced by cross-linking HA with BDDE,

resulting in a three-dimensional network. Barrigel does not require pre-mixing prior to use.

- **SpaceOAR System** is comprised of synthetic polyethylene glycol (PEG); a hydrophilic polymer, that when cross-linked produces a three-dimensional hydrogel. SpaceOAR is prepared by mixing PEG powder with a Diluent solution which is mixed with a salt-buffer accelerator solution during injection.

- Syringe:
  - **Barrige**l utilizes a single sterile glass syringe containing 3 ml of Barrigel cross-linked HA material in buffered saline solution.
  - **SpaceOAR System** utilizes a dual syringe system containing 10 ml of hydrogel material: One syringe is a mixture of PEG powder (provided in a separate vial) with a Diluent solution which is then combined during injection with second syringe containing an accelerant solution of buffered saline. The two syringes are injected together via a Y-connector attached to the two syringes.
- Process:
  - **Barrigel** does not require hydro-dissection prior to injection.
  - **SpaceOAR System** requires hydro-dissection prior to injection.
- Absorption:
  - **Barrigel** – As only a limited number (6% = 6/98) of patients were followed to complete resorption at 18 months, it is unknown if there are potential late complications or side effects of incompletely resorbed gel. Table 1 below, represents resorption data available for 96 patients at the 3-month visit, 55 patients at the 12-month visit, and 20 patients at the 18-month visit. There is currently no evidence that reflects potential late complications or side effects of incompletely resorbed gel.
  - **SpaceOAR -** Completely absorbed approximately 6 months after implantation.

Table 1. Resorption of Barrigel over Time (as reflected by patient visit)

Visit	Statistic	Percent Resorption
Immediate Post-Injection	N (patients)	98
	MIN	0%
	MAX	0%
	MEAN	0%
	STANDARD DEVIATION	0
3-Month Visit	N (patients)	96
	MIN	-11.4%*
	MAX	66.8%
	MEAN	18.4%
	STANDARD DEVIATION	15.4
12-Month Visit	N (patients)	55
	MIN	20.4%
	MAX	90.3%
	MEAN	57.2%
	STANDARD DEVIATION	16.8
18-Month Visit	N (patients)	20
	MIN	35.0%
	MAX	93.9%
	MEAN	73.6%
	STANDARD DEVIATION	15.5

* Negative resorption in some subjects due to the hydrophilic nature of Barrigel and the temporary increase in water present at the point of injection.

The technological characteristics of the subject device are substantially equivalent to the predicate device based on the intended use, delivery system and mode of operation of both devices. Differences between the predicate and subject devices are the base device material, syringe configuration, additional pre-injection process step, and rates of absorption.

Both the subject and predicate devices have long histories of safe use and differences that may exist in the effectiveness of Barrigel are well addressed by the biocompatibility, performance, and clinical data. The safety profile of Barrigel has been previously reviewed as part of IDE G190206.

Injectable NASHA products such as Barrigel possess a safety profile based on more than 40 million patient treatments over the past 20 years of aesthetic, therapeutic and spacing indications. Barrigel is approved and has been used in over 1,250 treatments for the recommended indication in the EU and Australia with no reports of serious, device related adverse events.

5.9 Biocompatibility

Biocompatibility testing of Barrigel was performed per applicable standards on both irradiated and non-irradiated Barrigel samples, addressing the following evaluation endpoints:

- Cytotoxicity
- Sensitization
- Irritation/intracutaneous Reactivity
- Acute Systemic Toxicity
- Material Mediated Pyrogenicity
- Subacute/Sub-chronic Toxicity
- Genotoxicity
- Implantation
- Chronic Toxicity
- Carcinogenicity

Tests for reproductive and developmental toxicity, toxicokinetics, immunotoxicity and carcinogenicity were determined to not be applicable to Barrigel since Barrigel does not contain any levels of materials considered hazardous; does not contain materials of toxicological significance; and is non-immunogenic. It was further determined that use of Barrigel does not represent a risk of tumor development and therefore does not present a cancer risk.

Examination of the risk-based biocompatibility assessment indicates Barrigel met the acceptance criteria of the biocompatibility endpoint tests listed above.

5.10 Performance Testing – Bench

Nonclinical testing was performed on Barrigel components and materials. These tests included physio/chemical characteristics of Barrigel injectable gel and were performed utilizing three (3) production lots of Barrigel to ensure consistency and reproducibility throughout the manufacturing process. Physio/chemical characterization was performed in accordance with EN ISO 10993-18 and included the following:

- HA Content
- Gel Content
- Extractable Carbohydrates
- Swelling Factor
- pH
- Particle Size Distribution
- Bacterial endotoxins
- Sterility
- Viscoelastic Properties
- Osmolality
- Elemental Impurities
- Residual Proteins
- Enzymatic Degradation
- Extrusion Force

Results of the physio/chemical characterization indicated all acceptance criteria were met and illustrated that there is minimal variation between production lots.

5.11 Performance Testing – Animal

A rabbit implantation study involving subcutaneous injections of both irradiated and non-irradiated Barrigel was conducted to identify early tissue response, local effects secondary to degradation as well as characterization and degree of resorption over the 52-week test period.

Test results demonstrated minimal to no reaction to irradiated Barrigel when compared to the non-irradiated control. In addition, and using the standard set forth in ISO 10993-6, Barrigel Injectable Gel can be considered completely absorbed, when material is significantly resorbed (≥ 90%) and tissue reactivity has subsided.

5.12 Performance Testing – Clinical

IDE G190206 is a clinical study conducted to determine the extent to which Barrigel Injectable Gel is able to mechanically increase the distance between the prostate and the rectum and thereby decrease the exposure of the rectum to the radiation dose in patients receiving definitive radiation therapy for localized prostate cancer. The study is a randomized, controlled, single-blinded multicenter study, conducted over 14 study sites. The Barrigel IDE was conducted to support the 510(k) submission and represented the first stage of a two-stage study.

In the second stage of the study and upon approval, all study subjects will continue with a post-market surveillance (PMS) study for longer-term follow-up.

All study subjects were treated with transrectal, ultra-sound guided trans-perineal prostate fiducial marker placement. Randomly assigned subjects followed fiducial placement with Barrigel injection between the rectum and the prostate. Study subjects not receiving Barrigel are the control group. All subjects received radiation therapy using IMRT.

The primary effectiveness endpoint for the Barrigel subjects in the study is the achievement of a 25% reduction in the volume of the rectum receiving 90% of the prescription radiation dose.

The key secondary safety objective for the study is determination that the Barrigel spacer does not increase the evidence of acute Grade 2+ GI toxicity within the first 3 months following treatment, assessed using the proportion of subjects experiencing one or more incidents of acute Grade 2+ toxicity within the first 3 months following treatment.

The primary effectiveness endpoint of the study was met and demonstrated that the proportion of subjects achieving a 25% reduction in the volume of the rectum receiving 90% of the prescribed radiation dose (based on pre-injection and immediate post-treatment CT and MRI scans), was greater than the minimally acceptable success rate of 70%, established by the De Novo application of the predicate device. The success rate for stage 1 of the Barrigel IDE indicates that 98.6% of the complete cases in the Barrigel group achieved at least a 25% reduction in the volume of the rectum receiving 90% of the prescription dose, the lower boundary of the 95% confidence interval (LCL) is 0.923 and the one-sided p-value is < 0.0001.

Therefore, study success has been demonstrated and has been shown to be effective in achieving a clinically relevant reduction in rectal radiation

The key secondary safety objective, demonstrating that the proportion of subjects with one or more acute Trade 2+ GI toxicities at 3 months for the Barrigel group is no worse than (non-inferior to) the proportion of subjects in the control group, using a non-inferiority margin of 10%, has been met.

The proportion of subjects with one or more acute Grade 2 or higher toxicities was 0.028 in the Barrigel group and 0.147 in the control group. The upper limit of the one-sided 95% CI (UCL) is for the difference in proportions (Barrigel minus control), -0.1189 and the two-sided Fisher's Exact p-value for the differences in proportion was 0.0348. As the UCL was less than the non-

inferiority margin of 0.10, Barrigel is shown to be non-inferior to the control and study success is demonstrated. In addition, as the two-sided Fisher's Exact test is < 0.05, Barrigel is shown to be superior to the control.

As indicated, per study protocol a sensitivity analysis of the key secondary safety objective was performed, and the safety objective was met. This supports the robustness and study success finding of the key secondary safety results. To assess any difference in treatment effect across subgroups, the key secondary safety objective was analyzed separately for three factors: ADT usage, erectile quality, and study site. The results show that Barrigel is consistently safe in all subgroups analyzed. These sensitivity and subgroup analysis support the robustness and study success finding of the key secondary safety results.

There were no reports of unexpected adverse device effects (UADEs) or Barrigel-related adverse events.

Resorption of Barrigel following implantation was determined based on clinical data from independent retrospective and prospective clinical studies (Goñi and RPAH1) of Restylane SubQ, which is identical in all respects to Barrigel except the amount of product contained in syringes of each product: 3 ml per syringe for Barrigel and 2 ml per syringe for Restylane SubQ. The typical amount of both Barrigel and Restylane SubQ per treatment is 9 ml, with variation according to individual patient physiology and at the discretion of the administering physician.

The Goñi data represented 27 male subjects who underwent perirectal injections of Restylane SubQ (2-6 ml) with subsequent radiotherapy and/or brachytherapy for prostate cancer. Follow-up MRIs were performed at a minimum of 60 months post injection. The MRIs indicated complete resorption, as evidenced by the absence of detectable gel by MRI, at 60 months post-injection. There were no indications of any adverse tissue reaction during degradation and absorption of the gel.

The RPAH1 clinical study represented 36 male subjects injected with Restylane SubQ (10 ml) prior to IMRT (intensity-modulated radiation therapy) and IGRT (image-guided radiation therapy) for prostate cancer. Follow-up digital rectal examinations indicated material stability for the first 6 months following treatment with complete gel resorption for 18.5% of patients at 1-year post-treatment and complete gel resorption for 42.3% of patients after 2 years. No adverse tissue reactions were reported.

5.13 Substantial Equivalence

Biocompatibility and performance testing of Barrigel Injectable Gel, combined with results of the clinical studies, indicate that Barrigel is effective compared to control without increased risk and is substantially equivalent to the findings that supported FDA's approval and subsequent clearance of the predicate device.

Considering the complications and symptomology of rectal toxicity associated with radiation treatment for prostate cancer, which may last 6-18 months post-therapy, the benefits of Barrigel considerably outweigh the risks.
Both the subject and predicate device are low-to-moderate risk devices that are neither life-supporting nor life-sustaining, with risks that can be mitigated with appropriate use by medical professionals.

It is therefore reasonable to conclude that while Barrigel may have some different technological characteristics when compared to SpaceOAR, the benefits outweigh the potential risk of injury when used in accordance with the published instructions for use. The use of Barrigel does not represent new questions of safety or effectiveness and all attendant risks have been addressed by the provided test data and results.

Based on this information, Barrigel is substantially equivalent to SpaceOAR in terms of intended use and technological characteristics. Performance data summarized above supports that any differences in technology do not affect the safety and effectiveness of Barrigel and the risk/benefit profile for Barrigel supports substantial equivalence with the proposed predicate device.