September 17, 2018

Suzhou Hengrui Callisyn Biomedical Co., Ltd.
Xiao Chen
Regulatory Affairs Manager
Building 9, No. 8 Jinfeng Road, New District
Suzhou, Jiangsu Province 215163
China

Re: K173871
Trade/Device Name: CalliSpheres Embolic Microspheres, 8Spheres Embolic Microspheres
Regulation Number: 21 CFR§ 870.3300
Regulation Name: Vascular Embolization Device
Regulatory Class: II
Product Code: KRD, NAJ
Dated: August 13, 2018
Received: August 15, 2018

Dear Xiao Chen:

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/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); 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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). 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 (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Sharon M. Andrews -S

for
Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
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)*
K173871

Device Name
CalliSpheres Embolic Microspheres, 8Spheres Embolic Microspheres

Indications for Use *(Describe)*
Callispheres Embolic Microspheres and 8Spheres Embolic Microspheres are intended to be used for the embolization of arteriovenous malformations (AVMs) and hypervascular tumors, including uterine fibroids.

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.

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510(k) Summary

CalliSpheres Embolic Microspheres, 8Spheres Embolic Microspheres

(per 21 CFR 807.92)

1 Submitter

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Date Prepared: September 11, 2018

2 Proposed Device

Name of Device: CalliSpheres Embolic Microspheres, 8Spheres Embolic Microspheres

Common or Usual Name: Polyvinyl Alcohol Embolic Microspheres

Classification Name: Vascular Embolization Device (21 CFR 870.3300)

Classification: Class II

Panel: Cardiovascular

Product Code: KRD (device, embolization, arterial), NAJ (agents, embolic, for treatment of uterine fibroids)

3 Predicate Device

Device Name: Bead Block™

510(k) number: K150876

Manufacturer: Biocompatibles UK Ltd.

Regulation Number: 21CFR 870.3300

Product code: KRD (device, embolization, arterial),

NAJ (agents, embolic, for treatment of uterine fibroids)

The predicate device has not been subject to any design-related recall.

4 Device Description

CalliSpheres and 8Spheres Embolic Microspheres are compressible hydrogel microspheres with a regular shape, smooth surface, and calibrated size, which are formed as a result of chemical modification on polyvinyl alcohol (PVA) materials. CalliSpheres and 8Spheres Embolic Microspheres consist of a macromer derived from polyvinyl alcohol (PVA), and are hydrophilic, non-resorbable, and are available in a range of sizes. The preservation solution is 0.9% sodium chloride solution. The water content of fully polymerized microsphere is 91% ~ 94%. Microspheres can tolerate compression of 30%. CalliSpheres Embolic Microspheres are dyed blue to aid in the visualization of the microspheres in the delivery syringe. 8Spheres Embolic Microspheres are undyed and with natural color. CalliSpheres and 8Spheres Embolic Microspheres are supplied sterile and packaged in sealed glass vials.

CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres are intended to be used for the embolization of arteriovenous malformations (AVMs) and hypervascular tumors, including uterine fibroids. By blocking the blood supply to the target area, the tumor or malformation is starved of nutrients and shrinks in size.

CalliSpheres and 8Spheres Embolic Microspheres can be delivered through typical microcatheters in the 1.7- 4 Fr range. At the time of use, CalliSpheres and 8Spheres Embolic Microspheres are mixed with a nonionic contrast agent to form a suspension solution. CalliSpheres and 8Spheres Embolic Microspheres are intended for single use and are supplied sterile and non-pyrogenic. The device configurations of

CalliSpheres and 8Spheres Embolic Microsphere are described in Table 1 and Table 2 below. Product codes beginning with “B” represent CalliSpheres, while product codes beginning with “U” represent 8Spheres. Among the various size ranges of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres, the size ranges that can be used for uterine fibroid embolization are 500-700μm, 700-900μm and 900-1200μm.

Table 1: Device configurations of CalliSpheres Embolic Microspheres

Product Code	Calibrated Size (μm)	Quantity	Indication	
			Hypervascular Tumors/ Arteriovenous Malformations	Uterine Fibroid
B107S103	100-300	1ml microspheres : 7ml 0.9% sodium chloride	Yes	No
B107S305	300-500	1ml microspheres : 7ml 0.9% sodium chloride	Yes	No
B107S507	500-700	1ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
B107S709	700-900	1ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
B107S912	900-1200	1ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
B207S103	100-300	2ml microspheres : 7ml 0.9% sodium chloride	Yes	No
B207S305	300-500	2ml microspheres : 7ml 0.9% sodium chloride	Yes	No
B207S507	500-700	2ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
B207S709	700-900	2ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
B207S912	900-1200	2ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes

Table 2: Product configurations of 8Spheres Embolic Microspheres

Product Code	Calibrated Size (µm)	Quantity	Indication	
			Hypervascular Tumors/ Arteriovenous Malformations	Uterine Fibroid
U107S103	100-300	1ml microspheres : 7ml 0.9% sodium chloride	Yes	No
U107S305	300-500	1ml microspheres : 7ml 0.9% sodium chloride	Yes	No
U107S507	500-700	1ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
U107S709	700-900	1ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
U107S912	900-1200	1ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
U207S103	100-300	2ml microspheres : 7ml 0.9% sodium chloride	Yes	No
U207S305	300-500	2ml microspheres : 7ml 0.9% sodium chloride	Yes	No
U207S507	500-700	2ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
U207S709	700-900	2ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes
U207S912	900-1200	2ml microspheres : 7ml 0.9% sodium chloride	Yes	Yes

5 Indications for Use

CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres are intended to be used for the embolization of arteriovenous malformations (AVMs) and hypervascular tumors, including uterine fibroids.

6 Comparison of Technological Characteristics with the Predicate Device

The subject devices and predicate device have identical / similar technological characteristics as shown in Table 3.

Table 3: Performance Characteristics Comparison Table of CalliSpheres & 8Spheres Embolic Microspheres verses Predicate Devices

Items	Proposed Device	Predicate Device	Discussion of Differences
Device Name	CalliSpheres Embolic Microspheres & 8Spheres Embolic Microspheres	Bead Block ™	N/A
510(k) Number	K173871	K150876	N/A
Product Code	KRD, NAJ	KRD, NAJ	Identical
Intended Use / Indications For Use	CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres are intended to be used for the embolization of arteriovenous malformations (AVMs) and hypervascular tumors, including uterine fibroids.	Bead Block microspheres are intended to be used for the embolization of hypervascular tumors, including uterine fibroids and arteriovenous malformations (AVMs).	Identical: Indications for use of the proposed device is identical to that of Bead Block (K150876).
Materials	Polyvinyl alcohol (PVA), N-acryloylaminoacetaldehyde dimethyl acetal (NAAADA), 2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt, 0.9% Sodium Chloride Solution, Reactive Blue Dye #4 (only for CalliSpheres Embolic Microspheres)	Polyvinyl alcohol (PVA), N-acryloylaminoacetaldehyde dimethyl acetal (NAAADA), 2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt, buffered Saline, Reactive Blue Dye #4	Identical
Polymerization Method	Suspension polymerization	Suspension polymerization	Identical
Resorption	Non-resorbable	Non-resorbable	Identical

Appearance	Hydrogel microspheres with regular shape, smooth surface and calibrated size, CalliSpheres: Blue dyed 8Spheres: Undyed	Hydrogel microspheres with regular shape, smooth surface and calibrated size, Bead Block: Blue dyed	CalliSpheres are identical in appearance to Bead Block, 8Spheres are undyed. 8Spheres are identical to CalliSpheres except for the color. The lack of dye in 8spheres does not raise different questions of safety and effectiveness from the predicate.
Size Range (μm)	100-300 300-500 500-700 700-900 900-1200	100-300 300-500 500-700 700-900 900-1200	Identical
Sizes indicated for UAE (μm)	500-700 700-900 900-1200	700-900 900-1200	Different. CalliSpheres and 8Spheres of 500-700um are indicated for UAE. The difference in size does not raise different questions of safety and effectiveness.
Water content of microspheres	91% ～ 94%	Approximately 90-95%	Similar. Water content range of proposed device is narrower than that of predicate device. The slight difference of water content does not raise different questions of safety and effectiveness.
Storage media	0.9% sodium chloride solution	Phosphate buffered saline (PBS)	Similar. Both 0.9% sodium chloride solution and phosphate buffered saline (PBS) can be used for injection.
Quantity of Microspheres	1mL, 2mL	1mL, 2mL	Identical

Quantity of Storage Media	Both CalliSpheres and 8Spheres have the following two quantities: 1) 1ml microspheres in 7ml 0.9% sodium chloride solution to form a total volume of 8mL 2) 2ml microspheres in 7ml 0.9% sodium chloride solution to form a total volume of 9mL.	Bead Block Compressible Microspheres have the following two quantities: 1) 1 mL microspheres in 6ml PBS to form a total volume of 7mL 2) 2 mL microspheres in 5ml PBS to form a total volume of 7mL.	Similar, the slight difference of saline quantity does not raise different questions of safety and effectiveness.
Packaging	Both CalliSpheres and 8Spheres are sealed in borosilicate glass vial.	Bead Block is sealed in polycarbonate syringe	Similar. Packaging has been verified by packaging compatibility testing and does not raise different questions of safety and effectiveness.
Compressibility	30% by diameter	Approximately 30% by diameter	Identical
Suspension	The time taken to achieve suspension is less than 10 min, and the time maintaining suspension is longer than 4 mins.	The time taken to achieve suspension is less than 4 min, and the time maintaining suspension is longer than 4.5 mins.	Similar. The slight difference of time does not raise different questions of safety and effectiveness.
Delivery Method	Delivered to target position by micro-catheter under DSA.	Delivered to target position by micro-catheter under DSA.	Identical
Compatible Delivery Catheter	1.7-4Fr	1.5-5Fr	Similar. The specification for CalliSpheres and 8Spheres lies within the range of the predicate. The slight difference does not raise different questions of safety and effectiveness.
Radiopacity Method	Mixed with non-ionic contrast agent prior to injection	Mixed with non-ionic contrast agent prior to injection	Identical
Method of Supply	Sterile and single use	Sterile and single use	Identical
Shelf Life	Two years	Two years	Identical
Sterilization	Moist heat and non-pyrogenic	Moist heat and non-pyrogenic	Identical

Overall, the differences in technological characteristics between the subject and predicate do not raise different questions of safety and effectiveness.

7 Summary of Non-clinical Performance Testing

The device is subject to Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices issued on 29 December 2004 and was evaluated accordingly. The safety and effectiveness of CalliSpheres and 8Spheres have been evaluated by non-clinical testing including:

7.1 In-Vitro Bench Testing

The test items, methods and method references of CalliSpheres and 8Spheres Embolic Microspheres are as follows:

No.	Test items	Test methods and basis	Result
1	Appearance	USP 39 NF34 （2016）<1> Injections and Implanted Drug Products (Parenterals) -Product Quality Tests and <790> Visible Particulates In Injections	Met predefined acceptance criteria
2	pH test	USP39 NF34（2016）- <791> pH	Met predefined acceptance criteria
3	Size range confirmation	Method adapted from ISO 13322-1:2014 Particle size analysis – Image analysis methods – Part 1: Static image analysis methods. The particle sizes of Callispheres and 8spheres Embolic Microspheres were measured and confirmed by optical microscope, digital camera and corresponding particle size measurement software which have been calibrated and validated.	Met predefined acceptance criteria
4	Compressibility Test	A texture analyzer was used to test the compressibility of microspheres; microspheres were compressed of 30% by diameter and maintained for 10s. After the compression, the microspheres	Met predefined acceptance criteria

		were inspected by microscope for maintenance of shape and breakage.	
5	Catheter deliverability test	Particles were delivered through 1.7Fr - 4.0Fr microcatheters to evaluate the potential for clogging and breakage of spheres. The size of the microcatheter was selected based on the size of the microspheres. In order to simulate the tortuosity of the catheters used in clinical practice, the microcatheters were inserted into a model simulated to human hepatic artery to conduct the catheter deliverability test. Clogging was assessed during the test, and microspheres were inspected microscopically following delivery for signs of breakage or changes in shape.	Met predefined acceptance criteria
6	Water content test	USP 39 NF34 （2016）- <731> Loss on Drying	Met predefined acceptance criteria
7	Impurities and Residual Solvents Test	USP39 NF34（2016）- <1086> Impurities in Drug Substances and Drug Products，<467> Residual Solvents，<621> Chromatography，<857> Ultraviolet -Visible Spectroscopy	Met predefined acceptance criteria
8	Suspension	A suspension study of all variants of CalliSpheres and 8Spheres Embolic Microspheres was conducted with three commercially-available nonionic contrast agents based upon the following study: Lewis AL et. al. Comparative in vitro evaluation of microspherical embolization agents. J Mater Sci Mater Med. 2006 Dec: 17(12):1193-204.	Met predefined acceptance criteria
9	Sterility Test	USP 39 –NF34 （2016）<71> Sterility Tests	Met predefined acceptance criteria
10	Bacterial	USP39 -NF34 （2016）- <85>	Met predefined acceptance

	Endotoxins Test	Bacterial Endotoxins Test	criteria

Samples of CalliSpheres and 8Spheres Embolic Microspheres passed the performance tests listed above, indicating that device performance met the design requirements and is acceptable for the intended use.

7.2 Packaging Integrity and Shelf Life

CalliSpheres and 8Spheres Embolic Microspheres are supplied as sterile devices and packaged in sealed borosilicate glass vials.

According to ASTM F1980-16, accelerated aging tests equivalent to 2 years of shelf life were carried out on Callispheres and 8Spheres Embolic Microspheres, with 3 batches of each tested for all device specifications. Accelerated aging tests for package integrity were also carried out on the packaging materials including the bottles, rubber closures and aluminum-plastic covers.

The results of the performance tests of Callispheres and 8Spheres microspheres after accelerated aging demonstrated all samples met specifications. Therefore, the results support a 2 year shelf life of Callispheres and 8Spheres Embolic Microspheres.

7.3 Sterilization and Shelf Life

CalliSpheres and 8Spheres Embolic Microspheres are labeled as “Sterile” and “non pyrogenic.” CalliSpheres & 8Spheres Embolic Microspheres are sterilized by moist heat sterilization with validated parameters (121℃, 30 min) after sealing the vials. Sterilization validation was completed to a sterility assurance level (SAL) of 10^{-6} using the Overkill Approach per ANSI/AAMI/ISO 17665-1:2006(R)2013.

Callispheres and 8Spheres were tested for bacterial endotoxins per USP <85> Bacterial Endotoxins Test to a level of not more than 0.5EU/mL in accordance with the requirements of FDA guidance document: Guidance for Industry: Pyrogen Endotoxins Testing: Questions and Answers, issued June 2012.

7.4 Chemical Characterization

Chemical characterization testing was conducted on the CalliSpheres and 8Spheres Embolic microspheres and the saline preservation solution. The testing consisted of exhaustive extraction of the CalliSpheres and 8Spheres Embolic microspheres in purified water, ethanol, and hexane and analyzing the extracts using FTIR, ICP/MS, GC/MS, GC/MS headspace, and UPLC/MS. A risk analysis using a worst case risk

assessment approach was conducted based upon the findings of the exhaustive extraction. Using this approach, it was determined that the margins of safety (MOS) for potential chemical exposures indicated a low risk of chronic toxicity and carcinogenicity.

7.5 Biocompatibility Evaluation

Tests for biocompatibility were conducted in accordance with ISO 10993-1 and ASTM standards.

The conducted biocompatibility testing is shown in the following table, and the subject devices were demonstrated to be biocompatible.

Biocompatibility Evaluation	Summary
Cytotoxicity Study Using the ISO Elution Method	The test article, CalliSpheres Embolic Microspheres, was evaluated for potential cytotoxic effects using an *in vitro* mammalian cell culture test. This study was conducted following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity. The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity).
ISO Intracutaneous Study in Rabbits	The test article, CalliSpheres Embolic Microspheres, was evaluated for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article met the requirements of the test.
ISO Maximization Sensitization Study	The test article, CalliSpheres Embolic Microspheres, was evaluated for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.
ISO Systemic Toxicity Study	The test article, CalliSpheres Embolic Microspheres, was evaluated for acute systemic toxicity in mice. This study was conducted based on ISO 10993-11, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity. There was no mortality or evidence of systemic toxicity from the extracts injected into mice. Each test article extract met the requirements of the study.

Modified ASTM Hemolysis Study	The test article, CalliSpheres Embolic Microspheres, was evaluated for the potential to cause hemolysis. This study was conducted based on ASTM F756, Standard Practice for Assessment of Hemolytic Properties of Materials and ISO 10993-4, Biological evaluation of medical devices - Part 4: Selection of tests tor interactions with blood. The hemolytic index tor the test article in direct contact with blood was 0.6% and the direct contact was non-hemolytic.
ASTM Partial Thromboplastin Time	The test article, CalliSpheres Embolic Microspheres, was evaluated to determine the potential to cause an effect on the coagulation cascade via the intrinsic coagulation pathway. The study was conducted in accordance to ASTM F2382: Standard Test Method for Assessment of Circulating Blood-Contacting Medical Device Materials on Partial Thromboplastin Time (PTT). The test article average clotting time was lower and was not statistically different than the negative reference material. The test article met the requirements of the test.
SC5b-9 Complement Activation Assay	The test article, CalliSpheres Embolic Microspheres, and sponsor provided control (SPC), Embospheres, were evaluated for the potential to activate the complement system. This study was conducted based on ISO 10993-4, Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood. The test article, SPC, and comparative control were incubated in normal human serum (NHS) and SC5b-9 was measured in the exposed serum using an enzyme immunoassay. The test article was not considered to be a potential activator of the complement system.
USP Rabbit Pyrogen Study	The test article, CalliSpheres Embolic Microspheres, was evaluated for material mediated pyrogenicity in rabbits. The test was conducted based on USP, General Chapter <151>, Pyrogen Test. The procedure is recommended in ISO 10993-11, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity. The total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP requirements. The test article met the requirements for the absence of pyrogens.
Genotoxicity: Bacterial Reverse Mutation Study	The test article, CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres, were evaluated for the potential to cause mutagenic changes at the histidine locus of the *Salmonella typhimurium* tester strains TA98, TA100, TA1535. And TA1537 or at the tryptophan locus of the *Escherichia coli* tester strain WP2wv/v4. The study was conducted in the presence and absence of S9 metabolic activation based on ISO 10993-3, Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity and OECD 471, Guideline for Testing of Chemicals, Bacterial Reverse Mutation

	Test. The test article was extracted in dimethyl sulfoxide (DMSO) and saline. The DMSO and saline test article extracts were considered to be nonmutagenic to *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1537. and to *E. coli* tester strain WP2*uvrA.*
Genotoxicity: Mouse Lymphoma Assay	The test article, CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres, were evaluated for mutagenic potential using the mouse lymphoma forward gene mutation assay. The mouse lymphoma L5178Y/TK+/' cell line, heterozygous at the thymidine kinase (TK) locus, was used for this assay. The test article was extracted in serum-free cell culture medium (RPMIo) and dimethyl sulfoxide (DMSO). The RPMIo and DMSO test article extracts did not cause a 2-fold or greater increase in the mean mutant frequency of the L5178Y/TK+/' cell line either in the presence or absence of metabolic activation. The test article was not mutagenic.
ISO Muscle Implantation Study in Rabbits, 4 Weeks	The test article, CalliSpheres Embolic Microspheres, was implanted in muscle tissue of the rabbit to evaluate the local tissue response in accordance with ISO 10993-6, Biological evaluation of medical devices - Part 6: Tests for local effects after implantation. Sterile implant test articles were aseptically prepared. Negative control articles were sterilized by steam. The test article and negative control were intramuscularly implanted and animals were euthanized 4 weeks later. Muscle tissues were excised and the implant sites examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response. The macroscopic reaction was not significant as compared to the negative control article. Microscopically, the test article caused a slight reaction as compared to the negative control article.
ISO Systemic Toxicity Study in Rats Following Subcutaneous and Muscle Implantation, 13 Weeks	The test article, CalliSpheres Embolic Microspheres, was surgically implanted in the gluteal muscle and subcutaneous tissue of the rat to evaluate potential systemic toxicity and local tissue response at the implantation sites. A separate group of animals was similarly implanted with high density polyethylene (HDPE) to serve as the control group. Twenty male and 20 female rats were randomly assigned to either the test or control group (10/sex/group). There were no changes in hematology or clinical chemistry values considered related to implantation with the test article. Microscopic evaluation of collected organs revealed no evidence of a systemic test article related response. Microscopic evaluation of the implantation sites indicated no difference in the local tissue response between the control and test articles. There was no evidence of systemic toxicity from the test article following

	subcutaneous and muscle implantation in the rat. Microscopically, the test article was classified as causing a minimal to no reaction in both the subcutaneous tissue and the gluteal muscle.
Chronic Systemic Toxicity and Carcinogenicity Evaluation	We conducted a biological risk assessment for chronic toxicity and carcinogenicity of proposed device based upon chemical extractable/leachable analysis (described above). The CalliSpheres and 8Spheres Embolic Microspheres are not considered to have chronic systemic toxicity and carcinogenicity risk. To evaluate the biological safety of the device, consideration was given to the following: type of patient contact; potential hazards of the materials of construction, the history of clinical use and testing of the materials of construction, biocompatibility and chemical characterization testing on the device; and other information available in the literature.

8 Summary of Animal Performance Testing

An animal study was conducted to evaluate the safety and effectiveness of CalliSpheres and 8Spheres Embolic Microsphere. The animal study was intended to simulate the clinical application of the embolization microspheres by interventional procedure for partial renal artery embolization. A pig model was chosen, with Embosphere Microspheres, manufactured by Biosphere Medical, Inc. (K021397) selected as the control group.

Random grouping method was used to assign treatment in the animals. The lower polar second branch artery and subordinated branch artery of 12 swine (female and male) were selected for embolization by CalliSpheres Embolic Microspheres (300-500um), and the other 12 swine (female and male) were selected for embolization with Embosphere microspheres (300-500um) in the lower polar second branch artery and subordinated branch artery. Several preoperative and postoperative observation time points were selected, including 2, 7 and 28 days after embolization. At these time points, the change of blood routine, coagulation function, renal function and liver function were tested, the results of DSA angiography and histopathological results were checked, and the performance differences of CalliSpheres embolic microsphere and Embosphere microspheres were compared. Finally, the safety and effectiveness of CalliSpheres embolic microsphere were comprehensively evaluated.

The assessment items for this animal study are as follows:

(1) Compare the recanalization of the vessels/durability of occlusion of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres

(2) Compare the local and systemic foreign body reactions of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres

(3) Compare the embolization effectiveness of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres

(4) Compare the ease of delivery of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres

(5) Compare the rupture or puncture of the blood vessels of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres

(6) Compare the non-target embolization /device migration of CalliSpheres Embolic Microspheres and 8Spheres Embolic Microspheres

The monitoring indexes of the animals were normal during preoperative adaptation period and postoperative observation period; there was no difference between the test group and the control group. Embolic agents from both groups were easily delivered to the target vessels, and neither of the two embolic agents showed vascular rupture or perforation during embolization. Both the subject and control devices were shown to achieve complete embolization effectively with the same number of embolic target vessels and amount of embolic materials. In addition, both embolic agents had had comparable non-target embolization. Animal evaluation indexes of CalliSpheres Embolic Microspheres on day 2, day 7 and day 28 after embolization were comparable to those from the Embosphere group. Tissue reactions of both CalliSpheres and Embospheres were found to be mild and comparable. Preoperative and postoperative clinicopathological examination results demonstrated that there was no significant difference between test group and control group with respect to adverse reactions.

Overall, the results of the study demonstrate that CalliSpheres Embolic Microspheres are as safe and effective as the cleared device Embosphere (K021397).

9 Conclusions

As described above, the subject devices have the same intended use as the predicate device. The differences in technological characteristics between the subject devices and the predicate do not raise different questions of safety and effectiveness. To evaluate the impact of the technological differences, performance testing was conducted as described above. The results of the testing demonstrate that the subject devices, CalliSpheres and 8Spheres Embolic Microspheres, are as safe and effective

as the predicate device. Therefore, CalliSpheres and 8Spheres Embolic Spheres are substantially equivalent to the predicate.