June 22, 2023

INVO Bioscience, Inc.
℅ Wanda Carpinella
Regulatory Affairs Consultant
Avania, LLC
100 Crowley Drive, Suite 100
Marlborough, MA 01760

Re: K222932
Trade/Device Name: INVOcell Intravaginal Culture System
Regulation Number: 21 CFR§ 884.6165
Regulation Name: Intravaginal Culture System
Regulatory Class: II
Product Code: OYO
Dated: May 18, 2023
Received: May 19, 2023

Dear Wanda Carpinella:

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,

Michael T. Bailey -S

For
Monica D. Garcia, Ph.D.
Assistant Director
DHT3B: Division of Reproductive,
Gynecology and Urology Devices
OHT3: Office of GastroRenal, ObGyn,
General Hospital and Urology Devices
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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K222932

Device Name
INVOcell Intravaginal Culture System

Indications for Use *(Describe)*
The INVOcell Intravaginal Culture System consists of the following components:

The INVOcell Culture Device is indicated for use in preparing, holding, and transferring human gametes or embryos during In Vitro Fertilization/Intravaginal Culture (IVF/IVC) and Intra-Cytoplasmic Sperm Injection Fertilization/ Intravaginal Culture (ICSI/IVC) procedures. The INVOcell Culture Device is indicated for use with the INVOcell Retention Device. The INVOcell Culture Device is not indicated for incubation periods exceeding 120h.

The INVOcell Retention Device is indicated for use with the INVOcell Culture Device to aid in retention of the INVOcell Culture Device in the vaginal cavity during the incubation period. The INVOcell Retention Device is not indicated for use exceeding 120h.

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
K222932

INVOcell® Intravaginal Culture System

I. **Submitter**

INVO Bioscience, Inc.
5582 Broadcast Court
Sarasota, FL 34240

Contact Person

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CEO INVO Bioscience, Inc.
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Date Prepared June 20, 2023

II. Device

Trade name	INVOcell Intravaginal Culture System
Common name	Intravaginal Culture System
Regulatory Name	Intravaginal Culture System
Classification Name:	21 CFR 884.6165
Product Code(s):	OYO (Culture, Intravaginal, Assisted Reproduction)
Regulatory Class:	II

III. Predicate Device

INVOcell Intravaginal Culture System (DEN150008) from INVO Bioscience, Inc.

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

IV. Description of the Device

The INVOcell Intravaginal Culture System consists of the INVOcell Culture Device and the INVOcell Retention Device.

The INVOcell Culture Device is a radiation sterilized, single-use polystyrene container that holds and maintains the gametes and/or embryos during intravaginal culture for a maximum duration of 120 hours. The INVOcell Culture Device consists of three components: Inner Vessel, Outer Rigid Shell, and Retention Device.

The Inner Vessel holds the culture medium along with the gametes and /or embryos. It has a rotating valve at its top, which allows for access to the chamber when loading and retrieving gametes/embryos and provides a seal during incubation. At the bottom of the Inner Vessel, there is a physical stop to limit the penetration depth of the retrieval catheter into the Inner Vessel to protect embryos during retrieval.

The Outer Rigid Shell that is made of polystyrene, protects the Inner Vessel from the vaginal environment when the device is in use. The Inner Vessel fits into the bottom portion of the Outer Rigid Shell and is sealed in position by the top portion of the Outer Rigid Shell cap with a silicone O-ring, which provides a liquid-tight seal to prevent contamination of the Inner Vessel.

The Retention Device aids in the retention of the INVOcell Culture Device during incubation in the vaginal cavity for a maximum duration of 120 hours. The Retention Device is single-use and provided non-sterile. It is a 70 mm diameter cup-shaped silicone retention device that includes holes to allow flow of vaginal secretions during use.

V. Indications for Use

The INVOcell Intravaginal Culture System consists of the following components:

The INVOcell Culture Device is indicated for use in preparing, holding, and transferring human gametes or embryos during In Vitro Fertilization/Intravaginal Culture (IVF/IVC) and Intra-Cytoplasmic Sperm Injection Fertilization/Intravaginal Culture (ICSI/IVC) procedures. The INVOcell Culture Device is indicated for use with the INVOcell Retention Device. The INVOcell Culture Device is not indicated for incubation periods exceeding 120h.

The INVOcell Retention Device is indicated for use with the INVOcell Culture Device to aid in retention of the INVOcell Culture Device in the vaginal cavity during the incubation period. The INVOcell Retention Device is not indicated for use exceeding 120h.

VI. Substantial Equivalence Comparison:

A comparison of the intended use and technological features of the subject and predicate devices are described in the table below:

	K222932 **Subject Device**	**DEN150008** **Predicate Device**	**Comparison**
Indications for Use	The INVOcell Intravaginal Culture System consists of the following components: The INVOcell Culture Device is indicated for use in preparing, holding, and transferring human gametes or embryos during In Vitro Fertilization/Intravaginal Culture (IVF/IVC) and Intra-Cytoplasmic Sperm Injection Fertilization/Intravaginal Culture (ICSI/IVC) procedures. The INVOcell Culture Device is indicated for use with the INVOcell Retention Device. The INVOcell Culture Device is not indicated for incubation periods exceeding 120h. The INVOcell Retention Device is indicated for use with the INVOcell Culture Device to aid in retention of the INVOcell Culture Device in the vaginal cavity during the incubation period. The INVOcell Retention Device is not	The INVOcell Intravaginal Culture System consists of the following components: The INVOcell Culture Device is indicated for use in preparing, holding, and transferring human gametes or embryos during In Vitro Fertilization/Intravaginal Culture (IVF/IVC) and Intra-cytoplasmic Sperm Injection Fertilization/Intravaginal Culture (ICSI/IVC) procedures. The INVOcell Culture Device is indicated for use with the INVOcell Retention Device and the INVOcell Holding Block. The INVOcell Culture Device is not indicated for incubation periods exceeding 72h. The INVOcell Retention Device is indicated for use with the INVOcell Culture Device to aid in retention of the INVOcell Culture Device in the vaginal cavity during the incubation period. The	The indications for use statements for the subject and predicate devices are not identical; however, the intended uses of the subject and predicate devices are the same.

	indicated for use exceeding 120h.	INVOcell Retention Device is not indicated for use exceeding 72h. The INVOcell Holding Block is indicated for use with the INVOcell Culture Device to aid in temperature maintenance of the INVOcell Culture Device during loading and collection procedures and to aid in positioning and observation of the INVOcell Culture Device during human gamete/embryo loading and collection procedures.	
Components	Inner chamber, outside rigid shell, retention device	Inner chamber, outside rigid shell, retention device, holding block	**Different:** The subject device does not include a holding block. Differences in components do not raise different questions of safety and effectiveness (S&E).
Fully Assembled Dimensions	1.8" length x 1.1" diameter	1.8" length x 1.1" diameter	**Same**
Sterilization	Gamma sterilized	Gamma sterilized	**Same**
Endotoxin (LAL)	< 20 EU/device	< 20 EU/device	**Same**
Mouse Embryo Assay	One-cell: ≥ 80% reaching the expanded blastocysts at 120 h	Two-cell: ≥ 80% hatched/expanded blastocysts at 72 h	**Different:** The subject device uses the one-cell system, and the testing time is longer than that of the predicate device. The differences identified in MEA methods do not raise different questions of S&E.
Vaginal Incubation Period	120 hours	72 hours	**Different:** The subject device has a longer vaginal incubation time than the predicate device. Differences in the vaginal incubation time do not raise different questions of S&E.
Culture Conditions	0.7 ml of IVF culture medium with mineral oil overlay	1.08 ml of IVF culture medium	**Different:** The culture conditions for the subject device include a lower volume of medium and a mineral oil overlay. Differences in the culture conditions do not raise different questions of S&E.
Shelf-Life	6 years	3 years	**Different:** The subject device has a longer shelf-life than

			the predicate device. Differences in shelf-life do not raise different questions of S&E.

As shown in the table above, there are differences in the indications for use statements and technological characteristics of the subject and predicate devices. However, as stated in the table, the differences in indications for use do not represent a new intended use and the differences in technological characteristics do not raise different questions of safety and effectiveness.

V. Summary of Non-Clinical Performance Testing

The following non-clinical performance testing was conducted on the INVOcell Culture Device:

- Shelf-Life Testing – The following testing was conducted following real-time aging in support of the six-year device shelf-life:
  - Mouse Embryo Assay (MEA) per the 2021 FDA guidance *Mouse Embryo Assay for Assisted Reproduction Technology Devices*: 1-Cell MEA: ≥80% embryos developed to expanded blastocyst at 120h.
  - Seal Integrity Testing: No contamination inside and outside the vessel after 120h of incubation.
  - pH Stability: pH of test medium in device remained within the specified range after 120h of incubation.
  - Vessel Wall Optical Clarity: No obscured views after 120h of incubation.

- Sterilization Validation – The gamma irradiation sterilization and validation methods for the predicate device (ISO 11137:2006) are being relied on in support of this submission.

- Packaging Integrity Testing – Testing was conducted after accelerated aging. Testing included bubble leak testing (ASTM F2096) and seal strength testing (ASTM F88) on the INVOcell packaging to qualify the 6-year expiration date.

VII. Summary of Clinical Performance Testing

Two clinical studies were conducted to support extension of the culture duration to 120 hours, the revised culture conditions, and substantial equivalence to the predicate device. A summary of the two studies are shown below:

Study 1: INVOcell Culture System Comfort and Retention

This was a single center, open label trial to evaluate Comfort and Retention of the INVOcell Intravaginal Culture System during 120 hours of intravaginal incubation. After device removal and final speculum exam, study participants also completed a questionnaire to assess their discomfort, device expulsion, or incidence of vaginal discharge, spotting, or itching during the 5-day use of the subject device. There were no reports of INVOcell Culture Device expulsion in the 29 subjects evaluated. One subject reported the system was felt to be dislodged and the subject successfully readjusted the device to maintain the system in place. This results in an overall retention rate of 96%, which demonstrated the INVOcell Retention Device performed as intended.

There were no clinically relevant vaginal findings (e.g., lesions, ulcerations, erythema, or bleeding) identified after device wearing for 120 hours. These results demonstrated the safety of wearing the device for the longer 120 hour duration.

Study #2: Retrospective Analysis of the INVOcell Culture System (IVC) in Comparison with traditional IVF and ICSI for 5 Day Incubation

This was a multicenter, retrospective cohort study that compared safety and effectiveness of the INVOcell Culture System (IVC/IVF and IVC/ICSI) to traditional IVF and ICSI procedures for 5 Day incubation. The study provided real-world evidence to support the expanded indication to 120h incubation and use of the revised device loading procedure, including a lower medium volume and a mineral oil overlay. Data was collected from four fertility clinics in the U.S. for the 3-year period of January 2017 to December 2019.

The data collection effort was focused on evaluating the outcomes of INVOcell day 5 transfer (IVC/IVF and IVC/ICSI) compared to historical outcomes of INVOcell day 3 transfer (IVC/IVF and IVC/ICSI). Rates of embryo development to the designated stage were also examined after day 5 incubation.

The four sites contributed a total of 240 fresh embryo transfers in the INVOcell arm (IVC/IVF and IVC/ICSI) and 685 fresh embryo transfers in the traditional IVF and ICSI arm. Patient demographics and fertility diagnoses were comparable between both cohorts.

Effectiveness

When comparing the data of day 3 INVOcell (IVC/IVF and IVC/ICSI) using the original loading procedure to day 5 INVOcell (IVC/IVF and IVC/ICSI), which used the revised loading methods, the day 5 embryo development is more advanced, and the clinical pregnancy and live birth rates are higher for day 5 incubation in the INVOcell device for both IVF and ICSI cohorts.

While the INVOcell ICSI (IVC/ICSI) method produced lower rates of embryos developed to the blastocyst stage than traditional ICSI produced, the rates of embryos developed to the blastocyst stage using the IVC/IVF and traditional IVF methods were similar. The rates of embryo transfer, clinical pregnancy, implantation, miscarriage, live birth, and pre-term birth using the IVC/IVF and IVC/ICSI methods were similar to the day 5 traditional IVF and ICSI methods. The data supports that embryos suitable for transfer can be formed by incubation in the INVOcell device with 120h incubation and use of the revised device loading methods.

Safety

The type of maternal and offspring adverse events experienced in both the IVC (IVF and ICSI) cohort and traditional IVF and ICSI cohort were similar. There were a total of 2 birth defects reported in 2 subjects in the IVC (IVF and ISCI) cohort (out of 104 births with known outcomes) and 9 birth defect in 9 subjects in the traditional IVF and ICSI cohort (out of 273 births with known outcomes). The data supports that incubation in the INVOcell device with 120h incubation and use of the revised device loading methods did not result in increased adverse events or outcomes.

VIII. Conclusion

The results of the performance testing described above demonstrate that INVOcell Culture System is as safe and effective as the predicate device and supports a determination of substantial equivalence.