DE NOVO CLASSIFICATION REQUEST FOR
INVOCELL™ INTRAVAGINAL CULTURE SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Intravaginal Culture System: An intravaginal culture system is a prescription device intended for preparing, holding, and transferring human gametes or embryos during intravaginal in vitro fertilization or intravaginal culture procedures.

NEW REGULATION NUMBER: ***21 CFR 884.6165***

CLASSIFICATION: ***II***

PRODUCT CODE: ***OYO***

BACKGROUND

DEVICE NAME: ***INVOCELL INTRAVAGINAL CULTURE SYSTEM***

SUBMISSION NUMBER: ***DEN150008***

DATE OF DE NOVO: ***FEBRUARY 23, 2015***

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REQUESTER'S RECOMMENDED CLASSIFICATION: ***II***

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/Intra Vaginal 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 INVOcell Retention Device is not indicated for use exceeding 72 hours.

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.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR §801.109.

The INVOcell Intravaginal Culture Device is indicated to be utilized as part of a system. It is not indicated to be utilized independently of the INVOcell Retention Device and the INVOcell Holding Block.

The device was evaluated for up to 72 hours of incubation. It is not indicated for incubation periods to exceed 72 hours. No data were provided to support longer incubation times.

The INVOcell Intravaginal Culture Device and INVOcell Retention Device are single-use only. The only components able to be reprocessed are the INVOcell Holding Block and the Retention Device fitting kit.

The INVOcell procedure should only be performed by physicians with expertise in assisted reproductive technology and techniques including oocyte retrieval, clinical embryology, and embryo transfer, and with access to all necessary equipment (listed in the Instructions for Use).

The culture media utilized with the device should have phenol red to aid in the determination of acceptable pH maintenance and antibiotics to mitigate possible contamination of media in the inner chamber.

The INVOcell devices should be handled in an aseptic fashion to reduce the risk of contamination of the culture media.

The device should only house up to 7 oocytes or embryos. The majority of clinical data consisted of cases where <5 oocytes or embryos were utilized. However, there were cases in which up to 7 were utilized, and live births resulted from the embryos collected.

The INVOcell Intravaginal Culture Device is only compatible with embryo retrieval catheters with tip outer diameters from 1.0mm to 1.85mm.

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

DEVICE DESCRIPTION

The INVOcell Intravaginal Culture System is comprised of three parts: the INVOcell Intravaginal Culture Device, the INVOcell Retention Device, and the INVOcell Holding Block. All devices are designed to be utilized together.

INVOcell Intravaginal Culture Device

The INVOcell Intravaginal Culture Device is a single-use plastic container that serves to house and protect the gametes and/or embryos during intravaginal culture. It is provided sterile. The culture device consists of two components: the inner chamber and the outer shell (Figure 1).

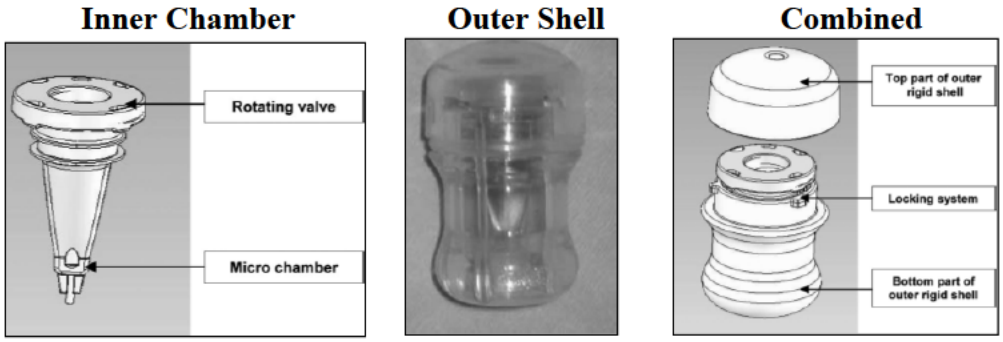

Figure 1: Schematic/Picture of the INVOcell Intravaginal Culture Device, showing the inner chamber, outer shell and combined.

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

The outer shell serves to protect the inner vessel from the vaginal environment. The inner vessel fits into the bottom portion of the outer shell. The top portion of the outer shell can then be screwed onto the bottom portion. A silicone O-ring separates the bottom and top portions of the outer shell, and aids in reducing contamination of the inner vessel.

INVOcell Retention Device

The INVOcell Retention Device (Figure 2) aids in the retention of the INVOcell Intravaginal Culture Device during incubation in the vagina. It is a single-use device that is provided non-sterile. The device is a cup-shaped silicone piece that includes holes to allow flow of vaginal secretions. The device comes in four sizes (65, 70, 75, and 80 mm). It is accompanied by a fitting kit, which is utilized to determine the appropriate diameter of the INVOcell Retention Device to ensure appropriate retention, and is intended to be reprocessed.

Figure 2: Picture of the INVOcell Retention Device and the combined INVOcell Intravaginal Culture Device situated inside the INVOcell Retention Device.

INVOcell Holding Block

The INVOcell Holding Block (Figure 3) is designed to hold and maintain temperature of the inner vessel of the INVOcell Intravaginal Culture Device during loading and retrieval procedures. The block does this passively by serving as a heat sink. Prior to use, the block is preheated to body temperature. The block then can be utilized to hold the Intravaginal Culture Device inner vessel, and will maintain appropriate temperature for short periods of time. The block is solid stainless steel, with a conical hole in the top for the inner vessel. The block also includes a glass window on the side, to allow viewing of the embryos in the inner vessel during retrieval.

Figure 3: Picture of the INVOcell Holding Block

Device Usage

In the INVOcell procedure, gametes (for IVF) or intracytoplasmic sperm injected (ICSI) embryos are deposited into the Intravaginal Culture Device inner vessel when the inner vessel is held vertically with the aid of a pre-warmed Holding Block. Once the gametes or embryos are within the inner vessel, the inner vessel is closed and placed within the outer shell. The complete Intravaginal Culture Device is inserted into the patient's vagina, and the Retention Device is placed proximal to the Culture Device in the vagina to ensure the Intravaginal Culture Device stays in place. The devices are left in the vagina for 72 hours, where fertilization and/or development of the embryos occurs. At 72 hours, the retention device and Intravaginal Culture Device are removed from the patient. The Retention Device and the outer shell of the Intravaginal Culture Device are discarded, and the inner vessel is placed into a pre-warmed Holding Block. The embryos are then extracted from the inner vessel via a retrieval catheter, washed and graded Embryos may then be utilized for transplantation, or may be stored for use later.

For complete detailed instructions, refer to the Instructions for Use.

SUMMARY OF NONCLINICAL/BENCH STUDIES

Test	Purpose	Methods	Acceptance Criteria	Results
Sterilization, Cleaning, and Disinfection				
Sterilization	Evaluate the sterility level of device components provided sterile (outer shell and inner vessel of the Intravaginal Culture Device)	ISO 11137:2006 Sterilization of Healthcare Products	The sterility assurance level (SAL) shall be 10^{-6}	Passed
Reprocessing: cleaning and disinfection validation	Evaluate the cleaning and disinfection protocols for reprocessed components (Holding Block) to ensure that bacterial contamination is not transferred between used and new devices	Holding blocks were soiled with test soil, and cleaned and disinfected per the instructions for use. After cleaning and disinfection, surfaces of the devices were swabbed and tested for the presence of microorganisms	Greater than 6-$\log_{10}$ reduction in microorganism counts	Passed
Biocompatibility				
Cytotoxicity	Determine if the Intravaginal Culture Device or Retention Device polar and non-polar extracts elicit a cytotoxic response	ISO 10993-5 Tests for Cytotoxicity: *in vitro*; b(4) method; Performed on Intravaginal Culture Device and Retention Device	-	Grade 0 (non-cytotoxic)
Rabbit Muscle Implantation	Determine the toxic effects of the Intravaginal Culture Device or Retention Device in direct contact with living tissue	ISO 10993-6: Tests for Local Effects after Implantation; Performed on Intravaginal Culture Device and Retention Device	-	No significant difference from negative control (no signs of toxic response)
Vaginal Irritation	Determine if polar and non-polar extracts of the Intravaginal Culture Device or Retention Device elicit a hypersensitive response	ISO 10993-10: Biological Evaluation of Medical Devices: Tests for Irritation and Sensitization; Performed on Intravaginal Culture Device and Retention Device	-	No signs of macroscopic or microscopic irritation from polar and non-polar extracts

Sensitization	Determine if polar and non-polar extracts of the Intravaginal Culture Device or Retention Device cause a hypersensitive response	ISO 10993-10: Biological Evaluation of Medical Devices: Tests for Irritation and Delayed Type Hypersensitivity; Performed on Intravaginal Culture Device and Retention Device	-	No signs of sensitization from polar and non-polar extracts
Acute Systemic Toxicity	Determine if polar and non-polar extracts of the Intravaginal Culture Device are acutely systemically toxic	ISO 10993-11: Biological Evaluation of Medical Devices Tests for Systemic Toxicity; Intravaginal Culture Device	-	No evidence of mortality or systemic toxicity from test material extracts
Bench Testing				
Volumetric Capacity	Determine if the inner vessel chamber meets volume specifications and if it can be filled without formation of air bubbles. This test ensures that bubbles/air pockets are not formed, which may damage the embryos during incubation.	Inner vessels were filled to overflow with water, closed, and blotted dry. Samples were observed during filling for bubble formation. The water in the filled vessels was extracted and weighed.	Inner vessel volume shall meet specification and no bubbles or air pockets shall be formed during filling	Passed. No bubbles or air pockets were observed
Fluid Contact Surface Finish	Determine the quality of the surface finish of the surface of the inner vessel in contact with media to ensure that embryos are not exposed to rough surfaces, leading them to "stick" to the vessel walls.	Impression media was used to create replicas of the surfaces of inner vessels. Scanning electron microscopy utilized to visualize the replica surfaces.	No surface imperfections ≥ 50 microns shall be observed	Passed
Illumination and Optical Properties	Evaluate if embryos can be observed post-incubation through the illumination port of the Holding Block to ensure that embryos are appropriately accounted for after incubation and during extraction.	90 micron microspheres b(4) Microsphere solution was added to the inner vessels of the Intravaginal Culture Device, which were placed in the Holding Block. Microspheres were observed at 12 positions and given a score from 1-5 on	-	No obscured views, 89% of samples were scored 5/5, 11% were 4/5.

		clarity.		
Temperature Maintenance of Holding Block	Evaluate the time required to heat the Holding Block and the heat retention time to ensure that embryo media maintains appropriate temperature during loading and extraction procedures.	Blocks were heated to 37C and allowed to cool. Temperature of the media within the inner vessel was monitored continuously	Media inside inner vessel shall maintain a temperature of >34˚C for >10 minutes to allow for adequate procedure time	Passed; Block maintains temperature of inner vessel of the Intravaginal Culture Device (>34 C) for 12 minutes
pH maintenance	Determine if media maintains pH during the incubation period to ensure that embryos are not exposed to damaging changes in pH during incubation.	pH of media (containing gametes) within the inner vessel of the Intravaginal Culture Device was monitored over a simulated incubation period of 72 hours	pH shall remain within ±0.2 of the controls (legally marketed assisted reproduction labware)	Passed
Seal integrity	Determine the device's ability to resist bacterial ingress and maintain sterility of the culture media during incubation and extraction to ensure embryos will not be exposed to bacteria during vaginal incubation.	Sterile bacterial media was deposited in the inner vessels of the Intravaginal Culture Devices. b(4)	Culture media within the inner vessel shall remain sterile during incubation and extraction	Passed; 30/30 samples maintained culture media sterility during incubation and extraction
Mouse Embryo Assay (Embryo compatibility)	Determine if the device is compatible with embryos	Twenty-one 2-cell embryos were incubated in each of 9 (3 samples from 3 lots) INVOcell Intravaginal Culture Devices for 72 hours. Legally marketed assisted reproduction labware were used as the control (n=3). After 72 hours,	>80% embryos shall reach expanded blastocyst stage	Passed; >90% of embryos reached expanded blastocyst stage

		embryos were scored for development		
Endotoxin Testing	Determine if bacterial endotoxins are within acceptable limits to ensure that embryos are not exposed to high levels of endotoxins	USP 31 NF 26 2008 <85> Bacterial Endotoxins Test	The endotoxin level shall be < 20 EU/mL	Passed; < 2.4 EU/ device
Shelf Life				
Package integrity (Bubble emission leak test)	Evaluate the sterile packaging integrity to ensure that devices remain sterile throughout the shelf-life	ASTM F2096-11	-	No bubbles observed in 30 samples
Package integrity (visual inspection)	Evaluate the sterile packaging integrity to ensure that devices remain sterile throughout the shelf-life	ASTM F1886-09	-	No channels observed in 60 samples
Physical testing of seals (peel strength)	Evaluate the sterile packaging integrity to ensure that devices remain sterile throughout the shelf-life	ASTM F88-09	-	Seal strengths were in excess of 1.63 lbf/in
Mouse embryo assay	Evaluate the embryo compatibility of the device at the end of shelf-life to ensure the device maintains embryo compatibility at the end of shelf life	Twenty-one 2-cell embryos were incubated in each of 9 (3 samples from 3 lots) INVOcell Intravaginal Culture Devices for 72 hours. Legally marketed assisted reproduction labware were used as the control (n=3). After 72 hours, embryos were scored for development	>80% of embryos shall reach the blastocyst stage	Passed, >90% reached blastocyst stage
pH maintenance	Evaluate media pH during the incubation period to ensure that the devices retain their pH-maintaining properties at the end of the shelf life. This test is an indicator for the CO_2 permeability of the device.	Twenty-one 2-cell embryos were incubated in each of 9 (3 samples from 3 lots) INVOcell Intravaginal Culture Devices for 72 hours. The pH of the media within the vessels after incubation was measured with an electrochemical probe. Legally marketed assisted reproduction labware were used as controls.	pH shall remain within ±0.2 of the control	Passed

Clarity of vessel wall	Evaluate the clarity of the vessel wall at the end of the shelf-life to ensure that aging of the plastic does not adversely affect the ability to count embryos	After incubation of mouse embryos during the Mouse Embryo Assay, visually inspect the inner vessels of the Intravaginal Culture Devices and count the number of embryos	Ability to identify and count embryos accurately	Passed
Seal integrity	Determine the device's ability to resist bacterial ingress and maintain sterility of the culture media during incubation and extraction in worst-case scenario (immersion in bacterial broth) at the end of shelf-life	Sterile bacterial media was deposited in the inner vessels of the Intravaginal Culture Devices. Ten samples each from three lots were tested. b(4)	Culture media within the inner vessel shall remain sterile during incubation and extraction	Passed; 30/30 samples maintained culture media sterility during incubation and extraction

SUMMARY OF CLINICAL INFORMATION

The sponsor performed two clinical investigations to demonstrate a reasonable assurance of safety and effectiveness for the INVOcell Intravaginal Culture System.

Study 1: INVOcell Outside the US (OUS) Safety and Efficacy

Objective of the study

Evaluate rate of fertilization (IVF only), embryo quality, successful transfer rates, and live birth rates resulting from embryos incubated using the INVOcell device.

Methods

The sponsor conducted clinical investigations at assisted reproductive facilities in Peru, Colombia, Bolivia, and Brazil. The INVOcell devices (INVOcell Intravaginal Culture Device, Retention Device, and Holding Block) were utilized for both gamete incubation (IVF) and intracytoplasmic sperm injection (ICSI). In all cases, a mild ovarian stimulation protocol was utilized to harvest oocytes. The study population is summarized in Table 1 below:

Table 1: Study Population at OUS sites in INVOcell Safety and Efficacy Study

Site	Number of Subjects	IVF cycles/ICSI cycles/Total Cycles	Age Range	Average Age
Lima, Peru	134	138/0/138	36-43	35
Bogota, Colombia	220	125/100/225	21-45	34
Sao Paulo, Brazil	40	20/20/40	29-44	35
Cochabamba, Bolivia	48	48/0/48		34

Results

Effectiveness:

For comparison of effectiveness of the INVOcell device to traditional IVF and ICSI procedures, the sponsor pooled the results from the investigational sites. The sponsor examined embryo fertilization and cleavage rates, embryo quality, as well as the clinical outcomes resulting from transfer of embryos.

The fertilization and cleavage rates of embryos developed with the INVOcell devices was compared to a literature report by Bergh *et al.* in the journal Human Reproduction,[1] which reports on fertilization and cleavage rates in traditional IVF and ICSI. Fertilization and cleavage rates from the Brazil site were unavailable, as the site did not create individual summary reports of each cycle. The comparison of fertilization and cleavage rates is summarized in Table 2 below:

Table 2: Fertilization and Cleavage Rates of Embryos from the INVO Procedure

	Bergh IVF	INVO IVF Total	INVO IVF Colombia	INVO IVF Peru	INVO IVF Bolivia	Bergh ICSI	INVO ICSI Colombia
Cycles	**200**	**310**	125	137	48	**175**	**100**
Inseminated Oocytes	**2,279**	**1,388**	520	640	228	**1,880**	**376**
Fertilized Oocytes	**1,536**	**897**	331	404	162	**1,365**	**295**
Cleaved Embryos	**1,437**	**894**	328	404	162	**1,268**	**290**
Fertilization rate	**67.3%**	**64.6%**	63.7%	63.1%	71%	**72.7%**	**78.5%**
Cleavage rate	**63.1%**	**64.4%**	63.1%	63.1%	71%	**67.4%**	**77.1%**

[1] Bergh C, Broden H, Lundin K, Hamberger L. Comparison of fertilization, cleavage and pregnancy rates of oocytes from large and small follicles. Hum Reprod, 1998; 13: 1912-15

Fertilization rates and cleavage rates of embryos are not statistically different between the INVOcell incubated embryos and those reported in Bergh *et al.* for traditional IVF and ICSI. In addition, there is no statistical difference between IVF and ICSI fertilization and cleavage rates for the INVOcell procedure. However, there is less data available on ICSI cycles using INVOcell compared to IVF cycles using INVOcell. Overall, cleavage and fertilization data from embryos cultured in the INVOcell device supports that the INVOcell procedure can result in reasonable fertilization and cleavage rates.

The quality of embryos formed and/or incubated utilizing the INVOcell device were compared to results of a study conducted by Lundin *et al.* in the journal Reproduction.[2] It is important to note that the quality of embryos is difficult to compare between centers and studies due to differences in grading systems. However, both the literature study and the INVO study sites utilized similar criteria for the scoring of embryos for quality, which included the grade of fragmentation, cytoplasmic appearance and number of blastomere per embryo. The embryo quality assessment is summarized in Table 3 below:

Table 3: Embryo quality after intravaginal incubation in INVOcell device

Embryo Quality	Lundin IVF/ICSI	INVO IVF/ICSI Total	INVO IVF/ICSI Colombia	INVO IVF/ICSI Peru	INVO IVF Bolivia
Number of 6 cells, Grade 1 and 2		192	89	63	40
Number of 8 cells, Grade 1 and 2		462	224	191	47
Number of 10 cells or greater, Grade 1 and 2		74	51	16	7
Number of good quality embryos	4,496	728	364	270	94
Number of cleaved embryos	10,798	1,184	618	404	162
Good quality embryo rate	41.6%	61.5%	58%	66.8%	58%
Clinical pregnancy rate per cycle		137/410 33.4%	79 35.1%	42 30.7%	16 33.3%
Miscarriage rate	17.3%*	33/137 24.1%	15 19%	14 33.3%	4 25%
Birth rate per cycle	27.8%	98/410 23.9%	63 28%**	23 16.8%***	12 25%

*Lundin *et al*. used an ovarian stimulation with a long protocol combining Gn-Rh agonist and FSH. This is in contrast to the mild ovarian stimulation protocol used in the INVOcell study.
**The outcome of one INVO/IVF was unknown.
***The outcome of 5 clinical pregnancies was unknown, which explains in part the low birth rate reported at the Peru site.

In general, embryos incubated with the INVOcell device were of good quality (i.e., being graded 1 or 2 with 6 to 8 cells at day 3). However, the rate of good quality embryos in INVOcell subjects could be due, in part, to the use of the mild ovarian stimulation protocol. The study by Lundin *et al.*

[2] Lundin K, Bergh C, Hardarson T. Early embryo cleavage is a strong indicator of embryo quality in human IVF. Hum Reprod, 2001; 16: 2652-57

did not utilize the same stimulation protocol. The author instead utilized a hyper-stimulation protocol, which may have resulted in more immature oocytes being harvested for IVF/ICSI, and therefore lower quality embryos. While direct comparisons are difficult given the differences in stimulation protocol, the data support that quality embryos can be produced from the INVOcell procedure at reasonable rates.

Effectiveness indicators such as clinical pregnancy rate, miscarriage rate, multiple pregnancy rate, and birth rates resulting from use of the INVOcell device are presented in Table 4 below:

Table 4: Pooled outcomes data from INVOcell clinical use

	INVO cycles (IVF + ICSI)
Cycles	450
Clinical Pregnancies	146
Clinical Pregnancy Rate	32.4%
Miscarriage Rate	22.6%
Multiple Pregnancy Rate	15.1%
Birth Rate	23.8%
Multiple Birth Rate	17.8%
Triplet Births	6
Twin Births	13
Births from Singleton Pregnancies	88
Triplet Pre-term Births (%)	6 (100%)
Twin Pre-term Births	7 (53.8%)
Singleton Pre-term Births from Single Pregnancies	0
Pre-term Birth Rate	21.4%

The relevant effectiveness of the INVOcell device is available to physicians as part of the INVOcell labeling.

Safety:

There were no observed device-related serious or non-serious adverse events associated with the use of the INVOcell Intravaginal Culture Device or the Retention Device during the study. Adverse pregnancy outcomes such as miscarriage and pre-term births were reported in the effectiveness section above as these are primarily related to the effectiveness of the device (i.e., the successful pregnancy and live birth rates).

Study 2: INVOcell Intravaginal Culture Device Comfort and Retention Study

Objective of the study

Evaluate the rates at which the INVOcell Intravaginal Culture Device is lost from the vagina during incubation with and without the INVOcell Retention Device. Additionally, the study reported on comfort wearing the device during incubation.

Methods

The study was a non-random, prospective study of 29 women to assess device retention. Of the women in the study, 12/29 used the Intravaginal Culture Device and Retention devices, and the rest (17/29) utilized the Intravaginal Culture Device alone. Women were instructed to wear the device(s) for 72 hours, and report on any expulsion or readjustments/repositioning. In addition, the women were asked to rate their comfort with the device.

Results

The sponsor reported that retention of the device for the full 72 hours occurred in 25/29 women. None of the women utilizing the Retention Device reported device expulsion during the incubation period. Of the expulsions, two were reported during urination or bowel movement, and two were reported without any associated cause. Of the 25 with maintained retention, eight reported slippage with successful repositioning. None of the women using the Retention Device reported slippage.

For the majority of subjects, the device(s) were well tolerated. All but two of the subjects reported minimal discomfort. The remaining two had moderate to severe discomfort, with one asking for device removal prior to the 72 hour wear time. There were no reports of erythema, ulceration or lesions in any of the subjects.

Based upon the results of this study, the Retention Device is effective in retaining the Intravaginal Culture Device for the 72 hour incubation period. For most patients, the device should cause minimal discomfort. The device labeling informs the users that the device may cause discomfort in some patients and discourages its use in patients that may not be able to tolerate the device for the full 72 hour incubation period. Additionally, it is important to note that the INVOcell Retention Device was utilized in the INVOcell Safety and Efficacy Study (Study 1 above) in over 500 subjects, with no reports of serious and non-serious adverse events.

LABELING

The labeling for the INVOcell Intravaginal Culture System comprises physician labeling and patient labeling, which both include the device indications for use, a description of the device, warnings and precautions, clinical data on the performance of the device, and instructions for the safe and effective use of the device.

The labeling satisfies the requirements of 21 CFR 801.109 Prescription devices. The patient labeling also follows the principles identified in FDA's guidance entitled "Medical Device Patient Labeling" (issued April 2001).

The Instructions for Use (IFU) for the INVOcell device includes information on the required equipment/accessories for culturing of gametes and embryos, as well as explicit instructions on

the handling of each device component and the cleaning/disinfection of the components intended to be reprocessed.

The following warnings and precautions were included in the labeling:

Warnings:

- The INVOcell Culture Device and INVOcell Retention Device are single use only. Do not reuse.
- Do not use if product or package appears damaged. If the packaging is damaged, the product may no longer be sterile.
- Do not use the INVOcell culture device in patients with demonstrated hypersensitivity to medical grade silicone or polystyrene. Ensure that the embryo retrieval catheter complies with the tip outer diameter specifications that are compatible with the INVOcell device.
- Proper handling is extremely important to the safe and effective use of the INVOcell Intravaginal Culture Device. Do not begin clinical use of the INVOcell Intravaginal Culture System without establishing competency by reading and practicing these instructions for use.
- INVOcell Intravaginal Culture System should be handled under aseptic conditions at all times.
- After the INVOcell Intravaginal Culture Device has contacted the vaginal environment, the surfaces of the device, including those of the inner vessel, should be handled as if contaminated by vaginal flora.
- Utilize a legally-marketed ART culture medium that will support continued embryonic development for up to 72 hours.
- Culture media utilized with the INVOcell system MUST contain antibiotics to mitigate the risk of contamination of media in the inner chamber.
- Culture media utilized with the INVOcell system should have phenol red to aid in the determination of acceptable pH maintenance.
- Using the INVOcell Culture Device and INVOcell Retention Device, embryo development is first evaluated at the end of the incubation period at 72 hours post fertilization. Any abnormalities that would have been detected at an earlier stage (pro-nuclei stage) may no longer be apparent when the embryos are evaluated for transfer. As a result, there may be an increased risk that an abnormal embryo could be transferred to the uterus compared to traditional IVF.
- Do not use a 0-200 μL tip to add oocytes to the INVOcell Culture Device as the oocytes may stick in the tip and/or become damaged.
- Ensure that the embryo retrieval catheter complies with the list of catheters and the tip outer diameter requirements listed in the accessory section on page 3 of the IFU.

Precautions:

- INVOcell procedures should only be conducted by physicians with expertise in assisted reproductive technology and techniques including oocyte retrieval, clinical embryology, and embryo transfer, and with access to all equipment listed in the Required Accessories section.

- It is recommended that the INVOcell Intravaginal Culture system be utilized with a mild ovarian stimulation protocol.
- The recommended upper limit on number of oocytes or ICSI fertilized embryos to be placed in the INVOcell Culture Device is seven. Verify that the outer rigid shell and inner chamber of the INVOcell Culture Device are correctly locked before placement of the INVOcell Culture Device and the INVOcell Retention Device in the vaginal cavity.
- Do not touch the surface of the rotating valve of the inner chamber of INVOcell Culture Device during installation into the outer rigid shell to reduce the potential for contamination of media within the inner chamber via the inner chamber access port of the INVOcell Culture Device.
- Verify that the outer rigid shell and inner chamber of the INVOcell Culture Device are correctly locked before placement of the INVOcell Culture Device and the INVOcell Retention Device in the vaginal cavity.
- Advise the patient to avoid the following activities while the INVOcell Culture Device and the INVOcell Retention Device are in the vaginal cavity: sexual intercourse, strenuous physical activity, swimming, bathing in a tub (a shower is permissible), use of a douche, sauna, or any activity that may alter the temperature of the vaginal cavity.
- Instruct the patient to contact the physician if any of the following are observed: discomfort, bleeding, movement of the INVOcell Culture Device or INVOcell Retention Device, unusual vaginal secretions, or vaginal odor.
- Instruct the patient not to remove the INVOcell Culture Device and the INVOcell Retention Device from the vaginal cavity and to avoid manipulation of the INVOcell Culture Device and the INVOcell Retention Device.
- Provide the patient with instructions for replacement of the INVOcell Culture Device and the INVOcell Retention Device in the event it moves from its original position.
- If obvious contamination of culture medium is observed when the INVOcell Culture Device is removed from the vaginal cavity the embryos should be discarded.
- The working environment in the laboratory should be at a minimum of 22 °C to maintain the culture media temperature in the holding block at or above 34°C for 10 minutes during the loading process and embryo aspiration process.

RISKS TO HEALTH

Table5 below identifies the risks to health that may be associated with use of the Intravaginal Culture System and the measures necessary to mitigate these risks.

Table 5: Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Measure**
Damage to gametes and/or embryos or disruption of the IVF process	Non-clinical performance testing Shelf life testing Clinical testing Sterilization validation Labeling
Patient injury (e.g., hypersensitivity, toxicity, abrasion, discomfort)	Non-clinical performance testing Shelf life testing Biocompatibility

	Clinical testing Sterilization validation Labeling
Infection	Sterilization validation Reprocessing validation Non-clinical performance testing Shelf life testing Clinical testing Labeling
Transfer of incorrect embryos to patient	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the INVOcell Intravaginal Culture System is subject to the following special controls:

1. Clinical performance testing must demonstrate the following:
    a. Comfort and retention of the intravaginal culture device
    b. Adverse vaginal tissue reactions associated with intravaginal culture
    c. Maximum number of gametes and/or embryos that can be placed in a device
    d. Rates of embryo development to the designated stage, implantation rates, clinical pregnancy rates, live birth rates, and any adverse events or outcomes.
2. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be demonstrated:
    a. Mouse Embryo Assay (MEA) testing to assess embryotoxicity by evaluating the gamete and embryo-contacting device components effect on the growth and development of mouse embryos to the blastocyst stage
    b. Endotoxin testing on gamete and embryo-contacting components of the device
    c. Cleaning and disinfection validation of reusable device components
    d. Sterility maintenance of the culture media within the device throughout the vaginal incubation period and subsequent embryo extraction
    e. Ability of the device to permit oxygen and carbon dioxide exchange between the media contained within the device and the external environment throughout the vaginal incubation period.
3. The patient-contacting components of the device must be demonstrated to be biocompatible.
4. Performance data must demonstrate the sterility of the device components intended to be provided sterile.
5. Shelf-life testing must demonstrate that the device maintains its performance characteristics and the packaging of device components labeled as sterile maintain integrity and sterility for the duration of the shelf-life.
6. Labeling for the device must include:
    a. A detailed summary of the clinical testing, including device effectiveness, device-related complications, and adverse events

b. Validated methods and instructions for reprocessing of reusable components
c. The maximum number of gametes or embryos that can be loaded into the device
d. A warning that informs users that the embryo development is first evaluated following intravaginal culture
e. A statement that instructs the user to use legally-marketed assisted reproductive technology media that contain elements to mitigate the contamination risk (e.g., antibiotics) and to support continued embryonic development over the intravaginal culture period.

7. Patient labeling must be provided and must include:
    a. Relevant warnings, precautions, and adverse effects and complications
    b. Information on how to use the device
    c. The risks and benefits associated with the use of the device
    d. A summary of the principal clinical device effectiveness results.

BENEFIT/RISK DETERMINATION

The risks of the device are based on risks associated with assisted reproductive technology (ART) procedures accompanying the use of the device, as well as the placement of the device in the vagina for 72 hours. No serious adverse events associated with device usage were reported in the clinical studies described above. However, serious risks such as ovarian hyperstimulation syndrome (OHHS) due to elevated response to gonadotropin stimulation utilized in oocyte extraction, pain/discomfort related to oocyte retrieval via transvaginal aspiration, infection related to oocyte aspiration, failure of gametes to fertilize or embryos to develop (requiring additional stimulation protocols and extractions), and psychological injury due to failed embryo development and cancellation of transfer, could occur, but are not directly related to the device. Non-serious risks associated with device usage include discomfort wearing the device, involuntary expulsion of the device, change in vaginal flora secondary to wearing the device, and spotting due to vaginal irritation. In addition, usage of the device carries the risk that embryonic abnormalities that would normally be detected during the 72 hour incubation, may not be noticed, leading to the possible transfer of an abnormal embryo during transplantation. Changes in vaginal flora and spotting were not reported in the clinical evaluation of the device. If they occur, these events would be expected to resolve soon after the 72 hour incubation period. During the device retention study, 14/15 women reported no or mild discomfort while wearing the device. If a woman cannot tolerate wearing the device, the device may be easily removed, but the device will need to be placed in an incubator to maintain temperature. The effectiveness of the device when placed in a laboratory incubator has not been evaluated.

The primary probable benefit of using the device, considering that there are alternative treatments for infertility (depending on the underlying cause) and devices (e.g. traditional ART culture dishes), is the ability for a woman to "carry" the couple's own gametes/embryos. This benefit is psychological in nature, and is based primarily on patient desire for a holistic approach to IVF. Therefore, this benefit will be dependent on patient preference. In addition, this benefit is based upon expert clinical opinion, rather than patient preference data.

Additional factors to be considered in determining probable risks and benefits for the INVOcell Intravaginal Culture System include: the overall risks associated with device use are few and

minor, and serious adverse events are expected to be rare. The live birth outcomes of the INVOcell Intravaginal Culture System are similar to conventional IVF.

In conclusion, given the available information above, the data support that for intravaginal IVF and culture of gametes/embryos, the probable benefits outweigh the probable risks for the INVOcell Intravaginal Culture System. The device provides substantial benefits to patients desiring a holistic approach to IVF and who are uncomfortable allowing their gametes/embryos to reside in a laboratory environment out of their control. The risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* request for the INVOcell Intravaginal Culture System is granted and the device is classified under the following:

Product Code: OYO
Device Type: Intravaginal Culture System
Class: II
Regulation: 21 CFR 884.6165