K100367
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Appendix D

510(K) SUMMARY
Summary of Safety and Effectiveness Information
Supporting a Substantially Equivalent Determination

Submitted by: ORIGIO a/s
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Date Submitted: August 24, 2010

Device Identification
Trade Name: MediCult Vitrification Cooling and MediCult Vitrification Warming
Common Name: MediCult Vitrification Cooling (Cat. No. 1228) and Warming (Cat. No. 1229)

Classification Name: Reproductive media and supplements (21 CFR 884.6180, Product Code MQL)

Predicate devices:
RapidVit™ Cleave (K080446)
RapidWarm™ Cleave (K080446)

Description
The ORIGIO MediCult Vitrification Cooling (1228) and Warming (1229) media consist of two freezing and four warming media which are intended to be used sequentially. All the media are based on modified human tubal fluid (mHTF) buffered with HEPES supplemented with human serum albumin (12 mg/mL) and gentamicin sulphate (10 mg/L).

MediCult Vitrification Cooling (1228) media contains the cryoprotectants ethylene glycol and 1,2-propanediol. The concentration of the cryoprotectants increases in the two sequentially media, to increase the osmotic stress to withdraw water from the cell. The two sequential cooling media are:

- Vial 1: Equilibration Medium (1222)
- Vial 2: Vitrification Medium (1223)

The Equilibration Medium contains 7.5% (v/v) ethylene glycol and 7.5% (v/v) 1,2-propanediol. The Vitrification Medium contains 15% (v/v) ethylene glycol and 15 % (v/v) 1,2-propanediol.

The MediCult Vitrification Warming (1228) media contains sucrose in decreasing concentrations in four dilution steps. The four sequential warming media are:

- Vial 1: Warming Medium (1224)
- Vial 2: Dilution Medium 1 (1225)
- Vial 3: Dilution Medium 2 (1226)
- Vial 4: Washing Medium (1227)

The four warming vials, Warming Medium, Dilution Medium 1, Dilution Medium 2, and Washing Medium contain 1M, 0.5M, 0.25M, and 0M sucrose, respectively.

MediCult Vitrification Cooling (1228) and Warming (1229) are supplied in transparent polypropylene plastic vials with screw top closures in a volume of 1-2 ml. All the media are colorless, viscous solutions, sterile, and ready to use by professionals within assisted reproduction. All media are quality control tested before release for pH, sterility, mouse embryo assay, endotoxin, and osmolality.

The vitrification media, MediCult Vitrification Cooling (1228) and Warming (1229) are modifications of former versions (MediCult Vitrification Cooling (Cat. No. 1218) and Warming (Cat. No.1219)) which have been commercially available in Europe since 2006 but not in U.S. The new version differ from the current vitrification products in two ways: 1) the media contain 12 mg/mL HSA instead of 10 mg/mL Plasmanate, 2) the media contain gentamicin instead of penicillin and streptomycin.

Intended use
MediCult Vitrification Cooling (1228) is for vitrification of human, day 3 cleavage-stage embryos.

MediCult Vitrification Warming (1229) is for warming of vitrified human, day 3 cleavage-stage embryos.

Technological Characteristics
The MediCult Vitrification Cooling (1228) media is designed to facilitate efficient dehydration of day 3 cleavage-stage embryos prior to the vitrification procedure and the MediCult Vitrification Warming (1229) media is designed to facilitate controlled re-hydration during the warming procedure of vitrified day 3 cleavage-stage embryos.

Generally, vitrification in cryopreservation is a process where human cleavage-stage embryos are preserved by cooling to low sub-zero temperatures typically in liquid nitrogen. In the process water is withdrawn from the cell by use of cryoprotectant. The cryoprotectants act like antifreeze by lowering the freezing temperature. They also increase the viscosity. Instead of crystallizing, the syrupy solution turns into an amorphous ice, i.e., it vitrifies.

Later, the embryos can be warmed, fertilized, and transferred to the uterus. In the warming process sucrose functions as an external "osmotic buffer" by restricting the inflow of water when the external concentration of cryoprotectant is reduced during the rehydration process.

The technological characteristics of MediCult Vitrification Cooling (1228) and Warming (1229) are essentially similar to the predicate device RapidVit™ Cleave and RapidWarm™ Cleave (K080446), i.e. they have the same intended use and use ethylene glycol, 1,2-propanediol, and sucrose as cryoprotectants.

As base medium Medicult Vitrification Cooling (1228) and Warming (1229) use modified human tubal fluid (mHTF) buffered with HEPES. The predicate devices use G-MOPS as the buffer. However, both media contain amino acids and physiological salt solutions as the base composition.

Both devices contain gentamicin and HSA at the same concentration levels. However, the RapidVit™ Cleave also contains Ficoll and Hyaluronan. The functions of hyaluronan and Ficoll in vitrification are supposed to be as extra cellular cryoprotectives; hence, the predicate device RapidVit™ Cleave contains slightly more macromolecules than MediCult Vitrification Cooling (1228). Commercially available vitrification and warming media contain HSA in the range of 8-12 mg/mL and the total macromolecule content is between 10-22 mg/mL. Hence, both devices are within these limits. Additionally, no clinical data indicates that vitrification media containing increasing content of HSA or other macromolecules, affects the safety and effectiveness of the media. Therefore the MediCult Vitrification Cooling (1228) and Warming (1229) are as safe and effective as the predicate.

Thus, the intended use, the technology, and composition of MediCult Vitrification Cooling (1228) and Warming (1229) is considered to be the same as the predicate devices and they are subject to the same quality control tests before release, storage conditions, and sterility assurance level.

Therefore, Medicult Vitrification Cooling (1228) and Warming (1229) are considered substantially equivalent to the predicate devices.

Performance data - bench
Preclinical bench testing has been performed with MediCult Vitrification Cooling (1228) and Warming (1229) on bovine embryos.

The bovine study used three different cooling and warming vitrification media: MediCult Vitrification Cooling and Warming (1218, 1219) with 10 mg/mL Plasmanate, MediCult Vitrification Cooling and Warming (1228, 1229) with 12 mg/mL HSA, and with 50 mg/mL HSA, respectively. The results showed no significant differences in blastocyst rates, cleavage rates, or survival rates between the 3 vitrification media. However, the supplementation of 50 mg/mL HSA in MediCult Vitrification Cooling and Warming (1228, 1229) appears to have a slightly positive effect as evidenced by faster development and better morphology of the bovine embryos.

The non-significant positive trend of increased HSA (50 mg/mL) substitution in MediCult Vitrification Cooling and Warming (1228, 1229) on development and better morphology of the bovine embryos was not supported by the clinical data.

Performance data – clinical
In order to evaluate the safety and efficiency of MediCult Vitrification Cooling (1228) and Warming (1229) on human embryos an evaluation of clinical data regarding the intended use of the media has been conducted. The evaluation was based on: a retrospective clinical study, published in peer-reviewed literature, along with market experience on MediCult Vitrification Cooling and Warming (1218, 1219) supplemented with Plasmanate.

The clinical output (deliveries) obtained in the retrospective clinical study with MediCult Vitrification Cooling (1228) and Warming (1229) media supplemented with 50 mg/mL HSA were 23.3% per started thawing cycle and 23.7% per transfer cycles in the study. In comparison,

deliveries have been reported by ASRM/SART to 21% per thawing cycle and 23.5% per transfer cycle and by ESHRE to 12.0% per thawing cycle and 13.1% per transfer cycle. The miscarriage rate in the retrospective clinical study was 6.3% which is in line with previous described miscarriage rates after vitrification.

Clinical results reported by Balaban et al. (2008)[1] using the predicate device, obtained relative high pregnancy and implantation rate of 49.3% and 29.7%, respectively, compared to 32% and 15% in the retrospective clinical study. However, pregnancy and implantation rate obtained in the retrospective study is in line with pregnancy- and implantation rates reported in other published studies. The results reported by Balaban et al. (2008) could be explained by different patient profiles and conditions. For instance the study reported by Balaban et al. (2008) includes only patients who undergo the first assisted reproduction treatment cycle. In contrast the clinical data obtained in the retrospective study is based on routine data; in addition the average ages of the patients were relative high (35.1 years). It is well known that the age of the patient affects the probability for pregnancy.

The evaluation of published peer-reviewed literature, documents that vitrification media containing a wide range of HSA concentrations (and other macromolecules) are able to safely vitrify and effectively give rise to acceptable pregnancy rates and numbers of babies born. No clinical data indicate that using media containing 12 mg/mL HSA instead of 50 mg/mL HSA affects the safety and effectiveness of the media. Additionally, good performance and safety have been demonstrated in published studies that have used the MediCult Vitrification Cooling (1218) and Warming (1219) media which contain 10 mg/mL plasmanate, resulting in pregnancy rates between 28- 44.6 % and implantation rates between 17-23.4 % which is comparable to the predicate devices.

Several reviews have compared the safety and performance of cleavage-stage embryo vitrification. The reviews conclude that promising results for neonatal outcome and with no increase in birth defects compared to fresh embryo transfer are to be expected.

In summary:

- **MediCult Vitrification Cooling** and Warming (1228, 1229) have the same indication for use as predicate.
- **MediCult Vitrification Cooling** and Warming (1228, 1229) have similar technology, contain the same components, and are subject to the same control methods as the predicate devices. They have the same sterility assurance level and storage conditions.
- **MediCult Vitrification Cooling** and Warming (1228, 1229) are considered to be as safe, as effective, and perform as well as the predicate devices.

Based on the literature review, the market experience, the retrospective clinical study, and comparison with the predicate device, it is concluded that MediCult Vitrification Cooling (1228) and Warming (1229) media are safe and effective in use for vitrification of human day 3 cleavage-stage embryos.

[1] Balaban B, Urman B, Ata B, Isiklar A, Larman MG, Hamilton R, and Gardner DK (2008). A randomized controlled study of human Day 3 embryo cryopreservation by slow freezing or vitrification: vitrification is associated with higher survival, metabolism and blastocyst formation. Hum Reprod, 23, 1976-1982.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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AUG 27 2010

Re: K100367
Trade Name: MediCult Vitrification Cooling and MediCult Vitrification Warming
Regulation Number: 21 CFR §884.6180
Regulation Name: Reproductive media and supplements
Regulatory Class: II
Product Code: MQL
Dated: August 3, 2010
Received: August 5, 2010

Dear Dr. Leonardi:

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. 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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 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 the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Herbert P. Lerner, M.D., Director (Acting)
Division of Reproductive, Gastro-Renal
and Urological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

K100367

Indications for Use

510(k) Number (if known): **K100367**

Device Name: **MediCult Vitrification Cooling**

Indications for Use:

MediCult Vitrification Cooling is for vitrification of human, day 3 cleavage-stage embryos.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K100367

K100367

Indications for Use

510(k) Number (if known): **K100367**

Device Name: **MediCult Vitrification Warming**

Indications for Use:

MediCult Vitrification Warming is for warming vitrified human, day 3 cleavage-stage embryos.

Prescription Use ___X___ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

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