under paragraph (a) of this section and does not change the amount to be deducted from the family benefit or payment. The increase is simply added to what amount, if any, is payable. If a new beneficiary becomes entitled to monthly benefits on the same earnings record after the increase, the amount of the reduction is redistributed among the new beneficiaries entitled under section 202 of the Act and deducted from their current benefit rate.

(k) *Effect of changes in the amount of the workers' compensation/public disability benefit or payment.* Any change in the amount of the workers' compensation/public disability benefit or payment received will result in a recalculation of the reduction under paragraph (a) of this section and, potentially, an adjustment in the amount of such reduction. For those individuals described in paragraph (a)(1) of this section who do not meet the conditions specified in paragraph (a)(2) of this section, any increased reduction will be imposed effective with the month after the month the Commissioner received notice of the increase in the workers' compensation benefit or payment (it should be noted that only workers' compensation can cause this reduction). Adjustments due to a decrease in the amount of the workers' compensation/public disability benefit or payment will be effective with the actual date the decreased amount was effective. For individuals described in paragraph (a)(2) of this section, any increase or decrease in the reduction will be imposed effective with the actual date of entitlement to the new amount of the workers' compensation/public disability benefit or payment.

(l) *Redetermination of benefits*—(1) *General.* In the second calendar year after the year in which reduction under this section in the total of an individual's benefits under section 223 of the Act and any benefits under section 202 of the Act based on his or her wages and self-employment income was first required (in a continuous period of months), and in each third year thereafter, the amount of those benefits which are still subject to reduction under this section are redetermined. The redetermination will be made unless it results in any decrease in the total amount of benefits payable under title II of the Act on the basis of the workers' wages and self-employment income. The redetermined benefit is effective with the January following the year in which the redetermination is made.

(2) * * *

(i) The ratio of the average of the total wages (as defined in § 404.1048(c)) of all persons for whom wages were reported to the Secretary of the Treasury or his delegate for the calendar year before the year in which the redetermination is made, to the average of the total wages of all persons reported to the Secretary of the Treasury or his delegate for calendar year 1977 or, if later, the calendar year before the year in which the reduction was first computed (but not counting any reduction made in benefits for a previous period of disability); and

* * * * *

[FR Doc. 97–23506 Filed 9–3–97; 8:45 am]

BILLING CODE 4190–29–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 884

[Docket No. 97N–0335]

Obstetric and Gynecologic Devices: Reclassification of Medical Devices Used for In Vitro Fertilization and Related Assisted Reproduction Procedures

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify instrumentation intended for use in in vitro fertilization (IVF) and related assisted reproduction procedures from class III to class II. FDA is also proposing to reclassify assisted reproduction microscopes and microscope accessories from class III to class I and to exempt this device from the requirement of premarket notification. This reclassification is being proposed on the Secretary of Health and Human Services' own initiative, based on new information. This action is being taken under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) and the Safe Medical Devices Act of 1990 (the SMDA).

DATES: Written comments by December 3, 1997. FDA proposes that any final regulation based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Elisa D. Harvey, Center for Devices and Radiological Health (HFZ–470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–1180.

SUPPLEMENTARY INFORMATION:

I. Background

A. Regulatory Authorities

The act (21 U.S.C. 201 *et seq.*), as amended by the 1976 amendments (Pub. L. 94–295) and the SMDA (Pub. L. 101–629), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are: Class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the act, to a predicate device that does not require premarket approval. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

Section 513(f)(2) of the act provides that FDA may initiate the reclassification of a device classified into class III under section 513(f)(1) of the act, or the manufacturer or importer of a device may petition the agency to reclassify the device into class I or class II. FDA's regulations in § 860.134 (21

CFR 860.134) set forth the procedures for the filing and review of a petition for reclassification of such class III devices. In order to change the classification of the device it is necessary that the proposed new class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. FDA relied upon ''valid scientific evidence,'' as defined in section 513(a)(3) of the act and 21 CFR 860.7(c)(2), in the classification process to determine the level of regulation for devices. For the purpose of reclassification, the valid scientific evidence upon which the agency relied must be publicly available. Publicly available information excludes trade secret and/or confidential information, e.g., the contents of premarket approval applications (PMA's) (see section 520(c) of the act (21 U.S.C. 360j(c)).

Section 513(d)(2)(A) of the act authorizes FDA to exempt, by regulation, a generic type of class I device from, among other things, the requirement of premarket notification in section 510(k) of the act after stating the reasons for making such a requirement inapplicable. Such an exemption permits manufacturers to introduce into commercial distribution generic types of devices without first submitting a premarket notification to FDA. If FDA has concerns about certain types of changes to a particular class I device, the agency may grant a limited exemption from premarket notification for that generic type of device.

B. Regulatory History of the Devices

Devices specifically intended for IVF and embryo transfer (ET) were developed and studied after enactment of the 1976 amendments. The first premarket notification submission (510(k)) for a device with an IVF indication for use was submitted to FDA in 1986. FDA found this device, and several subsequent to it, not substantially equivalent to preamendments devices because the IVF indication for use constituted a new intended use for these devices. Consequently, these devices were classified into class III by statute.

On January 29, 1988, FDA convened the Obstetrical and Gynecological Devices Panel (the Panel), an FDA advisory committee, to identify and discuss medical devices used for IVF or gamete intrafallopian transfer (GIFT), and to identify the data required for the evaluation of safety and effectiveness, in order to assist FDA in developing a regulatory strategy for medical devices used for IVF and related assisted reproductive technology (ART) procedures (Ref. 12). The Panel considered a wide variety of medical devices already being used by IVF clinics. Besides the overall quality and sterility of these devices, the Panel focused on one key concern that applied to many of the devices used for IVF, namely possible material toxicity of the device to gametes or embryos. The Panel agreed with many of the guest speakers that there was a general need to evaluate many of these IVF devices using the mouse embryo assay (MEA).

The MEA had been shown to be highly predictive of material safety. The Panel discussed what devices should be subjected to a variety of test regimens. The Panel agreed that, in general, IVF had been shown to be safe and effective for properly selected patients, and that many of the generic types of devices used in IVF/ART procedures could be adequately regulated by special controls. The Panel believed that each generic type of device used for IVF/ET was a candidate for reclassification if certain recognized testing, specifications, and/or labeling requirements were imposed.

Reclassification of devices can be initiated following a petition from a manufacturer, and FDA encouraged interested manufacturers to do so following the 1988 Panel meeting. However, no such petition was submitted to FDA, and devices intended for use in IVF remained in class III. Use of IVF/ART procedures in the United States continued to grow. A variety of assisted reproduction technologies and procedures, including IVF/ET and GIFT, are now considered the standard of care for treatment of infertility in a selected population of patients (Refs. 1, 6, 8, 17, 18, 20, 32, and 35).

On October 21, 1995, FDA reconvened the Panel to reconsider the safety and effectiveness of these devices (Ref. 13). At the October 1995 meeting, the Panel considered a new list of generic device names and identifications. FDA asked for scientific and clinical input on important design, manufacture, and use characteristics of these devices (Ref. 7). After presentations by FDA-invited guest speakers, industry, and professional societies, the Panel reviewed the background materials on these devices and made suggestions about appropriate testing requirements for each.

The individual devices used for IVF/ET, such as oocyte retrieval needles, reproductive media, labware, and ET catheters, each perform a part of a multistaged procedure. The ultimate success of the assisted reproduction procedure (pregnancy) depends on the safety and effectiveness of each individual medical device used, as well as operating procedures within the IVF clinic and patient selection/exclusion criteria. The 1988 and 1995 Panels agreed that premarket approval is not necessary to provide reasonable assurance of the safety and effectiveness of the individual medical devices used for IVF/ET.

In accordance with section 513(f) of the act and § 860.134, based on new information with respect to the device, FDA, on its own initiative, is proposing to reclassify the following instrumentation for assisted reproduction: (1) Needles; (2) catheters; (3) accessories; (4) microtools; (5) micropipette fabrication instruments; (6) micromanipulators and microinjectors; (7) labware; (8) water and water purification systems; and (9) reproductive media and supplements, from class III to class II when intended for the uses specified below in the device description section. Additionally, in accordance with section 513(f) of the act and § 860.134, based on new information with respect to the device, FDA, on its own initiative, is proposing to reclassify the assisted reproduction microscopes and microscope accessories from class III to class I when intended to enlarge images of gametes or embryos. Furthermore, FDA is proposing to exempt assisted reproduction microscopes and microscope accessories used for IVF and related assisted reproduction procedures from premarket notification requirements.

Consistent with the act and the regulation, and because the Panel had been consulted earlier in the process and offered input on appropriate design and test requirements, FDA did not refer the proposed reclassification back to the Panel for its recommendation on the requested change in classification.

II. Device Descriptions

The following is a list of medical devices, with their respective identifications, covered by this reclassification. It is important to note that these requirements apply only to products that are intended for use in assisted reproduction. General purpose devices (e.g., incubators, freezers, and water purification systems), which are not intended for use in assisted reproduction, are not subject to the regulatory controls described later in this proposed rule.

1. *Assisted reproduction needles*: Assisted reproduction needles are devices used to either obtain gametes from the body, or introduce gametes, zygote(s), preembryo(s), and/or embryo(s) into the body. This generic

type of device may include a single or double lumen needle and component parts, including needle guides such as those used with ultrasound.

2. *Assisted reproduction catheters*: Assisted reproduction catheters are devices used to introduce or remove gametes, zygote(s), preembryo(s), and/or embryo(s) into or from the body. This generic type of device may include catheters, cannulae, introducers, dilators, sheaths, and component parts.

3. *Assisted reproduction accessories*: Assisted reproduction accessories are a group of devices used during assisted reproduction procedures, in conjunction with assisted reproduction needles and/or assisted reproduction catheters to aspirate, incubate, infuse, and/or maintain temperature. This generic type of device may include:

(a) Powered aspiration pumps, used to provide low flow, intermittent vacuum for the aspiration of eggs (ova).

(b) Syringe pumps (powered or manual), used to activate a syringe to infuse or aspirate small volumes of fluid during assisted reproduction procedures.

(c) Collection tube warmers, used to maintain the temperature of egg (oocyte) collection tubes at or near body temperature. A dish/plate/microscope stage warmer is a device used to maintain the temperature of the egg (oocyte) during manipulation.

(d) Embryo incubators, used to store and preserve gametes and/or embryos at or near body temperature.

(e) Cryopreservation instrumentation and devices, used to contain, freeze, and maintain gametes and/or embryos at an appropriate freezing temperature.

4. *Assisted reproduction microtools*: Assisted reproduction microtools are pipettes or other devices used in the laboratory to denude, micromanipulate, hold or transfer human gametes, or embryos for assisted hatching, intracytoplasmic sperm injection (ICSI), embryo biopsy, or other assisted reproduction methods, including preimplantation diagnosis.

5. *Assisted reproduction micropipette fabrication instruments*: Assisted reproduction micropipette fabrication devices are instruments intended to pull, bevel, or forge a micropipette or needle for ICSI, IVF, or other similar procedures.

6. *Assisted reproduction micromanipulators and microinjectors*: Assisted reproduction micromanipulators are devices intended to control the position of an assisted reproduction microtool. Assisted reproduction microinjectors include any device intended to control aspiration or expulsion of the contents of an assisted reproduction microtool.

7. *Assisted reproduction labware*: Assisted reproduction labware consists of laboratory equipment or supplies intended to prepare, store, manipulate, or transfer human gametes or embryos for IVF or other assisted reproduction techniques. These include syringes, IVF tissue culture dishes, IVF tissue culture plates, pipette tips, dishes, plates, and other vessels that come into physical contact with gametes, embryos, or tissue culture media.

8. *Assisted reproduction water and water purification systems*: Assisted reproduction water purification systems are devices intended to generate high quality sterile, pyrogen-free, distilled, deionized water for reconstitution of media used for aspiration, incubation, transfer or storage of gametes or embryos for IVF or other assisted reproduction procedures. They may also be intended as the final rinse for labware or other assisted reproduction devices that will contact the gametes or embryos. This device also includes bottled water that is specifically intended for reconstitution of media used for aspiration, incubation, transfer or storage of gametes or embryos for IVF or other assisted reproduction procedures.

9. *Reproductive media and supplements*: Reproductive media ad supplements are products that are used for assisted reproduction procedures. Media include liquid and powder versions of carious substances that come in direct physical contact with human gametes or embryos (including oil used to cover the media) for the purposes of preparation, maintenance, transfer or storage, and supplements include specific reagents added to media to enhance specific properties of the media (e.g., proteins, sera, antibiotics, etc.).

10. *Assisted reproduction microscopes and microscope accessories*: Assisted reproduction microscopes and microscope accessories (excluding microscope stage warmers, which are classified under Assisted Reproduction Accessories) are optical instruments used to enlarge images of gametes or embryos. Variation of microscopes and microscope accessories used for these purposes would include phase contrast microscopes, fluorescence microscopes, dissecting microscopes, and inverted stage microscopes.

III. Proposed Reclassification

FDA is proposing that assisted reproduction: (1) Needles; (2) catheters; (3) accessories; (4) microtools; (5) micropipette fabrication instruments; (6) micromanipulators and microinjectors; (7) labware; (8) water and water purification systems; and (9) reproductive media and supplements; with the intended uses specified in section II of this document, be reclassified from class III to class II. FDA believes that class II, with the following special controls, would provide reasonable assurance of the safety and effectiveness of these devices: (1) The MEA (see Davidson et al., 1988 (Ref. 4); May, 1996 (Ref. 10)); (2) endotoxin testing (see Nagata and Shirakawa, 1996; and United States Pharmacopeia (USP), 23d ed. (Ref. 10)); (3) design specifications; (4) labeling; (5) clinical studies; and (6) voluntary standards (College of American Pathologists (CAP) Reproductive Laboratory Accreditation Program (Ref. 16), Society for Assisted Reproductive Technology (SART, Refs. 22 through 31)). In addition, FDA is developing a policy addressing regulation of tissue culture media for a variety of in vivo applications, including assisted reproduction. Guidance for performance and labeling of such products, based on differing claims, is being evaluated with input from industry. For general claims, it is expected that minimum performance data (based on toxicologic, microbiologic, and chemical studies) will be required. More specific clinical claims will require additional data.

FDA also proposes that assisted reproduction microscopes and microscope accessories used for IVF and related assisted reproduction procedures be reclassified from class III to class I. FDA believes that class I general controls are sufficient to provide reasonable assurance of the safety and effectiveness of these devices. Furthermore, FDA is proposing to exempt assisted reproduction microscopes and microscope accessories from premarket notification requirements.

IV. Risks to Health

Because the inception of IVF and related ART procedures in the early 1980's, a wealth of literature regarding the safety and effectiveness of this technology has become available (Refs. 1, 5, 6, 8, 11, 18, 20, 22 through 30, 35, 37, and 38). The long history of use of devices for assisted reproduction and the large amount of published literature have demonstrated that the potential risks from use of these devices are now well-known and extensively documented. The following is a summary of the overall general potential risks that may be associated with the use of assisted reproduction devices to the gametes or embryo and the patient,

including background information, and identification of the general or special controls that FDA believes address each risk. The risks may or may not apply to each individual device. Risks to health with the devices mentioned in section II of this document may involve trauma or damage to the patient (see discussion below), to gametes or embryos.

A. Gamete or Embryo Damage

Gamete or embryo damage could occur which would render them viable but damaged, or nonviable. This could occur with the knowledge of the gynecologist, so that affected gametes or embryos would not be used in the procedures, or without the knowledge of the gynecologist, in which case damaged or nonviable gametes or embryos could be used in assisted reproductive procedures. This could result in cycles lost or potential development of damaged embryos, which may result in later loss of pregnancy or congenital defects. Nevertheless, if recommended testing procedures are followed, there is reasonable assurance that the risk of damage to gametes or embryos is small. The assisted reproduction devices most likely to present this risk are assisted reproduction needles, assisted reproduction catheters, assisted reproduction accessories, assisted reproduction microtools, assisted reproduction micromanipulators and microinjectors, and reproductive media and supplements. The special controls for these devices that would mitigate this risk would be the MEA, device sterilization validation, water quality testing, design specifications, labeling, and voluntary standards (in which techniques for using these devices are described).

B. Pain

The incidence of pain or discomfort associated with assisted reproduction procedures has been estimated at 0 to 11.6 percent (Refs. 2 and 9), depending on the specific procedure or part of the procedure being done. Typically it is associated with percutaneous abdominal needle puncture for oocyte retrieval, and it may be tolerable to the patient. In the event that the pain is intolerable, it may be mitigated by the use of local anesthetic. The assisted reproduction devices most likely to present this risk are assisted reproduction needles and assisted reproduction catheters. The special controls for these devices that would mitigate this risk would be labeling (specifically, instructions for use), design specifications, and voluntary standards (in which techniques for using these devices are described).

C. Hematuria

The incidence of hematuria has been estimated at 0.4 to 13.3 percent (Refs. 2, 9, 19, 34, and 39). This may occur due to the aspiration needle penetrating a filled bladder, and it may be accompanied by extravasation of urine or transient dysuria. These are short-term problems that typically resolve spontaneously within 24 hours. The assisted reproduction devices most likely to present this risk are assisted reproduction needles and assisted reproduction catheters. The special controls for these devices that would mitigate this risk would be labeling (specifically, instructions for use), design specifications and voluntary standards (in which techniques for using these devices are described).

D. Infection (Uterine, Urinary Tract Infection (UTI), Exacerbation of Pelvic Inflammatory Disease (PID), and Cystitis)

The incidence of infection occurring as a consequence of an assisted reproduction procedure has been estimated at 0.5 to 6.9 percent (Refs. 2, 9, 19, 34, and 39). If a needle puncture traverses the bladder, cystitis is a possible sequela. Infection may be introduced via needle puncture, or the use of any contaminated (unsterile) device, as well as by lack of adherence to strict sterile technique. For these reasons, antibiotics are prophylactically administered. These complications can also be minimized with close attention to sterile technique and careful screening for preexisting active or latent pelvic infections. The assisted reproduction devices most likely to present this risk are assisted reproduction needles, assisted reproduction catheters, assisted reproduction accessories, assisted reproduction microtools, assisted reproduction micromanipulators and microinjectors, and reproductive media and supplements. The special controls for these devices that would mitigate this risk would be the MEA, endotoxin testing, device sterilization validation, water quality testing, design specifications, labeling, and voluntary standards (in which techniques for using these devices are described).

E. Bleeding

The incidence of bleeding during assisted reproduction procedures has been estimated at 3.5 to 17 percent (Refs. 2, 9, 19, 34, and 39), and typically is associated with transvaginal oocyte retrieval or trauma secondary to insertion of a catheter through the cervix. Bleeding can usually be easily controlled with direct pressure. The assisted reproduction devices most likely to present this risk are assisted reproduction needles and assisted reproduction catheters. The special controls for these devices that would mitigate this risk would be design specifications, labeling, and voluntary standards (in which techniques for using these devices are described).

F. Puncture of Blood Vessels, Uterus, or Bowel

The incidence of inadvertent puncture of intra- or retro-abdominal structures is estimated at 0.2 to 5.1 percent for blood vessels, 0.9 to 1.9 percent for bowel, and 1.9 to 2.6 percent for the uterus (Refs. 2, 9, 19, 34, and 39). This can occur during oocyte retrieval procedures and is most often due to incorrect needle placement or inadequate knowledge of pelvic and abdominal anatomy by the operator. Incidence of these complications is minimized with increasing experience of the operator. Should any of these adverse events occur, surgical correction may be necessary to avoid further complications. The assisted reproduction devices most likely to present this risk are assisted reproduction needles and assisted reproduction catheters. The special controls for these devices that would mitigate this risk would be design specifications, labeling, and voluntary standards (in which techniques for using these devices are described).

G. Other (Ectopic Pregnancy, Multiple Gestation, or Chromosomal and Congenital Abnormalities)

Ectopic pregnancy, multiple gestation, or chromosomal and congenital abnormalities are also risks of assisted reproduction procedures, though not specifically related to any device. Rather, the occurrence of these events is related more to the inherent risk of assisted reproduction procedures in general, patient factors, and the specific clinical practices employed. Nevertheless, special controls of labeling and voluntary standards will help to ensure that the user includes appropriate patient education that informs patients of these risks as well as the specific procedures to be performed and devices to be used.

SART collects data from all of its members annually on success rates and the incidence of adverse events such as those listed above. According to SART's 1996 report (Ref. 30), the incidence of ectopic pregnancy following assisted reproduction procedures has

consistently remained in the range of 0.6 to 1.3 percent of all transfers performed (approximately 4 percent of established pregnancies) in the United States for several years. This is somewhat higher than the incidence of ectopic pregnancies (around 1.7 percent) in the general U.S. population (Ref. 15). The increased incidence of ectopic pregnancy following IVF procedures correlates strongly with tubal damage, which is a major cause of infertility in IVF patients. Other potential but less substantiated causes of ectopic pregnancy include the use of clomiphene, or ET techniques that use high intrauterine positioning of the catheter tip (near the tubal ostium) or large amounts of fluid. Heterotopic (simultaneous intrauterine and extrauterine) pregnancies are also a known complication following assisted reproductive procedures (Ref. 33) with an estimated incidence of up to 1.4 percent of pregnancies in IVF patients, compared to the general population's rate of 0.003 to 0.038 percent (Ref. 31). Risk factors for this complication also include tubal pathology and replacement of multiple embryos, as well as the other previously mentioned factors. Early transvaginal sonography has greatly improved the ability to detect ectopic or heterotopic pregnancies with nearly 100 percent sensitivity and specificity. The assisted reproduction devices most likely to present this risk are assisted reproduction needles and assisted reproduction catheters. The special controls for these devices that would mitigate this risk would be design specifications, labeling, and voluntary standards (in which techniques for using these devices are described).

Multiple gestation is the most common complication of assisted reproductive procedures, and it is obviously related to the number of embryos transferred per procedure or cycle, as well as the efficiency of implantation at a particular IVF facility. In the general U.S. population, twinning occurs in about 1.2 percent of deliveries, and triplets constitute 0.01 to 0.02 percent. The incidence of twins following assisted reproductive procedures ranges from about 20 to 35 percent, and 2 to 6 percent for triplets or higher order births. (Refs. 27 through 30). Risks associated with multiple gestation include increased chance of prematurity, increased perinatal morbidity and mortality, and increased maternal risks such as gestational hypertension (Ref. 1). These risks are not related per se to the medical devices used in accomplishing the procedure, but the practice of implanting multiple embryos to maximize the chance of achieving pregnancy. Various approaches to dealing with this problem have been suggested, including limiting the number of transferred zygotes or embryos to three or four, cryopreservation techniques for preserving extra zygotes or embryos for future use, and selective embryo reduction techniques. Early ultrasonographic monitoring of IVF patients provides the best method for documenting and following multiple gestation pregnancies in order to best treat these patients.

SART estimates with its data from 1996 (Ref. 30) that the incidence of birth defects is between 1.8 to 2.7 percent of neonates, which approximate those seen in the general U.S. population (Ref. 3), especially when adjusted for maternal age. Because the incidence of these abnormalities increased with maternal age, this rate would be expected due to the advanced age of many IVF patients. This one factor accounts for most abnormalities, although other potential procedure-related causes could be defects induced through ovulation stimulation, in vitro manipulations of gametes, or the lack of elimination of abnormal gametes via normal biological mechanisms.

V. Summary of Reasons for Reclassification

FDA believes that the instrumentation for assisted reproduction: (1) Needles; (2) catheters; (3) accessories; (4) microtools; (5) micropipette fabrication; (6) micromanipulators and microinjectors; (7) labware; (8) water and water purification systems; and (9) reproductive media and supplements should be classified into class II because special controls, in addition to general controls, can provide reasonable assurance of the safety and effectiveness of the devices, and there is sufficient information to establish special controls to provide such assurance. FDA believes that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these devices.

FDA believes that assisted reproduction microscopes and microscope accessories should be classified into class I because general controls would provide reasonable assurance of safety and effectiveness. Furthermore, FDA is proposing to exempt assisted reproduction microscopes and microscope accessories used for IVF and related assisted reproduction procedures from premarket notification requirements. These devices do not have a significant history of false or misleading claims or risks associated with their inherent characteristics such as device design or materials. In addition, the characteristics of these devices necessary for their safe and effective performance are well established.

VI. Summary of Data Upon Which the Reclassification is Based

The number of IVF and other assisted reproduction procedures performed annually in the United States has grown considerably in recent years. In 1994, the most recent year from which statistics are available, about 33,000 IVF cycles were initiated, with approximately 9,500 live-birth deliveries (Ref. 30).

Success rates for standard IVF procedures have increased somewhat between 1991 and 1994, from about 15 to 21 percent per cycle initiated (see Table 1), while tubal transfer techniques such as GIFT and zygote intrafallopian transfer (ZIFT) have somewhat higher success rates in the range of 28 percent (Refs. 27 through 30). These include micromanipulation techniques such as ICSI, which is successful in treating male factor infertility, and assisted hatching. No consensus exists as to the explanation for the difference in success rates, but these techniques do reflect different patient populations and diagnostic categories. About 250 ART programs report data to a registry of SART (Ref. 30), published annually in *Fertility and Sterility* (Refs. 22 through 30). Data reporting is mandatory for SART membership, and it is believed that most programs in the United States doing ART are reporting their data to SART.

Adverse outcomes, such as ectopic pregnancy, pregnancy loss, stillbirth, and structural or functional anomalies, have remained steady over the period of 1991 to 1994. Ectopic pregnancy rates are about 1.5 to 4.0 percent of established pregnancies, or 0.6 to 1.3 percent of ET's done. Pregnancy loss, most of which occurs during the first trimester, has remained around 20 percent. Stillbirths comprise approximately 1 percent of clinical pregnancies established, and congenital anomalies make up approximately 2 percent of neonatal outcomes. The incidence of prematurity was not recorded. The incidence of multiple gestations, a common feature of ART, was recorded, with 60 to 67 percent (depending on the particular ART technique used) of births being singleton deliveries, about 29 percent of births being twin gestations, about 5 percent being triplet gestations, and less than 1 percent of multiple births being

quadruplets or greater (Refs. 27 through 30).

The potential health benefit to be derived from the use of assisted reproductive devices is considerable. Infertility, defined as the inability to become pregnant within 1 year, is common in the United States today. Estimates range from 8.5 percent to 14 percent in couples over 30 years of age. IVF, an assisted reproductive technique wherein oocytes are retrieved from the ovaries and fertilized extracorporeally with subsequent embryo replacement (Ref. 1), was developed to treat infertility. In 1981, Elizabeth Carr became the first child born in the United States using IVF technology (Norfolk, VA). Since then, the number of IVF clinics in the United States has grown so that today approximately 250 specialized IVF clinics report their results to the SART registry. The use of these devices and their associated techniques provides the chance for restoration of reproductive function to those who would otherwise remain infertile (Ref. 25). Many advances have been made in assisted reproductive technology over the past two decades which have permitted treatment for more patients, including the ability to place oocyte aspiration needles transvaginally under ultrasonic guidance. This increases the ease and accuracy of the procedure and decreases procedure time and patient discomfort. It also decreases or avoids risks associated with general anesthesia and laparotomy or laparoscopy.

TABLE 1.—ART SUCCESS RATES[1]

	1991	1992	1993	1994
Cycles Initiated[2]				
IVF	24,671 (15.2)	29,404 (16.8)	33,543 (18.3)	33,700 (20.7)
GIFT[3]	5,452 (26.6)	5,767 (26.3)	4,992 (28.1)	4,214 (28.4)
ZIFT[3]	2,104 (19.7)	1,993 (22.8)	1,792 (24.4)	926 (29.1)
Combination	714 (19.3)	791 (27.9)	882 (27.8)	550 (29.7)
Frozen ET[3]	4,838 (11.1)	5,814 (13.9)	6,869 (13.3)	7,046 (15.4)
Donor Oocytes	1,107 (25.6)	2,032 (31.3)	2,766 (30.2)	3,119 (46.8)
Total Deliveries	5,699	7,355	8,741	9,573
Number of Programs	215	249	267	249

TABLE 2.—ART ADVERSE EVENTS[1]

	1991	1992	1993	1994
Ectopic Pregnancies[4]				
IVF	223 (5.8)	272 (4.9)	288 (4.4)	246 (3.9)
GIFT	44 (2.9)	61 (3.6)	61 (4.0)	45 (3.2)
ZIFT	20 (4.5)	20 (3.9)	13 (2.8)	9 (3.1)
Combination	10 (4.5)	10 (3.9)	15 (5.3)	5 (2.7)
Frozen ET	28 (2.2)	2 (3.2)	10 (5.0)	17 (1.5)
Donor Oocytes	Nr[5]	NR	NR	NR
Pregnancy Loss (% of clinical pregnancies)				
IVF	20	20	19	19
GIFT	22	22	20	22
ZIFT	19	15	20	16
Combination	39	17	20	15
Frozen ET	19	15	20	15
Donor Oocytes	23	25	20	19
Stillbirths (% of clinical pregnancies)				
IVF	0.5	1.0	1.1	1.4
GIFT	1.0	0.6	1.1	1.0
ZIFT	NR	NR	NR	NR
Combination	NR	NR	NR	NR
Frozen ET	NR	NR	NR	NR
Donor Oocytes	0.3	0	NR	NR
Anomalies[6]				
IVF	57 (1.5)	109 (1.9)	164 (2.3)	174 (2.7)
GIFT	17 (1.1)	41 (2.4)	19 (1.2)	25 (1.8)
ZIFT	4 (0.8)	14 (2.5)	20 (2.8)	7 (2.4)
Combination	NR	NR	NR	26 (2.1)
Frozen ET	1 (2.0)	0 (0.0)	32 (3.1)	NR
Donor Oocytes	5 (0.8)	NR	18 (1.7)	34 (2.6)

[1] See references 26 through 29.
[2] In parentheses = % deliveries per retrieval.
[3] GIFT = gamete intrafallopian transfer; ZIFT = zygote intrafallopian transfer; ET = embryo transfer.
[4] In parentheses = % of established pregnancies.
[5] NR = none reported.
[6] In parentheses = defects/100 neonates.

These data compare to recent ectopic pregnancy rates of approximately 1.7 percent of all pregnancies (Ref. 15), overall (preclinical, clinical, and stillbirth) pregnancy loss rates of approximately 25 percent (Ref. 1), and an incidence of anomalies (congenital defects) of approximately 2 percent of all births in the general U.S. population (Ref. 3).

VII. Special Controls

The following special controls are proposed for the assisted reproduction devices being proposed for reclassification into class II. These must be addressed, where appropriate, in any 510(k) premarket notification submitted to FDA.

A. Guidance Document

FDA plans to develop a guidance document that would address the following:

1. Mouse Embryo Assay (Davidson et al., 1988 (Ref. 4); May, J. V., 1996 (Ref.10))

The MEA should be used for toxicity and functionality testing of reproductive media, labware, and other devices coming into contact with gametes and/or embryos (Refs. 4 and 10). The rationale for requiring this test as a special control for class II assisted reproduction devices is that it is a good surrogate indicator of potential toxicity of materials used in assisted reproduction devices to gametes and/or embryos. Both one-cell and two-cell assays are used, and these are identical except that one-cell embryos are flushed from the mouse oviduct earlier than two-cell embryos. There are advantages to either test. Some believe that a two-cell MEA is preferable because it assures that one is testing a viable cleaving embryo from the onset. If cleaving does not proceed to the expanding or hatching blastocyst stage, then the test material is suspect for toxicity to the embryo. A one-cell MEA may not be as reassuring because lack of cleavage may be due either to embryo toxicity or to an intrinsically compromised embryo. The two-cell MEA is also easier to use because of timing of oviductal flushing and the fact that the embryos release easily from their mass of cumulus cells. Others believe that one-cell embryos are more sensitive to toxic conditions and better represent the actual conditions of IVF and embryo development than the two-cell embryo. Whether a one-cell or two-cell MEA is used, the bioassay should duplicate, as closely as possible, the procedures used for human IVF, including the acquisition, maintenance, culture, transfer (relocation), and cryopreservation of embryos (Refs. 4 and 10). FDA will not dictate to the manufacturer which MEA should be used during the manufacture of a particular product, or even whether any MEA is used. Rather, if the MEA is used, the manufacturer should provide clear information to the user about how the assay was performed and the assay results, both on the label and in the labeling. If no MEA is used, then this information must also be clearly provided to the user.

2. Endotoxin Testing (Nagata and Shirakawa, 1996 (Ref. 14); USP, 23d ed., 1995 (Ref. 36))

The rationale for requiring endotoxin testing as a special control for class II assisted reproduction devices is that it will provide a mechanism for ensuring that devices coming into contact with gametes, embryos, and/or the patient have been tested for levels of endotoxin released from gram-negative bacteria, which is the major pyrogen of concern. Of primary concern, endotoxin can be harmful to embryos and thus potentially affect development of the embryo, implantation, and pregnancy rates (Ref. 14). An established USP endotoxin assay using the limulus amebocyte lysate (LAL) test (Ref. 36) must be performed on any device, including needles, catheters, labware, water (including bottled water or water purification systems), and media.

3. Sterilization Validation

The rationale for requiring sterilization validation as a special control for class II assisted reproduction devices is that it will provide a mechanism for ensuring that devices coming into contact with gametes and/or embryos are sterile to a sterility assurance level (SAL) of 10^{-6}. Established sterilization validation testing must be performed on all devices according to American Association Medical Instrumentation (AAMI) guidelines.

4. Water Quality (May, J. V., 1996 (Ref. 10))

The rationale for requiring this test as a special control for class II assisted reproduction devices is that water quality is critically important to successful assisted reproductive technology procedures (Ref. 10). Water used to reconstitute reproductive media and to wash and rinse labware, whether generated in-house using purification systems or obtained in bottled form from vendors, should be sterile, pyrogen-free, type I reagent grade (CAP or American Society for Testing Materials (ASTM)) or greater. Water purification systems typically can generate even purer water with increased resistivity (18 megohm) relative to type I water. For general laboratory use, type II and higher can be used. Any item coming into contact with human gametes or embryos should have a final rinse with type I water or better. As stated earlier, general purpose water purification systems, not intended for use in assisted reproduction, will not be affected by this proposed rule.

5. Design Specifications

Particular design specifications may be identified for each type of device that assure minimally acceptable standards. The rationale for including design specifications as a special control for class II assisted reproduction devices is that it will help to reduce the incidence of adverse events such as bleeding, pain, or perforation that could be due to suboptimal device design. For example, assisted reproduction needles may be specified to be 16 to 18 gauge, 22 to 23 centimeters long, 45 to 60 degree beveled stainless steel and sterile to assure safe and adequate access to ovarian follicles.

6. Labeling

Specific labeling that identifies the intended use, indication for use, contraindications, precautions, warnings, and instructions for use will be required. The rationale for including labeling as a special control for class II assisted reproduction devices is that it will ensure that devices are used properly, that the user is adequately informed, that the intended use of the device is clearly understood, and that claims by the manufacturer do not exceed the intended use of the device. For instance, assisted reproduction catheters will require labeling that specifies its intended use as ''For transvaginal retrieval of oocytes,'' or ''For delivery of embryos into the fallopian tube.'' Labeling will also indicate whether a one-cell or two-cell MEA, or no assay at all, was performed.

7. Clinical Studies

Certain device designs may not conform to conventional configurations used in assisted reproduction today, e.g., a specially-configured ET catheter. Although the device designs envisioned for this special control do not raise new types of safety and effectiveness questions, additional testing may be necessary to validate clinical performance.

B. Voluntary Standards (CAP) Reproductive Laboratory Accreditation Program (Ref. 15), SART, Refs. 22 through 31))

The rationale for including voluntary standards by CAP and SART as a special control for class II assisted reproduction devices is that these organizations have already identified many important standards regarding various aspects of assisted reproduction, including recommended tests and equipment, as well as acceptable techniques in the use of many assisted reproduction devices. Voluntary standards issued by individual laboratories, and both CAP and SART, address many aspects of the use of these devices for assisted reproduction techniques, including water quality, type of laboratory equipment to be used, and various quality control techniques including MEA previously identified (Refs. 10, 11, 16, 21, 37, and 38). For example, CAP conducts comprehensive inspections of reproductive laboratories for quality assurance and control measures, specimen (sperm, oocytes, and embryos) handling and processing, documentation, equipment, reagents, personnel, glassware washing, communications, and laboratory safety (Ref. 16). SART publishes guidelines for human embryology and andrology laboratories (Ref. 31), and maintains an annually updated data base from all of its members (the great majority of IVF programs in the United States have membership in SART) on all assisted reproduction procedures conducted in the United States (Refs. 22 through 30). Statistics on the total numbers of ART procedures are kept, including IVF, GIFT, ZIFT, donated oocytes, frozen ET's, and micromanipulation procedures (e.g., ICSI, subzonal sperm insertion, assisted hatching). Outcome data on total numbers of clinical pregnancies, deliveries, and multiple gestations, as well as adverse events such as ectopic pregnancy, abortion, stillbirth, and congenital abnormalities are gathered.

Significant available literature has established the reasonable safety and effectiveness of assisted reproduction devices, and the potential complications. In addition, the preexisting recommendations (Ref. 16) already put in place by CAP Reproductive Laboratory Accreditation Program and SART (Refs. 22 through 31) provide excellent and comprehensive guidelines on the proper use of these devices and data reporting required by its members.

FDA believes that general controls and the special controls proposed for these devices are sufficient to provide reasonable assurance that these devices are safe and effective for their intended use.

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday:

1. Adashi, E. Y., J. A. Rock, and Z. Rosenwaks, *Reproductive Endocrinology, Surgery and Technology*, Lippincott-Raven, Philadelphia, 1996.
2. Ashkenazi, J. et al., ''Abdominal Complications Following Ultrasonically Guided Percutaneous Transvesical Collection of Oocytes for In Vitro Fertilization,'' *Journal of In Vitro Fertilization and Embryo Transfer*, 4(6):316–318, 1987.
3. Behrman, R. E., and R. M. Kliegman, *Nelson Essentials of Pediatrics*, 2d ed., W. B. Saunders, Philadelphia, p. 175, 1993.
4. Davidson, A. et al., ''Mouse Embryo Culture as Quality Control for Human In Vitro Fertilization: The One-Cell Versus the Two-cell Model,'' *Fertility and Sterility*, 49(3):516–521, 1988.
5. Davis, O. K., and Z. Rosenwaks, ''In Vitro Fertilization,'' *Infertility: Evaluation and Treatment*, edited by W. R. Keye and R. J. Chang, Saunders, pp. 759–771, 1994,
6. DeCherney, A. H., ''In Vitro Fertilization and Embryo Transfer: A Brief Overview,'' *Yale Journal of Biology and Medicine*, 59:409–414, 1986.
7. Letter from FDA to Manufacturers of Medical Devices Used for IVF/ET, September 1995.
8. Kerin, J. F. et al., ''The Way Forward for In Vitro Fertilization in Man,'' *Journal of Reproduction and Fertility*, Supplement, 36:161–172, 1988.
9. Lenz, S., and J. G. Lauritsen, ''Ultrasonically Guided Percutaneous Aspiration of Human Follicles Under Local Anesthesia: A New Method of Collecting Oocytes for In Vitro Fertilization,'' *Fertility and Sterility*, 38(6):673–677, 1982.
10. May, J. V., Recommendations to the FDA Obstetrics and Gynecology Devices Panel for Safety and Efficacy Parameters for Assisted Reproduction Labware and Reproductive Media, personal communication to Mike Kuchinski, 1996.
11. May, J. V., and K. Hanshew, ''Organization of the In Vitro Fertilization/Embryo Transfer Laboratory,'' *CRC Handbook of the Laboratory Diagnosis and Treatment of Infertility*, pp. 291–327.
12. Minutes, Obstetrics and Gynecology Devices Panel meeting, January 29, 1988.
13. Minutes, Obstetrics and Gynecology Devices Panel meeting, October 23, 1995.
14. Nagata, Y., and K. Shirakawa, ''Setting Standards for the Levels of Endotoxin in the Embryo Culture Media of Human In Vitro Fertilization and Embryo Transfer,'' *Fertility and Sterility*, 65(3):614–619, 1996.
15. Nederlof, K. P., H. W. Lawson, A. F. Saftlas, H. K. Atrash, and E. L. Finch, ''Ectopic Pregnancy Surveillance, United States, 1970–1987,'' *Morbidity and Mortality Weekly Reports (MMWR)*, 39(SS–4):9–17, 1990.
16. Inspection Checklist Section XC: Reproductive Laboratory, College of American Pathologists, Reproductive Laboratory Accreditation Program, pp. 1–50, 1993.
17. Palermo, G. D. et al., ''Intracytoplasmic Sperm Injection: A Powerful Tool to Overcome Fertilization Failure,'' *Fertility and Sterility*, 65(5):899–908, 1996.
18. Paulson, R. J., ''In Vitro Fertilization and Other Assisted Reproduction Techniques,'' *Journal of Reproductive Medicine*, 38(4):261–268, 1993.
19. Riddle, A. F. et al., ''Two Years Experience of Ultrasound-Directed Oocyte Retrieval,'' *Fertility and Sterility*, 48(3):454–458, 1987.
20. Seibel, M. M., ''A New Era in Reproductive Technology: In Vitro Fertilization Gamete Intrafallopian Transfer, and Donated Gametes and Embryos,'' *New England Journal of Medicine*, 318(313):828–834, 1988.
21. Seifer, D. B., ''Suggested Safety and Efficacy Parameters for FDA Reclassification Guidelines,'' personal communication to Colin Pollard, 1996.
22. Society for Assisted Reproductive Technology, The American Fertility Society, ''In Vitro Fertilization/Embryo Transfer in the United States: 1985 and 1986 Results From the National IVF–ET Registry,'' *Fertility and Sterility*, 49(2):212–215, 1988.
23. Society for Assisted Reproductive Technology, The American Fertility Society, ''In Vitro Fertilization/Embryo Transfer in the United States: 1985 and 1986 Results From the National IVF–ET Registry,'' *Fertility and Sterility*, 51(1):13–19, 1988.
24. Society for Assisted Reproductive Technology, The American Fertility Society, ''In Vitro Fertilization/Embryo Transfer in the United States: 1988 Results From the National IVF–ET Registry,'' *Fertility and Sterility*, 53(1):13–20, 1990.
25. Society for Assisted Reproductive Technology, The American Fertility Society, ''In Vitro Fertilization/Embryo Transfer in the United States: 1989 Results From the National IVF–ET Registry,'' *Fertility and Sterility*, 55(1):14–23, 1991.
26. Society for Assisted Reproductive Technology, The American Fertility Society, ''In Vitro Fertilization/Embryo Transfer in the United States: 1990 Results From the National IVF–ET Registry,'' *Fertility and Sterility*, 57(1):15–24, 1992.
27. Society for Assisted Reproductive Technology, The American Fertility Society, ''Assisted Reproductive Technology in the United States and Canada: 1991 Results From the Society for Assisted Reproductive Technology Generated From The American Fertility Society Registry,'' *Fertility and Sterility*, 59(5):956–962, 1993.
28. Society for Assisted Reproductive Technology, The American Fertility Society ''Assisted Reproductive Technology in the United States and Canada: 1992 Results Generated From The American Fertility Society/Society for Assisted Reproductive Technology Registry,'' *Fertility and Sterility*, 62(6):1121–1128, 1994.
29. Society for Assisted Reproductive Technology, The American Fertility Society,

''Assisted Reproductive Technology in the United States and Canada: 1993 Results Generated From The American Fertility Society/Society for Assisted Reproductive Technology Registry,'' *Fertility and Sterility*, 64(1):13–21, 1995.

30. Society for Assisted Reproductive Technology, The American Fertility Society, ''Assisted Reproductive Technology in the United States and Canada: 1994 Results Generated From The American Fertility Society/Society for Assisted Reproductive Technology Registry,'' *Fertility and Sterility*, 66(5):697–705, 1996.

31. Society for Assisted Reproductive Technology, The American Fertility Society, ''Guidelines for Human Embryology and Andrology Laboratories,'' *Fertility and Sterility*, 58(4) Supplement 1:1S–16S, 1992.

32. Surrey, E. S., and J. F. Kerin, ''Extended Techniques in Assisted Reproductive Technologies,'' *Infertility: Evaluation and Treatment*, edited by W. R. Keye and R. J. Chang, Saunders, pp. 788–797, 1994.

33. Tal, J. et al., ''Heterotropic Pregnancy After Ovulation Induction and Assisted Reproductive Technologies: A Literature Review from 1971 to 1993,'' *Fertility and Sterility*, 66(1):1–12, 1996.

34. Tan, S. L. et al., ''Surgical Techniques of Oocyte Collection and Embryo Transfer,'' *British Medical Bulletin*, 46(3):628–642, 1990.

35. Trounson, A., ''Recent Progress in Human In Vitro Fertilization and Embryo Transfer,'' *Developmental Biology*, chapter 5, pp. 149–186, 1986.

36. United States Pharmacopeia, 23d ed., National Formulary, vol. 18, Bacterial Endotoxins Test, No. 85, pp. 1696–1697, 1995.

37. Utian, W. H. et al., ''Implementation of an In Vitro Fertilization Program,'' *Journal of In Vitro Fertilization and Embryo Transfer*, 1(1):72–75, 1984.

38. Veeck, L. L., ''The Gamete Laboratory: Design, Management and Techniques,'' *Infertility: Evaluation and Treatment*, edited by W. R. Keye and R. J. Chang, Saunders, pp. 798–820, 1994.

39. Wikland, M. et al., ''Collection of Human Oocytes By the Use of Sonography,'' *Fertility and Sterility*, 39(5):603–608, 1983.

IX. Proposed Effective Date

The agency proposes that any final rule based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

X. Environmental Impact

The agency has determined under 21 CFR 25.24(e)(2) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of these devices from class III to class II and class I will relieve all manufacturers of the device of the cost of complying with the premarket approval requirements in section 515 of the act (21 U.S.C. 360e). Because reclassification will reduce regulatory costs with respect to this device, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The Commissioner of Food and Drugs therefore certifies that this proposed rule, if issued, will not have a significant economic impact on a substantial number of small entities. In addition, this proposed rule will not impose costs of $100 million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement of analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

XII. Submission of Comments

Interested persons may, on or before December 3, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 884

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 884 be amended as follows:

PART 884—OBSTETRICAL AND GYNECOLOGICAL DEVICES

1. The authority citation for 21 CFR part 884 continues to read as follows:

Authority: Secs. 501, 510, 513, 515, 520, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 360, 360c, 360e, 360j, 371).

2. Subpart G, consisting of §§ 884.6100 through 884.7000 is added to read as follows:

Subpart G—Assisted Reproduction Devices

Sec.
884.6100 Assisted reproduction needles.
884.6200 Assisted reproduction catheters.
884.6300 Assisted reproduction accessories.
884.6400 Assisted reproduction microtools.
884.6500 Assisted reproduction micropipette fabrication instruments.
884.6600 Assisted reproduction micromanipulators and microinjectors.
884.6700 Assisted reproduction labware.
884.6800 Assisted reproduction water and water purification systems.
884.6900 Reproductive media and supplements.
884.7000 Assisted reproductive microscopes and microscope accessories.

Subpart G—Assisted Reproduction Devices

§ 884.6100 Assisted reproduction needles.

(a) *Identification*. Assisted reproduction needles are devices used to obtain gametes or introduce gametes, zygote(s), preembryo(s), and/or embryo(s) into the body. This generic type of device may include a single or double lumen needle and component parts, including needle guides such as those used with ultrasound.

(b) *Classification*. Class II (special controls) (premarket notification guidance and voluntary standards).

§ 884.6200 Assisted reproduction catheters.

(a) *Identification*. Assisted reproduction catheters are devices used to introduce or remove gametes, zygote(s), preembryo(s), and/or embryo(s) into or from the body. This generic type of device may include catheters, cannulae, introducers, dilators, sheaths, and component parts.

(b) *Classification*. Class II (special controls) (premarket notification guidance and voluntary standards).

§ 884.6300 Assisted reproduction accessories.

(a) *Identification*. Assisted reproduction accessories are a group of devices used during assisted reproduction procedures, in conjunction with assisted reproduction needles and/

or assisted reproduction catheters, to aspirate, incubate, infuse, and/or maintain temperature. This generic type of device may include:

(1) Powered aspiration pumps, used to provide low flow, intermittent vacuum for the aspiration of eggs (ova).

(2) Syringe pumps (powered or manual), used to activate a syringe to infuse or aspirate small volumes of fluid during assisted reproduction procedures.

(3) Collection tube warmers, used to maintain the temperature of egg (oocyte) collection tubes at or near body temperature. A dish/plate/microscope stage warmer is a device used to maintain the temperature of the egg (oocyte) during manipulation.

(4) Embryo incubators, used to store and preserve gametes and/or embryos at or near body temperature.

(5) Cryopreservation instrumentation and devices, used to contain, freeze and maintain gametes and/or embryos at an appropriate freezing temperature.

(b) *Classification*. Class II (special controls) (premarket notification guidance and voluntary standards).

§ 884.6400 Assisted reproduction microtools.

(a) *Identification*. Assisted reproduction microtools are pipettes or other devices used in the laboratory to denude, micromanipulate, hold or transfer human gametes or embryos for assisted hatching, intracytoplasmic sperm injection (ICSI), embryo biopsy or other assisted reproduction methods, including preimplantation diagnosis.

(b) *Classification*. Class II (special controls) (premarket notification guidance and voluntary standards).

§ 884.6500 Assisted reproduction micropipette fabrication instruments.

(a) *Identification*. Assisted reproduction micropipette fabrication devices are instruments intended to pull, bevel, or forge a micropipette or needle for intracytoplasmic sperm injection (ICSI), in vitro fertilization (IVF), or other similar procedures.

(b) *Classification*. Class II (special controls) (premarket notification guidance and voluntary standards).

§ 884.6600 Assisted reproduction micromanipulators and microinjectors.

(a) *Identification*. Assisted reproduction micromanipulators are devices intended to control the position of an assisted reproduction microtool. Assisted reproduction microinjectors are any device intended to control aspiration or expulsion of the contents of an assisted reproduction microtool.

(b) *Classification*. Class II (special controls).

§ 884.6700 Assisted reproduction labware.

(a) *Identification*. Assisted reproduction labware consists of laboratory equipment or supplies intended to prepare, store, manipulate, or transfer human gametes or embryos for in vitro fertilization (IVF) or other assisted reproduction techniques. These include syringes, IVF tissue culture dishes, IVF tissue culture plates, pippette tips, dishes, plates, and other vessels that come into physical contact with gametes, embryos or tissue culture media.

(b) *Classification*. Class II (special controls).

§ 884.6800 Assisted reproduction water and water purification systems.

(a) *Identification*. Assisted reproduction water purification systems are devices specifically intended to generate high quality sterile, pyrogen-free, distilled, deionized water for reconstitution of media used for aspiration, incubation, transfer or storage of gametes or embryos for in vitro fertilization (IVF) or other assisted reproduction procedures. It may also be intended as the final rinse for labware or other assisted reproduction devices that will contact the gametes or embryos. This also includes bottled water ready for reconstitution available from a vendor that is specifically intended for reconstitution of media used for aspiration, incubation, transfer or storage of gametes or embryos for IVF or other assisted reproduction procedures.

(b) *Classification*. Class II (special controls).

§ 884.6900 Reproductive media and supplements.

(a) *Identification*. Reproductive media and supplements are products that are used for assisted reproduction procedures. Media include liquid and powder versions of various substances that come in direct physical contact with human gametes or embryos (including water, or oil used to cover the media) for the purposes of preparation, maintenance, transfer or storage, and supplements are specific reagents added to media to enhance specific properties of the media (e.g., proteins, sera, antibiotics, etc.).

(b) *Classification*. Class II (special controls) (premarket notification guidance and voluntary standards).

§ 884.7000 Assisted reproductive microscopes and microscope accessories.

(a) *Identification*. Assisted reproduction microscopes and microscope accessories (excluding microscope stage warmers, which are classified under Assisted Reproduction Accessories) are optical instruments used to enlarge images of gametes or embryos. Variations of microscopes and accessories used for these purposes would include phase contrast microscopes, fluorescence microscopes, dissecting microscopes, and inverted stage microscopes.

(b) *Classification*. Class I. The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter.

Dated: August 26, 1997.

D. B. Burlington,

Director, Center for Devices and Radiological Health.

[FR Doc. 97–23449 Filed 9–2–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 934

[ND–032–FOR; Amendment No. XXII]

North Dakota Regulatory Program

AGENCY: Office of Surface Mining Reclamation and Enforcement, Interior.

ACTION: Proposed rule; reopening and extension of public comment period on proposed amendment.

SUMMARY: The Office of Surface Mining Reclamation and Enforcement (OSM) is announcing receipt of a revision to a previously proposed amendment to the North Dakota regulatory program (hereinafter, the ''North Dakota program'') under the Surface Mining Control and Reclamation Act of 1977 (SMCRA). The revision for North Dakota's proposed rules pertain to individual civil penalties. The amendment is intended to revise the North Dakota program to be consistent with the corresponding Federal regulations.

DATES: Written comments must be received by 4:00 p.m., m.d.t., September 19, 1997.

ADDRESSES: Written comments should be mailed or hand delivered to Guy Padgett at the address listed below.

Copies of the North Dakota program, the proposed revision to the proposed amendment, the proposed amendment, and all written comments received in response to this document will be available for public review at the addresses listed below during normal business hours, Monday through Friday, excluding holidays. Each requester may receive one free copy of the proposed