AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
Formerly The American Fertility Society

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Food and Drug Administration
5630 Fishers Lane
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Re: Current Good Tissue Practice for Manufacturers of Human, Cellular and Tissue-Based Products; Inspection and Enforcement. Docket No. 97N-484P

The American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) are pleased to submit comments to the Food and Drug Administration (FDA) on the agency's proposed rule "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement." 66 Fed. Reg. 1508 (January 8, 2001) (FDA's Proposal or the Proposed Rule).[1] As FDA continues its development of a comprehensive regulatory scheme for human cellular and tissue-based products (HCT/Ps), ASRM and SART request that the agency balance its public health interest in preventing the spread of communicable diseases against the reproductive freedoms of infertile couples.

ASRM and SART agree with FDA regarding the importance of applying current good tissue practices (CGTPs) to appropriate HCT/Ps and believe that well-defined standards are the most effective method of protecting the public health and providing high quality patient care. ASRM and SART disagree, however, that FDA's Proposal should apply to HCT/Ps used to treat infertility where the treatment falls within the practice of medicine and there is no evidence that communicable diseases are transferred through the use of

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[1] To the extent they are applicable, the attached comments submitted by ASRM and SART on December 29, 1999, to FDA Docket No. 97N-484S ("Suitability Determination for Donors of Human Cellular and Tissue-Based Products" 64 Fed. Reg. 52696 (September 30, 1999)) and on August 12, 1998, to FDA Docket No. 97N-484R ("Establishment and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 Fed. Reg. 26744 (May 14, 1998)) are incorporated herein by reference. ASRM and SART's December 1999 comments provide a detailed description of the nature of reproductive tissue and the corresponding evidence for association with infectious organisms. The August 1998 comments provide a description of various assisted reproductive technology procedures.

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assisted reproductive technology. More specifically, ASRM and SART object to the imposition of the CGTPs set forth in the Proposed Rule to HCT/Ps used for insemination and HCT/Ps used in ART procedures between sexually intimate couples. Where infertility is treated solely with HCT/Ps of sexually intimate partners, whether through simple insemination or more complex ART procedures, no additional risk of exposure to communicable disease exists. Indeed, the risk is less than what is assumed during actual intercourse. Regarding insemination by donor sperm, ASRM and SART believe that FDA's public health concerns can be adequately met by subjecting sperm banks to the CGTPs set forth in the Proposed Rule. As described below, nearly all reproductive medicine is currently practiced in accordance with strict quality and processing standards. Subjecting individual medical practices and clinics to FDA's Proposal is unnecessary and represents an overly burdensome regulatory approach that offers no corresponding benefit to the public health.

While ASRM and SART object to the application of the Proposed Rule to all forms of insemination and those assisted reproductive technologies that use only HCT/Ps of sexually intimate partners, we acknowledge that for certain areas of reproductive medicine, application of the Proposed Regulation is appropriate. ASRM and SART request, however that changes be made to the rule as currently proposed in order to clarify its application to human reproductive technologies. These requested changes, described in detail below, are necessary to accommodate the unique nature of the practice of reproductive medicine and the HCT/Ps involved in the treatment of infertility. The requests for exemption and clarification are further justified by the current state of the practice of reproductive medicine in the United States, nearly all of which is conducted under standards that satisfy FDA's public health goal of preventing the spread of communicable diseases.

ASRM AND SART

ASRM is a non-profit organization dedicated to advancing knowledge and expertise in reproductive medicine and biology and is the foremost organization promoting the study of reproduction and reproductive disorders. ASRM has approximately 9,000 members throughout the United States and more than 110 foreign countries, the great majority of whom are physicians practicing in the fields of obstetrics, gynecology and urology. ASRM's membership also includes others involved in reproductive medicine, such as doctoral level scientists, nurses, and technicians.

SART is an affiliated society of ASRM whose members are medical practices actively engaged in performing assisted reproductive technologies (ART)—as defined by the Centers for Disease Control—as well as individuals who are participants in or employees of SART member practices. SART currently has over 370 ART practice members representing 48 states, the District of Columbia and Puerto Rico. SART programs are responsible for approximately 95% of the ART treatment cycles performed in the U.S. each year.

Both ASRM and SART have long been involved in developing and maintaining the highest standards of practice for health professionals involved in the field of reproductive medicine, including the development of practice guidelines and minimum standards for various ART procedures. Since 1989, SART and ASRM have been publishing both clinic-specific and national success rates for ART procedures. In addition, working with the College of American Pathologists (CAP), ASRM and SART have created an accreditation program for ART laboratories. Accreditation, by a nationally recognized accreditation organization (CAP/ASRM, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), or by the State of New York) is a mandatory membership requirement for all SART member practices. Thus, approximately 95% of the ART treatment cycles performed in the U.S. each year currently are performed in accredited ART laboratories.

BACKGROUND

FDA's Proposal is part of a new, comprehensive approach to the regulation of human cellular and tissue-based products. By this new approach, which sets forth a tiered regulatory scheme, FDA intends to impose levels of regulation commensurate with the degree of risk and need for FDA oversight associated with different HCT/Ps.[2] Among the product categories delineated by FDA are certain types of HCT/Ps that are minimally manipulated, and that will be regulated pursuant to the agency's authority under section 361 of the Public Health Service Act (42 U.S.C. § 264) to prevent the introduction, transmission or spread of communicable diseases. FDA has identified HCT/Ps used in the practice of reproductive medicine as falling within this category of "361 products." 21 C.F.R. § 1271.10(a)(4)(ii)(c).

Although ASRM and SART appreciate that FDA has correctly identified reproductive HCT/Ps as among those products requiring less regulatory oversight, we object to the proposed imposition of the CGTPs on many of the HCT/Ps used in the practice of reproductive medicine. The "Analysis of Economic Impacts" section of the Proposed Rule provides the greatest insight into FDA's basis for applying the proposed CGTPs to reproductive cells and tissues used for reproductive purposes. 66 Fed. Reg. at 1542-48. ASRM and SART strongly disagree with the claims contained in that section of FDA's Proposal relating to the risk of communicable disease from these types of HCT/Ps. First and foremost, ASRM and SART challenge FDA's reliance on the study cited by FDA as evidence of the risk of HIV transmission from infertility treatments. Additionally, as described in detail in our attached comments on FDA's Donor Suitability Rule, the risk of disease transmission with

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2 *See* FDA Documents "Reinventing the Regulation of Human Tissue" and "A Proposed Approach to the Regulation of Cellular and Tissue Based Products" (February 1997).

oocytes and embryos is immeasurably small. There is no evidence that isolated ovum or embryos can transmit any of the diseases indicated in FDA's Proposal, nor any documented case of such transmission.

As an extension of its concerns regarding reproductive HCT/Ps and communicable disease risks, FDA also asserts that:

> Adverse outcomes owing to problems with product quality can result from contamination that produces infection (e.g., HIV transmission) in the infertility patient (Ref. 21). Problems with ART facility processing of sperm or oocytes can also lead to reduced rates of fertilization, and unsuccessful IVF attempts, which would ultimately increase the number of transfer attempts. Each additional transfer attempt increases the risk of communicable disease with each attempt.

66 Fed. Reg. at 1435. ASRM and SART object most vigorously to this flawed logic. There is no evidence that FDA's Proposal will in any way improve outcomes, assure increased levels of patient safety, or reduce the risk of communicable disease. We base this position on the following:

(i) The notion that application of CGTPs to the practice of reproductive medicine will improve outcomes, decrease the number of treatment cycles, and thereby reduce exposure to communicable disease is irrelevant where no unaccounted for risk of disease transmission exists, as is the case for procedures using HCT/Ps of sexually intimate partners.

(ii) Since nearly all ART lab facilities already use procedures almost identical to the proposed CGTPs, the increased ART success described by FDA will not materialize. Success rates in the treatment of infertility are far more influenced by factors such as age than by laboratory practices. Surely FDA does not intend to suggest that by merely applying the Proposed Rule the agency can overnight increase ART outcomes beyond the current levels that reflect years of effort by countless experts in reproductive medicine, gamete physiology, and other related fields.

(iii) Some risk of infection is inherent in almost all forms of medical treatment. Regulation premised on the notion that multiple treatments increase the risk of disease or infection exposure could apply to many other areas of medicine. ASRM and SART disagree with a regulatory approach based on such a premise and do not believe that it represents a realistic balance between the agency's safety concerns and the medical needs of patients.

Not only does FDA's Proposal fail to establish that contemporary HCT/Ps used in the practice of reproductive medicine raise communicable disease concerns, but the agency has not adequately considered the current practices followed by ART laboratories, which are responsible for more than 95%

of the treatment cycles in the U.S. annually. ASRM and SART have long recognized good tissue practices as critical to good patient care and successful fertility procedures. Indeed, ASRM and SART have been involved in the drafting of several existing sets of standards. Among the detailed standards currently followed by ASRM and SART members are the joint CAP/ASRM standards and the standards issued by the JCAHO. More recently, the Centers for Disease Control and Prevention (CDC) published standards for the certification of embryo laboratories mandated under the Fertility Clinic Success Rate and Certification Act of 1992 (Fertility Clinic Act) (42 U.S.C. 293a-1 et seq.). Thus, several sets of standards already exist that address the realities of medical practice in the field of reproductive medicine. These standards, under which nearly all reproductive medicine currently is practiced, offer substantially more detail than the CGTPs contained in FDA's Proposal. Additionally, the standards that have been self-imposed by physicians and facilities actually practicing reproductive medicine, by their very nature, are more appropriate to medical practice in the unique area of human reproduction.

DISCUSSION

FDA's Proposal fails to provide adequate justification for imposing a new regulatory scheme on reproductive HCT/Ps used for reproductive purposes. In the preamble to the Proposed Rule FDA states:

> Because the safety concerns addressed by the proposed CGTP requirements apply to all human cellular and tissue-based products, no exceptions are being proposed for any particular category of product. Thus, banked cells and tissues for autologous use, and reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use, would be subject to the CGTP requirements.

66 Fed. Reg. At 1511. ASRM and SART object to FDA's blanket application of the Proposed Rule to all HCT/Ps.

As noted above, the Fertility Clinic Act required CDC to establish a model program for the certification of embryo laboratories. Under this Act, "assisted reproductive technology" is defined as "all treatments or procedures which include the handling of human oocytes or embryos, including in vitro fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, and such other specific technologies as the Secretary may include in this definition . . . "[3] 42 U.S.C. § 263a-7(1). The regulation implementing this section also included embryo cryopreservation, oocyte or embryo donation, and

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[3] CDC defines the terms "in vitro fertilization," "gamete intrafallopian transfer," and "zygote intrafallopian transfer" in its final notice. 64 Fed. Reg. 39374, 39383 (July 21, 1999).

gestational surrogacy in the definition of ART.[4] 64 Fed. Reg. 39374, 39383 (July 21, 1999). In establishing this definition of ART, Congress, CDC, and other interested parties carefully considered all the different infertility procedures and the risks associated with them and determined that only the subset of procedures listed above warranted regulation.

Rather than reinvent the wheel and establish a new definition that is inconsistent with CDC's definition, ASRM and SART believe that FDA should adopt the Fertility Clinic Act's definition of ART and limit its regulation to only those facilities and practitioners who are performing these procedures using donor HCT/Ps, and even then, only to appropriate ART procedures. Even if FDA does not decide to adopt CDC's definition of ART, the Proposed Rule clearly should not be applied to the specified infertility procedures for the reasons outlined below.

As described in detail below, the safety concerns expressed by the agency simply do not apply to HCT/Ps used in certain specified reproductive procedures. HCT/Ps from sexually intimate partners raise no new disease risks. Donor sperm used for insemination, when obtained from a facility that complies with the proposed CGTPs will already have been adequately screened and processed to ensure any risk of disease transmission has been minimized. FDA's other articulated concern, cross contamination between HCT/Ps in the laboratory setting, also fails to raise any risk of disease sufficient to justify application of the Proposed Rule to HCT/Ps used in these reproductive practices. While cross-contamination from one patient to another is of course of grave concern with any reproductive procedure, there are only a few reports in the medical literature that describe ART patients that have been infected with communicable disease:

(i) Transmission of hepatitis C was reported by a French clinic in 2000 (Lesourd et. al. 2000 Human Reproduction 15, 1083). After a careful investigation the authors concluded that *"the contamination occurred outside the direct practice of IVF . . . possibly through procedures practiced by ancillary staff."*

(ii) A hepatitis B epidemic occurred among women at a Dutch IVF center. The epidemic was caused by a human serum pool contaminated with hepatitis B virus (van Os et. al. 1991 Am. J. of Obstet. Gynecology 165, 152-159). Currently in the United States, IVF serum protein supplements used in ART culture media are purchased from commercial vendors that meet FDA requirements for blood product safety.

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[4] The terms "embryo," "cryopreservation," and "oocyte" also are defined in this final notice. Id.

Thus, FDA's cited references do not support application of the Proposed Rule to the HCT/Ps and procedures identified herein. Additionally, current reproductive laboratory practices rely on disposable materials to the greatest extent possible, and utilize FDA approved ancillary materials, eliminating many of the avenues where cross-contamination could occur. ART procedures are also conducted serially, one patient at a time, further reducing the possibility of inadvertent cross-contamination. Indeed, in the more than 20 years that ART procedures have been conducted in the United States, no documented occurrence of cross-contamination has occurred, nor is ASRM or SART aware of any instance of cross-contamination.

I. HCT/Ps used for insemination should be exempt from the Proposed Rule.

In the context of insemination, the HCT/Ps addressed by the Proposed Rule refer solely to semen and isolated sperm cells. ASRM and SART acknowledge that under certain conditions, HCT/Ps used in the insemination process may act as a vector for the transmission of disease, and we support application of the Proposed Rule to sperm banks that provide practitioners with donor sperm. ASRM and SART object, however, to the uniform application of the Proposed Rule to all HCT/Ps used for insemination because it far exceeds the amount of regulation necessary to achieve FDA's public health goals and would significantly interfere with the practice of reproductive medicine.

Artificial insemination procedures, both intracervical insemination (ICI)[5] and intrauterine insemination (IUI),[6] are among the most basic treatments for infertility and are often used as a first line therapy for couples that have difficulty conceiving. ICI and IUI are routinely offered by OB-GYN practices throughout the United States. ASRM and SART are deeply concerned that many OB-GYNs will stop offering insemination services for their patients if they are forced to incur the administrative costs (both financial and time) to comply with the Proposed Rule. Although some patients can be treated just as conveniently and cost effectively in a more comprehensive ART clinic, many patients are not

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5 ICI is a procedure by which semen is placed into a woman's cervical canal with a syringe near the time of ovulation. A speculum is used in the procedure, and sometimes a cap or plastic-coated sponge is placed in the woman's vagina before the speculum is removed to keep the sperm near the cervix. The sponge or cap typically is removed after two to six hours.

6 IUI is similar to ICI except that specially "washed" sperm are used and the sperm are placed directly into the uterus. To "wash" the sperm, the semen is diluted with a sterile fluid, and then the sperm are separated from the liquid component. Before the insemination procedure, the sperm are returned to a small amount of the sterile liquid. This process removes prostaglandins and other chemicals and bacteria from the semen. It also may increase the sperm's ability to fertilize the egg.

located within close proximity to one of these facilities and will face insurmountable hurdles in seeking treatment elsewhere. For example, a couple in Montana would have to travel to Fargo, North Dakota; Spokane, Washington; or Fort Collins, Colorado to receive insemination at an ART clinic. Because insemination frequently takes several attempts to result in a pregnancy, traveling this distance to seek treatment is not a realistic option and is more likely to induce more risk for patients. Moreover, there is no increased risk associated with insemination at the individual OB/GYN practice level where donor sperm is procured from a sperm bank—which ASRM and SART agree should be required to comply with the Proposed Rule. By regulating artificial insemination at the level of practice encompassed by FDA's Proposal, some patients will be denied access to these critical, first line services. ASRM and SART do not believe that curtailing patient access is warranted given the very limited public health and safety benefit that would be achieved by regulating insemination at this level.

Furthermore, ASRM and SART believe that regulating these insemination procedures violates the "practice of medicine exemption" to the Federal Food, Drug and Cosmetic Act and interferes with physicians' treatment of their patients.[7] FDA should follow through with its commitment to free physicians from FDA regulation of the practice of medicine by excluding insemination procedures from the Proposed Rule.[8]

A. Insemination with the HCT/P of a sexually intimate partner

Where the source of sperm used for insemination is from a sexually intimate partner, there are no public health or safety concerns that warrant intrusion into a physician's treatment of an infertile couple. Thus, the Proposed Rule should not apply to this category of HCT/Ps.

FDA has already recognized the logic of exempting HCT/Ps used for reproductive purposes in its proposed rule "Suitability Determination for Donors of Human Cellular and Tissue-Based Products" 64 Fed. Reg. 52696 (September 30, 1999), which includes a specific exception for:

> Reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use.

Proposed 21 CFR §1271.90; 64 Fed. Reg. 52723. FDA's rationale for excepting HCT/Ps from the donor testing and screening (*i.e.*, suitability) procedures under those circumstances applies equally to the insemination process:

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7 *Cheney v. Heckler,* 718 F.2d 1154 (D.C. Cir., 1983), revised on other grounds, 470 U.S. 821 at 1180.

8 48 Fed. Reg. 26720 (June 9, 1983); 52 Fed. Reg. 8799, 8802-03 (March 19, 1987).

> In this case, the recipient will likely have been routinely exposed to the donor's semen or other body fluids. Although some screening and testing of the donor and recipient may be appropriate, FDA believes that this should be the responsibility of the attending physician and the donor and the recipient.

Id. At 52707. Similarly, artificial insemination with semen from a sexually intimate partner does not raise any new communicable disease concerns. Indeed, artificial insemination poses less risk of disease transmission than does unprotected intercourse; requiring compliance with FDA's proposed CGTPs would not increase the safety of insemination procedures as far as the transmission of communicable disease is concerned. Thus, the Proposed Rule should extend the exception articulated in proposed 21 CFR §1271.90 to insemination procedures for purposes of compliance with CGTPs.

In addition to the public health concerns that the CGTPs are intended to address, FDA must also consider the practicality of enforcement when it issues a regulation. FDA's Final Rule on Establishment Registration and Listing excepts from the provisions of that rule an establishment that:

> does not recover, screen, test, process[9], label, package, or distribute, *but only receives or stores HCT/P's solely for implantation*, transplantation, infusion, or transfer within the facility; or
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> only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

21 CFR §§1271.15(d) and (e). As noted above, many insemination procedures fall within these exemptions. ASRM and SART applaud FDA for recognizing that these types of procedures raise few new infectious disease concerns and that no regulatory purpose would be served by subjecting establishments that engage in such procedures to registration and listing. *See* 66 Fed. Reg. at 5460. We question, however, how—having exempted these establishments from the registration and listing requirements—FDA intends to ensure compliance with the Proposed Rule and indeed, what purpose applying the Proposed Rule to these establishments and situations would serve.

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[9] ASRM and SART note that the term processing as it is used by FDA in the context of all tissue related rulemaking should not be deemed to include the thawing and washing of sperm, which raises no product quality or disease concerns.

B. Insemination with HCT/P from a donor source

Where problems with a partner's sperm are a suspected cause of infertility, couples often choose to undergo artificial insemination using donor sperm. As noted above, semen is recognized as a leukocyte rich tissue capable of transmitting certain communicable diseases. Thus, ASRM and SART agree with FDA that donor sperm should be subject to CGTPs at the sperm bank level. Once received by a physician for insemination, however, donor sperm should be exempt from the Proposed Rule. Such exemption would be consistent with FDA's Final Rule on Establishment Registration and Listing. 66 Fed. Reg. 5447, that excepts from the provisions of that rule an establishment that:

> does not recover, screen, test, process, label, package, or distribute, *but only receives or stores HCT/P's solely for implantation*, transplantation, infusion, or transfer within the facility.

21 CFR §§1271.15(d). Thus, for purposes of registration and listing FDA has recognized that end-user establishments do not play a significant role in ensuring the HCT/Ps they use do not raise any infectious disease concerns. *See Id.* at 5460. Physicians who receive sperm from a sperm bank for artificial insemination purposes depend upon the good tissue practices of their suppliers; ASRM and SART have no objection to imposition of the Proposed Rule upon these HCT/P sources. We do, however, strenuously disagree that any additional benefit to the public health will be achieved by extending the reach of the Proposed Rule to the practice of reproductive medicine as occurs at the actual insemination level of the female recipient.

II. HCT/Ps used in ART procedures between sexually intimate couples should be exempt from the Proposed Rule.

As in the case of artificial insemination, other assisted reproductive technologies that involve manipulations outside the uterus, but that only use the HCT/Ps of sexually-intimate partners, also should be exempt from the Proposed Rule. ASRM and SART support the same exception for those situations as FDA has proposed for donor suitability determinations:

> Reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use.

Proposed 21 CFR §1271.90; 64 Fed. Reg. 52696 (September 30, 1999). As illustrated by this exception, FDA recognizes that where HCT/Ps are shared between sexually intimate partners, any communicable disease risks are already known to the parties and their attending physician and have been assumed by the embryo recipient. Thus, as in the case of insemination with sperm from a sexually intimate partner, exempting ART procedures conducted with the HCT/P

of a sexually intimate partner from FDA's CGTPs will not increase the risk of transmitting communicable disease.

III. FDA should clarify the Proposed Rule as it applies to the use of HCT/Ps in ART procedures that are not otherwise exempt from the Proposed Rule.

ASRM and SART recognize that FDA's Proposal is designed to accommodate a wide variety of situations and to provide flexibility in the implementation of good tissue practices. Among the foreseeable problems in applying FDA's Proposal to the practice of reproductive medicine, however, is that many fertility procedures do not fit the basic constructs that the agency has relied on throughout its rulemakings for human cellular and tissue-based products. To the extent FDA intends to apply the Proposed Rule to ART procedures that extend beyond those described above, ASRM and SART request that FDA carefully consider the impact of its requirements and ensure that the final language of the regulations does not unnecessarily restrict the practice of reproductive medicine. The following comments discuss each area of FDA's Proposal where ASRM and SART believe accommodations for reproductive medicine are appropriate and where clarification of the requirements is requested in the final rule.

Sec. 1271.3 Definitions. The need for clarification regarding application of FDA's Proposal to the practice of reproductive medicine is obvious in the context of the definitions used in the proposed regulations. Among the definitions that ASRM and SART have identified as problematic are the following:

(gg) Adverse reaction.

FDA's Proposal defines an adverse reaction as a "noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out)." In the area of reproductive medicine such a definition could encompass all manner of reactions including spontaneous miscarriages and ectopic pregnancies. Even non-pregnancy technically could fall within the definition of an unintended response related to the "product" since fertility treatments are intended to result in pregnancy. ASRM and SART seriously doubt that FDA envisions the reporting of such events under proposed 21 C.F.R. 1271.350 and request that FDA provide written clarification of its intent in the final rule.

(kk) Product deviation.

FDA's Proposal includes within its definition of a product deviation "an unexpected or unforeseeable event that may . . . adversely affect the function or integrity of the product." Proposed 21 C.F.R. §1271.3 (kk). Again, a literal

application of this definition to the practice of reproductive medicine would likely encompass many events not intended to be included within the scope of a "product deviation." For example in cases where eggs do not fertilize, it may, or may not, suggest a problem with donated material. Since it is almost impossible to discern the precise cause of any particular failure to achieve fertilization, ASRM and SART do not believe the concept of product deviation should be applied to the practice of reproductive medicine and request an appropriate exemption from the definition for outcomes related to reproductive HCT/Ps.

(rr) Validation.

ASRM and SART agree with the reproductive medical experts consulted by FDA that "the process validation requirement would have limited application to this industry because the tissues involved in laboratory processes (e.g., sperm and ova) are not uniform in quality." 66 Fed. Reg. at 1533.

Sec. 1271.150 Current good tissue practice: general.

The term "manufacturing" as it is traditionally understood in the context of biological products, does not accurately describe the types of procedures associated with reproductive medicine. In assisted reproduction, the materials used—sperm and eggs—are made by individuals and utilized without significant change. Closely associated with the notion of manufacturing is the application of CGTPs to "products," another basic precept that does not necessarily fit the practice of reproductive medicine. Among the "products" manufactured for the treatment of infertility are embryos (fertilized oocytes), that clearly are not products in the traditional sense. As discussed in each of the sections identified below, ASRM and SART request changes in the Proposed Rule to better accommodate the unique nature of reproductive materials and the practice of reproductive medicine.

Sec. 1271.160 Quality program.

Proposed 21 CFR § 1271.160(b)(7) would require establishments to investigate and document all product deviations in manufacturing. ASRM and SART would like clarification on the term "product deviation" as it applies to human gametes and embryos. Further, the proposal indicates that an event that "adversely affects the function or integrity of the product" would be required to be investigated and documented. ASRM and SART are concerned about how FDA intends to define adverse function in human beings and how the agency expects clinics to collect information on offspring, which could fall within the definition of reproductive products, in light of the fact that patient treatment is spread out over three different levels of medical care: (1) Fertility care; (2) Obstetric care; and (3) Pediatric care. There is currently no national system for tracking patient care and no way of forcing patients to share medical information.

Also among the requirements in this section is for a comprehensive quality audit to be performed at least once a year. ASRM and SART are very concerned that the imposition of an annual FDA audit on ART facilities will result in unnecessary disruption of patient treatment and interference with the delicate timing surrounding treatment cycles, without any corresponding benefit to patients or the public health. Currently, all ASRM and SART members are inspected by CAP every 2 years and by JCAHO every 3 years. ASRM and CAP also require a self-inspection and report during the interim year. Additionally, the CDC conducts random audits every year of approximately 10% of ART facilities. Included in the reproductive medicine standards are the audit procedures that are currently imposed upon ASRM and SART members. All of these auditing organizations are careful to ensure that they do not negatively impact treatment cycles at the facilities they visit. We urge FDA to acknowledge the adequacy of these audits and to work with the current reproductive medicine groups to ensure that to the extent any separate audits are conducted by the agency, they are part of a coordinated effort to preserve the rights of patients undergoing fertility treatments.

Sec. 1271.220 Process Controls.

The process controls described in the Proposed Rule also reveal a fundamental disconnect in the application of the proposed regulation to the practice of reproductive medicine. For example, regarding "pooling," the Proposed Rule provides "[h]uman cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing." Proposed 21 C.F.R. §1271.220(c). Because the combination of egg and sperm from separate donors is at the very heart of many fertility procedures, it is our understanding that FDA does not intend the prohibition on pooling to apply to that particular practice of reproductive medicine. Even, however, if FDA limits the pooling restriction in the Proposed Rule to combinations of like tissues, without further clarification, a variety of practices in the treatment of infertility still technically could be prohibited as "pooling." Among the common ART procedures that need to be addressed are those that combine:

- donor egg with the sperm of a male couple;
- donor sperm with the eggs of a female couple; and
- embryos created from different egg or sperm sources that are placed in a catheter for a single implantation.

ASRM and SART also request that FDA clarify the prohibition of pooling in the context of embryo storage. Currently, common practice includes the storage of embryos in separate vials within a single liquid nitrogen tank. ASRM and SART strongly support this continued practice. Requiring separate tanks would substantially increase costs for clinics and patients, making some reproductive medicine procedures unaffordable for infertile couples desperate to have a child. This is of particular concern to ASRM and SART because the only case report of cross-contamination through liquid nitrogen occurred with bone

marrow and peripheral blood stem cells. (Tedder et. al. 1995 Lancet 346 137-40). ASRM and SART again remind FDA that washed sperm, oocytes and embryos are not know vectors for transmission of infectious disease. Thus, the purely theoretical risk of contamination through liquid nitrogen does not merit the significant increase in costs to patients that would result from imposing a separate storage tank requirement.

Sec. 1271.230 Process Validation.

FDA's Proposal also includes provisions for process validation that ASRM and SART request the agency specifically address in the context of reproductive medicine. As noted above, validation—as a general concept—does not apply to assisted reproductive technologies and human embryos due to the materials involved and the nature of human reproduction, in which every procedure includes circumstances that are unique to the individuals involved. Moreover, ASRM and SART believe that with respect to certain processes used in the practice of reproductive medicine, "validation" (as we understand that term to be used by FDA), may be impossible due to the government ban on embryo research. Greater clarity regarding FDA's intended application of proposed 21 C.F.R. §1271.230 is necessary.

Sec. 1271.260 Storage.

Among other things, this section requires expiration dating "where appropriate." ASRM and SART note that since it is impossible to determine if and when the viability of reproductive HCT/Ps ever expire, this requirement would not be applicable to reproductive HCT/Ps.

Sec. 1271.265 Receipt and distribution.

Among the receiving activities identified in this section is the requirement to inspect incoming HCT/Ps. ASRM and SART note, however, that reproductive HCT/Ps, such as embryos, are microscopic and request that FDA confirm that for these materials, inspection of the actual containers for physical damage will suffice.

This section also addresses procedures required in making HCT/Ps available for distribution. §1271.260(c). ASRM and SART note that the concept of preventing the release of HCT/Ps that have deteriorated should not apply to reproductive HCT/Ps. For example, as part of the practice of reproductive medicine physicians often make decisions about whether to implant embryos that show some evidence of deterioration. Given the unique nature of these materials, physicians must remain free, in consultation with the patients they are treating, to rely on their best judgment regarding the use of particular reproductive HCT/Ps. Similarly, the notion of establishing procedures under which reproductive HCT/Ps may be "returned to inventory" is not applicable to the normal practice of reproductive medicine. Thus, ASRM and SART request

that FDA clarify in the final rule that the requirements regarding release specifications and return to inventory procedures do not apply to reproductive HCT/Ps.

Sec. 1271.290 Tracking.

ASRM and SART request that FDA confirm that for reproductive HCT/Ps the tracking obligation extends only as far as the transfer of the HCT/P to the possession of the recipient, which may or may not encompass actual implantation of the material.

Subpart E—Additional Requirements

Adverse reaction reporting requirements are included within this section. FDA's Proposal defines an adverse reaction as a "noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out)." Under the reporting provision in this section, an establishment must report:

> [a]ny adverse reaction involving the transmission of a communicable disease, product contamination, or failure of the product's function or integrity if the adverse reaction:
>
> (i) Is fatal;
> (ii) Is life-threatening;
> (iii) Results in permanent impairment of a body function or permanent damage to body structure; or
> (iv) Necessitates medical or surgical intervention.

Proposed 21 C.F.R. §1271.350(a). As noted above, in the area of reproductive medicine such a definition could encompass all manner of reactions, including spontaneous miscarriages and ectopic pregnancies that require medical intervention and often surgery, and could result in death. Similarly, the requirement for reporting product deviations does not, as currently drafted, reasonably apply to the practice of reproductive medicine. There is no discernible standard by which to judge reproductive HCT/Ps as "normal"—wide variations occur naturally in such materials. ASRM and SART request that FDA clarify the reporting parameters under this section.

This section also sets forth labeling requirements for HCT/Ps. ASRM and SART note that as currently drafted the proposed regulation refers to information that "shall appear on the product label." Proposed 21 C.F.R. §1271.370(a)(2). It is our understanding that under the Federal Food, Drug and Cosmetic Act the "label" of a product refers to the immediate container. 21 U.S.C. §321(k). On the other hand, labeling" refers to all labels and other materials "accompanying" the product. *Id.* at §321(m). Given the small size of

the vials that generally are used to store reproductive HCT/Ps, it would be impossible to include all of the required information on individual product containers. Thus, ASRM and SART request that FDA clarify that the information requirements under this section will be deemed satisfied for reproductive HCT/Ps if the information is included in the "labeling" of the product.

Subpart F—Inspection and Enforcement

As discussed above, all ASRM and SART members are inspected by CAP every 2 years and by JCAHO every 3 years. The CDC also conducts random audits every year of approximately 10% of ART facilities. This section authorizes FDA to conduct inspections, with or without notice, and at a frequency to be determined by the agency. Proposed 21 C.F.R. § 1271.400. Even more than the audit provisions of the Proposed Rule, this inspection authority raises the potential for serious disruption of the practice of reproductive medicine. ASRM and SART urge FDA to impose some requirement for coordination of such inspections with responsible personnel to ensure that fertility treatments are not unceremoniously interrupted in a manner that impacts the potential success of the treatment involved. Infertility is a devastating condition, and patients undergoing fertility treatments tend to undergo tremendous psychological stress and emotional turmoil. Surprise FDA inspections only would exacerbate these feelings, potentially even decreasing the likelihood of a pregnancy.

Aside from inspection authority, this section also addresses the import of HCT/Ps. Proposed 21 C.F.R. § 1271.420. ASRM and SART request an exemption from any import restrictions for reproductive HCT/Ps imported under the authority of the owner of the reproductive materials. This is necessary to ensure that United States citizens overseas retain control over their reproductive HCT/Ps and that their access to all available fertility treatment options are protected. For example, a member of the United States armed services may have cryopreserved embryos in Germany that were created during his or her tour of duty there. Rather than being forced to return to Germany to have the embryos implanted, the couple should have the option of bringing the embryos to the United States to complete the procedure in this country.

Regarding the retention, recall and other provisions included in proposed 21 C.F.R. § 1271.440, ASRM and SART request that FDA acknowledge the limitations on corrective actions arising from the ownership status of reproductive HCT/Ps as well as from their unique status as a potential starting point for new human life. Neither the raw materials (egg and sperm), nor the result (an embryo), are owned by the fertility clinic or physician. As upheld by the courts, it is the couple seeking treatment that retains ownership rights and that exercises control over any reproductive materials. *Davis v. Davis*, 842 S.W.2d 588, 597 (Tenn. 1992). *See also York v. Jones*, 717 F.Supp. 421, 425 (E.D. Va. 1989).

The issue of when human life begins is one of the most explosive in our society today. Without attempting to resolve that question, we can recognize that human reproductive tissue is more than an ordinary medical "product." At a minimum, these tissues possess a special potential as the starting point for new human life. Before finalizing this regulation, FDA needs to fully explore the ethical ramifications of its ability to take possession of and destroy a violative reproductive HCT/P. Would the agency truly advocate destruction of the "violative" cryopreserved sperm of a cancer patient who is now sterile when the sperm presents the patient and his wife with their only hope to have a child who is genetically related to them? Likewise, would the FDA really advocate destruction of a "violative" embryo over the opposition of the couple for whom it was created? Unlike other HCT/Ps, reproductive HCT/Ps cannot always be replaced. Often they are a couple's only chance to have genetically related offspring. Currently, there is no documented case of transmission of disease through eggs, washed sperm, or embryos, and, even on a theoretical level, risk of transmission is minuscule. Thus, at this time, ASRM and SART do not believe there is any instance in which the FDA should be able to take possession and destroy a violative reproductive HCT/P. At a minimum, FDA should clarify its intent regarding application of the Proposed Rule to the "products" associated with reproductive medicine in its final rule.

Effective Date

FDA proposes that any final rule that it may issue based on this proposal become effective 180 days after the date of its publication in the Federal Register. Unless FDA adopts the current standards in lieu of the framework set forth in the proposed rule, ASRM and SART believe that it will be extremely difficult for its members to comply with a final rule within 180 days. Thus, we request that FDA extend the compliance deadline to one year after the publication of the final rule.

Conclusion

ASRM and SART believe that adequate justification exists, both legally and from a public health perspective, for its objection to application of the Proposed Rule to all forms of insemination, including insemination with donor sperm *acquired for a bank that complies with FDA's CGTPs*. Similarly, reproductive HCT/Ps shared between sexually intimate partners in ART procedures should not have to comply with the Proposed Rule. For those HCT/Ps used in the practice of reproductive medicine that would be subject to the Proposed Rule, ASRM and SART urge FDA to consider using the current standards used by nearly all reproductive medical practices in lieu of the framework set forth in the proposed CGTPs. As the specific comments above illustrate, attempting to apply generally understood notions of good tissue practices to reproductive HCT/Ps will inevitably lead to unintended consequences and inappropriate regulation.

ASRM and SART recognize that our current standards are voluntary. Nothing, however, prevents FDA from adopting them and making compliance with them mandatory. Indeed, such adoption would fall squarely within FDA's Guiding Principles for Leveraging at FDA and ASRM and SART would welcome the opportunity to work with FDA in publishing an appropriate guidance. The application of CGTPs to reproductive medicine provides an excellent opportunity for FDA to utilize outside resources to achieve the agency's public health goals in this area without interfering with the practice of medicine. In addition, adopting current reproductive medicine standards would substantially decrease compliance costs. ASRM and SART intend to contact the Tissue Reference Group in the very near future regarding efforts to partner with the agency on the specific issue relating to the regulation of reproductive HCT/Ps.

Sincerely,

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