DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Date: May 4, 2001

To: FDA Dockets Management Branch, HFA-305

From: Martha Wells, CBER, Human Tissue Staff, HFM-305 mw

Concerning: Submission to Docket No. 97N-484P, Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-based Products

Please accept to the docket, the attached:

1. 3/30/2001 email from the American Society for Reproductive Medicine (ASRM) requesting a meeting with FDA about the GTP proposed regulation
2. 4/11/2001 email from ASRM concerning issues they wished to clarify at the meeting
3. FDA drafted minutes of the 4/16/2001 meeting with ASRM

97N-484P

LET 1

Minutes
Meeting between FDA and ASRM
Regarding Current Good Tissue Practice Issues

April 16, 2001

WOC-1, Conference Room 2

Present:

FDA: CBER; Antonio Pereira, Jay Epstein, Astrid Szeto, Kay Lewis, Jill Warner, Phil Noguchi, Deb Hursh, Joyce Frey, Jerome Davis, Martha Wells, OCC; Areta Kupchyk

External: Jacob Mayer, ASRM Public Affairs Committee; Sean Tipton, ASRM Public Affairs Director; Ben Younger, ASRM Executive Director; David Hoffman, SART President; Vicki Girard, Hogan and Hartson

The American Society for Reproductive Medicine (ASRM) requested this meeting with FDA to discuss the proposed regulation on "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement", published for public comment on January 8, 2001 as it applies to the practice of reproductive medicine. The purpose of the meeting was to understand FDA's intent on specific sections of the proposed regulation to be able to respond effectively to the public docket.

ASRM started the meeting with a discussion of general concerns that reproductive medicine is unique and the provisions of the regulation do not appear to apply because it is designed to apply to all tissues and cells. Reproductive medicine is focused on infertility treatment of couples where the concepts of product and manufacturing are not relevant. ASRM requested that flexibility be addressed as related to reproductive practices to assure that access is not impaired. FDA explained that it has responded to the use of the word product in the preamble and the revised title for the final rule on "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing", published on January 19, 2001. The term manufacture is considered a term of art and is also discussed in the final rule as pertaining to the activities or steps involved in preparing a cell or tissue for transplantation. Though many comments to the docket were received concerning this definition, no alternative was suggested and FDA was unable to come up with a better term.

ASRM requested clarification on how the prohibition on pooling (1271.220c) would apply to the practice of reproductive medicine such as the combination of egg and sperm from separate donors, and how does pooling apply to embryos stored in liquid nitrogen. FDA responded that under the proposed rule, combining a sperm and an egg would not be considered pooling, however pooling of sperm from different donors for an insemination would. ASRM indicated that this is not current practice though there is no industry standard prohibiting this practice. They requested that flexibility be considered

for allowing pooling of embryos from different donor oocytes for an implantation when the situation is warranted. FDA discussed that liquid nitrogen storage of embryos in separate vials in the same liquid nitrogen tank would not be considered pooling under the proposed rule.

ASRM expressed concern with application of retention, recall and destruction pertaining to embryos. They explained that the couple and not the clinic owns the embryo. Even when known problems are identified such as possible CJD contamination of culture media, the clinic can only recommend disposition. Oocytes present similar issues as ownership is transferred immediately from the donor to the recipient. Once oocytes can be reliably frozen like sperm the issues of ownership will become easier. FDA explained that an Order for Retention, Recall, and Destruction is one of a number of different enforcement actions the agency could pursue depending on the facts and circumstances surrounding a case. FDA stated that it's possible that the agency could order a firm to retain and/or recall tissue, without ordering destruction of the tissue. FDA also clarified that the mere notification of a consignee could be construed as a recall.

ASRM identified process validation as a term that is incompatible with reproductive practices. Use of embryos to validate a process is generally unacceptable and banned if using public funding and animal studies are rare since there is no support for such research. FDA indicated that validation should apply to the steps and procedures used in preparing tissue for use such as cryopreservation, and cleaning.

ASRM expressed concern on the issue that the GTP's appear to go beyond communicable disease issues and focuses on outcome issues such as success rates. ASRM believes that there is a lack of known disease transmission from oocytes and embryos and that the GTPs go beyond the risk/benefit approach initially proposed by FDA. Their concern is that FDA will use success rates in assessing GTP's for a specific clinic. FDA explained that the economic assessment section in the proposed rule is required to address the effects of the rule regardless of whether their intended purpose. FDA stated that it would not be assessing success rates on inspection.

ASRM requested clarification on how FDA will apply "adverse reactions" to reproductive tissue. This could be problematic as it could encompass spontaneous miscarriages, ectopic pregnancies and non-pregnancy. Similarly "product deviation" could be problematic as it could encompass eggs that may not fertilize. FDA explained that the proposed rule limits adverse reactions to those that result in permanent impairment or damage or necessitates medical or surgical intervention. FDA agreed that further examination of how these concepts should apply to reproductive tissue was warranted.

ASRM stated that the proposed requirements for labeling can not be applied to some reproductive tissues because for many donated embryos the donors name is on the frozen straw and can't be taken off. Also the information required would not fit on these straws. FDA explained that labeling included accompanying materials so that not all information would have to be on the vial or straw containing the tissue.

Concern was also expressed by ASRM with overlapping regulations and the need for multiple inspections. SART currently lists 367 fertility centers as members (15 other non-member establishments are known) and requires certification through CAP (every 2 years), JCAHO (every 3 years) or New York State. Membership also requires that success rate data be submitted to CDC every year. CDC and SART audit the success rate information from 10% of these establishments yearly. FDA discussed current inspectional policies that take into consideration the certification status of an establishment if known

ASRM requested clarification on what facilities are expected to register in 2003 and be subject to the regulations. Would all ob-gyn practices that perform inseminations be regulated or just the ART facilities? If a facility utilizes purchased sperm that is shipped to them, would they be regulated. FDA explained that several exceptions to the regulation that pertain to reproductive practices are found in the final rule in 1271.15. These include if the establishment only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor. The 1271.15d exemption for establishments if they only receive or store purchased sperm would also apply. Concern was also raised by ASRM on potential liability on already collected tissue. FDA explained that the regulations would not apply to tissue procured before the effective date. FDA explained that there is a Q and A on the CBER web site concerning registration and an email address is given to request information.

ASRM suggested that industry drafted standards be utilized as a way of leveraging resources. They proposed that ASRM explore drafting such guidance based on industry standards and certification requirements for the elements in the GTPs. FDA expressed enthusiasm for the idea of ASRM developing reproductive tissue specific guidance for GTP's requirements indicating that there are precedents for FDA reviewing and then issuing such guidances under appropriate administrative procedures as FDA guidance. ASRM indicated that they would review this concept and discuss it further with FDA.

Wells, Martha

From: Sean tipton [stipton@asrm.org]
Sent: Wednesday, April 11, 2001 5:19 PM
To: 'Wells Martha'
Subject: meeting letter - questions and comments

April 11, 2001

Ms. Martha A. Wells
Human Tissue Program
CBER
Food and Drug Administration
HFM 305
1401 Rockville Pike
Rockville, MD 20852-1448

Dear Ms. Wells:

The American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) intend to submit formal 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). ASRM and SART agree with FDA regarding the importance of ensuring that all manufacturers of human cellular and tissue-based products comply with current good tissue practices (CGTPs). Indeed, ASRM and SART believe that well-defined standards are the most effective method of protecting the public health and providing high quality patient care. ASRM and SART are concerned, however, that FDA's Proposal does not adequately describe the manner in which the proposed regulations would apply to human reproductive technologies given the unique nature of the practice of medicine in that context. As the examples detailed below demonstrate, FDA's Proposal includes numerous provisions and concepts that simply do not make any sense when applied to the field of human reproductive medicine. In order to understand FDA's intent and to be able to respond effectively to FDA's Proposal, we are requesting a meeting with appropriate CBER officials to review the application of the Proposed Rule to the practice of reproductive medicine.

Reproductive Tissues are Unique

ASRM agrees that "good tissue practices" should apply to the practice of reproductive medicine. However, FDA needs to recognize that its notion of "product quality" does not necessarily apply where the "product" refers to human reproductive materials, and the "patient" generally refers to a couple

seeking treatment for infertility, rather than to an individual. Additionally, as FDA continues its development of a comprehensive regulatory scheme for human cellular and tissue-based products, 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. A careful balancing is especially critical in the area of reproductive medicine where there is no evidence that communicable diseases are transferred through the use of assisted reproductive technology.

Issues Under FDA's Proposal Requiring Clarification.

Among the foreseeable problems in applying FDA's Proposal to the practice of reproductive medicine 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. For example, "manufacturing" as that term 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), which clearly are not products in the traditional sense. 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). FDA's intent regarding application of the Proposed Rule to the "products" associated with reproductive medicine requires clarification before ASRM and SART can effectively respond to ownership related issues. For example, it is unclear to ASRM and SART whether, and how, FDA anticipates applying orders of retention, recall and destruction under proposed 21 C.F.R. § 1271.440 to reproductive materials such as human embryos.

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. sec. 1271.220(c). Because the combination of egg and sperm from separate donors is at the very heart of many fertility procedures, ASRM and SART cannot believe that the agency intends the prohibition on pooling to apply to the practice of reproductive medicine in the same manner as it applies to other tissue and cellular products. However, without further clarification, such result would occur under a literal interpretation of the Proposed Rule. Clarification on FDA's intent to prohibit pooling is also necessary to establish whether embryos would need to be kept in separate liquid nitrogen tanks or merely separate vials as is the current practice. If separate tanks are required, this could substantially increase costs for clinics and patients, potentially making some reproductive medicine procedures unaffordable for infertile couples desperate to have a child.

FDA's Proposal also includes provisions for process validation that ASRM and SART find difficult to envision in the context of reproductive medicine. Validation—as a concept—does not apply to assisted reproductive technologies and human embryos due to the materials involved and the nature of human reproduction, where 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 they 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 in order to allow ASRM and SART to respond to FDA's Proposal.

The need for clarification regarding application of FDA's Proposal to the practice of reproductive medicine can also be seen 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:

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)." Proposed 21 C.F.R. sec. 1271.3(gg). 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, but seek clarification from the agency on that issue.

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. sec. 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 may not fertilize, does this mean donor component is faulty and must be reported? Unfortunately, it will very difficult to discern the precise cause of the failure, we cannot assume there is a problem with the donated material.

Conclusion

Good tissue practices have long been recognized by ASRM and SART 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. Rather than develop a new and possibly inadequate set of standards, we urge FDA to take advantage of existing programs and standards.

Among the detailed industry standards currently followed by ASRM and SART
members are the joint College of American Pathology (CAP)/ASRM standards and
the standards issued by the Joint Commission on Accreditation of Healthcare
Organizations (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 (42 U.S.C. 293a-1 et seq.). Thus, several sets of
industry standards already exist that address the realities of medical practice in the field of reproductive medicine. These standards, under which a majority of reproductive medicine already is practiced, offer substantially more detail than the CGTPs contained in FDA's Proposal. Moreover, the standards that have been self-imposed by industry, by their
very nature, are more appropriate to medical practice in the unique area of
human reproduction.

ASRM and SART intend in their formal comments to urge FDA to consider using
the current industry standards in lieu of the framework set forth by FDA in
the Proposed Rule. Although we recognize that these standards currently are
voluntary, there is nothing to prevent FDA from adopting them and making compliance with them mandatory. Such adoption of industry standards falls
squarely within FDA's Guiding Principles for Leveraging at FDA. 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 industry standards would substantially decrease compliance costs

Alternatively, if FDA is unwilling to partner with industry in this area,
it is critical that ASRM and SART fully understand the agency's intended application of the Proposed Rule to reproductive technologies. Only by meeting with CBER prior to submitting comments to the docket can ASRM

and
SART be sure to address all of the applicable areas of the rule in an appropriate and helpful manner. We look forward to our discussion.

Sincerely

J. Benjamin Younger, MD
Executive Director

Wells, Martha

From: Sean tipton [stipton@asrm.org]
Sent: Friday, March 30, 2001 10:52 AM
To: 'Wells Martha'
Subject: meeting request - hard copy in mail

March 30, 2001

Ms. Martha A. Wells
Human Tissue Program
Food and Drug Administration
HFM 305
1401 Rockville Pike
Rockville, MD 20852-1448

Dear Ms. Wells:

I am writing to request an opportunity to meet with you and your colleagues regarding regulation of human reproductive tissue. Specifically, several key members of the American Society for Reproductive Medicine (ASRM) leadership will be in Washington April 16 and we would very much like to arrange a meeting for that day.

ASRM has appreciated the opportunity to provide input into FDA's proposals regarding human reproductive tissue thus far and hope our dialogue can continue.

Specifically, we would like the opportunity to get some clarification as to FDA's intent before we submit our comments on the good tissue practice proposed rule.

Thank you for your consideration. I will contact you soon regarding scheduling details.

Sincerely,

Sean Tipton
Director, Public Affairs

cc. Kathryn C. Zoon, Ph.D
Director CBER
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