U.S. ART Practitioners Soon to Begin Their Forced March into a Regulated Future

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INTRODUCTION

A Brief History of U.S. Government Regulation of Infertility Treatment

In the 1980s and early 1990s, the Food and Drug Administration (FDA) showed little interest in human reproduction. When in vitro fertilization (IVF) was a relatively novel procedure, success rates were lower than they are now, causing some congressional concern. The 100th and 101st Congresses held hearings on this topic (1). It was never suggested at these hearings that the FDA had the authority to regulate fertility clinics or any aspect of the IVF process itself. When Congress finally enacted some regulation of fertility treatment, in the form of the Fertility Clinic Success Rate and Certification Act of 1992 (2), the agency charged with implementing the law was not FDA, but rather the Centers for Disease Control and Prevention (CDC).

This law required annual reporting of pregnancy success rates by ART programs and the development of a model program for the certification of embryo laboratories. This law specifically states that in developing the model certification program, "the secretary [of Health and Human Services] may not establish any regulation, standard or requirement which has the effect of exercising supervision or control over the practice of medicine and assisted reproductive technology programs" (3). States which choose

to adopt the model certification program are also prohibited from establishing any such regulations, standards, or requirements (4).

For many years, the U.S. FDA has various regulated human cellular and tissue-based products (HCT/Ps), such as blood, on a piecemeal basis. FDA's first formal foray into this area came in 1993. It took the form of a notice concerning human somatic cell and gene therapy products (5). FDA outlined the types of cells that would be subject to licensure as biological products (for example, autologous or allogenic bone marrow transplants). FDA indicated that establishments involved in manufacturing, preparing, or processing such biological products are also subject to licensure. That year, FDA also published an interim rule on human tissue for transplantation (6). That rule required certain infectious disease testing, donor screening, and record keeping to help prevent the transmission of the HIV and hepatitis viruses through human tissue. The rule specifically excluded semen and reproductive tissue from its oversight. It defined as its subject "any human tissue derived from a human body and intended for transplantation into another human."

In 1997, FDA's Center for Biologics Evaluation and Research (CBER) published its thoughts on a comprehensive program for the regulation of all HCT/Ps, for the first time identifying semen and reproductive tissue as a regulatory target (7). FDA's stated goal for this comprehensive program was "to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products." The degree of regulation, FDA said, would be commensurate with the

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public health risk presented. As with the regulation of human tissue intended for transplantation, FDA claimed that the legal authority for such regulation is based on Section 361 of the Public Health Service (PHS) Act, which permits it to make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the states or from foreign countries into the United States (8). Since HCT/Ps are derivatives of the human body, they pose a risk of transmitting infectious disease.

The 1997 announcement also indicated that FDA's approach would also provide protection from the risks of therapies that may be ineffective or dangerous (9). To implement this approach, FDA has developed three separate rules: the Establishment Registration Rule (10), the Donor Suitability Rule (11), and the Good Tissue Practices (GTP) Rule (12). Each rule is discussed below.

THE ESTABLISHMENT REGISTRATION RULE

A final Establishment Registration rule, promulgated on January 19, 2001, imposes a registration requirement and other obligations on an estimated 400 assisted reproductive technology (ART) clinics and 110 sperm banks. The initial January 21, 2003 effective date of this rule has been postponed and it will now take effect January 21, 2004 (13), by which time the related GTP Rule and Donor Suitability Rule will also have been finalized.

The rule requires initial registration and annual reregistration. It requires the filing of an updated list of the establishment's HCT/Ps twice a year if a change has been made from the previously submitted list (14). Regulated establishments will also have to report changes in the ownership or location of the establishment within 5 days of the change (15). An establishment which manufactures HCT/Ps that are regulated solely under the authority of Section 361 must register and comply with the Part 1271 requirements whether or not its particular HCT/P enters into interstate commerce (16).

An FDA spokesperson has indicated that facilities subject to registration can expect unannounced FDA inspections usually during normal business hours about every 2 years (17). The inspections will generally involve document review, interviewing and observation of employees, and physical inspection of equipment, products, labeling, and facilities. Of

course, records that are required to be maintained may be reviewed and copied. Thus, ART clinics should expect that greater emphasis will be placed on their policies and procedures and the extent to which staff follow standard operating procedures. As in many regulatory schemes, the importance of documentation may come to equal or exceed the importance of the activity being documented.

In order for an ART-related HCT/P establishment to "take advantage of" the less onerous regulation available under Part 1271, the ART establishment must assert that the HCT/P in question is regulated "solely under § 361 of the PHS Act," or, in other words, that it meets the criteria set forth in 21 C.F.R. § 1271.10, i.e. that it is:

1. minimally manipulated;
2. intended only for homologous use;
3. not combined with a drug or device, except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P (18); and
4. for reproductive use.

Reproductive tissue not meeting these criteria are deemed to raise more significant clinical safety and effectiveness concerns and will be regulated as drugs, biological products, or devices. In other words, more than minimally manipulated tissue will have to go through the investigational new drug (IND) application process governed by 21 C.F.R. Parts 50, 56, and 312. An establishment wishing to use such a "product" must file the IND and wait for 30 days. If FDA takes no action, the use may proceed. If FDA has questions about the product, FDA can put a hold on use until the questions are resolved. This approach is supposed to provide flexibility in the early phase to assure the quality of the investigational study design and the safety and rights of the patient; and in later phases to permit evaluation of safety and effectiveness (19).

When the Establishment Registration Rule was in the proposal stage, FDA received many comments, including a number from the American Society of Reproductive Medicine (ASRM), some presented in meetings (20) and other submitted in writing (21). The final rule reflects some, but by no means all, of these comments. ASRM, for example, made presentations to FDA indicating that there is a lack of known disease transmission from oocytes and embryos and that the proposed GTPs go beyond the risk/benefit approach initially proposed by FDA. Furthermore, problems

related to disease transmission via sperm appear to have been largely eliminated by voluntary compliance with the testing, quarantine, and repeat testing recommendations of professional societies, such as ASRM, and the American Association of Tissue Banks (AATB) and the CDC. This information did not alter FDA's course.

ASRM also argued that the concepts of "product" and "manufacturing" have little relevance to the treatment of infertile couples. FDA's response to this argument was simply to expand the title of the rule, changing it from "human cellular and tissue based products" in the proposed version to "human cells, tissues, and cellular and tissue based products" in the final. FDA kept the term "manufacture," as it could not come up with a better alternative term. This term is defined in the rule as including but not limited to, "any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue and the screening or testing of the cell or the tissue donor" (22). The FDA regards this as an umbrella term covering all the different steps an HCT/P establishment might take in preparing HCT/Ps for use.

In response to one comment, FDA did create an exemption for establishments that only recover reproductive cells and "immediately transfer them" into a sexually intimate partner of the cell donor (23). Because the only exemption in the rule is so limited, all of the following establishments would be subject to registration and regulation:

1. an ART clinic that cryopreserves a couple's IVF-created embryos for later use by that same couple;
2. an ART clinic that facilitates the donation of cryopreserved embryos not needed by one couple to another couple;
3. a sperm bank that collects and cryopreserves sperm for provision, on an anonymous basis to patients seeking infertility treatment in ART clinics and other locations;
4. an egg bank that does the same thing; and
5. an ART clinic that solicits egg donors to anonymously provide one or more eggs for use in an IVF attempt by an infertile donee couple, even if no cryopreservation is involved.

The Establishment Registration Rule was finalized first because of FDA concern about the safety of human tissue in the "rapidly growing tissue industry" (24). But, after finalizing the rule, FDA concluded it was better not to put it into effect

until the related rules were also in effect. A full discussion of the related and yet to be finalized GTP and Donor Suitability rules is beyond the scope of this paper. Their requirements are described briefly below.

The Donor Suitability Rule will require specific communicable disease testing such as for HIV I/II, Hepatitis B/C, HTLV I/II, CMV, *Chlamydia trachomatis*, *Neisseria gonorrhea*, and *Treponema pallidum*. Donors will also need to be screened for risk factors and clinic evidence of diseases such as HIV, Hepatitis B/C, CJD, *Chlamydia trachomatis*, and *Neisseria gonorrhea*. The Donor Suitability Rule will include quarantine and retest provisions for anonymous semen donors and labeling and record-keeping requirements. These requirements will be imposed prospectively and will not apply to HCT/Ps procured before the effective date of the regulation. Current thinking is that while semen will require a 6-month quarantine and a retest, oocytes will only require an initial test. Embryos would require an initial test or screen of both gamete providers with a 6-month quarantine until the retest of the semen donor. Clients of an ART clinic who deposit their own ovarian tissue or semen intended for their own use or use with their sexually intimate partner will not be subject to screening requirements.

The proposed GTP Rule will contain provisions on facilities and environmental controls, storage, receipt, distribution, labeling, processing controls, tracking, and reporting of adverse reactions. ART clinics will be subject to a significant portion of this rule. Some of the provisions will be similar to those now pertaining to the joint College of American Pathologists/ASRM Reproductive Laboratory Accreditation Program, to the CDC Model Embryo Certification Program and/or to the standards promulgated by the American Association of Tissue Banks.

ENFORCEMENT

Under Section 368(a) of the PHS Act, any person who violates a regulation prescribed under Section 361 may be punished by imprisonment for up to 1 year (25). Individuals can also be punished for violations of regulations by a fine of up to \$100,000 if death has not resulted from the violation or up to \$250,000 if death has resulted (26). Violations of the regulations can also be enjoined by a federal district court (27).

IS FDA REGULATING THE PRACTICE OF MEDICINE? IF IT QUACKS LIKE A DUCK...

Although FDA states that an ART clinic will require no more than 30 minutes to report on the seemingly simple FDA Form 3356 (28), in fact this form calls for a complex legal determination that an establishment makes at its peril. FDA indicated in promulgating the final rule that at the present time it considers as examples of HCT/Ps that have been "minimally manipulated," those that have been subjected to cryopreservation or freezing (29). Much is left unsaid by this statement. FDA has indicated that it is in the process of trying to get a sense of where to draw the line between "minimally manipulated" reproductive tissue and other reproductive tissue (30).

ART medical practice may already be the most closely scrutinized area of medical practice in the United States, given that clinics must report their success rates on an annual basis. Those success rates are audited, compiled, and posted on a government website (31). Few, if any, other medical procedures are subject to a similar reporting requirement.

In 2001, approximately 95% of all U.S. ART clinics were members of SART and thus required to undergo certification through the College of American Pathologists (CAP) every 2 years, through the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) every 3 years or through New York State (32).

In response to assertions that the Establishment Registration Rule constitutes for regulation of the practice of medicine, particularly reproductive medicine, FDA stated;

We are not attempting to govern practitioners' use of HCT/Ps, but rather to ensure that HCT/Ps that would be used by practitioners in their treatment of patients are in compliance with the applicable regulations, including regulations designed to prevent the transmission or spread of communicable diseases (33).

This seemingly benign claim is belied by recent incursions by FDA into the field of ART, namely its approach to "ooplasm transfer," a procedure designed to improve the development and fertilization capacity of oocytes from patients with recurrent IVF failures, and the coculture of human embryos.

The ooplasm transfer procedure involves injections of 5–10% of the ooplasm from a donor oocyte into a patient's oocyte. CBER sent letters on July 6, 2001, to six ART programs, informing them that the use

of ooplasm containing mitochondrial genetic material constituted a clinical investigation and that the submission of an IND would be required before they could proceed with ooplasm transfer procedures (34). FDA indicated that an IND would have to be approved before any procedures were performed which would combine genetic material in any other way than the "union of gametic nuclei." The genetic materials cited in this FDA letter also include cell nuclei, oocyte nuclei, and genetic material containing a genetic factor. FDA claimed authority for this action based on the October 1993 rule discussed before, governing cell and gene therapy products (35), a rule suddenly discerned as applying to fertility practices. Curiously, the October 14, 1993, proposed rule contained no occurrences of the words: infertility, reproductive, sperm, or oocytes. FDA also based its authority on the comprehensive regulatory program for regulation of HCT/Ps described before. The July 6, 2001, letters were described by at least one reporter as marking the FDA's "first significant foray into regulating the fertility field (36)."

FDA sent out a similar Dear Colleague letter asserting jurisdiction over the coculture of human embryos cocultured with living nonhuman animal cellular material such as bovine tubal cells or Vero cells. FDA considers this activity to be within the definition of xenotransplantation even if the feeder layer cells have been irradiated to render them nonproliferative. Once again, the FDA demanded the submission of an IND before such activities could proceed. It cited the same bases for its jurisdiction as mentioned above (37).

The introductory comments to the final January 19, 2001, establishment registration rule make it clear that as of January 2001, reproductive cells and tissues were not currently regulated as drugs, devices, and/or biological products (38). However, it appears that it would be but a short step from regulation under Part 1271 to the much more burdensome regulation under Section 351 of the PHS Act and the Food, Drug and Cosmetic (FDC) Act as a drug, device, and/or biological product. All that would be needed would be for FDA to conclude that some reproductive tissue is more than "minimally manipulated"; or that it is not intended only for "homologous use"; or that it is being combined with an agent that raises clinical safety concerns. For example, a modification of currently used IVF culture media, a change in culture procedures, or perhaps the intracytoplasmic sperm injection (ICSI) procedure could be deemed not to meet the criteria of 21 C.F.R. § 1271.10 and thus subject to regulation

as drugs/biological product. Processing of cells may be more than minimal manipulation “when adequate information does not exist to determine whether the processing will alter the biological characteristics of the cell or tissue (39).”

As the FDA says “this action is a first step in the regulation in the rapidly evolving industry of human cells and tissues . . . this will enable the agency to more efficiently monitor the industry, distribute new requirements such as guidances, policies, or requirements, and identify entities that may be subject to FDA oversight (40).” FDA’s efforts to regulate reproductive technology may exceed agency authority because such efforts could easily be construed as stepping over the boundaries prohibiting the FDA from regulating the practice of medicine (41).

CONCLUSION

The past two decades have seen rapid advances in infertility treatment. Whether progress will continue at the same pace in the coming decades remains to be seen.

REFERENCES

1. Consumer Protection Issues Involving In Vitro Fertilization Clinics: Hearing Before the Sub-Committee on Regulation & Business Opportunities of the House Committee on Small Business, 100th Cong., 2d Sess. (1988). Consumer Protection Issues Involving In Vitro Fertilization Clinics: Hearing before the Sub-Committee on Regulation, Business Opportunities & Energy of the House Committee on Small Business, 101st Cong. (1989)
2. Pub. L. No. 102-493 (codified at 42 U.S.C. §§ 263a-1 to 263a-7) (Oct. 24, 1992)
3. 42 U.S.C. § 263a-2(i)(1), 2003
4. 42 U.S.C. § 263a-2(i)(2), 2003
5. Application of Current Statutory Authorities to Human Somatic Cell Therapy Products, and Gene Therapy Products, 58 Fed. Reg. 53248 (Oct. 14, 1993)
6. Human Tissue for Transplantation; Interim Rule, 58 Fed. Reg. 65514 or 53248 (Oct. 14, 1993) (codified at 21 C.F.R. Pt. 1270)
7. A Proposed Approach to the Regulation of Cellular and Tissue-Based Products, 62 Fed. Reg. 9271 (March 4, 1997)
8. 42 U.S.C. § 264, 2003
9. 62 Fed. Reg. 9721 (March 4, 1997)
10. The Establishment Registration Rule (Human Cells, Tissue, and Cellular and Tissue-Based Products; Establishment Registration and Listing) was published in proposed form on May 14, 1998 (63 Fed. Reg. 26744), and in final form on January 19, 2001 (66 Fed. Reg. 5447)
11. The Donor Suitability Rule (Suitability Determination for Donors of Human Cellular and Tissue-Based Products) was published in proposed form on Sept. 30, 1999 (64 Fed. Reg. 52696)
12. The GTP Rule (Current Good Tissue Practices for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement) was published in proposed form on January 8, 2000 (66 Fed. Reg. 1508)
13. 68 Fed. Reg. 2689 (2003)
14. 21 C.F.R. § 1271.21 April 1, 2002
15. 21 C.F.R. § 1271.26 April 1, 2002
16. 21 C.F.R. § 1271.1(b) April 1, 2002
17. Presentation of Martha A. Wells of FDA’s Center for Biologics, Evaluation and Research, University of Kentucky Workshop, Nov. 9, 2002
18. FDA has indicated that examples of acceptable sterilizing, preserving, and storage agents would include cryoprotectants (e.g., DMSO); chemicals used for sterilization (e.g. ethylene oxide); and storage solutions. 66 Fed. Reg. at 5459. Comment 30
19. FDA Workshop on Evidenced Based Assisted Reproductive Technologies, Sept. 18, 2002
20. www.fda.gov/cber/minutes/asrm041601.htm
21. The written comments are discussed in detail in the Preamble to the final Establishment Registration Rule, *supra* note 11
22. 21 C.F.R. § 1271.3(e) (April 1, 2002)
23. 21 C.F.R. § 1271.15 (April 1, 2002)
24. 68 Fed. Reg. 2689, 2690 (Jan. 21, 2003)
25. 42 U.S.C. § 271, 2003
26. 18 U.S.C. §§ 3559 and 3571 (c) 2000
27. See specifically the enforcement regulations contained in the proposed GTP Rule
28. Form FDA 3356 can be found on FDA’s website at <http://forms.psc.gov/forms/FDA/FDA-3356.pdf>
29. 66 Fed. Reg. 5457. “By “immediate use,” we mean that the reproductive materials are used promptly enough that cryopreservation is not necessary and is not performed. This exception is intended to cover an establishment that recovers semen for use in the artificial insemination of the donor’s sexually intimate partner. We believe that this situation raises few new infectious disease concerns. For this reason, we are excepting these establishments from registering and from the other requirements will be contained in Part 1271. The exception does not extend to the recovery of cells or tissues from close relative who are not sexually intimate partners, since an increased risk of communicable disease transmission exists in this situation.”
30. See minutes of Workshop on Evidence Based Assisted Reproductive Technologies. Sept. 18, 2002. (Remarks of Jill H. Warner)
31. www.cdc.gov/nccdphp/dhr/art.htm. The website includes the 2000 pregnancy success rate report as well as the five earlier reports published under the Fertility Clinic Success Rate and Certification Act
32. Data presented to FDA by SART
33. 66 Fed. Reg. 5452 (Jan. 19, 2001)
34. www.fda.gov/cber/ltr/cytotrans070601
35. 58 Fed. Reg. 53248 (Oct. 14, 1993)
36. Washington Post, July 11, 2001, A2. Weiss noted that this assertion of authority “differs in that it relates to fertility procedures. Medical procedures generally fall under the category of ‘the practice of medicine,’ which the FDA does not usually oversee out of respect for doctors’ freedom to treat their patients as they see fit.”

37. www.fda.gov/cber/ltr/humemb (March 2002)
38. 63 Fed. Reg. 5450 (Jan. 19, 2001)
39. Proposed Approach to Regulation of Cellular and Tissue Based Products, Docket Number 97N-0068 at p. 17
40. 66 Fed. Reg. 5462 (emphasis added) (Jan. 19, 2001)
41. See, e.g., *Linder v. United States*, 268 U.S. 5 (1925) (the direct control of medical practice is beyond the power of the federal government); *Federal Trade Commission v. Simeon Management Corp.*, 391 F. Supp. 697 (N.D. Cal. 1975)

(discussing the congressional intent as reflected in the legislative history of the 1938 Food, Drug and Cosmetic Act and the 1962 amendments to it—repeated statements that Congress did not intend the FDA to interfere with the medical practice); *United States v. Evers*, 453 F. Supp. 114 (M.D. Ala. 1978); *aff'd* 643 F.2d 1043 (5th Cir. 1981); *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). See also Rokosz, G.J., *Human Cloning: Is the Reach of FDA Authority Too Far a Stretch*, 30 Seton Hall L. Rev. 464 (2000)