

# FAQs

about

## 21CFR Part 1271

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### FDA REGULATION OF REPRODUCTIVE TISSUE LABS



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### 1. ARE IVF LABS REGULATED BY FDA UNDER PART 1271?

Any “establishment” that “manufactures” “human cells, tissues and cellular and tissue-based products” (HCT/P) is regulated by Part 1271. This includes almost all IVF labs.

### 2. WHAT ARE HCT/PS?

HCT/Ps include gametes, embryos and other reproductive tissues. HCT/Ps also include “hematopoietic stem/progenitor cells derived from peripheral and cord blood” BUT DOES NOT INCLUDE PRODUCTS (COVERED BY OTHER REGULATIONS) SUCH AS

- Vascularized human organs for transplantation (such as whole gonads)
- Whole blood or blood components for transfusion
- Bone marrow for transplantation

### 3. WHAT DOES “MANUFACTURE” ENTAIL?

An entity becomes a manufacturer and therefore an establishment when it evaluates tissue donors for infectious diseases or evaluates or processes HCT/Ps for clinical use. Specifically, “manufacture” includes any or all steps in the recovery, processing, storage, labeling, packaging or distribution of HCT/Ps, and the screening or testing of HCT/Ps, and the screening or testing of the HCT/P donor.

### 4. WHICH ESTABLISHMENTS MUST COMPLY WITH 1271 AND WHICH ARE EXEMPT?

Establishments that must comply with 1271 are those that “minimally manipulate” HCT/Ps or manufacture them for “homologous use.” *Minimal manipulation* is any process that does not alter the physiological function of the HCT/P. Examples of minimal manipulation mentioned by the FDA are cell culture, centrifugation and cryopreservation. If the processing of HCT/Ps goes beyond minimal manipulation so that physiological function is altered, the establishment must comply with 1271 and also comply with section 351 of the Public Health Service Act. Questions about whether a manufacturing step goes beyond minimal manipulation should be directed to the FDA’s Tissue Reference Group: [www.fda.gov/cber/tissue/trg.htm](http://www.fda.gov/cber/tissue/trg.htm). *Homologous use* refers to clinical transfer of the HCT/P so that the HCT/P functions in the recipient as it did in the donor. Exempt establishments are those that

- Use HCT/Ps solely for non-clinical scientific or educational purposes
- Remove HCT/Ps from an individual and implant such HCT/Ps from an individual during the same surgical procedure. This includes reproductive tissues immediately transferred into a sexually intimate partner.
- Receive or store HCT/Ps solely for (clinical use) within the establishment. These HCT/Ps must be obtained from an establishment regulated under 1271. The FDA list of registered establishments is at [www.fda.gov/cber/tissue/hctregestabl/htm](http://www.fda.gov/cber/tissue/hctregestabl/htm) or [www.fda.gov/cber/tissue/tissregdata.htm](http://www.fda.gov/cber/tissue/tissregdata.htm) (two different formats and levels of information).

### 5. WHAT IS THE EMPHASIS AND INTENT OF 1271?

- Control of “communicable” (infectious) diseases in transplantable human tissue to protect recipients (including offspring), other family members, health-care personnel, and anyone else who may come in contact with contaminated tissue.
- Quality principles of good tissue practices (GTP). For establishments processing reproductive tissues, FDA emphasizes GTPs related to donor eligibility.
- Enforcement.

## **6. WHAT IS INCLUDED IN PART 1271?**

*Subpart A:* Scope and Definitions

*Subpart B:* Registration – Requirement and Process

*Subpart C:* Donor Eligibility

*Subpart D:* Good Tissue Practices (GTP)

*Subpart E:* Additional Requirements

*Subpart F:* Inspection and Enforcement

## **7. WHERE CAN I FIND A COMPLETE TEXT OF 21 CFR PART 1271 ON THE WEB?**

The FDA of course has this:

- [http://www.access.gpo.gov/nara/cfr/waisidx\\_05/21cfr1271\\_05.html](http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr1271_05.html)

Xytex has annotated 1271:

- Go to [www.xytex.com](http://www.xytex.com)
- Click on “Physicians’ Info”
- Then click on the download of “1271” found on right side of screen.
- It is extremely important to note the date of the regulation you are using. Part 1271 has a history of volatility, sometimes changing within a month of the previous version. At this time (11 November 2005) the most recent version is 24 May 2005.

## **8. WHO CAN BE A DONOR OF REPRODUCTIVE CELLS OR TISSUES?**

Nearly anyone, depending upon circumstances. The circumstances are predicated on the closeness of the relationship between the intended recipient and the donor.

- The most limiting circumstances are for anonymous semen donors. These men must be negative by screening and testing of all “relevant communicable disease” at the time of donation. Furthermore, the semen must be held in quarantine until fresh specimens (blood, semen, urine) collected from these men at least six months after semen donation are also tested negative; only then can the original, quarantined semen be used clinically. (A second, abbreviated, screening is required.)
- Anonymous egg donors must be negative by screening and testing of all relevant communicable diseases within 30 days of egg retrieval, but quarantining of the eggs with donor re-testing is not required because eggs do not reliably survive cryopreservation.
- Screening and testing of the male and female providers of gametes used in anonymous donation of an embryo could theoretically be done in the same manner as required for the anonymous donations of the gametes, including quarantine of the embryo. In reality, most cryopreserved embryos for anonymous donation originally are intended for the private use of the gamete donors (sexually intimate partners called “client depositors”). The use of embryos outside of the partnership was never expected when the embryo(s) were created; the use of gametes and embryos within a sexually intimate partnership does not require screening and testing of the partners. If such embryos later become available for anonymous donation and one or both gamete providers can be screened and tested, this should be done; but if screening and testing of either or both donors are precluded for any reason, the embryo donation may proceed if the recipient consents after being informed of the risks for infectious disease transmission. The recipient should be informed as to recommended screening and testing, whether any screening and testing was done, and the outcome of these procedures. To notify physicians of the absence of required screening or testing of either embryo donor, special labels must be used with the embryos: see 1271.90 (b).
- Other circumstances may arise from sexually intimate client depositors. They usually are not required to be screened or tested in accordance with 1271. These donors should undergo appropriate screening and testing when someone outside of the sexual relationship is exposed to the risk of disease transmission posed by the reproductive cells. This may occur if a gamete or

embryo is transferred to a gestational carrier. Circumstance may be one of anonymous donation (requiring full screening and testing) or one of directed donation.

- Ostensibly “directed donation” is one in which the recipient “knows” the donor (1271.3) in the sense of a friend or acquaintance. Presumably both recipient and donor are aware of and agree to the intended pregnancy. In this circumstance, when the donated gamete is sperm, a six-month quarantine is not required by the FDA (1271.85(d)). The FDA expects the directed donors to be screened, tested and a donor eligibility determination made prior to clinical use of the reproductive cells, but a “positive” test or screen does not preclude the use of these cells provided proper labeling and informed consent of the recipient is obtained (1271.90).

#### 9. WHAT ARE THE REQUIREMENTS FOR “SCREENING” AND “TESTING”?

- “Screening” is evaluation of the donor for specific “relevant communicable diseases” (that is, relevant to the intended use of the tissue) by “reviewing the donor’s relevant medical records.” Relevant medical records include a current donor medical history interview, other medical records from any source pertaining to relevant communicable diseases, and a physical exam of the living donor. Note that the FDA prefers donors who have not received xenotransplants of any sort.
- “Testing” is the laboratory evaluation of the donor and/or the donor tissue for risk of transmission of relevant communicable diseases. This testing must be performed by a laboratory certified under CLIA to perform these specific tests using FDA-licensed, approved or cleared donor screening tests (when such tests are available). CLIA is administered by CMS of HHS; its regulations are at [www.phppo.cdc.gov/clia/pdf/42cfr493\\_2004.pdf](http://www.phppo.cdc.gov/clia/pdf/42cfr493_2004.pdf); also see [www.cms.hhs.gov/clia](http://www.cms.hhs.gov/clia). CLIA labs must be inspected and certified, but not necessarily by CMS; CMS has authorized a few accreditation agencies such as College of American Pathologists (CAP) and The Joint Commission for Accreditation of Healthcare Organizations (JCAHO) to do this as well as some states.
- Documentation of screening and testing as prescribed by 1271.

#### 10. WHAT ARE THE CAUSATIVE AGENTS OF “RELEVANT COMMUNICABLE DISEASES”?

- For all human cells and tissues
  - Human immunodeficiency virus, types 1 and 2
  - Hepatitis B virus
  - Hepatitis C virus
  - Prions causing human transmissible spongiform encephalopathy, including C-J disease (evaluated by screening, not testing, of living donors)
  - *Treponema palladium*
  - Zoopathogens transmissible by xenomaterials (evaluated by screening). Of concern to the FDA but not listed in 1271
- For viable, leukocyte-rich cells (namely, semen)
  - Human T-lymphotropic virus, types I and II
  - Cytomegalovirus
- For reproductive cells or tissues that could be contaminated by organisms prevalent in the genital or urinary tract
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhoea*
- AND ALSO ANY OTHER serious infectious disease for which there may be a significant risk of transmission by an HCT/P either to the tissue recipient or to people handling the tissue. The FDA intends to publish its ideas of additional diseases meriting screening and testing as it did in the Federal Register Vol. 69, page 29835 for 25 May 2004 ([www.fda.gov/cber/guidelines.htm](http://www.fda.gov/cber/guidelines.htm)).

**11. WHAT OTHER ASPECTS OF 1271 ARE SPECIFIC TO REPRODUCTIVE TISSUE LABORATORIES?**

Specifically, regulations in Subparts D and E are not being implemented for reproductive HCT/Ps. These two subparts describe how tissue is to be handled physically, not only in regards to processing, labeling and tracking, and documenting, but also in regards to personnel and facilities (space, equipment, and consumables). This allows reproductive labs to use homebrew media even when it includes devitalized hen's egg yolk. Should the FDA decide that problems in reproductive labs could be prevented by enforcing Subparts D and E, it will rescind the exemptions. In reality, the regulations in these two subparts represent "good practice" and should be voluntarily implemented by reproductive laboratories. One can imagine that this opinion might also be held by a court of law considering a dispute about the outcomes of a lab procedure.

**12. SINCE REPRODUCTIVE LABS ARE NOT REQUIRED TO PROCESS HCT/PS IN ACCORDANCE WITH GOOD TISSUE PRACTICES (GTP) IN SUBPARTS D AND E, DOES THIS MEAN THAT THESE LABS DO NOT HAVE THE SAME STRINGENT QUALITY PROCEDURES FDA REQUIRES OF OTHER TISSUE BANKS?**

Yes and No. FDA regulations for processing reproductive tissues are certainly more lenient than those for processing other HCT/Ps, but there is no leniency in evaluating and documenting tissue donors for relevant transmissible infectious diseases. FDA procedures for determining and documenting donor eligibility fall under GTPs in Subpart C and, in this regard, demand personnel trained and qualified in these procedures, documented standard operating procedures (SOPs); approval, review, and revision of procedures on an ongoing basis; records including labels; record retention and availability of records to users (clients). Deviations from SOPs must be documented.

**13. ARE THERE ALTERNATIVES TO AN INSPECTION BY THE FDA ITSELF?**

No, the FDA reserves this responsibility for itself, just as it does for blood establishments (banks!). The FDA requires involvement of both CBER and the Office of Regulatory Affairs in the overall inspection process. FDA investigators are trained for HCT/P inspections. The manual used by investigators is at [www.fda.gov/ora/inspect\\_ref/iom/](http://www.fda.gov/ora/inspect_ref/iom/); be sure to see subchapter 560. FDA has also recently published a Compliance Program Guide, 7341.002 for inspection of HCT/Ps at <http://www.fda.gov/cber/cpg/7341002tis.htm>.

**14. WHAT ENFORCEMENT ACTIONS CAN AN INVESTIGATOR TAKE?**

Procedures of due process have been developed within FDA and usually the first action is a request for a written plan of correction. However, if the investigator believes there is a serious risk for transmission of a communicable disease by a reproductive tissue establishment, there can be orders of tissue retention by the establishment, tissue recall or cessation of manufacturing.

**15. How did FDA get involved in reproductive tissue labs?**

The FDA, part of the Public Health Service (PHS) (Appendix A), has been regulating many human tissues (such as cornea, bone, heart valves, skin, but not reproductive tissues) since 1993 under 21 CFR Part 1270 through the mandate of the Public Health Service Act of 1944. It drafted Part 1270 in response to documented incidences of disease transmission by tissue transplants. These regulations incorporate principles of total quality management (TQM) arising from the work of Drs. William Edwards Deming and Joseph M. Juran and the more recent concepts of six sigma from the work of Dr. James P. Womack. It has intended for 1271 to supercede 1270.

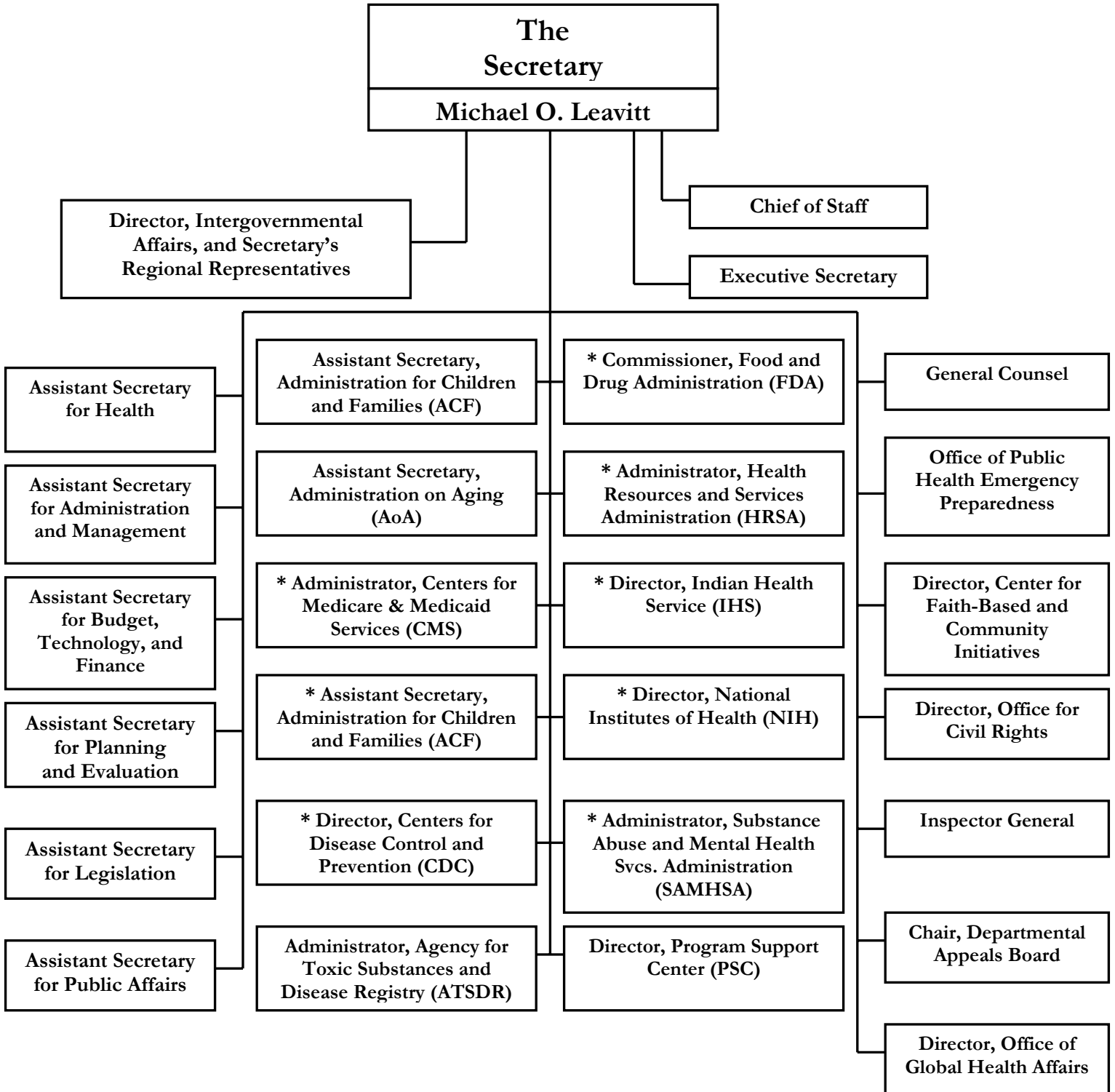
Blood has been regulated in the U.S. since 1946, first by NIH in the PHS, then FDA in 1972. However, biologics such as sera and vaccines have been regulated by the PHS since 1902. A "History of Federal Regulation of Human Reproductive Tissue in the U.S." is shown in Appendix B.

Prior to federal involvement, reproductive tissue labs were regulated to varying degrees by several states: e.g. California, Georgia, Maryland and New York. State regulations may go further than federal to include psychosocial and genetic evaluation of the donor.

Several voluntary organizations offer inspection and accreditation for reproductive laboratories. The emphasis here is education rather than enforcement. Notable is the collaborative program of the American Society for Reproductive Medicine (ASRM) with the CAP; CAP is the administrator. Also, the American Association of Tissue Banks (AATB) and JCAHO have inspection and accreditation programs.

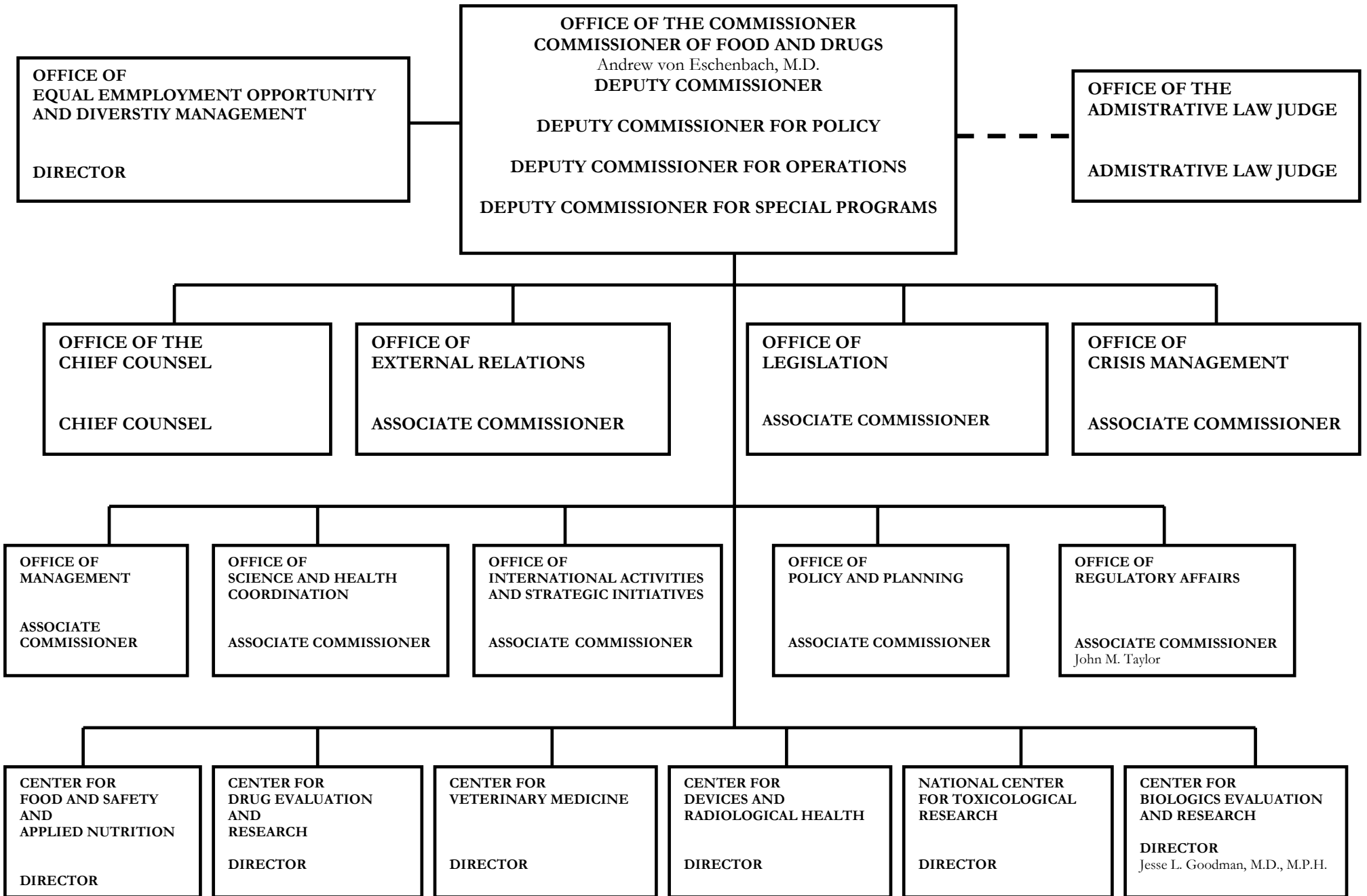
A worldwide organization promulgating total quality management and offering inspection and accreditation of tissue banks is the International Organization for Standardization. Its U.S. representative is the American National Standards Institute (ANSI). Members of ANSI include CAP, CDC, CMS and JCAHO. Inspection and accreditation by these voluntary organizations does not obviate a tissue bank from inspection by regulatory authorities.

**APPENDIX A**  
**DEPARTMENT OF HEALTH & HUMAN SERVICES (HHS)**  
**2005**



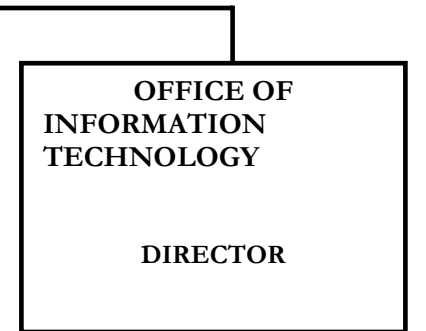
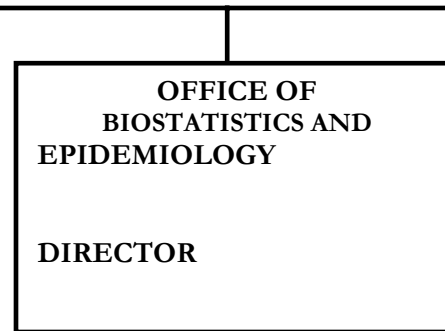
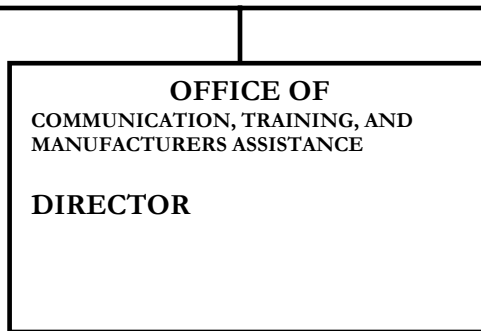
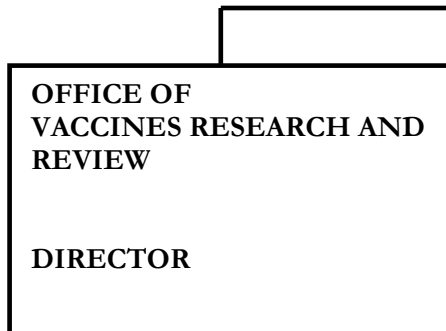
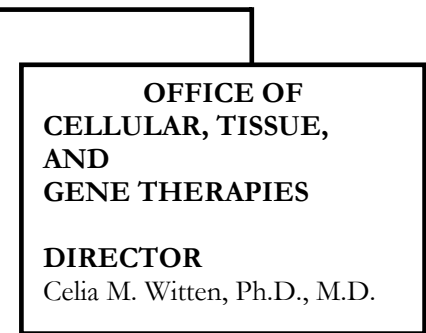
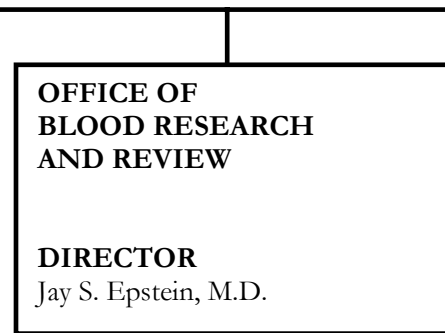
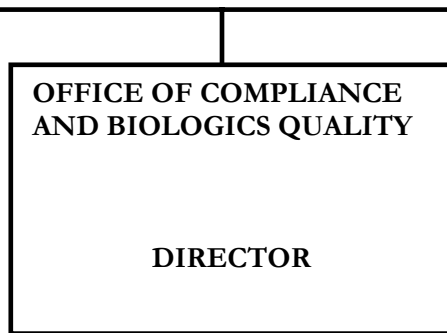
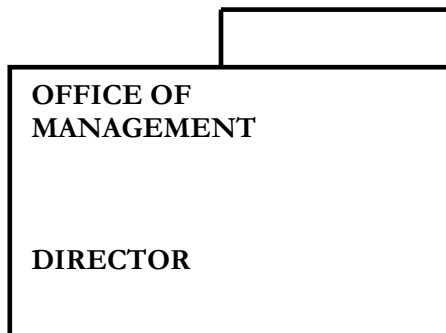
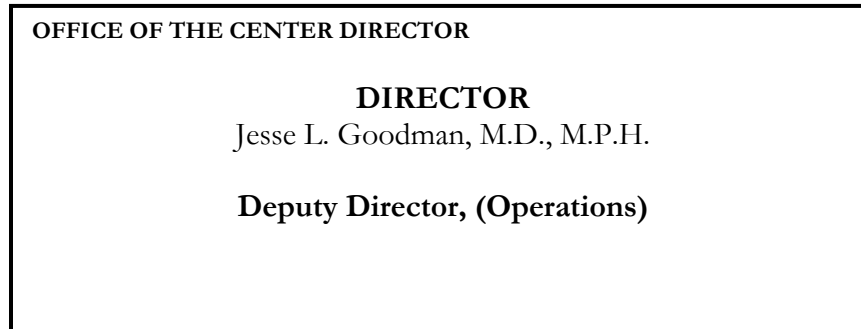
\*Components of Public Health Service (PHS); note that each reports to The Secretary. The PHS is one of several “uniformed services” of the U.S. government (including military and NOAA). Commissioned officers of PHS occasionally wear military-style uniforms. Also, there is a PHS Surgeon General.

**Appendix A Cont.**  
***FOOD AND DRUG ADMINISTRATION, HHS***  
***2005***



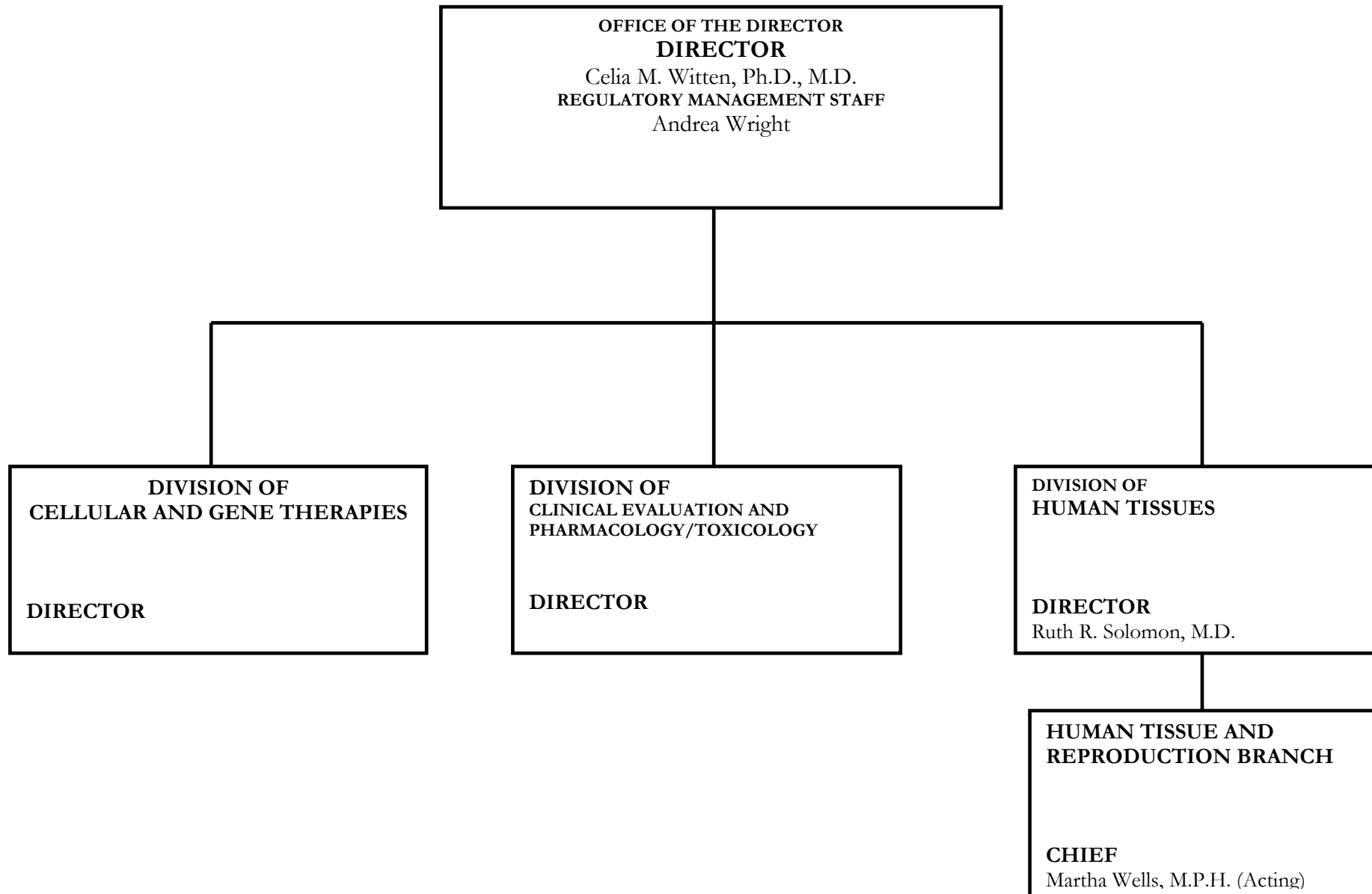
# Appendix A Cont.

## CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FDA *2005*



# Appendix A Cont.

## OFFICE OF CELLULAR, TISSUE AND GENE THERAPIES, CBER *2005*



## APPENDIX B

### HISTORY OF FEDERAL REGULATION OF HUMAN REPRODUCTIVE TISSUE IN THE U.S.

YEAR	HHS and PHS		SSA and MEDICARE/MEDICAID
	NIH and CDC	FDA	
1798	Marine Hospital Service (MHS) established by Congress		
1862		Department of Agriculture (DOA) and its Division of Chemistry established (President Lincoln)	
1870	MHS reorganized as a Bureau in the Treasury Department		
1887	Laboratory of Hygiene established for bacteriology research at the Marine Hospital, Staten Island, New York, later (1891) moved to Washington, headquarters of the MHS		
1901		Division of Chemistry renamed Bureau of Chemistry (BOC)	
1902	MHS name changed to Public Health and Marine Hospital Service (PHMHS)	Virus - Toxin Act/Biologics Control Act, administered by BOC	
	Public Law 244 regulates shipment of biologics (vaccines) administered by Hygienic Laboratory		
1912	PHMHS name changed to Public Health Service (PHS)		
1927		Food, Drug, and Insecticide Administration (FDIA) established for regulatory functions in DOA, independent of BOC	
1930	The Hygienic Laboratory becomes National Institute of Health (NIH)		
1931		FDIA becomes Food and Drug Administration (FDA)	
1935			Social Security Act creating Social Security Board (SSB), part of Treasury

## APPENDIX B (continued)

YEAR	HHS and PHS		SSA and MEDICARE/MEDICAID
	NIH and CDC	FDA	
1937	NIH organized into eight divisions, including Division of Biologics Control (DBC)		
1938		Food, Drug and Cosmetic Act	
1939-40	Federal Security Agency (FSA) created to bring together health, education and welfare. Includes SSB, PHS transferred (1939) from Treasury and FDA transferred (1940) from Agriculture		SSB transferred from Treasury to FSA
1944	Public Health Service Act includes biological products and communicable diseases		
1946	Communicable Disease Center (CDC) established as part of PHS		
	Philadelphia (PA) Blood Bank first to be licensed by NIH - DBC		
1953	FSA becomes Cabinet-level Department of Health, Education and Welfare (DHEW) including PHS and SSA but not FDA		
1955	DBC of NIH becomes Division of Biologics Standards (DBS)		
1965			Medicare and Medicaid programs established in SSA
1967	Clinical Laboratory Improvement Act (CLIA) administered by CDC		
1968		FDA becomes part of PHS	
1970	CDC renamed Center for Disease Control		
1972	Regulatory functions of NIH transferred to FDA, including DBS	FDA becomes responsible for registration, inspection and regulation of blood banks. Bureau of Biologics	

## APPENDIX B (continued)

YEAR	HHS and PHS		SSA and MEDICARE/MEDICAID
	NIH and CDC	FDA	
1973	The National Institute for Occupational Safety and Health becomes part of CDC		
1977			Health Care Financing Administration (HCFA) created within DHEW to manage Medicare and Medicaid separately from SSA.
1979	DHEW separated into Department of Health and Human Services (HHS) and Department of Education		HCFA manages clinical laboratories through CLIA
1980	CDC renamed Centers for Disease Control	Regulation of hospital transfusion services transferred to HCFA	
1985	CDC recommends HIV antibody testing of tissue donors MMWR 34:294		
1988	CDC recommends 6-month quarantine of semen donors MMWR 37 p.p. 56, 57, 63	FDA Act of 1988 officially established FDA as part of HHS	Clinical Laboratory Improvement Amendment (CLIA 88)
1991	CDC recommends voluntary screening of semen donors for hepatitis B and C. MMWR 40 (RR-1) p.p. 1-23		
	The Fertility Clinic Success Rate and Certification Act Public Law 102-493 requires CDC to collect and publish relevant statistics		
1992	CDC renamed Centers for Disease Control and Prevention (but retains acronym CDC)		
1993		FDA regulates many human tissues (but not reproductive) 21CFR Part 1270 FR 58 (238) pp 65514-21	

## APPENDIX B (continued)

YEAR	HHS and PHS		SSA and MEDICARE/MEDICAID
	NIH and CDC	FDA	
1994	CDC recommends voluntary screening and testing of semen donors for HIV. MMWR 43 (RR-8) pp 1-17		
1995			SSA becomes an independent agency
1999	CDC publishes "Proposed Model Program for the Certification of Embryo Laboratories" FR 64 (139) pp 39373-92		
2001		FDA final rule for 1271 subparts A and B (registration and listing of establishments) FR 66 p.p. 5447, amended FR69 (17) 3823 and (23) 5272 (2004)	Centers for Medicare and Medicaid Services (CMS) replaces HCFA
2004		FDA final rule for 1271, subpart C donor eligibility FR 69 p.p. 29785 - 29834	
		FDA final rule for 1271 subparts C, D, E current good tissue practice, inspection and enforcement FR69 p.p. 68611 – 68688	
2005		FDA interim final rule for 1271 (entirety) FR 70 p.p. 29949-29952	

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