

1 OBSERVATIONS ON THE EVOLVING REGULATORY PROGRAMME OF TISSUE BANKING BY THE FOOD AND DRUG ADMINISTRATION IN THE USA

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1. Introduction

The Food and Drug Administration (FDA), an agency of the Department of Health and Human Services of the US Federal Government, has recently proposed a comprehensive set of regulations aimed at manufacturers of human cells, tissues, and cellular and tissue-based products (“HCT/P’s”). The effort of the FDA in this direction began in 1997 when the regulatory plan was announced in two documents entitled “A Proposed Approach to the Regulation of Cellular and Tissue-Based Products” and “Reinventing the Regulation of Human Tissue (Department of Health and Human Services, 1997a,b). As a background to these proposals, it is important to know that the FDA had previously issued interim regulations (21 CFR 1270) effective December 14, 1993 based on Section 361(a) of the Public Health Service (PHS) Act, designed to prevent the spread of communicable diseases from

contaminated persons, animals and articles (Department of Health and Human Services, 1993). On July 29, 1997 the FDA issued final regulations (21 CFR 1270) that require facilities engaged in recovery, screening, testing, processing, storage or distribution of human tissue to ensure that medical screening and infectious disease testing have been performed and that records documenting this be available for inspection by the FDA. These regulations contain provisions for the retention, recall or destruction of human tissue for which documentation is not available (Department of Health and Human Services, 1997c).

Since 1997 the FDA has published three proposed rules to implement the approach. The first proposal, "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" was published on May 14, 1998 (Department of Health and Human Services, 1998). This proposal became a final rule, "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing", published on January 19, 2001 (Docket No. 97N-484R) (Department of Health and Human Services, 2001b). The rule was implemented effective April 4, 2001 and requires that all HCT/P establishments register with the agency and list their products.

The second proposed rule, "Suitability Determination for Donors of Human Cellular and Tissue-Based Products" was published on September 30, 1999 (Docket No. 97-484S) (Department of Health and Human Services, 1999). It represents FDA's plan to take over the wide and comprehensive regulation of donor screening and testing for risk factors and clinical evidence of communicable disease agents and disease in the cell and tissue banking industry.

The third proposed rule, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement" published on January 8, 2000 (Docket No. 97-484P) deals with establishing a programme of "Current Good Tissue Practice" (CGTP) requirements and inspection/enforcement provisions (Department of Health and Human Services, 2001a). All the FDA rules and proposals can be accessed by those interested in details at <http://www.fda.gov/> link "Federal Register" where they can be sorted by the given docket numbers.

It is evident that both the professionals engaged in cell and tissue banking and clinicians who use the banked cells or tissues will be affected by FDA regulation. One would like to pose the question as to why this type of government regulation is going forward. One would also want to examine the FDA proposals in light of professional standards that are already in place. Finally, one would like to have a look at the likely impact that such government control would have on providers and users of cells or tissues. As a clinical surgeon and scientist who spent most of a career close to the tissue banking and transplantation disciplines, I choose to look at this subject through the lens of a professional association that unites cell and tissue bankers and transplant clinicians, the American Association of Tissue Banks (AATB). Currently, the AATB represents 69 AATB-accredited tissue banks and 1200 individual professionals engaged in the procurement, processing, storage and distribution of human tissues. The AATB has been setting standards for tissue banking in the US on an ongoing basis since its formation in 1976 (Kaprisin and Woll, 2001). It is therefore more in the position than any other group or individual to shape and mold the evolving regulatory programme. The following observations will summarise a number of current issues that are debated while the government regulatory intent is taking shape.

2. Intent of the Proposed FDA Regulation

The proposed FDA regulation has arisen as a result of the agency's intent to provide oversight over a wide range of human cellular and tissue-based products that are intended for implantation, transplantation, infusion, or transfer, now and in the future. Clearly, the agency is acting with the intent to protect public health in the face of rapidly evolving technological innovations. The proposal intends to put in place comprehensive rules to regulate HCT/P's under section 361 of the PHS Act (42 U.S.C.264) rather than under section 351 of the PHS Act applicable to drugs, medical devices and biological products.

The urgency of establishing FDA regulation of human cellular and tissue-based products at this time is justified by the agency's concerns regarding compliance with industry standards by establishments across the country involved in the transplantation of reproductive tissues. Such tissues are donor oocytes or embryos used in assisted reproductive technology (ART) facilities and associated laboratories, and donor sperm distributed by sperm banks. It is unknown how many of the producers of reproductive tissues follow industry standards. The FDA acknowledges that a number of these facilities are in line with AATB or American Society of Reproductive Medicine (ASRM) standards but many others are not. Consequently, this particular industry poses increased risk to the population for disease transmission.

The risk of Human Immunodeficiency Virus (HIV) transmission by reproductive tissues should decrease with FDA oversight as it already has in the case of Therapeutic Donor Insemination (TDI) since HIV testing was recommended by the Center for Disease Control (CDC) in 1985 (Center for Disease Control, 1985). The benefits of FDA oversight are going to be most obvious for the risk of Hepatitis B (HBV) and Hepatitis C (HCV) transmission by reproductive cells. Given yearly prevalence rates of 27.6% for HBV and 9.8% for HCV in oocyte and sperm donors, the risk of transmission is very real. The population at risk each year is estimated to include 1600 to 4700 women undergoing *In Vitro* Fertilisation (IVF) with donor eggs, and 1300 newborns delivered as a result of that procedure, and 34 200 to 70 000 women receiving TDI, and 8800 newborns delivered as a result of that therapy. While these figures are alarming, even more concern is generated by the lack of uniform compliance of reproductive cell facilities with industry standards (Department of Health and Human Services, 1999). While the ASRM has published guidelines for donor screening, it does not provide oversight or accreditation of facilities involved in infertility treatment. Thus, it is clear that the intent of the FDA is to close loopholes and deficiencies rather than interfere with industry standards already in place.

The FDA acknowledges the current industry standards set by the professional associations representing manufacturers of non-reproductive tissue. These establishments include eye banks, tissue banks, marrow and peripheral blood stem cell donor centers, and cord blood banks. Professional associations such as the AATB, Eye Bank Association of America (EBAA), American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) have been setting standards and accreditation procedures for producers of non-reproductive tissues for years. Consequently, the FDA estimates that 100% of these entities are already in compliance with industry standards and thus will be impacted minimally by the proposed regulation (Department of Health and Human Services, 1999).

3. Suitability Determination — Proposed Rule

This will be discussed with focus on new concepts introduced by the FDA, which require critical input from tissue bankers and clinicians as the regulatory process evolves.

3.1. Purpose and scope

Under “Purpose and Scope” (Proposal 1271.1), the FDA proposes to distinguish between two groups of human cellular and tissue-based products. The first group will be products regulated solely under the authority of section 361 of the PHS Act (“361 products”). The second will be products regulated under both section 351 of the PHS Act as drugs, medical devices and/or biological products and section 361 of the PHS Act. The FDA proposes that “361 products” be “minimally manipulated”, intended for only “homologous use”, be not combined or modified by addition of a drug or device and must not have systemic effects. Thus it is clear that the regulation of “361 products” will be less burdensome and more streamlined than that of drugs, medical devices and/or biological products. However, the criteria proposed for defining these products are undergoing evolving re-evaluation.

3.2. Definitions

In “Definitions” (Proposal 1271.3) the FDA holds that “minimal manipulation” for structural tissue is processing that does not alter the original relevant characteristics of the tissue relating to its utility for reconstruction, repair or replacement. For cells or nonstructural tissues, “minimal manipulation” means processing that does not alter the relevant biological characteristics of cells and tissues. The FDA defines “homologous use” for structural tissue-based products as use of the tissue for the same basic function that it fulfills in its native state, in a location where such structural function occurs normally. For cellular and nonstructural tissue-based products “homologous use” is defined as use of the cells or tissues to perform the same functions that they performed in the donor. It comes immediately to mind of a tissue banker or a clinical surgeon that these definitions are problematic. We shall discuss this issue in more detail when analysing the AATB position.

3.3. General requirements

Under “General Requirements” the FDA includes proposals on: determination of donor suitability (1271.50), records of donor suitability (1271.55), quarantine pending determination of donor suitability (1271.60), and quarantine and disposition of human cellular or tissue-based products from an unsuitable donor (1271.65). Of note here are three *special exceptions* where the regulation would not bar the implantation, transplantation, infusion or transfer of unsuitable tissue: 1) the product is for family related allogeneic use, 2) the product contains reproductive tissue from a directed donor, and 3) there is a documented urgent medical need for the product. The FDA will require that such unsuitable products be labelled with a “BIOHAZARD” legend. These exceptions will not be valid for products coming from donors who are recipients of xenotransplants or have been in contact with recipients of xenotransplants (to prevent the transmission of unknown animal pathogens, including retroviruses). This latter concern and the exceptional circumstances listed above have no direct AATB Standard equivalent although

some of these issues are addressed under “exceptional release” rules of the AATB (American Association of Tissue Banks, 2001a).

3.4. Donor screening

“Donor Screening” (Proposal 1271.75) deals with the review of the donor’s medical history and the evaluation of risk factors for communicable disease. The FDA proposal consists of two parts related to donor screening: 1) General requirements, and 2) Specific communicable disease screening requirements.

It is stressed under the *general requirements* that a donor medical history means a documented dialog with the donor, if alive, or a documented interview with the next of kin or other individual knowledgeable about the donor, if not alive. This issue is particularly important to prevent transmission of transmissible bovine encephalopathies (TSE) including Creutzfeldt-Jakob disease (CJD). According to the FDA, behavioural or cognitive changes of a cell or tissue donor would uncover a possible indication of TSE when all other screening and testing procedures are negative.

The *specific requirements* stipulate screening of all donors for HIV, HBV, HCV, and TSE, including CJD. A special screening concern are donors of reproductive cells or tissues when those cells or tissues are recovered through methods that could lead to the transmission of sexually transmitted or genitourinary diseases. Another concern of FDA is to exclude donors who have received a xenotransplant or have been in close contact with a xenotransplant recipient. Of note here is that this rule would affect only recipients of live xenotransplants and not those recipients who are transplanted with nonliving biological products such as porcine heart valves or porcine insulin.

3.5. Donor testing

“Donor Testing” (Proposal 1271.80 and 1271.85) includes general and specific requirements to assure reducing the risk of communicable disease transmission by defining how to test donors of cells or

tissues intended for transplantation or implantation. *General requirements* state that a specimen from the mother of a foetal or neonatal donor would be acceptable for testing. It is proposed to require that the donor specimen be collected at the time of recovery of cells or tissues from the donor or within 48 hours after recovery. This is different from the current AATB standard which says 7 days prior to or after donation.

The FDA proposal defines exceptions to this requirement in living donors and allows collection up to 7 days prior to recovery if: 1) recovery is risky to the donor, 2) transplantation is necessary before results of testing at recovery are known, and 3) extensive processing is necessary before results of testing at recovery are known. There is no corresponding AATB standard for these exceptions (American Association of Tissue Banks, 2001a).

It is proposed that testing should be performed with FDA-licensed, approved or cleared donor screening tests. A proviso is made for *Chlamydia trachomatis* and *Neisseria gonorrhoea* for which there are no FDA-licensed screening tests available and thus tests labelled for the detection of these organisms may be used. The proposed rule holds that a donor whose specimen tests are repeatedly reactive must be determined unsuitable. Exceptions to this are repeatedly reactive tests to Cytomegalovirus (CMV) and non-*Treponemal* screening tests for syphilis.

In the former case, product information sent with the cells or tissue will be evaluated by the physician who will then make a decision about the use of the product. In the latter case, a negative specific *Treponemal* confirmatory test is needed to override the previous false positive result. The general requirements also address the plasma dilution problem after transfusion of blood, colloids or crystalloids. A specimen taken after blood loss but before transfusions or infusions is suitable. In certain instances, an algorithm may be used to calculate dilution (Department of Health and Human Services, 1999).

The *specific requirements* identify the tests to be done on all donors of viable and non-viable cells or tissue as follows: HIV type 1 (FDA-licensed screening test for anti-HIV-1), HIV type 2 (FDA-licensed screening test for anti-HIV-2), HBV (FDA-licensed

screening test for hepatitis B surface antigen “HbsAg”), HCV (FDA-licensed screening test for anti-HCV), and *Treponema pallidum* (FDA-cleared test for syphilis). In addition to these tests, donors of viable, leukocyte-rich cells or tissues (stem cells and reproductive cells or tissues) will have to be tested for evidence of infection with Human T-lymphotropic virus (HTLV) types I and II (FDA-licensed screening test for anti-HTLV I/II) and CMV (FDA-cleared test for anti-CMV).

Donors of reproductive cells and tissue will also have to be tested for infection due to genitourinary disease agents *Chlamidia trachomatis* and *Neisseria gonorrhoea*, unless it can be shown that procurement ensures freedom from contamination with organisms that may be present in the genitourinary tract. The proposed rule would require retesting of donors of reproductive cells or tissues that can be reliably stored at least 6 months after the date of donation, thus establishing a 6 months minimum quarantine on these cells and tissues.

Retesting for HBV is most appropriately done with the HBV core antibody screening test rather than the surface antigen test used for the original screening. For all other banked tissues and cells from living donors, the FDA recommends but does not propose to require that, where appropriate and feasible, all donors be retested 6 months after donation and that a 6-month quarantine period be used.

For donors of *dura mater*, the proposed rule advocates an assessment and testing protocol that includes a full brain autopsy with examination of the dura mater by a qualified neuropathologist, testing for protease-resistant prion protein (investigational at present), donor medical history interview relevant to TSE risk, prevention of cross-contamination, and use of a chemical protocol to reduce infectivity according to previously published guidelines (Department of Health and Human Services, 1999). For *corneal tissue*, such testing for TSE would be desirable but is not feasible because of the need to transplant corneas within days of procurement. The AATB has no corresponding standard for TSE prevention (American Association of Tissue Banks, 2001a).

3.6. Exceptions

Under “Exceptions” (Proposal 1271.90) the proposed rule addresses situations where donor suitability determination would not be required and defines certain labelling requirements. Two situations are described where a determination of donor suitability would not be required: 1) in the case where autologous cells and tissues are removed and stored for later use in the same patient, and 2) in cases where reproductive cells or tissues are donated by a sexually active partner of the recipient.

The FDA still recommends testing and screening as a safety measure in these circumstances and, while not required, recommends that they be done as part of CGTP standards or as felt appropriate by the attending physician. The labelling requirements proposed are: 1) in exceptions from determination of donor suitability requirement, the label “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” is to be used, 2) if any screening or testing in the case of “exceptions” is performed and indicates the presence of a disease agent the product is to be labelled with the “BIOHAZARD” legend, and 3) autologous banked cells and tissues are to be labelled “FOR AUTOLOGOUS USE ONLY” to prevent inadvertent allogeneic administration.

3.7. Drug and device amendments

“Drug and Device Amendments” contains the proposal to amend existing regulations 210 and 211, with respect to human cellular and tissue-based products regulated as drugs and/or biological products, and regulation 820, with respect to human cellular and tissue-based products regulated as devices, to incorporate CGTP standards and comply with the donor suitability procedures now being proposed.

4. Impact of Proposed Suitability Determination Rule

The FDA has prepared an “Initial Regulatory Flexibility Analysis” to look at the economic impact of the proposed rule on the

substantial number of small entities that likely would be affected. These entities are providers of non-reproductive tissue (eye tissue, conventional tissue, stem cell) and reproductive tissue (ART facilities and sperm banks). The donor suitability cost analysis determined a total one-time cost of \$252 800 to \$1 264 000, a recurring cost of \$723 000 to \$1 340 000, and a total annualised cost of \$759 000 to \$1 520 000. The annualised cost per facility analysis showed a very small increase ranging from 0.004 to 0.6% of annual revenues and therefore not significant (Department of Health and Human Services, 1999).

The FDA argues that the proposed regulation would enhance both public health and public confidence in the safety and utility of transplanted cells and tissues, while imposing a minimum burden on the affected industry sectors. The FDA proposed rule is subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995. The estimated annual reporting burden has been reported by FDA to be a total of 263 007.5 hours and the estimated annual record-keeping burden to be 25 200.5 hours. The FDA believes to be in compliance with the Paperwork Reduction Act of 1995 as the additional requirements for collection of information are seen as minimal. The FDA judges that the proposed rule has no significant impact on the human environment and thus has neither performed an environmental assessment nor provided an environmental impact statement.

5. Current Good Tissue Practice — Proposed Rule

This proposal is presented under multiple sections containing “Standard Operating Procedures” (SOP) and “Record-Keeping” provisions, and a “Regulation” section (Department of Health and Human Services, 2001a). This latter section is the core of the proposed rule delineating the FDA’s concept of good tissue practice.

Subpart D of the “Regulations” deals with general rules of CGTP, exemptions and alternatives, establishment and maintenance of a quality programme, organisation and personnel, procedures,

facilities, environmental control and monitoring, equipment, supplies and reagents, process controls, process changes, process validation, labelling controls, storage, receipt and distribution, records, tracking and complaint file.

Subpart E of the regulations addresses additional requirements for establishments described in 1271.10 and regulated solely under section 361 of the PHS Act and the regulations under this proposed part. It addresses applicability, reporting, labelling and claims.

Subpart F of the regulations describes inspection and enforcement of establishments under 1271.10. It covers applicability, inspections, human cellular and tissue-based products offered for import, orders of retention, recall, destruction, and cessation of manufacturing.

6. AATB Position and Response

The AATB is the most prominent professional association of tissue bankers and transplant physicians and surgeons in the US. With the exception of ocular tissue, the AATB member banks provide most of the commonly used structural tissues for clinical use in the US. As an individual surgeon member of the AATB and as a practicing orthopedic oncology surgeon, the author has had a close contact with the AATB over many years. Consequently, it is with great interest that he has been following the evolution of the governmental regulatory programme spearheaded by the FDA. The existing high professional AATB standards have already been in place for many years and are reviewed and re-adjusted on an ongoing basis (Kaprisin and Woll, 2001). It is well established on a national and international level that the AATB standards are the key to the accreditation of tissue banks in the US and are guiding standards for the world. It is implicit therefore that "Donor Suitability Determination" and "Good Tissue Practice" rules have been advocated and required for accreditation of tissue banks by the AATB in the US for many years.

One might now ask if the new FDA proposals differ significantly from the existing professional/accreditation AATB standard. The

answer is no, the differences are small and frequently related to simple terminology. A complete comparison of FDA-proposed Donor Suitability Requirements and CGTP regulations with AATB Standards for Tissue Banking has been compiled and published by the AATB (American Association of Tissue Banks, 2001a).

This comparison shows that one can find an AATB standard already in place for most of the FDA-proposed suitability and good tissue practice regulations. While this makes it relatively easy for AATB professionals and tissue banks to satisfy eventual government law, it behooves them to be proactive in shaping the final rulemaking and stay vigilant to recognise and correct faulty concepts or wrong terminology.

Nevertheless, the reader is hoped to get a feeling on how proposed government regulations are shaped and molded by professionals who are going to be affected by the very same regulations within the framework of a democratic society.

7. Donor Suitability Issues

The AATB supports strongly mandatory screening and testing to prevent the transmission of communicable diseases. However, in response to the proposed "Suitability Determination Rule" by the FDA, the AATB has come forward critically with regard to the FDA's means for implementation, terminology related to criteria used to classify cell and tissue products, and jurisdictional determination (American Association of Tissue Banks, 1999, 2000). The AATB objects to the definition of "Donor Medical History Interview" (1271.3(o)) as including only face-to-face dialogues and argues that other forms of communication such as written or telephone exchanges must be included.

With regard to the identification of additional "Relevant Communicable Disease Agents or Disease Means" (1271.3(y)), the AATB has asked the FDA to explain the procedures it will use to identify such and asks the FDA to consult with and use the resources of the AATB. The requirement in the proposed rule that the donor blood test specimen be collected "At the Time of Recovery or within

48 Hours" (1271.80(b)) concerns the AATB because it would exclude pre-mortem samples. The AATB argues for permitting pre-mortem testing of cadaver donors because such donors are generally hospitalised and undergo comprehensive documentation. Thus, the exposure of such donors to disease agents is limited.

The FDA has already proposed to permit testing of living donors up to seven days prior to recovery while the potential exposure of such donors to disease is greater because they are not hospitalised. Post-mortem samples are often affected by haemolysis and haemodilution and this problem gives validity for drawing samples pre-mortem. The requirement by FDA that testing be performed "Using Only FDA Licensed, Cleared or Approved Products" (1271.80(c)) is too broad and the AATB asks that the FDA clarify in what circumstances tissue establishments can use tests that are not FDA-licensed. The AATB has also asked that not only laboratories certified under the "Clinical Laboratory Improvement Amendments of 1998" (CLIA), but also laboratories certified by "State Departments of Health and Human Services" and some "Foreign Laboratories" be permitted to test provided that their requirements are equivalent or more stringent than the FDA's requirements.

The AATB has also brought up the important point that clinical laboratories certified under CLIA should not require registration with the FDA, because the proposed rule provides already that such laboratories should be used. Facilities whose only role in tissue processing is "testing" are excluded from registration and listing requirements because they are under contract to a registered establishment (per FDA proposed rule). Facilities engaged in "screening" of prospective tissue donors should be deemed "establishments" requiring registration and listing because they are not necessarily governed by CLIA.

The AATB has raised specific objections to FDA's criteria and procedure for jurisdictional determinations related to two definitions contained in the "Suitability Determination" proposal: "minimal manipulation" and "homologous use". In addition, the AATB has the questioned FDA's criteria and procedure related to the "Tissue Reference Group" (TRG).

The definition by the FDA of “minimal manipulation” is processing that does not alter the tissue’s original relevant utility for reconstruction, repair or replacement (for structural tissue) or does not change the biological characteristics of cells or tissues. The definition by the FDA for “homologous use” is the use of cellular or tissue-based products for replacement or supplementation when used for the same basic function they perform in the donor and in a location where such function normally occurs (for structural tissue products) (Department of Health and Human Services, 1999).

The AATB has put forward the view that these definitions offer imperfect and uncertain guidance for determining which tissues should be regulated as devices or drugs. While these definitions are debated, the AATB has been invited to give input on the “classification of bone dowels as medical devices”. It has become evident that the TRG representing individual product sponsors has been trying to issue “recommendations” for regulation by the FDA affecting an entire class of tissue-based products. Since such action coming from the TRG could have broad effects on the tissue industry, the AATB has recommended that: 1) TRG Meetings be announced in the Federal Register, 2) TRG meetings be open to the public, and 3) TRG standard operating procedures should direct the Executive Secretary of the Group to publish the group’s findings and the basis for its decisions and that the standard operating procedures should require the Group to explain jurisdictional determinations (American Association of Tissue Banks, 1999).

The AATB finds the “minimal manipulation” definition of the FDA very problematic (American Association of Tissue Banks, 2000). As defined, this could lead to the widespread classification and regulation of many currently available bone grafts as medical devices and thus disqualification from less stringent regulation as Section 361 products. The proposed criterion of “minimal manipulation” is very difficult to apply in a consistent and unbiased manner and it could be the source of legal challenges. Bone is processed and machined to shape in a variety of ways in a wide range from deep frozen to freeze-dried to demineralised forms. Since there is no evidence that such processing presents risks to patients and there is no “approved” processing technology, it is

the view of the AATB that the imposition of regulatory controls by the definition of “minimal manipulation” is not warranted.

The AATB has come forward with specific and detailed criticism of the definition “homologous use” (American Association of Tissue Banks, 2000). The criteria of the definition are based on the misconception that holds that, if a tissue is transplanted for the same use and in the same anatomical site from which it was recovered, its use is more basic and less risky. This misperception ignores the standards of surgical practice and tissue banking. Surgeons select tissues for qualities and characteristics that often do not take into account the “original basic function” of the tissue or its “anatomical site” but rather have the qualities that are best to treat a specific problem in a patient. Bone grafts originate from a variety of donor sites and are used routinely by orthopaedic surgeons in hip replacement, trauma and oncology. Bone grafts intended for use in spinal fusions are very common applications of grafting in both orthopaedic surgery and neurosurgery.

In these cases, the “homologous use” criterion would disqualify the bone graft because it is used in a different location and for a different function (fusion by bone instead of maintaining the joint between the vertebrae which is normally filled with cartilage). A similar confusion occurs in the case of a fusion of any joint in the body. Based on these considerations, the AATB has proposed that bone implants be considered and recognised as “tissues” (regulated as Section 361 tissues) when used for the same basic characteristics (not functions) that they have inherently, regardless of the anatomic site from which they were recovered or the site in which they are implanted.

8. Good Tissue Practice Issues

The AATB has provided detailed comments on the FDA’s proposed rule establishing CGTP requirements and inspection/enforcement provisions (Department of Health and Human Services, 2001a). The response of the AATB (American Association of Tissue Banks, 2001b) is organised in three parts: 1) a background reaffirming the Association’s consistent support for balanced government

regulation aimed at insuring the safe and successful clinical use of human tissues provided for transplantation, 2) reservations concerning some of the proposed CGTP regulations either because (a) "they impose requirements on the tissue community that are disproportionate to the level of risk associated with conventional tissues (Section 361)" or (b) "they are based upon provisions of AATB standards that are not intended to be mandatory", 3) reservations concerning the lawfulness of some of the provisions of the proposed rule.

The AATB endorses those provisions of the FDA's proposed CGPT rule that are specifically and directly designed to address the risk of disease transmission to prospective recipients from infected tissues. Provisions of the proposed CGPT rule found burdensome and unnecessary are requirements "to validate all software changes by tissue banks", a requirement that FDA has not established for drugs or medical devices.

The authority FDA claims, in this regard, exceeds the agency's powers with respect to drugs and medical devices under the Food, Drug and Cosmetic (FD&C) Act. This very fact contradicts the FDA's own expressed intention to subject "361 products" to regulatory requirements that are more modest than those applicable to products regulated as drugs or devices under the FD&C Act.

The AATB has noted that some provisions of the proposed CGTP rule have been borrowed from the AATB Standards for Tissue Banking (American Association of Tissue Banks, 2001a). While using AATB standards eases compliance with final regulations, it is inappropriate for the FDA to convert all the AATB standards into binding legal regulations without considering carefully the extent to which these requirements are essential to protect public health.

The AATB has voiced comments on specific provisions of the FDA proposal related to CGTP. In the following analysis, the AATB position is summarised according to the order in which the relevant provisions appear in the FDA proposal:

- Section 1271.3: the definition of "distribution" should indicate that it does not include intra-company transfers of human cellular or tissue-based products.

- Section 1271.150(a): the CGTP requirements include “the function and integrity” of the products. The AATB wishes this part to be deleted because it is too ambiguous.
- Section 1271.150(b): it is implied that establishments that engage other facilities for a step in the manufacturing process should be “responsible” for compliance of the FDA requirements. The AATB wishes this wording to be changed to indicate that establishments “must have a system in place” designed to ensure that the work is performed in compliance with FDA rules.
- Section 1271.155: dealing with exemptions, the FDA wording is deemed by the AATB to be inconsistent. The AATB recommends that the FDA address oral requests for exemptions through oral replies and that such exemptions have an immediate effect without the need for “written confirmation”.
- Section 1271.160(a): the FDA requires that establishments maintain a “quality programme”. The AATB thinks that these “quality programmes” should be commensurate with the manufacturing steps performed and the types of tissues involved. The AATB requests that the FDA include in the final regulation language that distinguishes between “quality programmes” with particular reference to products regulated under Section 361 as opposed to Section 351 of the FD&C Act applicable to drugs and medical devices.
- Section 1271.160(d): discusses audits and FDA inspection. The AATB requests that FDA clarify that internal audits are not subject to FDA inspection and refer to the previous general policy of not allowing access of inspectors to company audit records for other categories of medical products.
- Section 1271.160(e): requires “validation of computer software” and “validation of software changes”. The AATB has serious concerns about the term “validation” because it is vague and it is not clear whether it corresponds to existing AATB standards. The AATB would like to see “validation” to be tailored to the type of processing used for a particular tissue. Thus, in current AATB standards, validation is required for shipping containers intended for tissues that must be maintained at other

- than ambient temperature, while the standards require only verification or confirmation for other aspects of tissue processing.
- Section 1271.180: states that “any deviation from a procedure shall be authorised in advance by a responsible person, recorded, and justified”. The AATB position on this issue is that deviation cannot always be authorised in advance because of unforeseen circumstances. Technical staff is trained to make decisions and document deviations. The AATB proposes that deviations be recorded at the time of occurrence and that the specific deviation be approved by a responsible person prior to the release of the tissues affected by the deviation.
 - Section 1271.190: deals with provisions that try to define standards for the construction and maintenance of facilities that manufacture human cellular and tissue-based products. The AATB finds these provisions too broad and recommends that the language be modified to specifically define requirements to prevent the transmission of communicable disease agents and to ensure orderly handling without mix-ups.
 - Section 1271.200(a): describes requirements for equipment and states that: “it should not have any adverse effects on the products”. The AATB wants the reference to “adverse effects” deleted because, absent a demonstration of effect on the risk of contamination with communicable disease agents, equipment selection and placement is not an appropriate focus of regulatory concern for tissues regulated under Section 361.
 - Section 1271.200(e): deals with requirements for records of maintenance for individual pieces of equipment and the need to have maintenance records available “at each piece of equipment”. The AATB finds these provisions extremely burdensome for the tissue community and unnecessary to protect public health. Items that are subject to control according to lot numbers and simple or disposable items should be exempt from record keeping requirement. Records should not have to be available “at” but rather “for” each of the pieces of equipment as there is no public health justification to keep records in close physical proximity to equipment.

- Section 1271.220: the FDA puts forward provisions for ensuring that human cellular or tissue-based products are not contaminated and “maintain their function and integrity”, furthermore that processing material be removed or limited to an amount that “does not adversely affect the product’s “function and integrity”. The AATB requests that references to “function and integrity” be deleted from this section and that instead the provisions should simply state that the products are not contaminated and will not transmit disease. The AATB also argues that tissue establishments should be allowed to determine whether residues elicit adverse reactions and label products regarding the presence of residues while procedures are in place for the removal of potentially toxic processing materials.
- Section 1271.220(d): deals with rules that prohibit pooling of cells or tissues from two or more donors. The AATB has proposed clarification to the term “pooling” which refers to commingling biological material from more than one donor in a single immediate container.
- Section 1271.230(a): states that in cases where the results of a process cannot be “fully” verified by subsequent inspection and tests, the process shall be validated and approved according to established procedures. The AATB requests the deletion of the term “fully” from this provision, as it is too broad and subject to inconsistent application. Once a process has been validated, and changes are required that do not increase the risk of disease transmission, a written justification should be sufficient.
- Section 1271.230(b): states: “a claim for sterility or viral inactivation shall be based on a validated process”. The AATB recommends that the FDA recognise that claims for sterility for bone and soft tissue grafts may be based on determination by verification, not validation, if validation is not feasible.
- Section 1271.230: deals with validation for reduction of transmission of TSE while preserving the clinical utility of grafts. The AATB disagrees with this provision because no safe levels of TSE are known presently and it would be inappropriate to imply that processing can produce safe tissue.

- Section 1271.260(b): deals with storage temperatures and durations stating that these must ensure “product function and integrity” to prevent “product deterioration”. The AATB has problems with the wording used by the FDA because concepts such as these are undefined and beyond the FDA’s legal authority to ensure prevention of transmission of communicable diseases.
- Section 1271.270(e): describes rules for the retention of records for 10 years. The AATB recommends simplification of the language of this provision and has put forward the proposal that tissue establishments that cease to exist use their best efforts to maintain records rather than being compelled to do so.
- Section 1271.290: describes “product tracking” and the assignment of “identification codes”. The AATB proposes to use the term “tracing” in the place of “tracking” to avoid confusion with medical device tracking regulation. The AATB would like the provisions of this section modified so that it recognises current practices of the industry and limitations that tissue establishments have in obtaining tracing information. The AATB requests that the FDA clarify that a single identification code may be used for an entire lot of structural tissue of the same type from the same donor even if distributed in more than one immediate container.
- Section 1271.320: deals with complaint procedures and their review, evaluation and documentation. The AATB requests that this section define that the complaint requirements apply only to tissues that are released for distribution. The AATB objects to the references to “tissue function and integrity” related to the definition of “complaint” in this section.
- Section 1271.420: describes provisions applicable to the importation of human cellular and tissue-based products and states that the importer must notify the director of the district of the FDA having jurisdiction over the port of entry through which the product is imported or his designate. The AATB has requested a small modification of the wording of this section to clarify that these requirements apply solely to tissues intended for “clinical use” and not to products intended for research.

In the preamble to the whole set of CGTP rules, the FDA requests “consultation from the States on preemption issues raised by the proposed CGTP rule”. The AATB wants that the FDA clearly state in the final rule that its provisions “preempt state tissue regulations”.

The AATB indicates clearly that some of the labelling provisions of the CGTP proposal exceed FDA’s statutory authority because their relationship to the prevention of disease transmission is too attenuated. The provisions that aim to assure “function and integrity” are, according to the AATB, beyond the agency’s authority under Section 361(a) of the PHS Act. Furthermore, the AATB alleges that certain of the proposed investigative and enforcement provisions of the FDA are invalid either because they cannot be justified by the disease transmission purpose of Section 361(a), or because they represent unlawful attempts to claim powers that Congress has only selectively conferred on the FDA in the FD&C Act.

Section 361 of the PHS Act is a 1944 re-codification of two quarantine laws passed in 1890 and 1893, respectively. The first law passed in 1890 authorised the President to direct the Secretary of the Treasury to effectuate rulemaking to prevent the spread of four specified infectious diseases (cholera, yellow fever, smallpox or plague), once introduced into the US. The second law passed in 1893 enabled the Secretary of Treasury to make rules and regulations that are necessary to prevent the introduction of the four specified diseases into the US.

Congress enacted the PHS Act in 1944 because of increasing air travel and the nation’s involvement in World War II. This legislation reorganised and codified several scattered laws dealing with public health, including the 1890 and 1893 laws. The legislative history of the 1944 PHS Act, according to the AATB, demonstrates that the intention of Section 361(a) is to authorize federal action in the context of quarantine measures and their enforcement.

Congress enacted the precursor to the modern FD&C Act in 1906 giving the federal government limited enforcement powers with respect to food and drug articles. Thereafter, when Congress

intended for the federal government to exercise greater authority to enforce laws related to safety, efficacy or labelling of food or therapeutic products, it conferred new authority specifically and narrowly without giving the federal government omnibus authority.

However, another provision in the 1944 statute, Section 351, empowers the federal government specifically to exercise authority to enforce the labelling and packaging of biological products. Section 361 contains no such directive and therefore, the AATB postulates that Congress did not intend for Section 361 to empower the federal government to impose product-labelling requirements (American Association of Tissue Banks, 2001b).

The FDA purports to rely on Section 361(a) of the PHS Act to support the enforcement provisions of the proposed CGTP rule. Since that statute was enacted before the FDA existed, several of the authorities claimed by the FDA in the CGTP proposal have no counterpart in the FDA's enabling statute, the FD&C Act. The AATB argues that Congress has been selective and often reluctant in granting the FDA investigative and enforcement authorities. Therefore, the interpretation of Section 361(a) as permitting the FDA to assert powers of investigation and enforcement, according to the AATB, is faulty and not compatible with the general strategy of Congress to grant such powers only for specific categories of products in specific circumstances.

The proposed CGTP rule would give the FDA unlimited authority to examine records with the use of photographs and videotapes. The AATB argues that historically, the FDA's efforts toward obtaining inspection authority over the years have been repeatedly curtailed by Congress. Thus, efforts by FDA to assert authority to inspect shipping records in the 1940s was rebuffed by the 1952 Cardiff decision of the Supreme Court (US Supreme Court, 1952).

Initially, trials by the FDA to win inspection authority under the FD&C Act failed in 1961 but eventually in 1962 legislation was enacted which gave the FDA explicit authority to inspect manufacturing facilities for prescription drugs but not for over-the-counter (OTC) drugs or other products regulated under the FD&C

Act (US Congress, 1962a). Similarly, initial efforts by the FDA to obtain inspection authority for medical devices were initially rejected by Congress in 1974 and 1975 (US Congress, 1974, 1977).

Eventually, in 1976 Congress enacted the Medical Device Amendment legislation, which gave the FDA some very limited inspection authority for restricted medical devices, specifically denying power to inspect financial, sales, pricing, personnel or research data (US Congress, 1976a,b). Over the last decade, during the Bush and later the Clinton administrations, the FDA tried but did not succeed in winning additional investigative and enforcement authority. The AATB believes, based upon knowledge of congressional intent over the years, that the FDA's request for broad, unrestricted authority via Section 361(a) of the PHS Act is unjustified and must only be considered if directly related to the disease prevention goal of Section 361(a).

The proposed CGTP rule also includes provisions related to submit "adverse reaction" and "product deviation" reports. Specifically, these reports are not limited to the "transmission of communicable diseases" but also include "product contamination" and "product function and integrity".

Historically, Congress has given the FDA mandatory reporting authority only in respect to certain products and always carefully tailored in form of amendments to the FD&C Act. Under the Drug Amendments of 1962, drug manufacturers were required to report data "relating to clinical experience" and data "otherwise obtained", a response to the thalidomide scare (US Congress, 1962b). The Safe Medical Devices Act of 1990 provided for the reporting of most serious adverse events regarding medical devices, a response to the fatal strut fractures in the replacement heart valves manufactured by Shiley in the late 1980s (US Senate, 1990). The AATB argues that it is inappropriate and illegitimate for the FDA to require tissue establishments to submit reports concerning all adverse reactions and product deviations. The reporting requirements must be linked to the disease prevention goal of Section 361(a) and not to issues of "product deviation" or "function and integrity".

The CGTP proposal in section 1271.440 would give the FDA officials authority to issue administrative orders requiring tissue

establishments to cease their operations when found non-compliant with the rules. Although a provision is made for the facilities to be able to request a hearing within 5 days after issuance of the order, there is no provision for opportunities for a challenge of the question of lacking compliance, and the order is of potentially infinite duration. In the view of the AATB, this administrative injunction provision is unconstitutional because it does not meet the most minimal standards of Due Process. AATB members have a constitutional right to practice their occupation and the deprivation of this right without giving the opportunity to present the case that the government action is unwarranted constitutes, in the view of the AATB, violation of the Due Process Clause (US Supreme Court, 1973). The AATB foresees a need for a legal challenge of this provision if the FDA does not change it.

The AATB has put forward a proposal for a co-operative mechanism whereby the FDA could use existing resources of professional accrediting organisations such as the AATB for the co-ordination of inspection activities. This is in line with a recommendation by the Office of the Inspector General at the Department of Health and Human Services. The co-operation would include the joint training of inspectors, recognition of AATB accreditation as fulfillment of CGTP requirements, extension of inspection cycles for accredited tissue banks and other joint resources aimed at saving time and expense for the FDA (American Association of Tissue Banks, 2001b).

The AATB argues against the proposed 180 days implementation requirement post publication of the final rule and is in favor of a phased implementation over 1 year to ensure an orderly transition.

10. Conclusion

The continuing dialog between the government represented by the FDA and the professionals of cell and tissue banking represented by the AATB is a great source of information reflecting directly the state-of-the-art of current knowledge in the field of cell and tissue banking. The analysis of the evolving regulatory programme

proposal of cell and tissue banking by the FDA, as it is continually molded and shaped by critical input by the AATB, allows one to understand the complexity of problems associated with the science and clinical practice of cell and tissue banking. This very analysis is also the natural history and evolution of a much needed government regulation of cell and tissue banking in the US. The purpose of such regulation at this particular point in time is to assure the continuing safety of recipients of cells and tissue-based products against the transmission of communicable diseases.

While the FDA is working to implement this rulemaking under Section 361(a) of the PHS Act, it has proposed criteria such as "homologous use" and "minimal manipulation", and provisions such as "product function and integrity", that are not related or aimed at disease transmission risk and therefore beyond the authority granted to FDA under Section 361(a) by its statutory provision. Continuing critical interchange between government and professional associations will shape the future regulation towards implementation to achieve the ultimate safety goal to the advantage of our patients.

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