# American Association of Tissue Banks

***The leader in support of quality, safety and availability of cells and tissue***

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

The American Association of Tissue Banks (AATB) welcomes the opportunity to provide comments on FDA's proposed rule establishing current good tissue practice (CGTP) requirements and inspection/enforcement provisions for human cellular and tissue-based products, published in the Federal Register on January 8, 2001.[1]

## I. Background

AATB was formed in 1976 to support the development of tissue banking in the United States. By educating its members and developing standards, and through other means, AATB works to help ensure that human tissues intended for transplantation are safe and free of infectious disease, of uniform high quality, and supplied in quantities sufficient to meet national needs. The Association's membership currently includes about 1,200 individual professionals and 69 accredited U.S. tissue banks engaged in the recovery, processing, storage, and distribution of human tissue. Most of the major tissue banks in the U.S., including all of AATB's member banks, have obtained AATB accreditation. With the exception of ocular tissue, AATB members provide most of the commonly used structural tissues for clinical use in the United States.

[1] 66 Fed. Reg. 1,507.

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AATB has consistently supported balanced government regulation aimed at assuring the safe and successful clinical use of all human tissues provided for transplantation in the United States. In 1993, AATB publicly supported FDA's establishment of interim disease transmission requirements for human tissues.[2]

Since the interim requirements were promulgated in final form in 1997,[3] FDA has issued three proposed rules applicable to tissue banks. In May 1998, FDA proposed regulations requiring tissue establishments to register and list their products with FDA.[4] In September 1999, FDA published a proposed rule governing suitability determinations for prospective tissue donors.[5] FDA has now proposed to establish comprehensive CGTP requirements, and to subject tissue establishments to new inspection and enforcement requirements.

AATB endorses those provisions of FDA's proposed CGTP rule that are specifically and directly designed to address the risk of disease transmission to prospective recipients directly from infected tissues. As discussed in greater detail in Part II of these comments, however, AATB has reservations about some of the provisions of FDA's proposed rule, either because: (a) they impose requirements on the tissue community that are disproportionate to the level of risk associated with conventional tissues (Section 361), as recognized by FDA's own risk-based scheme for regulating tissue-based products (i.e., FDA's "Proposed Approach to Regulation of Cellular and Tissue-Based Products," February 28, 1997); or (b) they are based upon provisions of AATB's own standards that are not intended to be mandatory.

AATB also has serious reservations about the lawfulness of some provisions of the proposed rule. As discussed in Part III, the cited statutory basis for the proposed rule, Section 361(a) of the Public Health Service Act (PHS Act), only authorizes regulations that are specifically designed to prevent the spread of communicable diseases from contaminated persons, animals, or articles. Some provisions of the CGTP proposal are not sufficiently linked to this objective to be legally supportable and, therefore, exceed FDA's authority under this provision. In addition, the provision of the proposed rule that purports to authorize FDA officials to issue ex parte administrative orders requiring tissue establishments to cease their operations, violates the Due Process Clause of the Fifth Amendment to the United States Constitution. (See Part IV.)

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2 58 Fed. Reg. 65,514 (1993).

3 62 Fed. Reg. 40,429.

4 63 Fed. Reg. 26,744. The final rule was published in the Federal Register earlier this year. 66 Fed. Reg. 5,447 (2001).

5 64 Fed. Reg. 52,696.

AATB is submitting these comments as part of its continuing effort to assist FDA in devising an effective but reasoned program of government regulation for the tissues.

## II. Some Provisions of the Proposed CGTP Rule Are Unnecessary or Unduly Burdensome

As noted above, some of the provisions of the proposed CGTP rule impose burdens on the tissue community that are unwarranted and unnecessary. For example, AATB believes FDA should not require tissue banks to validate all software changes. Validation is unnecessary for relatively minor changes to software that have no potential adverse effect on tissues. An unyielding validation requirement might actually drive tissue banks to retain manual record keeping systems, reducing their ability to access data quickly in emergency situations.

Many provisions of the proposed rule would establish for conventional tissues regulatory requirements that are similar to, or in some cases even more stringent than, the requirements applicable to drugs and medical devices under the FD&C Act. For example, proposed section 1271.160(e) purports to require tissue establishments to validate all software -- a requirement that FDA has not established for drugs or medical devices. As discussed in greater detail below, the authority FDA claims in the proposed investigative and enforcement provisions also significantly exceeds the agency's powers with respect to drugs and medical devices under the FD&C Act. This conflicts with FDA's own expressed intention to subject conventional tissue that are subject to regulation exclusively under Section 361(a) to regulatory requirements that are more modest than those applicable to products regulated as drugs or devices under the FD&C Act.[6]

Some provisions of the proposed CGTP rule appear to have been borrowed from AATB's own Standards for Tissue Banking.[7] Verbal consistency with

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[6] In the "Proposed Approach" document, FDA mentioned Section 361 of the PHS Act but never signaled its intention to advance the broad interpretation of that provision that FDA claims provides the basis for the proposed CGTP rule. FDA said only that it "would have authority to inspect facilities . . ., and to take actions to prevent transmission of communicable disease (e.g., orders of retention, recall, and destruction . . .)." Proposed Approach at 14. FDA also did not disclose its intention to impose reporting requirements that are as broad and burdensome as the reporting obligations outlined in the proposed CGTP rule. Id. See also 66 Fed. Reg. at 1,510 ("Products that the agency is proposing to regulate solely under section 361 of the PHS Act and proposed part 1271, would be subject to less rigorous agency oversight than products also regulated under the [FD&C] act and/or section 351 of the PHS Act.").

[7] 66 Fed. Reg. at 1,511.

AATB standards may help reduce the practical difficulties of complying with the final regulations. It is inappropriate, however, for FDA to convert all of the AATB standards into binding legal regulations without considering carefully the extent to which these requirements are essential to protect public health, consistent with the risk-based approach, and adequately supported by the statutory provision on which the agency purports to rely.

FDA is a government agency with significant enforcement authority. The consequences of a tissue bank's failure to comply with an AATB standard differ significantly from the consequences of violating a FDA regulation. If, as the proposed rule contemplates, FDA inspectors are to have significant discretion to select from among a wide range of enforcement options, including, according to the proposal, the option of ordering a tissue establishment to cease operations, it is critically important that AATB standards are imported into FDA regulations only to the extent necessary to meet public health goals and only to the extent permitted by FDA's statutory mandate.

The following comments address the operational issues presented by specific provisions of FDA's proposal. For convenience, the comments are presented in the order the relevant provisions appear in FDA's proposal.

## A. Proposed Section 1271.3

*Provision*. Subsection (jj) of proposed section 1271.3 states:

> Distribution means any conveyance or shipment of human cellular or tissue-based products (including importation and exportation), whether or not such conveyance or shipment is entirely intrastate and whether or not possession of the product is taken.

*Recommendation*. AATB requests that FDA clarify that intracompany transfers of human cellular or tissue-based products are not included within the definition of "distribution" in the proposed CGTP rule. This is consistent with FDA's policy with respect to other medical products.[8]

## B. Proposed Section 1271.150(a)

*Provision*. Subsection (a) of proposed section 1271.150 states (in relevant part):

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[8] See, e.g., 21 C.F.R. § 807.3(b)(1).

> The CGTP requirements are intended to prevent the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by helping to ensure that the products do not contain communicable disease agents; that the products do not become contaminated during manufacturing; and that the function and integrity of the products are not impaired through improper manufacturing.

*Recommendation*. FDA should delete the "function and integrity" language from this proposed provision. The proposed rule contains no definition of "function and integrity," and the words themselves are too ambiguous to provide the tissue community or FDA inspectors with meaningful guidance. Moreover, to the extent that other provisions of the proposed rule establish more specific requirements, it is unnecessary to include language in this general, descriptive provision that could be misinterpreted as imposing an independent obligation on tissue establishments.

## C. Proposed Section 1271.150(b)

*Provision*. Subsection (b) of proposed section 1271.150 states (in relevant part):

> . . . [A]n establishment that engages another establishment under a contract, agreement, or other arrangement, to perform any step in the manufacturing process, is responsible for ensuring that the work is performed in compliance with the requirements in this subpart and subpart C of this part.

*Recommendation*. It is unreasonable to hold an establishment responsible for the actions of another entity, itself subject to FDA regulation, engaged by contract to perform some aspects of manufacturing. AATB requests that FDA replace the underscored language with the following: "must have a system in place designed to ensure that the work is performed in compliance with the requirements in this subpart and subpart C of this part."

## D. Proposed Section 1271.155

*Provision*. Proposed section 1271.155 states (in relevant part):

> (d) Form of request. A request for an exemption or alternative shall ordinarily be made in writing or electronically. However, in limited circumstances such a request may be made orally, and an exemption or alternative may be granted orally by the Director. An oral

> request and approval shall be followed by an immediate written request and written acknowledgement of approval.
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> (e) Operation under exemption or alternative. An establishment shall not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted in writing. An establishment may apply for an extension of an exemption or alternative beyond its expiration date, if any.

*Recommendation*. Proposed subsections (d) and (e) are internally inconsistent. A request for an exemption made electronically or in writing is deemed effective when granted in writing. If the exemption or alternative is granted orally, however, an establishment cannot begin operating under the terms of the exemption until the exemption or alternative has been acknowledged in writing.

AATB recommends that FDA revise this proposed provision to clarify that oral requests should initially be addressed by FDA through oral replies, and that oral exemptions and alternatives have immediate effect without the need for subsequent written confirmation.

## E. Proposed Section 1271.160(a)

*Provision*. Subsection (a) of proposed section 1271.160 states (in relevant part):

> An establishment that performs any step in the manufacture of human cellular and tissue-based products shall establish and maintain a quality program that is appropriate for the specific human cellular and tissue-based products manufactured and the manufacturing steps performed and that meets the requirements of this subpart.

*Recommendation*. AATB agrees that an establishment performing any manufacturing activities for products should have a quality program and that the scope and depth of the quality program should be commensurate with the manufacturing steps performed and the types of tissues involved. AATB also endorses the statements in the preamble accompanying the proposed rule indicating FDA's intention to permit variations among tissue establishments' quality programs and to impose a lower level of regulatory supervision on tissue products subject to regulation under Section 361 than the agency has established for tissue products that are regulated under the Federal Food, Drug, and Cosmetic Act or under Section 351.[9] This is consistent with FDA's expressed intention to subject conventional tissues to more modest regulation than

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[9] 66 Fed. Reg. at 1,510.

other therapeutic products, reflecting the relative levels of risk associated with these categories of articles.

Consistent with these statements, AATB requests that FDA include in the final regulations language that distinguishes between "quality programs" as described in the proposed rule and other quality requirements. This will assure that tissue establishments are not held to unsuitable quality requirements.

## F. Proposed Section 1271.160(d)

*Provision*. Subsection (d) of proposed section 1271.160 states (in relevant part):

> All audits shall be conducted in accordance with procedures to assure that the quality program is operating effectively and to identify trends or recurring problems . . .
>
> .
>
> A documented report of the results of the audits and reaudits, where taken, shall be retained.

*Recommendation*. AATB requests that FDA clarify that records of internal audits are not subject to FDA inspection. FDA has generally agreed that inspectors do not have access to company audit records for other categories of medical products.[10] Without this assurance, the audit process will be significantly undermined.

## G. Proposed Section 1271.160(e)

*Provision*. Subsection (e) of proposed section 1271.160 states:

> If computers or automated data processing systems are used as part of the quality program, as part of manufacture or tracking, or for maintaining data or records related to the manufacture or tracking of human cellular or tissue-based products, the establishment shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.

*Recommendation*. AATB requests that this provision be modified to limit the scope of the requirement for software validation. Regulatory requirements for software validation should be tempered by an analysis of potential impact. Rather

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[10] E.g., CPG § 130.300 (CPG 7151.02) (revised Jan. 3, 1996).

than requiring that all software and software changes be validated, FDA should limit validation requirements to the most necessary areas in order to encourage the use of software programs in lieu of manual systems in record keeping. Reliance on manual systems in the quality program of tissue banks could result in a loss of system integrity and an inability to respond quickly in a recall situation.

AATB suggests the following language:

> All software and changes in software that controls tissue tracking information, is the sole source for any information necessary for donor suitability determinations, is the sole source for information used to release products for clinical use, or functions as an expert system in any phase of manufacture shall be validated.

AATB has serious concerns about FDA's use of the term "validation" throughout the proposed rule.[11] The proposed definition of "validation" provides only vague guidance to the tissue community with respect to the nature of the validation requirements in each of the provisions of the proposed rule in which it is used.

It is unclear whether FDA has substituted the concept of "validation" for other words used in analogous provisions of AATB's own standards. AATB's standards require a level of review that is tailored to the type of processing used for a particular tissue. Thus, for example, while validation is required for shipping containers intended for use in enclosing tissues that must be maintained at other than ambient temperature, AATB's standards require only verification or confirmation for other aspects of tissue processing.

AATB requests that FDA clarify that tissue establishments that comply with these provisions of AATB's standards will be deemed to comply with the validation requirements of the proposed rule.

## H. Proposed Section 1271.180

*Provision*. Proposed section 1271.180 states (in relevant part):

> Any deviation from a procedure shall be authorized in advance by a responsible person, recorded, and justified.

*Recommendation*. Deviations cannot always be authorized in advance, as they are often the result of unforeseen circumstances. Technical staff in the field at a procurement or even during processing may need to deviate from the specifics of a

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[11] E.g., proposed sections 1271.160(e), 1271.210(b), 1271.255(a), 1271.230, 1271.265.

procedure in unusual circumstances. These personnel are trained to make such decisions and document any deviations thoroughly. Authorization by a "responsible person" prior to the deviation may not be possible, and unyielding application of a prior approval requirement could result in an inability to release a tissue.

AATB requests that the proposed language be modified as follows:

> Any deviation from a procedure, together with the justification for the deviation, shall be recorded at the time of occurrence. The deviation shall be approved by a responsible person prior to release of the tissue or tissues affected by the deviation.

## I. Proposed Section 1271.190

*Provision*. Proposed section 1271.190 states (in relevant part):

> Any facility used in the manufacture of human cellular or tissue-based products shall be of suitable size, construction, and location to facilitate cleaning, relevant maintenance, and proper operations. The facility shall be maintained in a good state of repair. Adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities shall be provided . . ..
>
> Any facility used in the manufacture of human cellular and tissue-based products shall be maintained in a clean, sanitary, and orderly manner . . ..
>
> All significant cleaning and sanitation activities shall be documented, and records shall be maintained.

*Recommendation*. These provisions are too broad and open to inconsistent application. The requirements for facility design and size should be tailored to the processing steps being performed and to the risk of contamination.

AATB requests that this provision be modified to include language that relates the substantive requirements to preventing the transmission of communicable diseases from contaminated tissues to recipients. For example, the provision could state: "Facilities shall be of suitable design and sufficient size to perform necessary operations, prevent contamination with communicable disease agents, and ensure orderly handling without mix-ups."

## J. Proposed Section 1271.200(a)

*Provision*. Proposed section 1271.200(a) states (in relevant part):

> Equipment used in the manufacture of human cellular and tissue-based products shall be of appropriate design for its use, shall be suitably located and installed to facilitate operations, including cleaning and maintenance, and shall not have any adverse effect on the products.

*Recommendation*. The reference to "adverse effect" should be deleted from this provision. The phrase is undefined and ambiguous. To the extent FDA intends it to refer to the function and integrity of a tissue, it exceeds FDA's authority under Section 361 (as discussed in greater detail in Part III). 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 solely under Section 361.

## K. Proposed Section 1271.200(e)

*Provision*. Proposed section 1271.200(e) states (in relevant part):

> All maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with this section shall be documented and maintained. Records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be available at each piece of equipment. Records of the use of each piece of equipment, which shall include the identification of each human cellular or tissue-based product manufactured with that equipment, shall be maintained.

*Recommendation*. This provision is extremely burdensome to the tissue community and unnecessary to protect the public health. AATB requests that FDA clarify that the requirement to maintain records does not apply to simple items and manual surgical tools that can be washed and disinfected, or are disposable (e.g., vessels, stirring rods, scalpels). AATB requests further that FDA confirm that items that are subject to control according to lot number are exempt from the record keeping requirement, and that if an establishment has instituted a validated cleaning and disinfection process, equipment covered by the validated process is not subject to the record keeping requirement.

AATB also requests that FDA change "shall be available at each piece of equipment" to "shall be available for each piece of equipment." There is no public health justification for requiring tissue establishments to keep records in close physical proximity to equipment, and imposing such a requirement could necessitate burdensome facility modifications.

## L. Proposed Section 1271.220

*Provision*. Proposed section 1271.220 states (in relevant part):

> (a) General. Each establishment engaged in the processing of human cellular or tissue-based products shall develop, conduct, control, and monitor its manufacturing processes to ensure that each human cellular or tissue-based product conforms to specifications, is not contaminated, maintains its function and integrity, and is manufactured so as to prevent transmission of communicable disease by the product.
>
> (b) Processing material. Where a processing material could reasonably be expected to have an adverse effect on a human cellular or tissue-based product's function or integrity, the establishment shall establish and maintain procedures for the use and removal of such processing material to ensure that it is removed or limited to an amount that does not adversely affect the product's function or integrity. The removal or reduction of such processing material shall be documented.

*Recommendation*. AATB requests that the references to "function and integrity" be deleted from proposed section 1271.220. As noted above, this phrase is undefined, ambiguous, and inconsistent with FDA's risk-based approach to regulating conventional tissues. Also, a manufacturer may conclude that it is necessary to impair a tissue in some manner in order to decontaminate it. We recommend this provision be revised as follows: "each human cellular or tissue-based product is not contaminated and will not transmit communicable disease to the recipient."

AATB also requests changes to subsection (b). A tissue establishment should be allowed to determine, based on the use of published scientific data and established industry practice, whether a processing material or its residues may elicit an adverse reaction. Subsection (b) should also recognize that product labeling may be used to warn potential users with respect to the possible presence of residues. AATB requests the following language: "The establishment shall establish and maintain procedures for the use and removal of potentially toxic processing materials to assure that any residue is removed or limited to a non-toxic concentration."

## M. Proposed Section 1271.220(d)

*Provision*. Proposed section 1271.220(d) states (in relevant part):

> Human cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

*Recommendation*. AATB requests that the agency modify this provision to clarify that "pooling" refers to commingling biological material from more than one donor in a single immediate container. For example, the language could be revised as follows: "Human cells or tissue from two or more donors shall not be pooled (placed in direct physical contact, mixed or processed in a single container or receptacle) during manufacturing."

## N. Proposed Section 1271.230(a)

*Provision*. Proposed section 1271.230(a) states (in relevant part):

> 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 validation activities and results, including the date and signature of the individual(s) approving the validation, shall be documented.

*Recommendation*. AATB recommends deleting the word "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 communicable disease transmission to the recipient, a written justification for not revalidating should be sufficient. FDA has previously agreed in similar situations that validation is not always necessary.[12]

## O. Proposed Section 1271.230(b)

*Provision*. Proposed section 1271.230(b) states (in relevant part):

> Any process-related claim in labeling or promotional materials for a human cellular or tissue-based product, e.g., a claim for sterility or viral inactivation, shall be based on a validated process.

*Recommendation*. Sterility for some allografts, such as bone and soft tissue musculoskeletal grafts, is often determined by verification, not validation. The reasons for this practice are technical (i.e., the potentially destructive impact of some sterilization technologies on certain tissues). FDA should acknowledge this and allow

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[12] 61 Fed. Reg. 52,622, 52,628 (1996).

for sterility verification when technology limitations exist, and established manufacturing procedures have not led to clinical problems.

We propose that FDA modify the proposed language and add clarifying language so that this section will read as follows: "Any process-related claim in labeling or promotional materials for a human cellular or tissue-based product, e.g., a claim for sterility or viral inactivation, shall be based on a validated process, except that claims for product sterility may be based on a verified process if validation is not feasible."

**P. Proposed Section 1271.230(c)**

*Provision*. Proposed section 1271.230(c) states:

> Dura mater shall be processed using a validated procedure that reduces transmissible spongiform encephalopathy, while preserving the clinical utility of the product.

*Recommendation*. This proposed provision should be eliminated from the final rule. No safe level of TSE is known, meaning that it is inappropriate as a matter of public health for FDA to endorse, even implicitly, the practice of treating potentially infected material to reduce, but not eliminate, TSE. Rather than imply that the processing or testing of dura mater can produce a safe tissue, we recommend that FDA not endorse the concept of an acceptable level of TSE risk given the current state of scientific opinion on this issue.

**Q. Proposed Section 1271.260(b)**

*Provision*. Proposed section 1271.260(b) states:

> (1) Each establishment shall store human cellular and tissue-based products at an appropriate temperature and for no longer than the maximum storage period for the product.
>
> (2) Acceptable temperature limits for storage of human cellular and tissue-based products at each step of the manufacturing process shall be established to ensure product function and integrity, to prevent product deterioration, and to inhibit the growth of infectious agents.

*Recommendation*. AATB requests that FDA clarify that these provisions do not require tissue establishments to validate storage temperatures or storage periods. The tissue industry has established ranges of storage periods and temperatures for particular products based on experience.

In subsection (b)(2), AATB recommends the following modification of the proposed language: "Acceptable temperature limits for storage of human cellular and tissue-based products at each step of the manufacturing process shall be established to prevent the transmission of communicable disease to prospective recipients of the products." As stated above and discussed further in Part III of these comments, AATB objects to FDA's use of the phrase "product function and integrity" because these concepts are undefined and beyond FDA's legal authority. Also, AATB objects to the introduction of a new and heretofore undefined term, "deterioration," which AATB believes would introduce unnecessary complexity to the regulation of Section 361 products.

**R. Proposed Section 1271.270(e)**

*Provision*. Proposed section 1271.270(e) states:

> All records shall be retained 10 years after their creation. However, records pertaining to a particular human cellular or tissue-based product shall be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product, or if the date of implantation, transplantation, infusion, or transfer is not known, then records shall be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest. Records for archived specimens of dura mater shall be retained 10 years after the appropriate disposition of the specimens. The establishment shall make provisions for all records to be maintained for the required period in the event that the establishment ceases operation.

*Recommendation*. FDA's proposed language is unnecessarily complex and would lead to confusion in the tissue community. Tissue establishments cannot force clinicians to discard expired products or to provide notification with respect to the date of use. Also, it is not practical to try to compel a tissue establishment that has ceased to operate to expend resources on the maintenance of records; in AATB's view, it is adequate to require that they use their best efforts to maintain records.

AATB recommends that proposed subsection (e) be modified as follows:

> All records shall be retained for a minimum of 10 years after their creation. However, records pertaining to a particular cellular or tissue-based product shall be maintained for a minimum of 10 years after the product's expiration date. Records for archived specimens of dura

mater shall be retained 10 years after the appropriate disposition of the specimens. The establishment shall use best efforts for all records to be maintained for the required period in the event that the establishment ceases operation.

**S. Proposed Section 1271.290**

*Provision*. Proposed section 1271.290 states (in relevant part):

(b) Method of product tracking. (1) Each establishment shall establish and maintain a method of product tracking that enables the tracking of all human cellular and tissue-based products from:

(i) The donor to the recipient or final disposition; and

(ii) The recipient or final disposition to the donor.

(2) Alternatively, an establishment that performs some but not all of the steps in the manufacture of a human cellular or tissue-based product may participate in a method of product tracking that has been established and is maintained by another establishment responsible for other steps in the manufacture of the same product, provided that the tracking method complies with all the requirements of this section."

(c) Distinct identification code. As part of its tracking method, an establishment shall ensure that each human cellular and tissue-based product that it manufactures is assigned and labeled with a distinct identification code, e.g., alphanumeric, that relates the product to the donor and to all records pertaining to the product. Except in the case of autologous or directed donations, such a code must be created specifically for tracking and may not include an individual's name, social security or medical record number. An establishment may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process, or may assign a new code. An establishment that assigns a new code to a product shall establish and maintain

> procedures for relating the new code to the old code.

*Recommendation*. AATB strongly believes that proposed section 1271.290(b) should be modified to recognize the current practices of the industry and limitations that tissue establishments have in obtaining tracking information, especially if the establishments operate in a wide geographic area. AATB further believes that references to "tracking" in this proposed section should be changed to "tracing" to avoid confusion with medical device tracking regulations.

Tissue establishments should be required to establish and maintain methods of tracing tissues released by the establishment. The tracing requirement should extend to the donor and to the individual who orders and/or receives the tissue for clinical use.

AATB also requests that FDA clarify that a single identification code may be used for an entire lot of morselized structural tissue of the same type from the same donor, consistent with current practice, even if the lot is distributed in more than one immediate container.

## T. Proposed Section 1271.320

*Provision*. Proposed section 1271.320 states:

> Each establishment shall establish and maintain procedures for the prompt review, evaluation, and documentation of all complaints, as defined in § 1271.3(ii), and the investigation of complaints as appropriate.

*Recommendation*. AATB requests that proposed section 1271.320(a) be modified to include language recognizing that the complaint requirement applies only to tissues that have already been released for distribution. Further, AATB believes that the definition of "complaint" in proposed section 1271.3(ii) should be modified by deleting the reference to tissue function or integrity. As noted elsewhere in these comments, AATB believes that these terms are inappropriate and exceed FDA's statutory authority. Subsection (3) of the proposed definition of "complaint" should also be deleted.

## U. Proposed Section 1271.420

*Provision*. Proposed section 1271.420 states:

> (a) When a human cellular or tissue-based product is offered for entry, the importer of record shall notify the director of the district of the Food and Drug

> Administration (FDA) having jurisdiction over the port of entry through which the product is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part.
>
> (b) A human cellular or tissue-based product offered for import shall be held intact, under conditions necessary to maintain product function and integrity and prevent transmission of communicable disease, until it is released by FDA.

*Recommendation*. AATB requests that proposed subsection (a) be modified to provide:

> When a human cellular or tissue-based product intended for clinical use is offered for entry, the importer of record shall notify the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the product is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part.

AATB believes that the CGTP proposed regulations apply solely to tissues intended for human use, and that tissues and products intended solely for research uses should be exempt from these requirements.

### V. Preamble

*Provision*. In the preamble, FDA requests "consultation from the States on any preemption issues raised by the proposed CGTP rule . . . ."[13]

*Recommendation*. AATB requests that FDA clearly state in the final rule that its provisions preempt state tissue regulations.

## III. Some Provisions of the CGTP Proposal Exceed FDA's Statutory Authority

Some of the labeling provisions of the proposed rule (e.g., proposed section 1271.370(b))[14] exceed FDA's statutory authority because their relationship to

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13 66 Fed. Reg. at 1,508.

14 As noted above, by citing this particular proposed provision, AATB does not intend to concede that the other labeling provisions of the proposal are within FDA's statutory authority. While AATB does not necessarily disagree with labeling (continued...)

the prevention of disease transmission from tissue is too attenuated. The provisions that are aimed at reducing the indirect risk of disease transmission from repeated surgical procedures through assuring tissue "function and integrity" are also beyond the agency's authority under Section 361(a).[15] Secondly, certain of the proposed investigative and enforcement provisions are invalid, either because they cannot reasonably be linked to the disease transmission purpose of Section 361(a) or because they represent unlawful attempts to claim powers that Congress has, in the FD&C Act, only selectively conferred on FDA and then only after careful consideration.

### A. Section 361(a) Only Authorizes Regulations That Are Aimed at Preventing Disease Transmission Directly From Contaminated Articles

As its legislative history demonstrates, Section 361(a) authorizes regulations designed to prevent the transmission of communicable disease from a contaminated article to a human being. FDA may not rely on Section 361(a) to promulgate regulations that have other objectives.

Section 361 of the PHS Act is a 1944 recodification of two quarantine laws passed in the late nineteenth century. The first law, enacted in 1890, authorized the President to direct the Secretary of the Treasury to promulgate rules to prevent the spread of four specified contagious diseases among the States. The law provided, in relevant part:

> [W]henever it shall be made to appear to the satisfaction of the President that cholera, yellow-fever, small-pox, or plague exists in any State or Territory, or in the District of Columbia, and that there is danger of the spread of such disease into other States, Territories, or the District of Columbia, he is hereby authorized to cause the Secretary of the Treasury to promulgate such rules and regulations as in his judgment may be necessary to prevent the spread of such disease . . . and to employ such inspectors and

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requirements as a matter of policy, AATB has serious reservations about FDA's attempt to rely on Section 361(a) as the exclusive legal basis for such requirements. Moreover, a requirement that is tailored to the direct disease transmission prevention objective of Section 361(a) may nevertheless be invalid as applied in a particular case.

[15] FDA cites maintaining tissue function and integrity as the basis for proposed sections 1271.150(a), 1271.170(c), 1271.180, 1271.220, 1271.265(d), and 1271.420(b). In addition to product function and integrity, FDA cites the objective of assuring that tissue products conform with product specifications. Regulations premised on Section 361(a) may not be aimed at assuring conformity with product specifications, any more than they may aim at preserving tissue function and integrity.

> other persons as may be necessary to execute such regulations to prevent the spread of such disease. . . .[16]

Under the plain language of the legislation, the President could exercise his authority to effectuate rulemaking only upon a showing that one of the four specified contagious diseases already "exist[ed]" in one of the States, in a United States territory, or in the District of Columbia. The President could not instruct the Secretary to address the potential spread of one of these diseases. Nor did the legislation encompass disease transmission risks originating outside the United States.

Congress soon recognized the limitations of the 1890 law. By authorizing quarantine only after a contaminated article or person had actually entered the United States, the 1890 law failed to reach the root of the contagious disease problem: the introduction of communicable diseases from overseas.[17] Representative Rayner from Maryland explained:

> But that act, as I say, contains the unfortunate provision that the President must be satisfied that the disease exists, and then, when he finds that it does exist, what can he do? He can not stop it. He can not pass any regulation, and the Treasury Department can not pass any regulation that will take effect at the port of entry, but he can take measures to prevent it from going from one State into another. Now, that act could never be carried out. The Treasury officials knew they could not carry it out. They never made the slightest effort to carry out this act, because it did not apply to the emergency which existed last summer, or to the emergency with which we are threatened, and that is the appearance of the disease at a port of entry.

Another member of Congress declared that foreign diseases, like war or famine, would "convert your prosperous cities into a withering wilderness."[18]

Congress enacted new legislation in 1893. The law provided that if the States, acting with the assistance of the Supervising Surgeon General, could not take sufficiently protective measures, then the Secretary of the Treasury

> shall, if in his judgment it is necessary and proper, make such additional rules and regulations as are necessary to

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16 Act of March 27, 1890, 26 Stat. 31 (repealed July 1, 1944).

17 24 Cong. Rec. 751-52 (1893).

18 Id.

> prevent the introduction of . . . [the four specified] diseases into the United States from foreign countries, or into one State or Territory or the District of Columbia from another State or Territory or the District of Columbia . . . .[19]

The 1893 law eliminated the prerequisite for a showing that one of the four enumerated diseases "exist[ed]" before regulations could be promulgated.[20]

Nothing in the legislative history of either statute suggests that Congress intended to authorize federal regulations unrelated to preventing the transmission of communicable diseases from contaminated persons or articles.[21]

Federal quarantine legislation remained unchanged for more than a half-century. Then, prompted by the growing prevalence of air travel and the nation's involvement in World War II, both of which increased the risk that "strange" communicable diseases would be introduced from abroad, Congress enacted the Public Health Service Act (PHS Act) in 1944.[22]

The legislation reorganized and codified several scattered laws dealing with public health, including the 1890 and 1893 Acts.[23] But Congress made very few substantive changes in the law.[24] There is no evidence in the legislative history that

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[19] Act of February 15, 1893, 27 Stat. 449. Under Section 3 of the statute, if the States did not enforce the rules, the President

> shall execute and enforce the same and adopt such measures as in his judgment shall be necessary to prevent the introduction or spread of such diseases, and may detail or appoint officers for that purpose.

[20] 24 Cong. Rec. at 752.

[21] Debate over the 1893 Act focused mainly on Congress' power to enact health and safety statutes pursuant to the Commerce Clause. Section 3 in particular, which was the precursor to modern Section 361(a), was hotly debated because some believed it conferred too much power on the federal government or was unconstitutional.

[22] Pub. L. No. 78-410, 58 Stat. 682 (1944). See Laws Relating to the Public Health Service, Hearings on H.R. 4624 Before a Subcommittee of the Senate Committee on Education and Labor, 78th Cong. 6 (1944) (statement of Dr. Thomas Parran, Surgeon General); 90 Cong. Rec. 6,486 (1944) (statement of Sen. Thomas).

[23] Because the 1944 act was a recodification of existing law, the extent of federal authority under the 1890 and 1893 legislation is relevant in construing Section 361.

[24] Two changes to the 1890 and 1893 Acts are apparent from the text of the 1944 Act and from its legislative history. First, under the 1893 Act, federal foreign quarantine authority was somewhat limited if a state had a quarantine program. This potential limit on federal power was removed in 1944 because by then, the states had (continued...)

Congress intended to confer on any federal official or department authority beyond that originally delegated by the 1890 law and increased under the 1893 legislation. According to one Senator,

> The bill was given careful consideration by both the House committee and the Senate committee. It was carefully studied. It does not add to the law of the land, nor does it take away from the law of the land, but merely brings the law up to date, in such a way that one of the most vital and most necessary agencies of our Government may operate unhampered, at a time when our country is really imperiled.[25]

The legislative history of the 1944 legislation demonstrates that Congress intended for Section 361(a) to authorize federal action in the context of quarantine measures. Section 361 is included in the "Quarantine and Inspection" provisions of the PHS Act. According to the House Report, Section 361(a) authorized federal officials to destroy contaminated articles "as a part of interstate or foreign quarantine procedures, where such animals or articles are likely to infect human beings with a dangerous disease and no disposition other than destruction can safely be made."[26] According to the report, the inspection authority conferred by Section 361 would "authorize the Public Health Service to make inspections and take other steps necessary in the enforcement of quarantine."[27]

The House Report also indicates that one member advocated changing Section 361(a) to "more clearly provide for the disposition of animals and articles which are potential sources of infection."[28] Although the clarifying language regarding destruction of animals and articles was not added, the description of those items to be destroyed – potential sources of infection – is evidence that Congress

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withdrawn from the field of foreign quarantine regulation. Id. at 24; Public Health Service Code, Hearing on H.R. 3379 Before a Subcommittee of the House of Representatives Committee on Interstate and Foreign Commerce, 78th Cong. 139 (1944) (statement of Alanson W. Willcox, Asst. General Counsel, Federal Security Agency). Second, the 1944 enactment gave the Surgeon General the authority to promulgate regulations to prevent the spread across state lines of all communicable diseases rather than specified communicable diseases because "there would be no particular reason for selecting those four diseases for special legislation." Id.

25 90 Cong. Rec. 6,486 (1944) (statement of Sen. Thomas).

26 See H.R. Rep. No. 78-1364 at 3-4 (1944).

27 Id. (emphasis added).

28 Id.

intended Section 361 to serve as a mechanism by which the federal government could contain and destroy objects that themselves could spread disease. [29]

Historical context also supports the view that Section 361 was not intended to confer sweeping enforcement authority on the federal government. Congress enacted the precursor to the modern FD&C Act in 1906 -- more than a dozen years after the 1893 quarantine statute. The 1906 Act gave the federal government carefully limited enforcement powers with respect to food and drug articles. Thereafter, when Congress intended for FDA (or its predecessor) to exercise greater authority to enforce federal laws regarding the safety, efficacy, or labeling of food or therapeutic products, it conferred new authority specifically and narrowly. These carefully limited delegations would have been unnecessary had Congress believed it had already given the federal government omnibus authority to adopt whatever requirements circumstances seemed to justify.

Another provision of the 1944 statute explicitly empowers the federal government to exercise the type of authority that FDA claims is implied under Section 361. Section 351 provides that biologics may not be sold unless "each package of such [biologic] is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific results."[30] That section also provides: "No person shall falsely label or mark any package or container of any [biologic] nor alter any label or mark on any package or container of any [biologic] so as to falsify such label or mark."[31]

Section 361 contains no similar language. If Congress intended for Section 361 to empower the federal government to impose product-labeling requirements, it would have said so, as it had specifically for biological products.[32]

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[29] This interpretation is supported by FDA practice. The agency generally has used its power under Section 361 to regulate the spread of disease by articles or animals which are potentially contaminated and which, therefore, present a direct risk of transmitting an infectious disease to human beings. See, e.g., 21 C.F.R. Parts 110, 113, 114, 123, 129 (food and drinking water safety), Part 1240 (restrictions on movement of diseased persons or articles), Part 1250 (food and drinking water safety on air, land, and water vessels). The only reported judicial opinion involving Section 361 involved an FDA ban on the sale of small turtles based on the risk of salmonella transmission. See Louisiana v. Mathews, 427 F. Supp. 174 (E.D. La. 1977). The ban was upheld, and remains in effect in FDA regulations. See 21 C.F.R. § 1240.62.

[30] PHS Act § 351(a)(2).

[31] Id. § 351(b). See also Act of July 1, 1902, Pub. L. No. 57-244, 32 Stat. 728.

[32] In addition to legislative history and historical context, FDA's own prior statements regarding Section 361 support a more modest interpretation of that (continued...)

## B. Section 361(a) Cannot Legitimately Be Interpreted to Give FDA Investigative and Enforcement Powers That Congress Has Never or Only Selectively Conferred in the FD&C Act

To support the investigative and enforcement provisions of the proposed CGTP rule, FDA purports to rely on Section 361(a) of the PHS Act. That statute was enacted in the late nineteenth century, before FDA even existed. Several of the authorities claimed by FDA in the current proposal have no counterpart in FDA's enabling statute, the FD&C Act, and other provisions mimic specific and contextually limited grants of authority found there.

Since the agency was established, Congress has been selective, and often reluctant, in granting investigative and enforcement authorities. This long course of action is incompatible with an interpretation of Section 361(a) that would permit FDA to assert powers that Congress, in legislation specifically directed to the agency, has never conferred or has granted only for specific categories of products in specific circumstances. These more recent and focused laws are the best evidence of Congress' intent, and Section 361(a) must be interpreted consistently with them.

An additional limitation on FDA's authority under Section 361(a) is found in the legislative history and purpose of the PHS Act. As discussed more fully above, FDA cannot rely on Section 361(a) to assert enforcement and investigative authorities that are not clearly aimed at preventing the transmission of communicable diseases directly from contaminated tissues to prospective recipients.[33]

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provision than the interpretation advanced in the proposed CGTP rule. In the preamble accompanying the donor suitability proposed rule, FDA cited Section 361 as the legal basis for requirements designed to address the risk that a tissue intended for transplant could transmit a communicable disease directly to another person. 64 Fed. Reg. at 52,698. Nowhere in the Proposed Approach document or in the preambles accompanying the registration and listing and donor suitability regulations did FDA give any hint that it would, in the CGTP proposal, interpret Section 361 so expansively.

[33] In describing its authority to enforce Section 361, FDA has repeatedly stated that violations of regulations promulgated under that statutory provision may be enjoined by federal district courts. See 66 Fed. Reg. 1,522 (proposed CGTP rule); 64 Fed. Reg. 52,698 (proposed donor suitability rule); 63 Fed. Reg. 26,747 (proposed registration and listing rule). AATB does not concede that FDA has legal authority to seek such relief, and FDA cites no authority in support of its proposition.

## 1. FDA Could Not Assert Under the FD&C Act The Inspection Authority It Asserts Under the CGTP Proposal

The proposed CGTP rule would give FDA virtually unlimited authority to examine records and take photographs and make videotapes during inspections of tissue establishments. (Proposed Section 1271.400). Congress, however, has consistently denied FDA such far-reaching authority with respect to other medical products.

FDA's authority to conduct inspections of manufacturing facilities has been hard won. The FD&C Act, as originally crafted in 1938, contained no records inspection provisions. FDA nevertheless began asserting the authority to inspect shipping records in the 1940s, but the Supreme Court in the 1952 Cardiff decision rebuffed this initiative.[34]

Inspection refusals skyrocketed following Cardiff, and FDA began urging Congress to enact legislation restoring the agency's inspection powers and giving it records inspection authority. In House hearings in 1953, industry representatives vigorously contested FDA's claim that the agency needed access to complaint files and other records.[35] When Congress enacted inspection legislation, it was careful to limit the delegation so that it only returned FDA to its pre-Cardiff inspection authority.[36] Uninterested, perhaps, in litigating the issue again, FDA acknowledged publicly that the new legislation did not give it authority to examine records during establishment inspections.[37]

FDA resumed its efforts to win records inspection authority a few years later. In 1961, HEW Secretary Arthur S. Flemming asked Congress for amendments to the FD&C Act that would "extend the factory inspection provision of the [1938] act

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34 In 1950, the government initiated a prosecution against Ira Cardiff, an apple processor in Yakima, Washington, for violating Section 301(f) of the FD&C Act. The government sought a writ of certiorari in the United States Supreme Court, asserting in its petition a need for access to 15 types of information in the course of an establishment inspection, including "formula cards," personnel information, and complaint files. The Supreme Court invalidated Section 301(f) on vagueness grounds. United States v. Cardiff, 344 U.S. 174 (1952). See George McKray, Record Inspection 1906-1963, 18 Food Drug Cosm. L.J. 301, 306-07 (1963); Eugene M. Elson, Inspection of Records, 5 Food Drug Cosm. L.J. 755, 756 (1950).

35 See Food, Drug, and Cosmetic Act (Factory Inspections): Hearings on H.R. 2769, H.R. 3551, H.R. 3604 Before the House Comm. on Interstate and Foreign Commerce, 83d Cong. 94-96 (1953).

36 Pub. L. No. 83-217, 67 Stat. 476 (1953).

37 FDA, Press Release to Trade and Professional Journals, August 27, 1953, at 2.

(sec. 704) to all records, files, papers, processes, controls, facilities, and things bearing on violations, or potential violations of the act."[38] Congress did not enact legislation that year.

Congress did, however, include records inspection authority in the 1962 Drug Amendments. The 1962 legislation authorized FDA explicitly to compel manufacturers of prescription drugs to submit to inspection of "records, files, papers, processes, controls, and facilities."[39] This authority did not extend to OTC drugs or other products within FDA's regulatory authority under the FD&C Act.[40]

Efforts to extend FDA's inspection authority to medical devices were initially rebuffed by Congress. Legislation introduced in 1974 to give FDA broad authority to inspect device records and issue subpoenas was rejected.[41] A similar proposal failed in 1975.[42] Finally, in 1976, Congress enacted the Medical Device Amendments, which gave FDA some inspection authority for medical devices. As with drugs, the delegation was carefully limited. FDA could inspect factories, warehouses, or establishments in which restricted devices were manufactured, as well as the records, files, and papers associated with such devices.[43] Congress denied FDA the power to inspect "financial data, sales data (other than shipment data), pricing

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38 See Drug Industry Act of 1962: Hearings on H.R. 11581 and H.R. 11582 Before the House Comm. on Interstate and Foreign Commerce, 87th Cong. 131, 135 (1962) (testimony of H. Thomas Austern) (quoting letter).

39 Pub. L. No. 87-781, § 201, 76 Stat. 780, 792 (1962).

40 Congress rejected proposals to give FDA inspectional authority with respect to OTC drugs in 1978 and 1992. Congress finally gave FDA inspection authority with respect to OTC drug facilities in 1997, and only because the proposal had the support of the industry. See Pub. L. No. 105-115, § 412, 111 Stat. 2296, 2375 (1997). This authority was carefully limited to prevent FDA from applying it to cosmetics and to require FDA to extend uniformity to OTC/cosmetic products that were deemed OTC drugs for the purposes of inspection. See H.R. Rep. No. 105-399, at 103 (1997).

41 See S. 3012, 93d Cong. 124 (1974); Calendars of the United States House of Representatives and History of Legislation, 93d Cong. 137, 232 (1974); The Food, Drug, and Cosmetic Amendments of 1974 (FDA Talk Paper T74-11), Feb. 11, 1974.

42 See Medical Device Amendments of 1975, Hearings on H.R. 5545, H.R. 974, and S. 510 Before the Subcomm. on Health and the Environment of the House Comm. on Interstate and Foreign Commerce, 94th Cong. 212-18 (1975); Calendars of the United States House of Representatives and History of Legislation, 94th Cong. 136, 152 (1977).

43 Pub. L. No. 94-295, § 6, 90 Stat. 539, 581 (1976).

data, personnel data (other than that relating to the qualifications of technical and professional personnel), or research data."[44]

Congress rejected proposals for further expansion of FDA's inspection authority during the Bush Administration. In 1991, Representatives Waxman and Dingell introduced H.R. 2597, which was virtually identical to a bill drafted by FDA lawyers and approved by HHS Secretary Sullivan. According to Representative Waxman, then-Commissioner Kessler had indicated that "he needs these authorities." A June hearing on the bill was rescheduled. In the interim, Commissioner Kessler softened his support of the measure, reportedly because the Bush Administration did not support it.[45] Ultimately, the Commissioner stated that additional authorities were unnecessary for the agency to fulfill its mission.[46]

Support for H.R. 2597 eroded further as the Administration applied pressure at the departmental level and in Congress. In October, health subcommittee Republicans questioned the need for FDA to inspect food and cosmetic facilities and records, and objected to a provision authorizing FDA to photograph "apparent violations." Even Democrats on the subcommittee opposed giving FDA all of the authorities it had requested.[47] The House Commerce Committee marked up the weakened bill in July 1992 and reported it out in October, but the bill never reached the House floor.[48]

FDA's efforts to win additional investigative and enforcement authority also failed during the Clinton Administration. The Clinton transition team report complained that FDA operated under a 1938 statute that did not contain the same enforcement powers typically given administrative agencies today.[49] Although there is evidence that House staffers discussed additional powers with administration

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44 H.R. Rep. No. 94-853, at 46-47 (1976).

45 137 Cong. Rec. at E2123.

46 See FDA Enforcement Bill Hearing Postponed, Health News Daily, June 27, 1991, at 1; Barred Kessler Testimony Says FDA Seeks "Main Stream" Tools, Food Chem. News, Sept. 23, 1991, at 9; The Gold Sheet, July 1, 1991.

47 See New Version of the Enforcement Bill, Memorandum from Dave Keaney, Steve Sims, Bill Schultz, and Tim Westmoreland to Democratic Las, March 27, 1992.

48 See Calendars of the United States House of Representatives and History of Legislation, 102d Cong. 8-1, 8-45 (1993) (H.R. 3642). A companion bill in the Senate (S. 2135) also failed.

49 The Citizens Transition Project, Changing America: Blueprints for a New Democracy (Transition Report for America's 42nd President), Nov. 1992).

representatives, broad enforcement legislation similar to the 1991 proposals never materialized.[50]

This history confirms Congress' determination that FDA should not have unlimited authority to inspect manufacturing and other facilities and should not have unfettered access to all records held in those establishments. It would frustrate congressional intent, expressed repeatedly in the history of Congress' responses to FDA's requests for additional authority, to interpret Section 361(a) as authorizing FDA to conduct broad inspections, including unrestricted records inspection, the taking of photographs, and the making of videotapes, of tissue facilities. The scope of FDA's inspections of tissue establishments must be directly related and tailored to the disease prevention goal of Section 361(a).

### 2. FDA Could Not Require Adverse Reaction and "Product Deviation" Reports Under the FD&C Act

The proposed CGTP rule also includes a provision that would require tissue establishments to submit adverse reaction and "product deviation" reports for tissue products. Under proposed section 1271.350, tissue establishments will be required to report to FDA adverse reactions involving not only "the transmission of a communicable disease," but also "product contamination" and "failure of the product's function or integrity." Tissue establishments will also be required to report "product deviations," a defined term which encompasses a broad range of events in addition to those that present a risk of contagious disease transmission.[51]

Congress has given FDA mandatory reporting authority only with respect to certain products and only pursuant to explicit, and carefully tailored, statutory provisions in the form of amendments to the FD&C Act. Under the FD&C Act of 1938, FDA had no power to compel drug manufacturers to submit adverse event reports.[52]

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[50] A discussion draft of a bill that would have given FDA significant subpoena authority for all products was circulated but never introduced. Undated Discussion Draft of Title IX "Enhancing Consumer Protection," § 904.

[51] "Product deviation" includes, for example, deviations from CGTP requirements, "applicable standards, or established specifications." It also includes events that "may adversely affect the function or integrity of the product." Proposed Section 1271.3(kk).

[52] As then-Deputy Commissioner John L. Harvey stated in an address to the bar in August 1962, "Present law does not require drug manufacturers to notify the Government of reports they receive which attribute injuries to the use of their drugs. . . . FDA must learn of adverse side effects when they are first recognized. The present system is faulty because it does not require this." John L. Harvey, Deputy (continued...)

The need for adverse event reporting for drugs became a public issue in 1962, when reports surfaced of children with severe birth defects born to European mothers taking the drug thalidomide. The reports revived legislation, introduced several years earlier by Senator Kefauver. While originally intended to promote competition in the drug industry, the legislation became the vehicle for the establishment of several significant new requirements for drugs. Under the new legislation, named the Drug Amendments of 1962, manufacturers were required to report to FDA data "relating to clinical experience" as well as other data or information the manufacturer had received or "otherwise obtained" regarding the drug.[53]

Adverse event reporting for medical devices was also discussed in 1962.[54] H.R. 11582, which would have established for medical devices adverse event reporting requirements similar to those in the 1962 drug legislation, was the subject of House hearings in June 1962, but there was no further action on the bill. The subject arose again in connection with Congress' consideration of H.R. 5545 in 1975, but no legislation was adopted.[55]

In the late 1980s, reports of fatal strut fractures in replacement heart valves manufactured by Shiley highlighted the absence of any statutory requirement for device manufacturers to supply FDA with information concerning the incidence and consequences of device failure. The Shiley episode again drew Congress' attention to FDA's inability to require manufacturers to disclose information about product design, reports from physicians and patients, and other safety-related information about medical devices.[56]

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Commissioner, FDA, address to the American Bar Association, San Francisco, Aug. 8, 1962, reprinted in 108 Cong. Rec. 16,266, 16,267 (Aug. 13, 1962).

53 Pub. L. No. 87-781, 76 Stat. 780, 782 (1962).

54 John L. Harvey, Deputy Commissioner, FDA, Address to the American Bar Association, San Francisco, Aug. 8, 1962, reprinted in 106 Cong. Rec. 16,266, 16,271 (Aug. 13, 1962) (describing unsafe or quack devices and summarizing adverse event provisions of H.R. 11582).

55 Medical Device Amendments of 1975, Hearings Before the Subcomm. on Health and the Environment of the House Comm. on Interstate and Foreign Commerce, 94th Cong. 231 (1975) (testimony of Richard A. Merrill, FDA Assistant General Counsel).

56 See Staff of Subcomm. on Oversight and Investigations of the House Comm. on Energy and Commerce, 101st Cong., The Bjork-Shiley Heart Valve: "Earn as You Learn" 28 (Comm. Print 101R 1990). FDA's difficulty in getting information from manufacturers of silicone breast implants also contributed to the interest in adverse (continued...)

Congress included adverse event reporting provisions in the Safe Medical Devices Act of 1990. The legislation provided for the filing of adverse event reports by manufacturers of medical devices and required the submission of information relating to removals and field repairs. The legislation required manufacturers to establish and maintain records containing information specified by FDA in regulations.

Congress assured that FDA's adverse event reporting authority was limited. User facilities were required to report only the most serious adverse events, and requirements for reporting to FDA regarding device removals or corrective actions were carefully circumscribed to avoid "over-reporting."[57]

It would frustrate Congress' intent to interpret Section 361(a) as implicitly authorizing FDA to exercise, with respect to tissue products, the very powers that have been repeatedly withheld, or conferred in limited quantities only in response to specific public health concerns.[58]

Moreover, it is inappropriate and illegitimate for FDA to purport to require tissue establishments to submit reports concerning any and all adverse reactions and product deviations the agency deems necessary. The reporting requirements, like all of the provisions in FDA's proposal, must be clearly linked to the direct disease prevention goal of Section 361(a). The only adverse event reports that FDA may require tissue establishments to submit under Section 361(a) are those relating to contamination that presents a direct risk of communicable disease transmission. FDA may not legitimately compel tissue firms to submit "product deviation" or other reports that are based on a "function and integrity" justification, which is not within the scope of Section 361(a).

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event reporting requirements for medical devices. See The Grady Sheet, June 15, 1992.

57 S. Rep. No. 101-513, at 23 (1990).

58 Congress has never specifically given FDA authority under Section 361(a). FDA obtained authority under Section 361(a) from the Department of Health and Human Services (HHS) as a result of an executive branch reorganization begun in the 1960s. In 1966, the functions of the Surgeon General under the PHS Act were transferred to the Secretary of Health, Education, and Welfare (HEW) pursuant to Reorg. Plan No. 3 of 1966. At that time, 5 U.S.C. § 906 gave Congress 60 days to disapprove a reorganization plan before it became effective automatically. Congress never voted on the measure. HEW was redesignated the Department of Health and Human Services under Pub. L. No. 96-88, 93 Stat. 695. HHS then delegated its authority under Section 361(a) of the PHS Act to FDA. See 21 C.F.R. § 5.10.

## IV. The Ex Parte Administrative Injunction Provision is Unconstitutional

The CGTP proposal purports to give FDA officials virtually unfettered authority to issue administrative orders requiring tissue establishments to cease their operations. (Proposed Section 1271.440.) This proposed authority violates the Due Process Clause of the Fifth Amendment of the United States Constitution.[59]

Proposed Section 1271.440 allows an FDA representative, "[u]pon an agency finding that a human cellular or tissue-based product or an establishment is in violation of the regulations in this part," to "[s]erve upon the establishment an order to cease manufacturing until compliance with the regulations of this part has been achieved."[60] The written order must specify the regulations with which compliance is lacking, but the tissue bank is afforded no opportunity to challenge whether compliance is lacking before the order takes effect. Although the facility may request a hearing within five days the issuance of the order, the regulation does not provide a date on which such a hearing must be held (or that a hearing must be held at all) nor does it specify when a decision regarding the validity of the order is to be made. Finally, any order is of potentially infinite duration, lasting as long as the agency believes that regulatory compliance has not been achieved.

This process for closing down a facility under this section does not meet the most minimal standards of Due Process.

It is well established that the right to practice one's chosen profession is protected by the Due Process Clause.[61] Before the government can deprive a person of the right to practice his or her profession, it is generally assumed that the individual must be given notice and opportunity to present the case that the government's proposed action is unwarranted. "[I]t is fundamental that except in emergency situations . . . due process requires that when a State seeks to terminate an interest [pursuit of a profession], it must afford 'notice and opportunity for hearing appropriate to the nature of the case' before the termination becomes effective."[62] The Due

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59 U.S. Const. amend. V ("No person shall be . . . deprived of life, liberty, or property, without due process of law . . . ."). Authorizing FDA representatives to issue ex parte orders requiring a tissue establishment to cease operations is also wholly inconsistent with FDA's risk-based approach to the regulation of tissue-based products.

60 Proposed Section 1271.440.

61 See, e.g., Gibson v. Berryhill, 411 U.S. 564, 571 (1973); Bell v. Burson, 402 U.S. 535, 539 (1971); Barsky v. Board of Regents, 347 U.S. 442, 459 (1954) (Douglas, J., dissenting); Meyer v. Nebraska, 262 U.S. 390, 399 (1923).

Process Clause protects even a temporary suspension of the right to practice an occupation.[63]

Complete closure of a tissue bank not only would prevent the bank from distributing tissues to physicians who needed them, but also would prohibit the bank from receiving and processing tissue donations that might be needed in the future. A cessation of operations would harm not only the interest of the tissue bank owners, but also the interests of their employees.

AATB members have a constitutional right to pursue the occupation of tissue banking. While the government can impose requirements on persons who choose to pursue tissue banking, it cannot summarily deny those persons the right to pursue their occupation without due process of law.

The instances in which Congress has empowered a federal agency to close down a business without judicial involvement are rare, and even those have been carefully circumscribed to ensure fair notice and an opportunity to respond. The Internal Revenue Service has the authority to levy on property in order to collect overdue taxes without obtaining a court order.[64] In some circumstances, this power amounts to the power to close down a taxpayer's business. This authority, however, is subject to extensive process protections for the taxpayer, including prior filing of a tax lien against the property, notice of intent to levy on the property, and a 30-day opportunity for the taxpayer to seek a hearing before the levy.[65] During any hearing or appeal, the levy on the property is suspended. The Due Process Clause requires nothing less in the context of the tissue banking business.

AATB sincerely hopes that FDA will make the necessary changes now and not wait for a legal challenge.

## V. The FDA Should Include a Mechanism for Working With Professional Accrediting Organizations to Coordinate Oversight Activities

In the Supplementary Information accompanying the proposed rule, the FDA sought comments on "possible alternative inspection and enforcement provisions that would leverage agency resources, be cost-effective, and achieve the public health

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62 Bell, 402 U.S. at 542 (footnote and citations omitted). See also Gibson, 411 U.S. at 578. But see Barry v. Barchi, 443 U.S. 55 (1979) (holding that the hearing relating to suspension of a license can be held, when certain specific findings are made, promptly after the license is suspended).

63 Barry, 443 U.S. at 66.

64 26 U.S.C. § 6331.

65 Pub. L. No. 105-206, 112 Stat. 685, 746-50 (1998).

goals of the proposed rule." The agency also welcomed comments on types of programs and alternative approaches "that would help ensure compliance with the proposed rule."

The Office of the Inspector General (OIG) at the Department of Health and Human Services recommended a similar approach in its January report entitled, "Oversight of Tissue Banking," where it said:

> FDA should work with States and with professional associations that have inspection and accreditation programs to determine in what areas, if any, oversight activities could be coordinated.
>
> FDA, the industry, and the States with regulatory programs could benefit from examining where standards are in agreement, as well as areas in which standards might conflict. Following such an examination, determination could be made of whether formal partnership or other arrangements would be appropriate to maximize the effectiveness of the oversight process. Such arrangements could require enactment of legislation.

The OIG further stated that it recognized the effect of "resource constraints" of FDA's ability to inspect tissue establishments and the burden of "multiple inspection visits" on tissue establishments' operations.

AATB concurs with the OIG's recommendation and agrees that FDA should work with professional accrediting organizations to coordinate inspection activities. FDA and AATB have always enjoyed a collegial and professional working relationship. We recommend that the agency initiate discussions with the AATB to develop a mechanism to coordinate oversight activities that will serve the agency's interests and the AATB's mission. This could include the AATB's training of agency inspectors, or the joint training of inspectors by both organizations.

To maximize the agency's resources and budget, the AATB would recommend that FDA work with the Association to compare the AATB's Standards with the agency's CGTP requirements and to provide special recognition to those tissue establishments that are AATB accredited. For example, where both requirements are comparable, this could include FDA acceptance of AATB accreditation for those requirements. This would reduce the agency's time and expenses of on-site inspections. This special recognition might also include extending the agency's normal inspection cycle for tissue banks that are AATB accredited. This would save further time and expense.

## VI. FDA Should Provide For Phased Implementation of the CGTP Regulations

When a final rule is published in the Federal Register, the FDA proposes that it become final 180 days following publication.

Implementation of the final CGTP regulations will require a major educational effort by FDA and the tissue community. Tissue banks will need significant time to review their operating procedures, policies and manuals and to incorporate any necessary changes in order to meet the requirements of the new regulations. Likewise, FDA's compliance officials, particularly the inspectors in the field, will need time and on-site experience to become familiar with the new regulatory requirements, and how they are to be interpreted. As it has done with other major regulatory initiatives, FDA should provide for phased implementation of the CGTP regulations.

AATB recommends that FDA grant at least one year for this phase-in period. AATB would welcome the opportunity to work with the agency to educate tissue banks about the new regulations and to help ensure an orderly transition.

## VII. Conclusion

AATB recognizes FDA's hard work in drafting and publishing the proposed rule and comments the agency for continuing its efforts to develop a comprehensive and reasoned approach to the regulation of tissue products. AATB supports, in concept, many of the provisions of the proposed CGTP rule, and fully endorses requirements that are designed to prevent the risk of communicable disease transmission from infected donors to prospective recipients. There are, however, several provisions of the proposal that are both overly burdensome to the tissue community and unnecessary to achieve this objective.

In addition, some provisions of the proposed CGTP rule cannot reasonably be construed as effectuating the disease prevention purpose of Section 361(a). As the legislative history demonstrates, Section 361(a) was aimed at addressing the public health risks associated with the transmission of communicable diseases directly from a person (or article) to another person. The "product function and integrity" and labeling provisions, as well as the product deviation reporting provisions, are not aimed this type of transmission risk and are, therefore, beyond the authority granted to FDA under Section 361(a) by this statutory provision.

Since 1938, FDA has repeatedly requested, and Congress has consistently and deliberately declined to enact, legislation that would give FDA authority to inspect records, take photographs, and exercise other enforcement powers. It is unreasonable to interpret Section 361(a) as giving FDA the very powers that Congress repeatedly determined to deny the agency. And to do so in a way that

denies tissue banks the ability to defend their actions before they are forced to cease operations offends the Due Process Clause. Consequently, the provision of the proposed rule purporting to allow FDA to issue administrative cessation orders to tissue establishments is invalid and should be deleted from the regulations.

Sincerely,

Richard J. Kagan, M.D.
President

P. Robert Rigney, Jr., J.D.
Chief Executive Officer

RJK/PRRJr/br