TABLE 12.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]—Continued

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
SOP Maintenance (See previous list of 19 SOP's)	1,065	19	20,235	1	20,235
1271.155(f)	1,065	1	1,065	0.25	266
1271.160(b)(3)	483	2	966	6	5,796
1271.160(b)(7)	597	15	8,955	0.5	4,478
1271.160(d)(3)	558	1	558	13	7,254
1271.160(e)	597	5	2,985	0.25	746
1271.170(d)	483	1	483	1	483
1271.180	483	1	483	120	57,960
1271.190(c)(4)	558	12	6,696	1	6,696
1271.195(c)	822	12	9,864	1	9,864
1271.200(e)	483	12	5,796	1	5,796
1271.210(c)	597	12	7,164	1	7,164
1271.220(b) and (d)	91	781	71,070	0.08	5,686
1271.225(b)	1,065	2	2,130	1	2,130
1271.230(a)	755	1	755	1	755
1271.230(b)	980	1	980	1	980
1271.230(e)	1,065	1	1,065	1	1,065
1271.260(b)(3)	597	356	212,532	0.08	17,003
1271.260(d)	747	12	8,964	0.25	2,241
1271.265(a)	597	360	214,920	0.08	17,194
1271.265(b)	822	407	334,554	0.08	26,764
1271.270(a) and (c)	597	360	214,920	0.1	21,492
1271.270(f)	755	2	1,510	0.25	378
1271.290(e)	641	306	196,146	0.3	58,844
1271.290(f)	1,065	57	60,705	0.35	21,247
1271.320(b)	830	5	4,150	1	4,150
1271.350(c)	726	6	4,356	0.5	2,178
Total					563,380

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Standard operating procedures.

Under this proposed rule, 19 SOP's would be required as previously described. FDA is assuming that approximately 1,065 manufacturers would have to create up to 9 SOP's for a total of 9,585 records, and the agency estimates that it would take 16 hours per record to create 9 new SOP's for a total of 153,360 hours as a one-time burden. The agency estimates that up to 19 SOP's would already exist as a result of complying with current applicable regulations or following industry organizational standards. Approximately 1,065 manufacturers would have to review these 19 SOP's for compliance with the regulations, which would expend approximately 5 hours per SOP as a one-time burden. Annual SOP maintenance of existing SOP's is estimated to involve 1 hour annually per SOP, totaling 19 hours annually per recordkeeper.

In some cases, the estimated burden may appear to be lower or higher than the burden experienced by individual establishments. The estimated burden in these charts is an estimated average burden, taking into account the range of impact each proposed regulation may have. In estimating the burden, FDA compared the proposed regulations with the current voluntary standards of a number of industry organizations, such as, AATB, EBAA, AABB, FAHCT, and CAP, and the guidelines provided by ASRM. In those cases where a voluntary industry standard appears to be equivalent to a proposed regulation, FDA has assumed that any reporting or recordkeeping burden is a customary and usual business practice of establishments who are members of those organizations and no additional burden is calculated here. In some cases establishments affected by this proposed rule may already be required to comply with regulations for manufacturers of human drugs or biological products, e.g., parts 210, 211, 312, 314, and 606 (21 CFR parts 312, 314, and 606).

FDA has estimated the reporting (table 11) and recordkeeping (table 12) burdens based upon the agency's institutional experience with comparable recordkeeping and reporting provisions applicable to the human drug and biological product industries, recent information from trade organizations related to the manufacturing of products utilizing cells and tissues, and data provided by the Eastern Research Group (ERG), a consulting firm hired by FDA to prepare an economic analysis of the potential economic impact on sperm banks and ART facilities.

The agency has estimated that there are approximately 1,065 manufacturers of cellular and tissue-based products (approximately 110 manufacturers of conventional tissue, 114 manufacturers of eye tissue, 425 manufacturers of peripheral and cord blood stem cells, 350 manufacturers of reproductive tissue, and 66 manufacturers of cellular or tissue-based licensed biological products or devices). FDA obtained these estimates of manufacturers (including percentage of members and nonmembers) from the various trade organizations and the agency's registration systems for biological product and device manufacturers. The total number of respondents and recordkeepers, 1,065, in the tables is decreased for each provision by the number of establishments that follow, as usual and customary practice, the applicable established trade organizational standards comparable to the CGTP requirements, i.e., AATB, EBAA, FAHCT, AABB, or CAP. FDA based the estimated numbers for "Number of Respondents" and "Number of Recordkeepers" on information provided by the trade organizations.

FDA based the estimated numbers for "Annual Frequency per Response,"

"Total Annual Responses," "Annual Frequency per Recordkeeping," and "Total Annual Records" on information received from the trade organizations, institutional experience with similar requirements (good manufacturing practice), general information provided to FDA during inspections of manufacturers of human tissue intended for transplantation, and information gathered by ERG.

The estimates for "Hours per Response" or "Hours per Recordkeeper" were calculated using comparable burdens under drug GMP regulations, part 211, and GMP for blood and blood components, part 606, or by using the information provided by ERG, e.g., time spent on §§ 1271.190(c)(4) (documentation of cleaning and sanitation) and 1271.195(c) (documentation of environmental control and monitoring activities) was an estimate provided by ERG.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by February 7, 2001 to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

XI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has concluded that the proposed rule raises Federalism implications because it could preempt some States' laws regarding donated human cells and tissues. FDA currently is seeking comments from elected State and local government officials under Executive Order 13132 on: (1) The need for the proposed good tissue practice rule to prevent communicable disease transmission through human cellular and tissue-based products; (2) alternatives that would limit the scope of such national requirements or otherwise preserve State prerogatives and authority; (3) the proposed good tissue practice provisions; and (4) any other issues raised by this proposed rule possibly affecting State laws and authorities.

XII. Request For Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments on this proposal by May 8, 2001. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Comments received in response to the proposed GTP rule could support a change that will affect language in previously published proposed tissue rules. In the event that any tissue rule becomes effective before either or both of the remaining tissue rules become effective, FDA intends to make conforming amendments to those final rules at the same time the remaining tissue rules become effective.

List of Subjects in 21 CFR Part 1271

Human cellular and tissue-based products, Communicable diseases, HIV/AIDS, Reporting and recordkeeping requirements.

Therefore, under the Public Health Service Act, and under the authority delegated to the commissioner of Food and Drugs, it is proposed to amend 21 CFR Chapter I as follows:

Part 1271 as proposed in the **Federal Register** of May 14, 1998 (63 FR 26744) and September 30, 1999 (64 FR 52696) is amended as follows:

PART 1271—HUMAN CELLULAR AND TISSUE-BASED PRODUCTS

1. The authority citation for 21 CFR part 1271 is revised to read as follows:

Authority: 42 U.S.C. 216, 243, 263a, 264, 271.

2. Section 1271.3 is amended by adding paragraphs (ff) through (tt) to read as follows:

§ 1271.3 Definitions.

* * * * *

(ff) *Available for distribution* means that the human cellular or tissue-based product has been determined to meet all release specifications and to be suitable for distribution.

(gg) *Adverse reaction* means a noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out).

(hh) *Processing material* means any material or substance that is used in, or to facilitate, processing, but which is not intended by the manufacturer to be included in the human cellular or tissue-based product when it is made available for distribution.

(ii) *Complaint* means any written, oral, or electronic communication that alleges:

(1) That a human cellular or tissue-based product has transmitted or may have transmitted a communicable disease to the recipient of the product;

(2) That the function or integrity of a human cellular or tissue-based product may have been impaired; or

(3) Any other problem with a human cellular or tissue-based product that could result from the failure to comply with current good tissue practice.

(jj) *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.

(kk) *Product deviation* means an event that represents a deviation from current good tissue practice, applicable standards, or established specifications; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease agent or disease from a human cellular or tissue-based product to a recipient, or may lead to product contamination, or may adversely affect the function or integrity of the product.

(ll) *Establish and maintain* means define, document (in writing or electronically), and implement, then follow, review, and as needed, revise on an ongoing basis.

(mm) *Processing* means any activity other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution performed on a human cellular or tissue-based product, including but not limited to preparation, sterilization, steps to inactivate and remove adventitious agents, preservation for storage, and removal from storage.

(nn) *Quality audit* means a documented, independent inspection and review of an establishment's activities, including manufacturing and tracking, performed according to procedures, to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

(oo) *Quality program* means an organization's comprehensive system for manufacturing and tracking human cellular and tissue-based products. This program includes preventing, detecting, and correcting deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable disease.

(pp) *Recovery* means the process of obtaining from a donor cells or tissues that are intended for use in human

implantation, transplantation, infusion, or transfer.

(qq) *Storage* means holding human cellular or tissue-based products for future processing and/or distribution.

(rr) *Validation* means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or process validation, means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

(ss) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

(tt) *Importer of record* means the person, establishment, or its representative responsible for making entry of imported goods in accordance with all laws affecting such importation.

3. Subpart D, consisting of §§ 1271.150 through 1271.320, is added to part 1271 to read as follows:

Subpart D—Current Good Tissue Practice

Sec.

Subpart D—Current Good Tissue Practice

§ 1271.150 Current good tissue practice: general.

(a) *General.* Current good tissue practice (CGTP) requirements are set forth in this subpart and in subpart C of this part. CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. 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. The CGTP provisions specifically governing determinations of donor suitability, including donor screening and testing, are set out separately in subpart C of this part.

(b) *Compliance with applicable requirements.* (1) If an establishment engages in only some operations subject to the regulations in this subpart and subpart C of this part, and not others, that establishment need only comply with those requirements applicable to the operations in which it engages. However, an 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.

(2) The establishment that determines that a product meets release criteria and makes the product available for distribution, whether or not that establishment is the actual distributor, is responsible for ensuring that the product has been manufactured in compliance with the requirements of subparts C and D of this part and any other applicable requirements.

(c) *Compliance with parts 210, 211, and 820 of this chapter.* With respect to human cellular or tissue-based products regulated as biological drugs or devices under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act, the procedures contained in this subpart and in subpart C of this part and the current good manufacturing practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter, shall be considered to supplement, not supersede, each other unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the biological drug or device in question shall supersede any other requirements.

(d) *Where appropriate.* When a requirement is qualified by "where appropriate," it is deemed to be "appropriate" unless the establishment can document justification otherwise. A requirement is "appropriate" if nonimplementation could reasonably be expected to result in the product's not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable disease agents and diseases, or in the establishment's inability to carry out any necessary corrective action.

§ 1271.155 Exemptions and alternatives.

(a) *General.* An establishment may request an exemption or alternative from any requirement in subpart C or D of this part regarding a human cellular or tissue-based product.

(b) *Request for exemption or alternative.* A request under this section shall be submitted to the Director, Center for Biologics Evaluation and Research (the Director). The request shall be accompanied by supporting documentation, including all relevant valid scientific data. A request for an exemption shall contain information justifying the exemption. A request for an alternative shall contain a description of an alternative that satisfies the purpose of the requirement.

(c) *Criteria for granting exemption or alternative.* The Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of preventing the introduction, transmission, and spread of communicable disease and that:

(1) The information submitted justifies an exemption; or

(2) The proposed alternative satisfies the purpose of the requirement.

(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 acknowledgment of approval.

(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.

(f) *Documentation.* An establishment operating under the terms of an exemption or alternative shall maintain documentation of:

(1) FDA's granting of the exemption or alternative, and

(2) The date on which it began operating under the terms of the exemption or alternative.

§ 1271.160 Establishment and maintenance of a quality program.

(a) *General.* 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.

(b) *Functions.* Functions of the quality program shall include, but not be limited to:

(1) Ensuring that appropriate procedures are established and maintained, and ensuring compliance with the requirements of § 1271.180 with respect to procedures, including review, approval, revision, and archiving;

(2) Ensuring that procedures exist for receiving, investigating, evaluating, and documenting information received from other sources and for sharing with consignees and other establishments that are known to have recovered cells or tissue from the same donor any information pertaining to the integrity and function of a human cellular or tissue-based product, possible contamination of the product, or the potential transmission of communicable disease by the product. In the case of information received after the product is made available for distribution or shipped to the consignee, procedures shall include provisions for evaluating the effect this information has on the product and for the notification of all entities to whom affected product was distributed, the quarantine and recall of the product, and/or reporting to FDA, as necessary.

(3) Ensuring that appropriate corrective actions, including reaudits of deficiencies, are taken and documented, as necessary. Corrective actions shall be verified to ensure that such actions are effective and do not adversely affect the finished product. Where appropriate, corrective actions shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence. Documentation of corrective actions shall include where appropriate:

(i) Identification of the human cellular or tissue-based product affected and a description of its disposition;

(ii) The nature of the problem requiring corrective action;

(iii) A description of the corrective action taken; and

(iv) The date(s) of the corrective action.

(4) Ensuring the proper training and education of personnel;

(5) Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring);

(6) Establishing and maintaining a system for the maintenance of records in compliance with § 1271.270;

(7) Investigating and documenting all product deviations and making reports if required under § 1271.350(b) or other applicable regulations. Each investigation shall include a review and evaluation of the product deviation, the efforts made to determine the cause, and the implementation of corrective action(s) designed to address the product deviation and prevent recurrence. Each establishment shall also perform a periodic review and analysis of all product deviations, at least once each year, for the purpose of identifying trends and adopting appropriate preventive measures. This analysis shall be available for review upon inspection and for submission to FDA upon request; and

(8) Conducting evaluations, investigations, audits, and other actions necessary to ensure compliance with the requirements of this subpart.

(c) *Authority over program.* One or more designated persons shall have authority over and responsibility for ensuring that the quality program is effectively established and effectively maintained. This person shall report to management on the performance of the quality program on no less than an annual basis. If this person also performs other tasks in the establishment, he or she shall not have final oversight over his or her own work.

(d) *Audits.* (1) A comprehensive quality audit, as defined in § 1271.3(nn), shall be performed no less than once in a 12-month period. Special audits shall be performed as necessary. 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.

(2) Quality audits shall be conducted by individuals with sufficient knowledge, training, and experience to identify problems in the specific processes under review, but who do not have direct responsibility for the processes being audited.

(3) A documented report of the results of the audits and reaudits, where taken, shall be retained. Such reports shall be reviewed by management having responsibility for the matters audited, and this management review shall be documented.

(e) *Computers.* 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.

(f) *Procedures.* Procedures shall be established and maintained for a quality program, including quality audits.

§ 1271.170 Organization and personnel.

(a) *General.* Each establishment shall maintain an adequate organizational structure and sufficient personnel to ensure that the requirements of this part are met.

(b) *Competent performance of functions.* Each establishment shall have sufficient personnel with the necessary education and experience to assure competent performance of their assigned functions. Personnel shall perform only those activities for which they are qualified.

(c) *Training.* All personnel shall be trained, and retrained as necessary, to perform their assigned responsibilities adequately. Personnel shall be made aware of possible consequences of improper performance of their duties; e.g., the risk of transmission of communicable disease agents and diseases, and the hazards associated with those disease agents and diseases, and the risk of adversely affecting function and integrity of human cellular and tissue-based products.

(d) *Records.* A record of the education, experience, training, and retraining shall be maintained for all personnel.

§ 1271.180 Procedures.

Each establishment shall establish and maintain procedures for all significant steps that it performs in the manufacture of human cellular and tissue-based products. These procedures shall be designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by ensuring that the products do not contain relevant 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. Procedures shall be designed to ensure compliance with the requirements of this part. Prior to implementation, all procedures shall be reviewed and approved by a responsible person. At least once in a 12-month period, all procedures shall be reviewed and, if necessary, revised, and the

review shall be documented. Procedures shall be readily available to the personnel in the area where the operations to which they relate are performed, unless this is impractical. Any deviation from a procedure shall be authorized in advance by a responsible person, recorded, and justified. An establishment may adopt current standard procedures, such as those in a technical manual prepared by another organization, provided the procedures are consistent with and at least as stringent as the requirements of this part and appropriate for the operations conducted at the establishment. Obsolete procedures shall be archived for at least 10 years.

§ 1271.190 Facilities.

(a) *General.* 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.

(b) *Operations.* A facility used in the manufacture of human cellular or tissue-based products shall be divided into separate or defined areas of adequate size for each operation that takes place in the facility, or other control systems shall be established and maintained to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of human cellular and tissue-based products to communicable disease agents.

(c) *Facility cleaning and sanitation.* (1) Any facility used in the manufacture of human cellular and tissue-based products shall be maintained in a clean, sanitary, and orderly manner.

(2) Sewage, trash, and other refuse shall be disposed of in a timely, safe, and sanitary manner.

(3) Procedures for facility cleaning and sanitation shall be established and maintained. These procedures shall assign responsibility for sanitation and shall describe in sufficient detail the cleaning methods to be used and the schedule for cleaning the facility.

(4) All significant cleaning and sanitation activities shall be documented, and records shall be maintained.

§ 1271.195 Environmental control and monitoring.

(a) *General.* Where environmental conditions could reasonably be expected to have an adverse effect on the function or integrity of human cellular and tissue-based products, or to cause contamination or cross-contamination of products or equipment or accidental exposure of products to communicable disease agents, procedures shall be established and maintained to adequately control and monitor environmental conditions and to provide proper conditions for operations. Where appropriate, these procedures shall provide for the following control and monitoring activities or systems:

(1) Temperature and humidity controls;

(2) Ventilation and air filtration;

(3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations;

(4) Maintenance of equipment used to control conditions necessary for aseptic processing operations; and

(5) Environmental monitoring for organisms.

(b) *Inspections.* Each environmental control system shall be inspected periodically to verify that the system, including necessary equipment, is adequate and functioning properly. Appropriate corrective action shall be taken as necessary.

(c) *Records.* Environmental control and monitoring activities shall be documented, and records shall be maintained.

§ 1271.200 Equipment.

(a) *General.* 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. Any automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be capable of producing valid results.

(b) *Procedures and schedules.* Procedures shall be established and maintained for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, accidental exposure of human cellular and tissue-based products to communicable disease agents, and other events that could reasonably be expected to have an adverse effect on product function or integrity. Cleaning, sanitizing, and maintenance of equipment shall be performed according to established schedules.

(c) *Calibration of equipment.* All automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be routinely calibrated according to established procedures and schedules. Calibration procedures shall include specific directions and, where applicable, shall include limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for corrective action to reestablish the limits and to evaluate whether there were any adverse effects on any human cellular or tissue-based product.

(d) *Inspections.* Equipment shall be routinely inspected for cleanliness, sanitation, and calibration, and to assure adherence to applicable equipment maintenance schedules.

(e) *Records.* 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.

§ 1271.210 Supplies and reagents.

(a) *Receipt and verification.* Procedures shall be established and maintained for receiving supplies and reagents used in the manufacture of human cellular and tissue-based products. Supplies and reagents shall be verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable disease through product contamination or the impairment of product function or integrity, and shall not be used until such verification is completed. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent.

(b) *Reagents.* Reagents used in processing and preservation of human cellular and tissue-based products shall be of appropriate grade for the intended use and shall be sterile, if appropriate. Procedures for production of in-house reagents shall be validated and/or verified.

(c) *Records.* The following records pertaining to supplies and reagents shall be maintained:

(1) Records of the receipt of each supply or reagent, including the type, manufacturer, lot number, date of receipt, and expiration date;

(2) Records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a

certificate of analysis from the vendor; and

(3) Records of the use of each supply or reagent, which shall include the identification of each human cellular or tissue-based product manufactured with the supply or reagent.

§ 1271.220 Process controls.

(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.

(c) *Pooling.* 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.

(d) *In-process monitoring.* Procedures shall be established and maintained, where appropriate, to ensure that specified requirements of in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed or necessary approvals are received and documented. Sampling of in-process products shall be representative of the material to be evaluated.

§ 1271.225 Process changes.

(a) *Procedures.* Procedures shall be established and maintained for making changes to a process. Any such change shall be verified or validated, to ensure that the change does not create an adverse impact elsewhere in the operation, and shall be approved before implementation by a responsible person with appropriate knowledge and background.

(b) *Change records.* All changes to established processes shall be documented, including the rationale for the change and the date of implementation. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), approval date, and when the change becomes effective. Approved changes shall be communicated to the appropriate personnel in a timely manner.

§ 1271.230 Process validation.

(a) *General.* 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.

(b) *Claims.* 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. Validation shall be documented, and the documentation shall be maintained at the establishment and made available for review on inspection.

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

(d) *Procedures.* Procedures shall be established and maintained for monitoring and control of validated processes to ensure that the specified requirements continue to be met.

(e) *Changes and deviations.* When changes to or deviations from a validated process occur, the establishment shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

§ 1271.250 Labeling controls.

Procedures shall be established and maintained to control the labeling of human cellular and tissue-based products. These procedures shall be designed to ensure proper product identification and to prevent mix-ups. Procedures shall include verification of label accuracy, legibility, and integrity. Procedures shall ensure that each product is labeled in accordance with all applicable labeling requirements, including those in §§ 1271.55, 1271.65, 1271.75, 1271.90, 1271.290, and 1271.370, and that each product made available for distribution is accompanied by documentation of the donor suitability determination as required under § 1271.55.

§ 1271.260 Storage.

(a) *Control of storage areas.* Each establishment shall control its storage areas and stock rooms to prevent mix-ups, commingling, deterioration, contamination, and cross-contamination, of human cellular and tissue-based products and supplies, and any other condition that may adversely affect product function or integrity, and to prevent improper release for distribution.

(b) *Temperature.* (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.

(3) Storage temperatures for human cellular and tissue-based products shall be maintained and recorded. Recorded temperatures shall be reviewed periodically to assure that temperatures have not exceeded acceptable limits.

(c) *Expiration date.* Where appropriate, an expiration date shall be assigned to each human cellular or tissue-based product based on the following factors:

(1) Product type;

(2) Processing procedures, including the method of preservation;

(3) Storage conditions; and

(4) Packaging.

(d) *Corrective action.* Corrective action shall be taken and documented whenever proper storage conditions are not met.

§ 1271.265 Receipt and distribution.

(a) *General.* Procedures shall be established and maintained for the following activities: receipt, acceptance or rejection, distribution, and destruction or other disposition of human cellular or tissue-based products, and these activities shall be documented. Documentation shall include:

(1) Identification of the human cellular or tissue-based product;

(2) Activities performed and the results of such activities;

(3) Date(s) of activity;

(4) Quantity of human cellular or tissue-based product subject to the activity; and

(5) Disposition of the human cellular or tissue-based product (e.g., identity of consignee).

(b) *Receiving activities.* Procedures shall be established and maintained for

receiving and accepting or rejecting human cellular or tissue-based products for processing, distribution, or any other step in the manufacturing process. The status of each incoming human cellular or tissue-based product (e.g., with respect to quarantine, donor screening and testing, and processing) shall be determined and identified promptly after receipt, and each product shall be handled in a manner appropriate to its status. Each incoming human cellular or tissue-based product shall be inspected according to established procedures for damage, contamination, deterioration, or other indications that the integrity of the product has been impaired. Acceptance or rejection of incoming products shall be documented.

(c) *Availability for distribution.* Procedures shall be established and maintained for making human cellular and tissue-based products available for distribution. These procedures, which shall include release criteria, shall be designed to prevent the release of products that are in quarantine, are contaminated, have deteriorated, or otherwise have been manufactured in violation of current good tissue practice and, except as provided under §§ 1271.65 and 1271.90, products from donors who have been determined to be unsuitable or for whom a donor-suitability determination has not been completed. Prior to making a human cellular or tissue-based product available for distribution, the establishment shall verify and document that the release criteria have been met and shall review all records pertaining to the product. The determination that a human cellular or tissue-based product is available for distribution shall be documented and dated by a responsible person.

(d) *Packaging.* Packaging and shipping containers shall be designed, validated, and constructed to ensure product function and integrity and protect the product from damage, deterioration, contamination, or other adverse effects during customary conditions of processing, storage, handling, and distribution.

(e) *Shipping conditions.* Appropriate shipping conditions shall be defined for each type of human cellular or tissue-based product to be maintained during transit.

(f) *Return to inventory.* Procedures shall be established and maintained to determine if a product that is returned to an establishment is suitable to be returned to inventory.

§ 1271.270 Records.

(a) *General.* Records shall be maintained concurrently with the performance of each significant step required in this subpart and subpart C of this part. Any requirement in this part that an action be documented involves the creation of a record, which record is subject to the requirements of this section. All records shall be accurate, indelible, and legible. The records shall identify the person performing the work, the dates of the various entries, and shall be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular human cellular or tissue-based product involved. Record security systems shall be adequate to ensure the confidentiality of donors and recipients of human cellular and tissue-based products.

(b) *Records management system.* A records management system shall be established and maintained. Under this system, records pertaining to a particular human cellular or tissue-based product manufactured shall be maintained in such a way as to facilitate review of the product's history prior to making it available for distribution and, if necessary, subsequent to the product's release as part of a follow-up evaluation or investigation. Records pertinent to the manufacture of each type of human cellular or tissue-based product (e.g., procedures, specifications, labeling and packaging procedures, equipment logs) shall also be maintained and organized under the records management system. If records are maintained in more than one location, then the records management system shall be designed to ensure prompt identification, location, and retrieval of all records.

(c) *Other recordkeeping requirements.* Procedures shall be established and maintained to ensure compliance with the recordkeeping requirements in § 1271.55. Documentation of results and interpretation of all testing for relevant communicable disease agents in compliance with §§ 1271.80 and 1271.85 shall be maintained, as well as the name and address of the testing laboratory or laboratories. Documentation of the results and interpretation of all donor screening for relevant communicable disease in compliance with § 1271.75 shall be maintained in accordance with § 1271.270. Documentation of the donor-suitability determination, including the name of the responsible person who made the determination and the date of the determination, shall also be maintained. Information on the identity and relevant medical records of the donor, as defined in § 1271.3(v), shall be in English or, if in another language, shall be translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document.

(d) *Methods of retention.* Records required under this subpart may be maintained electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm, in which case suitable reader and photocopying equipment shall be readily available. Records stored in automated data processing systems shall be backed up. Electronic records and electronic signatures are subject to the requirements in part 11 of this chapter.

(e) *Length of retention.* 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.

(f) *Contracts and agreements.* Each establishment shall maintain records of any contract, agreement, or other arrangement with another establishment under which any step in the manufacturing process is performed by the other establishment. These records shall include the name and address of the other establishment and the responsibilities of each party to the contract, agreement, or other arrangement.

§ 1271.290 Tracking.

(a) *General.* Each establishment that performs any step in the manufacture of a human cellular or tissue-based product shall track each such product in accordance with this section.

(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.

(d) *Product information.* As part of its tracking method, an establishment shall ensure that the identifier and type of each human cellular or tissue-based product that is implanted, transplanted, infused, or transferred into a recipient is recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor.

(e) *Recipient information.* As part of its tracking method, an establishment shall document, and maintain records of, the disposition of each of its human cellular or tissue-based products, to enable tracking from the donor to the recipient or final disposition. The information to be maintained shall permit the prompt identification of the recipient of the product, if any.

(f) *Consignees.* At or before the time of distribution of a human cellular or tissue-based product to a consignee, an establishment shall inform the consignee in writing of the requirements in this section and of the tracking method that the establishment has established and is maintaining to comply with these requirements. Upon initial distribution of product to the consignee, the establishment shall document that the consignee agreed to participate in its tracking method and to take all necessary steps to ensure compliance with the requirements of this section.

(g) *Requirements specific to dura mater donors.* Appropriate specimens from each donor of dura mater shall be archived, under appropriate storage conditions, and for the appropriate duration, to enable testing of the archived material for evidence of transmissible sponiform encephalopathy, and appropriate disposition of any affected dura mater tissue, if necessary.

§ 1271.320 Complaint file.

(a) *Procedures.* 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.

(b) *Complaint file.* Each establishment shall maintain a record of each complaint that it receives in a file designated for complaints. The complaint file shall contain sufficient information about each complaint for proper review and evaluation of the complaint, including the identifier of the human cellular or tissue-based product that is the subject of the complaint. The complaint file shall be made available for review and copying upon request from an authorized employee of the Food and Drug Administration.

(c) *Review and evaluation of complaints.* Each complaint shall be reviewed and evaluated to determine if the complaint is related to a product deviation of a human cellular or tissue-based product or to an adverse reaction, and to determine if a report under § 1271.350 or another applicable regulation is required. Each complaint that represents an event required to be reported to FDA shall be promptly reviewed, evaluated, and investigated. A complaint that does not represent an event required to be reported shall be reviewed and evaluated to determine whether investigation is necessary; investigation may include referring a copy of the complaint to another establishment that performed manufacturing steps pertinent to the complaint. When no investigation is made, the establishment shall maintain a record that includes the reason no investigation was made, and the name of the individual responsible for the decision not to investigate.

4. Subpart E, consisting of §§ 1271.330 through 1271.370, is added to part 1271 to read as follow:

Subpart E—Additional Requirements for Establishments Described in § 1271.10

Sec.

Subpart E—Additional Requirements for Establishments Described in § 1271.10

§ 1271.330 Applicability

The provisions set forth in this subpart are applicable only to human cellular and tissue-based products described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act (the PHS Act) and the regulations in this part, and to the establishments that manufacture those products. Human cellular and tissue-based products described in § 1271.15 and regulated as drugs, devices, and/or biological products under the act and/or section 351 of the PHS Act, and the establishments that manufacture those products, are not subject to the regulations set forth in this subpart.

§ 1271.350 Reporting.

(a) *Adverse reaction reports.* (1) Any establishment that receives information about an adverse reaction, regardless of source, shall review the information to determine whether the adverse reaction is required to be reported. The establishment shall report any adverse reaction involving the transmission of a communicable disease, product contamination, or failure of the product's function or integrity if the adverse reaction:

(i) Is fatal;

(ii) Is life-threatening;

(iii) Results in permanent impairment of a body function or permanent damage to body structure; or

(iv) Necessitates medical or surgical intervention. Each report shall be submitted on an FDA Form-3500A to the address in paragraph (a)(4) of this section within 15 calendar days of initial receipt of the information.

(2) The establishment shall promptly investigate all adverse reactions that are subject of these 15-day reports and shall submit follow-up reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a follow-up report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

(3) Copies of the reporting form (FDA-3500A) may be obtained from the Center for Biologics Evaluation and Research (see address in paragraph (a)(4) of this section). Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785.

(4) The establishment shall submit two copies of each report described in this paragraph to the Center for

Biologics Evaluation and Research (HFM-210), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. FDA may waive the requirement for the second copy in appropriate circumstances.

(b) *Reports of product deviations.* (1) Any establishment that becomes aware of a product deviation in the manufacture of a distributed human cellular or tissue-based product shall immediately determine whether the product deviation is of the type that could reasonably be expected to lead to a reportable adverse reaction and, if it is, shall report the product deviation to the address in paragraph (b)(3) of this section as soon as possible.

(2) Each report shall contain a description of the product deviation and information on all corrective actions that have been or will be taken in response to the product deviation (e.g., recalls).

(3) Each report of a product deviation shall be reported to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (HFM-600), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

(c) *Records.* Reports and investigations required under this section shall be documented and records shall be maintained.

§ 1271.370 Labeling and claims.

(a) *Label information and accompanying materials.* (1) Each human cellular or tissue-based product made available for distribution shall be labeled clearly and accurately.

(2) The following information shall appear on the product label:

(i) Name and address of the establishment that determines that the product meets release criteria and makes the product available for distribution;

(ii) Description of the type of product; and

(iii) Expiration date, if any.

(3) The following information shall appear either on the product label or package insert:

(i) Storage temperature;

(ii) Warnings, where appropriate; and

(iii) Instructions for use.

(b) *Claims.* (1) All labeling, advertising, and promotional materials for a human cellular or tissue-based product shall be clear, truthful, and balanced in all respects, and may not be false or misleading in any particular.

(2) A labeling claim or promotional materials regarding the therapeutic or clinical outcome of a human cellular or tissue-based product (other than reconstruction, replacement, repair, or supplementation of cells or tissue) is considered a claim for a use other than a homologous use, as defined in § 1271.3(d), and the product, including labeling, shall be regulated under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act.

5. Subpart F, consisting of §§ 1271.390 through 1271.440, is added to part 1271 to read as follows:

Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

Sec.

Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

§ 1271.390 Applicability.

The provisions set forth in this subpart are applicable only to human cellular and tissue-based products described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act (the PHS Act) and the regulations in this part, and to the establishments that manufacture those products. Human cellular and tissue-based products described in § 1271.15 and regulated as drugs, devices, and/or biological products under the act and/or section 351 of the PHS Act, and the establishments that manufacture those products, are not subject to the regulations set forth in this subpart.

§ 1271.400 Inspections.

(a) An establishment subject to this part as described in § 1271.10, including any location performing contract services, shall permit an authorized representative of the Food and Drug Administration (FDA) to make at any reasonable time and in a reasonable manner such inspection of the establishment, including but not limited to its facilities, equipment, processes, products, procedures, labeling, and records, as may be necessary in the judgment of such representative to determine compliance with the provisions of this part. Such inspection may be made with or without notice and will ordinarily be made during regular business hours.

(b) The frequency of inspection will be at the agency's discretion.

(c) FDA's representative will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel of the establishment as the representative deems necessary.

(d) FDA's representative may review and copy any records required to be kept under this part and may take photographs or make videotapes.

(e) The public disclosure of records containing the name or other positive identification of donors or recipients of human cellular or tissue-based products will be handled in accordance with FDA's procedures on disclosure of information as set forth in part 20 of this chapter.

§ 1271.420 Human cellular and tissue-based products offered for import.

(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.

§ 1271.440 Orders of retention, recall, destruction, and cessation of manufacturing.

(a) Upon an agency finding that a human cellular or tissue-based product or an establishment is in violation of the regulations in this part, an authorized Food and Drug Administration (FDA) representative may take one or more of the following actions:

(1) Serve upon the person who distributed the human cellular or tissue-based product a written order that the product be recalled and/or destroyed, as appropriate, and upon persons in possession of the product that the product shall be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or the safety of the product is confirmed;

(2) Take possession of and/or destroy the violative human cellular or tissue-based product; or

(3) Serve upon the establishment an order to cease manufacturing until compliance with the regulations of this part has been achieved.

(b) A written order issued under paragraph (a) of this section will state with particularity the facts that justify the order.

(c)(1) A written order issued under paragraph (a)(1) of this section will

ordinarily provide that the human cellular or tissue-based product be recalled and/or destroyed within 5 working days from the date of receipt of the order. After receipt of an order issued under paragraph (a)(1) of this section, the establishment in possession of the human cellular or tissue-based product shall not distribute or dispose of the product in any manner except to recall and/or destroy the product consistent with the provisions of the order, under the supervision of an authorized FDA representative.

(2) In lieu of paragraph (c)(1) of this section, other arrangements for assuring the proper disposition of the human cellular or tissue-based product may be agreed upon by the person receiving the written order and an authorized official of FDA. Such arrangements may include, among others, providing FDA with records or other written information that adequately assure that the human cellular or tissue-based product has been recovered, processed, stored, and distributed in conformance with this part, and that, except as provided under §§ 1271.65 and 1271.90, the donor of the cells or tissue for the product has been determined to be suitable.

(d) A written order issued under paragraph (a)(3) of this section will specify the regulations with which compliance shall be achieved and will ordinarily specify the particular operations covered by the order. After receipt of an order issued under paragraph (a)(3) of this section, an establishment shall not resume operations without prior authorization of an authorized official of FDA.

(e) Within 5 working days of receipt of a written order for retention, recall, destruction, and/or cessation (or within 5 working days of the agency's possession of a human cellular or tissue-based product under paragraph (a)(2) of this section), the recipient of the written order or prior possessor of such product may request a hearing on the matter in accordance with part 16 of this chapter. An order of destruction will be held in abeyance pending resolution of the hearing request.

Dated: August 29, 2000.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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資料７

無菌医薬品の生産のための無菌的プロセッシングに関する規定（案）

Ⅰ．はじめに

Ⅱ．背景

Ⅲ．責任範囲

Ⅳ．施設が具備すべき機能的条件とその設計
- A. クリティカル・エリア（クラス１００）
- B. サポーティング・クリーン・エリア
- C. 各クリーン・エリアの分離について
- D. 空調（供給される空気の清浄度を保つための空気濾過）
  1. メンブラン（圧縮空気）
  2. HEPA (High Efficiency Particulate Air) フィルター
- E. 設計

Ⅴ．技術員訓練、資格、モニターリング
- A. プロセッシング技術員
- B. 細菌検査室などの技術員
- C. 技術員の技術をモニターリングするプログラム

Ⅵ．原料、容器・栓
- A. 原料
- B. 容器・栓

Ⅶ．エンドトキシン・コントロール

Ⅷ．種々の時間制限

Ⅸ．プロセス・バリデーションと機器の適格性評価
- A. プロセスシミュレーション
- B. 濾過効率
- C. 機器、容器、栓の滅菌

Ⅹ．検査室のコントロール
- A. 環境モニターリング
- B. 微生物学的培地とその評価
- C. フィルター通過前の生物学的負荷
- D. 空気中の浮遊粒子のモニターリング

XI. 無菌試験

A. 方法の選択
B. 培地
C. 技術員
D. サンプリングおよび培養
E. 無菌試験結果が陽性であった場合の対応

XII. バッチ記録の検査：作業管理記録

付記１：無菌操作無菌的クリーンルーム(註：プロセッシング施設の構造的機能を述べている)

A. メンテナンス
B. 設計
C. 供給物の移送
D. 除染〈Decontamination〉
E. 充填ラインの滅菌
F. 環境モニターリング
G. 技術員

付記２：ＢＦＳ(BLOW-FILL-SEAL)技術

A. 設備設計および空気清浄度
B. バリデーションと管理
C. バッチのモニターリングと管理

付記３：充填密閉作業前のプロセッシング

A. 製造工程初期の無菌的プロセッシング
B. 無菌的細胞プロセッシング

文献

用語解説

Ⅰ．はじめに

Ⅱ．背景

無菌医薬品の生産方法には、無菌的プロセッシングによる方法と、最終段階で滅菌することにより行う方法の２通りがある。

最終段階における滅菌操作による場合は、良好なバイオバーデン環境（生物学的負荷が低いが、無菌状態ではなくてもよい）で生産されたものに対して行なわれる。すなわち、良好なバイオバーデン環境で生産され、密閉された後、最終的に滅菌すれば良い訳である。たとえば、そのような方法には加熱滅菌やガンマー線照射、さらにはガス滅菌等があげられる。

しかし、最終産物ができてから加熱滅菌などの操作が可能な場合は良いが、加熱滅菌等が不可能な場合には、無菌的プロセッシングが必要である。多くの場合、いくつかの異なった滅菌過程（一部はガス滅菌、一部は加熱滅菌等）を経て無菌化されたものを組み合わせて、最終的に無菌医薬品を生産する場合には、無菌的プロセッシングを必要とする。この無菌的プロセッシングは、必然的に多くの工程から成りたち、各工程は適切に管理され、バリデートされる必要がある。この工程のなかでもし誤りが生じれば、コンタミネーションの可能性があるので、注意深い管理を行なわなければならない。最終製品に滅菌すれば良いだけの工程の場合は、コンタミネーションの可能性は減少する。

製造業者は、公衆の健康を守るため、無菌性の保証されない医薬品を出荷しないように留意しなければならない。cGMP 規制を遵守できなような製造設備は、最終的に患者の生命を脅かすことになる。

Ⅲ．責任範囲

本提案は、無菌的プロセッシングのすべての項目を網羅しているわけではない。原薬のプロセッシングから最終製品にいたるまでの、ごく限られた項目について言及している訳で、実際には、技術者の資格、クリーンルームの定義と種類、施設の設計、品質管理、環境のモニターリング、製造記録の査察など 1,987 個にも及ぶ指針がある。無菌的細胞プロセッシングに必要な安全キャビネットまたはクリーンベンチに関しても言及する。

本提案は製品の無菌的プロセッシングに関係する cGMP 基準について言及しているが、作業衣や医薬品の最終段階における無菌化については述べていない。というのは、無菌的プロセッシングは最終段階での無菌化が不可能な場合にのみ必要だからである（註：細胞プロセッシングは、この無菌的プロセッシングの範疇に入る)。

Ⅳ. 施設が具備すべき機能的条件とその設計

セクション211.42（設計と建設）
無菌操作は、明確に規定された適正な規模のエリア内で行われること。そして、汚染や混合を防止するために、個々の作業は別個のあるいは独立したエリアで行われねばならない。無菌操作工程においては、環境モニターリングおよび、無菌環境を維持するためのすべての機器を管理するシステムと同様に、陽圧環境下での高性能（HEPA）フィルターで濾過された空気の供給を行わねばならない。

セクション211.46（換気、空気濾過、空気加熱および冷却）
医薬品を製造、加工、包装あるいは保管する等の各々の工程に対して、その工程を行なう部屋の室圧、微生物、塵埃、湿度、および温度を適正に制御する必要がある。生産エリアへ適切に空気供給する際には、プレフィルターおよび粒子状物質捕集フィルター（中性能、HEPA フィルター等）を含む空気濾過システムを採用すべきである。

無菌的プロセッシングにおいては、独立した管理を必要とする様々な作業エリアがあり、個々のエリアの空気の品質は、その作業の性質により異なる。エリアの設計は、与えられたエリアで、定められた作業の実施と同様に、設備や原料の種類や製品の露出度合いによって規定され、微生物および微粒子の検出基準を満たすものでなければならない。

無菌操作工程におけるクリティカル・エリアおよびサポート・エリアは、既知の微生物および粒子のデーターによりクラス分けされて管理されなければならない。建設当初のクリーン・ルームの性能試験は完成された設備の静的な条件下で評価がされるが、最終的な作業エリアの清浄度分類は、動的な条件、すなわち技術者が存在し、機器がそこにあり、そして作業が実際に進行している状態から得られるデーターにより評価されなければならない。無菌工程における設備モニターリング・プログラムは、通常作業を行なっている動的な条件下において、定められたクリーン・エリアの清浄度分類に対する適合性で評価すべきである。

下記の表1は、クリーン・エリアにおける空気清浄度分類を要約したものである（参考文献1）。

表1-空気清浄度分類[a]

クリーン・エリア分類	≧0.5μm 粒子数・ft^3	≧0.5μm 粒子数・m^3	微生物限界値[b] cfu・$10ft^3$	cfu・m^3
100	100	3,500	<1[c]	<3[c]
1000	1000	35,000	≦2	≦7
10,000	10,000	350,000	≦5	≦18
100,000	100,000	3,500,000	≦25	≦88

a. すべての分類は、作業期間中に暴露された物、容器、栓等の近傍での測定値に基づいている。
b. 操作の特性からその妥当性が確立された場合は、代替可能な微生物基準を使用することが可能である。
c. クラス 100 の環境から得られたサンプルは、通常、微生物による汚染が認められてはならない。

2つのクリーン・エリアが無菌製剤品質に対して特に重要である。すなわち、クリティカル・エリアとそれに隣接するサポート・クリーン・エリアである。

A. クリティカル・エリア（クラス 100）

クリティカル・エリアでは、無菌医薬品、容器、梱包システムが、無菌性が保たれるように設計された環境に暴露されることになる。したがって、クリティカル・エリアでは、無菌性を維持できるよう設計された環境下で、無菌的マニュアル操作（たとえば、無菌的接続、無菌成分の添加等）を行なわなければならない。

このクリティカル・エリアが最も重要である理由は、中間容器に入れられた製品はそれ以上プロセッシングされることはなく、またクリティカル・エリアでの作業中の汚染に対して無防備なためである。製品の無菌性を維持するためには、無菌操作を行う環境は作業期間を通じてつねに適切な空気清浄度を保つべきである。環境における空気中の微粒子はそれらが製品に入り、物理的もしくは微生物のキャリアーとして働き、生物学的な汚染を引き起こす重要因子となる。クリティカル・エリアの微粒子数は適切な空調システムにより最小限に抑えなければならない。

無菌化された容器・栓が暴露される、および充填・閉塞作業を行うエリア環境中の空気に含まれる許容微粒子数量（作業中）は、通常、作業場所から1フィート以内のある場所において、0.5 ミクロン以上の微粒子数が 1 立方フィートあたり 100 個以下（クラス 100）でなければならない。このクリティカル・エリアにおいて、測定数値が基準値より超えている場合は、その原因を調査して結果を文書に記録しなければならない。

無菌的プロセッシング域の空気清浄度の測定は、無菌製品および容器・栓が暴露される場所で、気流の上流にパーティクル・カウンターのプローブを向けて行われなければならない。定期的モニターリングは作業ごと、その期間中に実行されるべきである。固定式のリモート・カウント・システムによる微粒子モニターリングは最も分かりやすい（信頼性のある）データーが得られるので、移動式の微粒子カウントユニットを施設内に持ち込んで測定するよりも望ましい（セクション X.D、微粒子モニターリングの項参照）（註：京大 CCMT ではリアルタイム式のものが備え付けてあるので、よりインテリジェントである）。

粉末充填作業は、その性質上、製品への汚染がないものの、高いレベルの粉末微粒子を生成する。この場合、１フィート以内のある特定点における空気清浄度を測定しても、粉末微粒子の「バックグラウンド・ノイズ」レベルを空気中の汚染物質から区別することは出来ない可能性がある。そのような場合、可能な範囲で、製品が曝露される、外部由来の真の微粒子汚染レベルを顕在化する方法で空気をサンプリグすべきである。実際の粉末充填作業を除いた動的条件下において予め検証を行うことにより、作業中における非製品由来の発塵に関するデーターを前もって得ておくべきである。クリティカル・エリアにおける空気は、充填・閉塞エリアから微粒子を押し流すに十分な風速で、作業期間中に気流の層流性を維持しうる HEPA フィルターを通過したラミナーフローとすべきである。所定場所における動的条件下で、正当かつ適切に層流性と空気清浄度が維持されるよう、個々の工程作業に応じた速度パラメーターを確立すべきである（参考文献２）（脚注３）。

適切に設計され、よくコントロールされれば、無菌操作工程やクリーン・ゾーンにおける、気流の乱れや空気の停滞を防止することができる。一旦、適切なパラメーターが確立されたら、気流パターンを調べて、気流の乱れがないかどうか評価すべきである。試験結果は文書化して記録されなければならない。ビデオテープまたは他の記録装置は、後の機器構成の変更に対する評価を容易にするのみでなく、建設初期の気流評価にも有益である。しかし、正しく性能検証されたシステムでさえ、未熟な作業者からの発塵や操作による発塵、メンテナンスにおける発塵により機能を損なうことがあることに留意するべきである。

クリティカル・エリアにおける空気モニターリングで、通常、微生物による汚染は認められるべきではない。この環境での汚染が見られた場合は、調査の必要があることを認識すべきである。

B. サポート・クリーン・エリア

サポート・クリーン・エリアは、様々にクラス分けされ、種々の機能を含む。多くのサポート・エリアは、非無菌原料、調剤済み製品、途中工程資材、機器、容器・栓を準備もしくは保管、搬送するゾーンとして機能する。これらのゾーンにおける環境は、最終製品への微粒子汚染物を最小化し、滅菌される前の資材および原料の微生物負荷（バイオバーデン（生物学的負荷））を制御できるように設計すべきである。

サポート・クリーン・エリアにおけるクリーン度分類は、実施される作業の性質に応じてなされるべきである。クラス１０万のエリアは、それほど重要ではない当初の容器準備等の作業に対して適応される。無菌操作工程に直接隣接するエリアは、動的条件下において少なくともクラス１万の基準（表 1 参照）を満たさねばならない。工程の作業内容によっては、製造者はこのエリアをクラス１、０００として規定することも、また無菌充填室全体をクラス１００として維持する選択を行うことも可能である。

C. 各クリーン・エリアの分離について

クリーン・エリアを適切に分離することは、作業エリア間における汚染を防止するために必要である。より高い清浄度エリアの空気清浄度を維持するためには、隣接する空気清浄度が低いエリアとの間に、適切な気流と圧力差を設定することが重要である。より高い清浄度の部屋は、隣接したより低い清浄度エリアに対して通常、少なくともドアを閉めた状態で 0.05 インチ水柱の差圧を設けるべきである。ドアを開けた場合、外へ向かう気流は汚染の進入を最小限とするのに十分でなければならない（参考文献３）。クリーン・ルーム間の差圧は、製造作業ごとにその期間中、高い頻度で連続的にモニターされるべきであり、設定された限界値からの逸脱が認められた場合は調査が必要である。

適正な換気回数はクリーン・ルームに応じて設定されるべきである。クラス１０万のサポート・クリーン・エリアでは、1 時間あたり最低 20 回の換気回数を十分達成しうる気流が一般的な許容レベルとされる。

設備モニターリング・システムは、設備環境に悪影響を及ぼす異常な変化を速やかに検出可能なものとすべきである。運転状態は、アクションレベルに達する以前に（すなわち、プロセッシングを開始する前に）、定められ検証されたレベルへ回復可能であるべきである。たとえば、差圧管理設備の仕様は、非清浄域空気の清浄域への侵入を防止するために、どのような緊急圧力低下に対しても速やかに検出（すなわちアラーム警報等）可能とすべきである。

D. 空調（供給される空気の清浄度を保つための空気濾過）

1. メンプレン（圧縮ガス）フィルター

圧縮ガスは、適切な純度（たとえば、油分および水蒸気を含有しない）を有し、その微生物および微粒子の品質についても、それが使用される環境における空気清浄度と同等あるいはそれ以上であるべきである。空気、窒素、二酸化炭素等の圧縮ガスは、クリーン・ルームでしばしば使われ、またパージ用あるいはガス膜用として頻繁に使用される。

メンブレン・フィルターは、圧縮ガスをろ過して適切な高品質基準に適合させることが出来る。無菌濾過されたガスは、無菌化された物にガスが接触する場合に使用される。特定の機器もまた、無菌濾過されたガスが供給されるべきである。たとえば、無菌化のための微生物捕集メンブレン・フィルターは、オートクレーブのエアー配管、真空凍結乾燥機の真空ブレーク配管、無菌化された物質を入れた容器、および乾熱滅菌機のベント等に使用されるべきである。無菌化されたタンクまたは液体は、微生物汚染防止のために、継続的に加圧された状態で保持されるべきである。メンブレン・フィルターを設置する予防手段は、非無菌空気や液体の逆流による汚染を引き起こす圧力変化への対策として適所に施すべきである。

ガス・フィルター（ベント・フィルターを含む）は乾燥状態であるべきである。ガス・フィルターの凝縮物はフィルターの詰まりや微生物汚染を起こす可能性がある。頻繁なフィルター交換、加熱、および疎水性フィルターの使用により、ガス供給システムの水分残留が防止できる。これらのフィルターは、取り付けられた状態で完全性試験を行い、そしてその後も定期的（たとえば、、使用後等）に試験すべきである。完全性試験が不合格となった場合は原因調査が必要である。

2. 高性能（HEPA）フィルター

無菌環境を保証するために、HEPA フィルターの完全性に対するメンテナンスは必須項目である。完全性試験は、シール・ガスケットの周囲からのリーク、フレームやフィルター・メディア上の多くのポイントからのリークを検出するために据付状態で実行すべきである。その後、完全性試験は無菌操作工程設備の HEPA フィルターに対して、適当な時間的間隔をあけて行うべきである。たとえば、そのような試験は、無菌工程室に対して、1 年に 2 回行うべきである。空気品質が許容値を下回った場合や、メディアフィルターの不適合もしくは製品の無菌試験の不適合に対する調査の一環として、付加的な試験が必要となる場合がある。完全性試験が必要とされるフィルターには、一般的にガラスバイアルを脱パイロジェン化するために用いられる乾熱滅菌トンネルのフィルター等も含まれる。

HEPA フィルターの完全性試験方法として認められている方法の 1 つが、dioctylphthalate （DOP） エアロゾルによる曝露試験試験である。代替エアロゾルの使用も許容される。粘度等の重要な物理化学的特性が要求される条件を満たしているのであれば、Poly-alpha-olefin の使用もまた許容される。試験を実施する環境への微生物汚染の危険があるため、いくつかの代替エアロゾル使用には疑問がある。これらの疑わしいエアロゾルを使用する場合は、微生物の発育を助長しないことを保証すべきである。

完全な HEPA フィルターは、直径 0.3 ミクロン以上の粒子を最低 99.97%捕集する性能を持っている。曝露試験試験に使用されるエアロゾルに、この粒径範囲の粒子が十分含まれていることを確認することが重要である。フィルター上流に導入するエアロゾルの粒径を把握せずに完全性試験を実施しても、リーク検出には無効である。DOP 曝露試験試験においては、フィルター設計風量で空気 1 リットルあたり 80～100 マイクログラムのエアロゾルを、フィルターの上流に供給すべきである。そして、フィルター下流側では 1 分あたり最低 1 立方フィートのサンプリングレートで、適切な光度計のプローブによって走査される。走査は、フィルター面から約 1～2 インチの点で全フィルター面とフレームに対して実施すべきである。HEPA フィルターに対するこの総合的な走査結果は確実に文書化すべきである。しばしば業者がこれらのサービスを提供するが、これらの必須の証明作業が満

足ゆくように実施されることについては、製薬メーカーがその責任を負う。フィルター上流濃度の 0.01%の値をひとつのプローブが示した場合、それは重要なリークを示唆していると理解すべきで、その結果、HEPA フィルターの交換もしくはフィルターの部分的な補修を行うべきである。その後の確認再試験はすべての補修エリアに対して実行すべきである。

フィルター完全性試験と効率試験には大きな違いがある。定期的に計画された完全性試験の目的は、フィルターメディア、フィルターフレーム、およびシールからのリークを検出することである。この曝露試験試験には、通常 1 ミクロンから 3 ミクロンに整粒された多拡散エアロゾルを使用する。試験はフィルターを取り付けた状態で、フィルター面をプローブで走査する。測定された下流のリーク量は、上流の粒子濃度に対するパーセントとして得られる。一方、効率試験はフィルター捕集効率を決定することのみを目的として実施される。

HEPA フィルター完全性試験だけでは、フィルター性能をモニターするのに十分ではない。この試験は通常年間 2 回の実施を基本としている。フィルター通過風速の均一性ならびに隣接するフィルターとの相関等のフィルター特性に対する定期的なモニターリングが重要である。これらの変化、たとえば、風速低下は気流の層流性に影響しうるので、風速の変化は一般に汚染の可能性を増大させる。気流速度は、フィルター面から 6 インチ離れたところ、または作業表面近傍の定められた場所において、各々の HEPA フィルターについて測定される。たとえば、無菌操作を行うクリーン・ゾーンに対しては、週 1 回程度の頻度でモニターリングを行うことが適切であろう。たとえば、目詰まりによる風量不足や、フィルター通過風速の不均一性が認められた場合は、HEPA フィルターを交換すべきである。

E. 設計

セクション 211.42：
無菌操作は、明確に定義された適正な大きさのエリア内で行われること。そして汚染や混合を防止するために、個々の作業は別個のあるいは定義されたエリアで行われなければならない。

セクション 211.42：
建物内における原料、製品コンテナ、栓、ラベル、中間品の流れ、および建屋そのものは、汚染を防止するよう設計されなければならない。そして、HEPA フィルターは適切に空気をろ過し、床と同様に壁および天井は、容易に清掃できるように平滑で堅い表面としなければならない。

セクション 211.63：
設備は適切に設計され、適正なサイズとし、意図される使用方法と清掃およびメンテナンスを容易とするよう使いやすく配置されねばならない。

セクション211.65：
公定書なあるいは他の特定基準を超えて、製品の安全性、本質、力価、品質、純度に変化を及ぼすような反応性、漫透性、吸収性が、原料、中間品、製品に接触する設備表面にあってはならない。

セクシション211.68：
自動機器設備および自動電気設備に対する要件。

セクシション211.113：
無菌化された製品に対する微生物汚染を防止するよう、計画され、適切に文書化された作業手順を確立し、それを遵守せねばならない。

無菌操作工程は、動的条件下において、無菌化された物の暴露と工程作業による潜在的な汚染の危険性を、最小化するように設計する。封栓前容器の暴露期間の制限、可能な限り高い能力の環境コントロールシステム、そして、より低い品質の空気がクラス 100 のゾーンに流れ込むことのないように設計された設計・設備が目標達成に必須である（参考文献３）。

無菌操作工程において、いかなる作業期間中の人的介在または装置の停止でも、汚染のリスクは増大しうる。露出した製品、容器・栓、あるいはその周囲環境への潜在的汚染を引き起こす不要な作業を防止するために、人およびモノの動線を最適化すべきである。設備レイアウトは、作業者の快適性と動作を最適化する人間工学に基づくべきである。無菌室への人の入退室頻度は制限されるよう設計すべきであり、無菌室内のクリティカル・エリアへの立ち入り制限はさらに重要である。低品質の空気が流れ込むような気流の変化を防止するために、クリティカル・エリア近傍での動作は制限されるべきである。たとえば、人的介在は、設備に一体化されたオンラインウェイトチェック装置の使用によって低減が可能であり、それにより、クリティカル・ゾーン内における繰り返しの手動操作をなくすことが出来る。また、無菌工程室内の作業人数を最小化することも重要である。

製品は、適切なクリーン・ルームの条件下で搬送すべきである。たとえば、真空凍結乾燥工程は、無菌充填され、部分的に封栓された容器の搬送工程を含む。汚染を防止するために、部分的に封栓された無菌製品は、クリティカル・エリア内だけで整列、搬送すべきである。充填ラインと真空凍結乾燥機との間のエリア、およびその搬送と入庫方法が、クラス 100 の環境を維持しうる設備を設計すべきである。

また、無菌の製品と容器・栓は、ライン近傍での作業からも保護されるべきである。無菌工程ラインを部分的に隔離するために、入念に設計されたカーテン、固定のプラスチック製シールド、もしくは他のバリアーを、適切に配置すべきである。

エアーロックとインターロックドアは、無菌工程エリアに通じる空気のバランスをより適切にコントロールする。エアーロックは、無菌工程エリア入口と隣接する非