

Chapter 1

REGULATORY MODELS FOR SAFETY AND QUALITY OF ALLOGRAFTS

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The difference in approach to regulatory control in USA and Europe is demonstrated in the two contributions. Is it appropriate to classify tissue, whether of human or animal origin as a DEVICE? No doubt the debate will continue. It is now for the Tissue Banking community to voice their opinions.

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1.1 REGULATORY MODELS FOR SAFETY AND QUALITY OF ALLOGRAFTS: EUROPE

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1. Introduction

The definition of a medical device is given in Article 1.2.a. of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD) and is as follows:

'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of

- diagnosis, prevention, monitoring, treatment, alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Heart valves, pericardial patches, ligaments, bone and dermal substitutes utilizing materials of animal origin are under the Council Directive 93/42/EEC by Article 1.5.g.

Human tissues are still not under a Directive of the Council of the European Communities. However, there is a proposal for a European Parliament and Council Directive on *in vitro* diagnostic medical devices, where in Article 19 "Amendment of Directives" changes are made in the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. The most important change is in Article 1.5.f. The complete text is as follows:

This Directive does not apply to:

- (f) transplants or tissues or cells of human origin, unless a device is manufactured utilizing tissues or substances derived from such tissues which are non-viable or rendered non-viable. In this case, the Directive shall not affect national regulations relating to the ethics of the collection of tissues or substances of human origin, as well as any regulations relating to the ethics governing distribution of given types of devices of such origin.

This proposal is amended by the European Parliament in the following way:

- (f) transplants or tissues or cells of human origin. It shall however apply to medical 'devices' manufactured utilizing cells or tissues of human origin and having undergone a process of transformation which removes the cellular organisation or the characteristic structure of the tissue of origin and renders them non-viable. In this case, the Directive shall not affect national regulations relating to the ethics of the collection of tissues or substances of human origin, as well as any regulations relating to the ethics governing distribution of given types of devices of such origin.

The European Parliament's version is accepted and taken up by Commissioner M. Bangemann. The initiative is accepted by the Council in order to make a common view, but as yet no Directive is in force covering this point.

2. Considerations

If this proposal is discarded, a particular situation will arrive that devices utilizing non-viable tissue from animal origin will be under the Medical Device Directive (MDD) and the same devices utilizing non-viable human tissue is not. Typical examples are heart valves (those from porcine origin are under the MDD and are classified as class III). The human valves, however, are not under the MDD and their status is unknown and dependent of the individual Member States. Glycerol preserved human cadaveric skin, Alloderm[®], Integra[®] are also not under the MDD. However, the skin substitutes from animal origin are again under the MDD.

The medical profession has a strong feeling that there must be a European regulation concerning human tissues and organs. In several countries problems have arised concerning the use of human tissues and organs because of the lack of appropriate regulations concerning safety, and so hampering the welfare of patients and the progress of research. The MDD and its related standards can serve as a framework for Tissue Bank standards.

3. The Medical Device Directive

A first step can be to accept non-viable human tissues in the MDD, guaranteeing a safe product and a free trade in the Member States, because of the following statements given in the MDD:

Whereas medical devices should provide patients, users and third parties with a high level of protection and attain the performance levels attributed to them by the manufacturer; whereas, therefore, the maintenance or improvement of the

level of protection attained in the Member States is one of the essential objectives of this Directive.

Member States are bound to implement the Council Directives in their national laws, creating an internal market without internal frontiers ensuring a free movement of goods, persons, services, and capital:

Article 4.1. Member States shall not create any obstacle to the placing on the market or the putting into service within their territory of devices bearing the CE marking provided for in article 17 which indicates that they have been the subject of an assessment of their conformity in accordance with the provisions of article 11.

The above-mentioned objectives have ethical values. Tissues can easily be transported over the Member States and the safety of the products are known to benefit patients. Moreover, the ethics of collection and distribution of human tissues is guaranteed by the clause of the new article 1.5.f:

The Directive shall not affect national regulations relating to the ethics of the collection of tissues or substances of human origin, as well as any regulations relating to the ethics governing distribution of given types of devices of such origin.

Moreover, the MDD and the related Standards from CEN (Comité Européenne de Normalisation) and ISO (International Standards Organisation) give a good framework for a quality system leading to an optimal safe product.

Article 3 of the MDD 'Essential Requirements' stated that devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned. Apart of general requirements there are stipulations concerning:

Section 7. Chemical, physical and biological properties

Section 8. Infection and microbial contamination

Section 13. Information supplied by the manufacturer

Article 11 referring to the Annexes II, III, IV, V, VI, VII and VIII gives support to implement a full quality assurance system, a production quality system and a product quality assurance.

4. European Standards

In order to demonstrate conformity with the essential requirements and to enable conformity to be verified, it is desirable to have harmonised European standards to protect against the risks associated with the design, manufacture and packaging of medical devices. These standards should retain their status as non-mandatory texts. The European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC) are recognised as the competent bodies for the adoption of harmonised standards. CEN/CENELEC members are the national standards bodies of Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration.

5. Quality Systems

Guidance in a quality assurance system, a product quality system and a product assurance system is given in the EN 46000 series in combination with the ISO 9000 series.

EN 46001 and EN 46002 respectively entitled Quality systems (Medical devices) Particular requirements for the application of EN 29001 (= ISO 9001) and Quality systems (Medical devices) Particular requirements for the application of EN 29002 (= ISO 9002).

These standards embrace all the principles of Good Manufacturing Practice (GMP). Both standards are not stand-alone standards.

This complex of standards give guidance in the requirements of a quality system ISO 9001/2 containing chapters about:

- Management responsibility with sections dealing with quality policy and organisation
- Quality system with sections about procedures and planning
- Contract review with sections about review, amendments and records
- Design control with sections about design and development planning, organisational and technical interfaces, design input, design output, design review, design verification, design validation, and design changes
- Document and data control with sections about document and data approval and issue, document and data changes
- Purchasing with sections about evaluation of subcontractors, purchasing data, verification of purchased product
- Control of customer-supplied product
- Product identification and traceability
- Process control
- Inspection and testing with sections about receiving inspection and testing, in-process inspection and testing, final inspection and testing, inspection and test records
- Control of inspection, measuring and test equipment with sections about control procedure, inspection and test status
- Control of non-conforming product with a section about review and disposition of non-conforming product
- Corrective and preventive action with sections about corrective action and preventive action
- Handling, storage, packaging, preservation and delivery with sections about handling, storage, packaging, preservation and delivery
- Control of quality records
- Internal quality audits

- Training
- Servicing
- Statistical techniques with sections about identification of need and procedures

EN 46001 and EN 46002 have an extended chapter about definitions. The chapter about the requirements of a quality system is the same as in ISO 9001/2 except for additions typical for medical devices. The additions can be rather extensive, as in Process control, for example.

6. Risk Analysis

EN 1441 specifies a procedure to investigate, by using available information, the safety of a medical device by identifying hazards and estimating the risks associated with the device.

7. Special Standards Concerning Animal Tissue

To comply with the Essential Requirements laid down in Article 8.2 and 8.3 of Annex I of the MDD 93/42, a committee CEN/TC 316 is given a mandate to write three standards:

- EN 12442-1 Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 1: Analysis and management of risk,
- EN 12442-2 Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 2: Sourcing, controls and handling,
- EN 12442-3 Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 3: Validation of the elimination and/or inactivation of viruses and other transmissible agents

All three standards are still in preparation.

EN 1441 is a general standard specifying risk analysis for medical devices, while EN 12442-1 provides additional requirements and guidance for the evaluation of medical devices manufactured utilising animal tissues or derivatives which are non-viable or have been rendered non-viable. For the management of risk, references are given.

Risks such as those related to bacteria, moulds and yeasts are referred to the following standards:

- Part 1 of EN 1174 Medical Devices — Estimation of the population of micro-organisms on a product
- EN 550 Sterilization of medical devices — Validation and routine control of ethylene oxide sterilization
- EN 552 Sterilization of medical devices — Validation and routine control of sterilization by irradiation
- EN 554 Sterilization of medical devices — Validation and routine control of sterilization by moist heat
- ISO/DIS 14160 Sterilization of Medical Devices — Validation and routine control of the sterilization of single-use medical devices incorporating materials of animal origin by liquid chemical sterilants

Risks related to viruses and transmissible agents such as unclassified pathogenic agents, prions and similar entities. To cope here with EN 12442 indicates the following possibilities:

- EN 12442-2 Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 2: Sourcing, controls and handling. Although EN 12442-2 is rather typicable for animals and hardly applicable for humans, the paragraphs concerning handling and collection can be useful.
- EN 12442-3 Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 3: Validation of the elimination and/or inactivation of viruses and other transmissible agents

A paragraph General Aspects gives guidance for the Manufacturing process referring to EN ISO 9001, 9002 and EN 46001, 46002 for general

aspects related to validation like documented procedures, personal referring to EN ISO 9004 — Guide to quality management and quality system elements, calibration and equipment. The core of this standard is the paragraph, “Validation of the inactivation of viruses and/or transmissible agents.” Guidance is given in literature search referring to a normative annex, inactivation during manufacture, validation report and re-validation of the validation report. Informative annexes are given as guidance in:

Scaling down — As it is hazardous to introduce viruses and/or transmissible agents like prions into production areas, validation of the inactivation study should be conducted in a separate laboratory equipped for virological work and performed by staff with the appropriate expertise. The scaled down process should be designed in such a way as to represent worst case conditions regarding the ability of the manufacturing process to eliminate and/or inactivate viruses and other transmissible agents.

Also the document CPMP/BWP/268/95: “Note for guidance on virus validation studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses” is very worthwhile and is used in the preparation of EN 12442-3.

The following two documents are of interest for spongiform encephalopathies:

- WHO Document: Report of the WHO consultation on public health issues to animal and human spongiform encephalopathies. Geneva, 12–14 Nov. 1991
- CPMP Document: Guidelines for minimising the risk of transmission of agents causing spongiform encephalopathies via medicinal products CPMP III/3298/91-EN, 11 Dec. 1991.

Risk related to undesired pyrogenic, immunological and toxicological reactions — To manage this risk, relevant parts of EN 30993 “Biological evaluation of medical devices” such as

Part 1: Guidance on selection of tests

- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- Part 4: Selection of tests for interaction with blood
- Part 5: Tests for cytotoxicity *in vitro* methods
- Part 6: Tests for local effects after implantation
- Part 7: Ethylene oxide sterilization residuals
- Part 9: Degradation of materials related to biological testing
Technical Report
- Part 10: Test for irritation and sensitization
- Part 11: Tests for systemic toxicity
- Part 12: Sample preparation and reference materials
- Part 16: General guidance on toxicokinetic study design for degradation products and leachables

can be used.

8. Discussion

The directives and standards discussed only deal with non-viable animal tissue and/or derivatives. There is only a proposal to take in account non-viable or rendered non-viable human tissue. If this proposal is accepted, new work items shall be mandated to CEN and CENELEC to write standards. Some of these standards will then be small extension of existing standards or standards under preparation.

Viable tissue from animal or human origin and hybrids of non-viable tissues and viable cells have not yet been discussed.

1.2 REGULATORY MODELS FOR SAFETY AND QUALITY OF ALLOGRAFTS: USA (HEART VALVES)

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1. Introduction

Heart valves in the United States are regulated as a Medical Device by the United States Food and Drug Administration (FDA). The FDA does not issue standards *per se*, but rather, they issue requirements and guidelines by which an organisation develops its own policies and procedures for operations which assure that the tissue processed is safe and effective.

This has been an FDA challenge because allograft heart valves were the first human tissue (besides blood) to be formally regulated by a system that was designed to oversee manufacturing of traditional devices, drugs and biologic products. At this time, other allograft tissues such as skin, bone and blood vessels are regulated as *Banked Human Tissues*. Allograft heart valves are the only “traditional” tissue to be regulated as a device.

Also, at this time there is no law which gives tissues a formal regulatory category designation. So the designation of *Banked Human Tissue* is derived at by the regulation of human tissues under broad powers given to the FDA under the communicable diseases provisions of the Public Health Service Act. This regulation is in the form of an *interim rule* defined in Volume 21 of the Code of Federal Regulations part 1270, referred to as 21 CFR 1270.

2. Overview of FDA Regulation

First, a brief overview of FDA Regulation. There are two major divisions of the FDA which deal with allografts and human tissues:

- 1) The Center for Biologic Evaluation and Research (or CBER), and biologic products.
- 2) The Center for Devices and Radiological Health (or CDRH) which regulates Devices and any product utilising radiation in its applications.

Devices are further classified as Class I, II or III depending on the degree to which the device has potential for causing injury or death, known as significant risk, to the patient due to a malfunction of the device, Class I having the least potential for harming the patient and Class III having the greatest significant risk.

The FDA does not issue product standards *per se*, but promulgates requirements and guidance points that the regulated party must follow to develop its own standards. The Code of Federal Regulations (CFR) contain these regulatory requirements and can be compared with the European Union Medical Device Directives.

3. FDA Regulation of the Tissue "Device"

The "Standards" for heart valve banking were initiated on June 26th 1991 when the FDA issued a notice of applicability which states that regulation applying to manufactured replacement heart valves would

also apply to allograft replacement heart valves. Furthermore, the allograft heart valves would be a Class III device, requiring Pre-Market Approval (PMA). In order to gather the safety and efficacy data needed for the PMA application, the tissue processor would also have to apply for an Investigational Device Exemption (IDE), so that the valve could be legally used to accumulate clinical performance data prior to obtaining the PMA.

This process for oversight of tissue processing was cumbersome and its need questionable, especially since the allograft heart valve had been in use for over 20 years at that time. A group of allograft heart valve processors brought a legal suit against the FDA to seek relief from Class III regulation and on October 7th 1994, a Federal court issued an injunction against the FDA stopping it from enforcing the Class III device, IDE and PMA requirements. The Federal Court instructed the FDA and the allograft heart valve processors to develop special controls for the purpose of regulating allograft heart valves as Class II devices. Class II devices do not have the degree of clinical detail requirements as with the Class III IDE and PMA.

4. FDA Regulation Contrasted with Technical Standards

4.1. The FDA method

The FDA method of regulation is also different from the method of Technical Standard setting, which many tissue banks are familiar with. FDA oversight can be considered process or outcome-based as opposed to procedure-based technical standards.

Effectively, the FDA wants to see proof that policies and procedures developed produce a safe and effective product. The FDA also wants to see that the organisation follows its stated policies and procedures on a uniform basis. The FDA, only on a broad sense, dictates the parameters for the policies and procedures you will use to produce the product. Contrast this with Technical Standards, where you will see specific procedures that must be followed in your operations in order to meet the oversight criteria.

In order to illustrate this further, I use the analogy of making a chocolate cake. The FDA wants to see how your process insures that every chocolate cake you make is delicious. Technical standards will give you an actual recipe and ingredients for a chocolate cake.

4.2. The ISO method

It would also be useful here to briefly discuss a regulatory process put forth by the International Organization for Standardization (ISO). The processing facility I am associated with, CryoLife, is ISO 9001, EN 29001 and EN 46001 registered and has also received the CE mark on a porcine valve that we manufacture. ISO and CE oversight is different again from FDA and technical standard procedure-based regulation. ISO places its focus upstream from dictating the specifications of the final product and requires documentation to support “**HOW** was the product processed vs. **WHAT** was produced.”

ISO 9000 standards require documented quality management systems for controlling the processes used to develop and produce products are aimed primarily at achieving customer satisfaction.

5. The Two Basic Functions of Heart Valve Banking

For the sake of regulation, Allograft heart valve banking can be separated into two basic functions, these being the physical recovery of the tissue and the preservation of the tissue.

The Tissue Recovery Function includes:

- Donor screening and selection
- Medical/social history review of the donor
- Surgical recovery and aseptic technique
- Donor tissue tracking

Requirements for the recovery of “Human Tissue Intended for Transplantation”, the first function, are spelled out in Volume 21 of the Code Federal Regulations, Part 1270 (21 CFR 1270). The FDA is

still in the process of developing final rules to be used in the medical and social history screening of the tissue donor.

The Tissue Preservation Function includes:

- The working of the tissue into a packaged, usable form or unit
- Quality assurance review
- Storage environment
- Transportation and distribution
- Recipient data and adverse event tracking

Requirements for the basic function of Tissue Preservation are mainly defined in 21 CFR 820, 807, 814 and 7 which spells out Good Manufacturing Practices (GMP), pre-market notification, facility registration and product recall.

5.1. Tissue recovery function

The Standards for Tissue Recovery are discussed in 21 CFR 1270 and contain the following considerations:

1. Donor Testing and Screening
 - Lists minimum required serology tests and serodilution factors
2. Medical and Social History
 - Requires confirmation of the donor's identity
 - Requirements for screening for clinical symptoms of and high risk behaviours associated with contracting HIV and Hepatitis
3. 21 CFR 1270, the Federal "Standards" for Tissue Recovery, also requires that there are written procedures describing donor screening for medical history and infectious disease screening.
4. There are general requirements for record keeping of donor results, tissue quarantine records and availability of records for transmission to wherever the tissue is if the records are not physically with the tissue.
5. Written procedures for interpreting donor testing and screening are required, as well as records of disposition of unacceptable tissue.

6. 21 CFR 1270 establishes FDA authority to inspect a tissue bank, as well as order the recall and destruction of tissue it feels may present a public health risk.

5.2. Tissue processing function

Tissue preservation requirements which are part of good manufacturing practices contain the following points of consideration:

1. Listing of responsible persons in the facility and policies on how they interact with each other.
2. Personnel policies which address matters of staff experience, training and hygiene.
3. Policies which ensure that there is sufficient space and proper environmental control to safely process tissue.
4. Procedures for validation of clean room areas and calibration of equipment and measuring devices.
5. Policies and procedures for the proper recovery, shipping and receiving of recovered tissue.
6. Procedures for tissue processing and all of the steps associated with tissue dissection and handling such as
 - aseptic technique
 - determination of tissue suitability and discard, if the tissue is not suitable
 - issuance of identification numbers or codes for tissue tracking
 - precise method to preserve the tissue
 - mechanisms for staff supervision and review of technical work performed
7. Procedures for the safe transportation and distribution of the tissue.
8. Tissue tracking records of tissue ordering and shipment, such as
 - what tissue has been shipped to what hospital
 - when the tissue was ordered and shipped
 - who ordered the tissue
 - when was the tissue shipped and when did it arrive

- when the tissue is used
9. Processing Control System, quality assurance
- * An overall Quality Assurance Policy and Procedure system must be detailed and specific so that there is no question as to how tissue has been processed and reviewed throughout the entire system to insure safety and efficacy. Some points to consider in the Q.A. System are
- Q.A. Personnel qualifications
 - the ongoing calibration and validation systems for equipment and facilities
 - supply and processing component material control and release system
 - donor and tissue review and release system
 - a system for reporting, investigating and correcting any errors and accidents
 - review and change of operational and organisational policies and procedures
10. Document control
- * A control mechanism to insure that the latest and most up to date documents are in circulation and that out of date documents have been retrieved and destroyed so that there is no confusion as to what are the correct and current procedure.
- procedures for the care and handling of all records and documents
 - mechanisms for internal auditing of operations
 - policies for reporting and recording reports of adverse events from the tissue implant site
 - an action plan for taking corrective action on reports of adverse occurrences from the field including mechanisms for recall of any other tissue which may be affected by an adverse event report
11. All of these policies and procedures must be easily available for review by any and all concerned staff members and regulating bodies.

6. Legislation

Regulatory efforts sponsored by the United States Government, such as 21 CFR 1270, have been undertaken as a response to perceived threats to public health by infectious disease from allograft tissues. These efforts are authorised under broad "emergency" powers granted to the FDA to protect the public from infectious disease transmission from any source. There is no present law which specifically requires the FDA regulation of tissue banking.

However, now there is legislation that has been introduced to the Congress designed to formally legislate the regulation of human tissue. Usually, no one involved in an industry is in favour of its regulation; but in this case it is possible that legislation is necessary to help make some sense out of a confusing and perhaps patchwork, regulatory situation.

The proposed legislation, called the *Human Tissues Safety Act of 1996* (introduced on October 3, 1996 by Senator Ronald Wyden {D-ORE}) would actually designate *Human Tissue* as a formal regulatory category under the jurisdiction of the FDA's CBER. Presently, the only formal regulatory category which exists for a "traditional" human tissue is for allograft heart valves and that is as a Device.

The proposed legislation calls for registration of all tissue banks and provides a detailed definition of exactly what is considered human tissue as opposed to a biologic product or an "engineered" tissue or cell. The Act also provides authority of facility inspection and enforced compliance of tissue bank operations with applicable operating standards. The Act would also provide that tissue banks maintain a patient registry if a tissue has not been commercially available for a period of five years.

As a point of relevance to this article, Under the *Human Tissues Safety Act of 1996*, the allograft heart valve would be reclassified as a human tissue. However, no action has taken place on this proposed law and, as of the date of this article, allograft heart valves remain regulated as a device and, as per the Federal Court Injunction which

we discussed earlier, special controls are being developed by an *ad hoc* group of heart valve processors for presentation and reconciliation with the FDA.