



Tissue and Cell Processing

AN ESSENTIAL GUIDE

EDITED BY

Deirdre Fehily, Scott A. Brubaker,
John N. Kearney and Lloyd Wolfinbarger



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Foreword

It gives me great pleasure to introduce this book, which covers the historical context of tissue and cell processing since the first allograft implantation was introduced clinically to current practice in tissue and cell banking. Its publication is timely – in the golden jubilee year of the first heart valve allograft (homograft) operation in 1962. Even then, it was clear that allografts had significant benefits over mechanical valves, which continue to require lifelong anticoagulation and carry the increased risk of stroke or bleeding, a particular problem in populations with limited medical staff and facilities. Our only disappointment was that it became apparent that the homograft did deteriorate over a number of years and would eventually need replacement. This led me, in 1967, to perform the pulmonary autograft, where the patient's pulmonary valve is transplanted to the aortic position and the pulmonary valve is replaced with a pulmonary allograft, where it is subjected to much lower pressures and therefore should have improved longevity. This continues to be *Work in Progress*. Research in tissue engineering and stem cells currently holds great promise for donated cardiac tissue.

From those early pioneering days we have seen the development of highly professional, uniform systems, embracing all aspects of organ and tissue transplantation, enshrined by the guiding principles issued by the World Health Organization.

This book describes parallel developments in other clinical specialties where tissues or cells have been donated for the benefit of others. It is not surprising that many common themes emerge across these specialties. It is a comprehensive guide to the level of technical complexity and precision required, where surgeons can be assured that the graft they receive for implantation will meet a particular specification. I have no doubt this publication will be regarded as a required handbook for tissue banks throughout the world.

Donald Ross



Preface

It was the development of techniques to preserve donated tissues and cells that gave life to the field of tissue and cell banking. This ability to store is what makes tissue banking different from organ transplantation. The banking activities of washing, cutting, shaping, cell separating, decontaminating, preserving, packaging, storing and distributing have become almost industrial in many countries, with large numbers of “products” being prepared and distributed internationally. But these are not like other healthcare products. Their human origin gives them a very particular nature, associated with the fact that they have been donated by people who want to help others and with the inescapable knowledge that they carry some risk for recipients, usually very small but sometimes unpredictable or undetectable. On the spectrum of healthcare substance processing, tissues and cells sit with blood components, somewhere between organ transplantation at one extreme and medicines manufacture at the other. This second book in a series of three explores those aspects of tissue and cell processing that aim to preserve and respect the special, emotional aspects tied to their human origin, while maximizing safety and quality through the application of quality standards and approaches similarly applied in other fields, such as the manufacture of aspirin or, for that matter, cars!

The development of methodologies to preserve tissues and cells brought with it a number of advantages. Once tissues could be made readily available for human application at a later date, shortages could be avoided with banked inventories providing various sizes and types as required. Better utilization of invaluable donations became achievable by making multiple grafts from single donations: the cortical bone of a femur could be used to prepare strong weight-bearing rings for spinal surgery while the cancellous bone of the same femur could be morcelized and provided as an effective packing material to fill bony defects. With this greater donation utilization came the opportunity to cut and shape certain graft types in advance, saving

time in the operating theatre. Allografts are not only transplanted, they can be infused, implanted or transferred, and prepared for specific applications. For example, the 120 mL of collected cord blood becomes 25 mL of concentrated progenitor cells, the placental membrane becomes a batch of clean 1 cm square patches for ocular surgery, and one semen donation becomes a series of aliquots of washed spermatozoa. But apart from this increase in efficient use of donations, tissue and cell banking brought opportunities to increase safety by removing those parts of the tissue or cell donation that were not necessary for clinical effectiveness or by applying decontamination or sterilization methods to remove bacterial, fungal or, in some cases, viral agents.

Tissue and cell processing brings these indisputable benefits but it also brings its own risks. The literature has documented rare but sometimes tragic results of environmental contamination and cross-contamination, of the extension of donor-derived risk to multiple recipients through large scale processing, of the accidental mixing of gametes or embryos or the reliance on sterilization methods that were not properly validated or effective. The potential for making profit from tissue and cell recovery and processing exacerbates the risk that income will be prioritized over safety and quality. For all these reasons, the world of tissue and cell processing is increasingly regulated. Professionals and regulators alike call on the field to maximize the benefits of processing and storage, while minimizing the risks, by applying the knowledge and tools of “manufacturing,” particularly those of the pharmaceutical industry, to achieve consistently high levels of quality and safety.

In this book, in line with the other two books in the series, we have drawn on the experience and expertise of international experts to capture and describe, in a didactic way, the key principles of safe and effective banking in this “industry” that is like no other. The regulatory framework is described and chapters address the scientific principles behind tissue and cell preservation, decontamination and sterilization – the added value of tissue and cell banking processes. Many of the processes that have been applied over the years have developed in a “cottage industry” way and been copied from bank to bank; Chapter 7 describes how facilities can meet today’s regulatory expectation that processes be properly validated and thoroughly documented. The importance of risk management, traceability and coding and personnel training are all addressed by experts who have learned through experience that these aspects are crucial to providing safe allografts. Finally, a series of chapters address the specificities of particular substance processing from skin or bone marrow to gametes and embryos.

Despite huge developments in science and technology, donated human tissues and cells are frequently still the best option for replacement of damaged or diseased tissues or cells in patients or for achieving successful pregnancy. In parallel, however, novel and creative approaches are being developed as described in Chapter 18. Traditional tissue and cell banking is

likely to co-exist well into the future, providing an essential clinical service, with exciting, more sophisticated new processes such as cell culture, gene therapy or tissue engineering.

The editors of this book are most grateful to all the authors who worked together, always trying to ensure that the “best practice” picture they presented reflected varying geographical and regulatory realities. Many of the authors who worked together to write these chapters had not known each other previously but have forged strong professional relationships through this collaboration. The editors would also like to thank Mr Donald Ross for writing the Foreword. Now retired, Donald Ross was a pioneering cardiac surgeon who performed the UK’s first heart transplant in 1968, having already been the first surgeon in the world to use an aortic homograft in 1962. He went on to advance the use of pulmonary homografts and originated the pulmonary autograft operation which is now known as the Ross Procedure. The first book in this series was published in 2009 and addressed tissue and cell donation. The third is published in parallel with this book and addresses tissue and cell clinical use. The editors hope that these three books together provide a comprehensive guide to the provision of safe and effective tissues and cells for human application through ethical and safe donation procedures, validated antimicrobial and preservation processes, and appropriate clinical application.

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1 Regulations and Standards

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Introduction

The primary purpose of statutory regulations is to serve as a common framework for ensuring with confidence the current state of the art on the quality and safety of tissues and cells for therapeutic benefit. Equally, the regulations and linked guidance should be compatible on a wider level to encourage equitable distribution between countries, where regulations may be similar and well established, in early development, or in their infancy. Many countries have implemented or are refining their healthcare services to provide a better standard of care to patients and to enhance the use of tissues and cells for clinical applications. The steps involved in the processing of tissues and cells are critical activities and require the application of specific controls to prevent contamination and cross-contamination, as well as to maintain quality and safety. This chapter gives an overview on the status, history, and scope of key regulations; the practical aspects of implementation; the interface with advanced therapy medicinal products (ATMPs); medical devices; biologics; and some global perspectives.

The therapeutic application of tissues or cells is preceded by a series of complex and inter-related activities, from donor selection and screening, infectious disease testing, tissue and cell recovery, processing, temporary or long-term storage, and distribution for use in the clinical setting. The organization and delivery of healthcare systems are structured and operate quite differently, according to resources and health programs, to address epidemiological characteristics of the endemic population. To encompass these

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diverse organizations, and their inter-linked activities, a tissue establishment can be defined as:

a tissue bank or a unit of a hospital or another body where the activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for the procurement or testing of human tissues and cells [1].

Organizations in healthcare services or the commercial sector performing one or typically more of these activities should be authorized by their national regulating body and are expected to verify compliance with appropriate requirements, so governing the quality and safety of tissues and cells.

Professionals working in the tissues and cells sector have not been wholly amenable to “allografts” being referred to as “products” or “devices;” and some have reservations regarding the use of the term “manufacturing” being applied in the context of human tissues and cells donated altruistically for the benefit of others. However, regulatory preferences and established terminology of other healthcare sectors often over-ride the human dimension in this donation-related work and such terms are commonly applied. This chapter discusses the requirements and language that affect professionals involved in the processing of tissues and cells for transplantation.

To assist all countries where cell and tissue banking activities are developing, and some without regulatory oversight, the World Health Organization (WHO) convened meetings in 2004 and 2005 with the participation of numerous experts and regulators from across all of the WHO regions. Global standards necessary for the development of safe tissues and equitable and ethical access to donation and transplantation of tissues and cells were discussed. This resulted in two useful aide-memoires for use by emerging health authorities, published in 2005 [2] and 2006 [3]. Among other key elements, both documents promote the benefits of quality systems and quality programs. The concept of a supplementary aide-memoire on the generic principles of inspection for tissue and cell establishments, including processing controls, was initiated in late 2009. Following this, in May 2010, the 63rd World Health Assembly endorsed a resolution on the WHO guiding principles for human cell, tissues and organs transplantation [4], which urged Member States to formulate and enforce their own policies, laws and, regulations on this subject.

Regulations – development, scope, and principles

Europe

The forerunner to the Tissue and Cell Directives (see below) was a comprehensive guidance document published by the European Health Committee

of the Council of Europe which defined the standards required, and quality assurances to be achieved, for the transplantation of organs, tissues, and cells. It was updated again in 2010 [5] and is a valuable source of scientific information and clinical practice guidance. The first legislative proposal to set binding requirements on the quality and safety of human tissues and cells by the European Commission was presented in 2002. Its objective was to facilitate the cooperation and collaborative activities between the health-care systems of the Member States. The regulation of substances of human origin, such as blood, tissues, cells, and organs, at a European Union (EU) level became legally possible when the Treaty of the EU was amended in 1995 by Article 152 of the Treaty of Amsterdam. This article extended the legal competence of the EU to certain aspects of healthcare stating that “Measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives” would be adopted. The legal basis would allow individual Member States to adopt more stringent requirements if they considered it appropriate. National representatives of the Member States, together with their experts, then negotiated a technical and political approach for the regulatory framework to control these activities for the greater protection of public health.

The entry into force for the principal Directive 2004/23/EC [1] was April 2006, which preceded Directive 2006/17/EC [6] in November 2006 and Directive 2006/86/EC [7] in September 2007. Collectively these are the “Tissue and Cell Directives” which address the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, distribution, and import/export of human tissues and cells. Since then the Member States have transposed the Directives into national laws and put in place the implementation measures for their application. Aspects of these Directives apply also to other manufactured products that are regulated as medicines but are wholly or partially derived from human tissues and cells. Specifically, donation, procurement and testing of the tissues and cells used for the manufacture of such products are regulated by the Tissue and Cell Directives. Tissues and cells used as an autologous graft in the same surgical procedure and those used for research studies not involving application to the human body, are excluded, as are organs, blood, and blood products. The Tissue and Cell Directives therefore regulate tissues for transplantation such as bone, skin, heart valves and corneas, cells such as hematopoietic stem cells from bone marrow, peripheral blood, or cord blood as well as other cells that are not extensively manipulated, plus gametes and embryos.

United States

As a comparison, tissue regulations in the USA were first introduced in the 1980s and aimed at processing requirements for the manufacture of two specific human tissue types, corneal lenticules and, separately, human dura mater. By mid-1991, cryopreserved allograft (replacement) heart

valves were singled out as a “product,” like man-made replacement heart valves, requiring data submission to demonstrate safety and effectiveness. These allografts were classified as medical devices by the Food and Drug Administration (FDA) and regulated by their Center for Devices and Radiological Health (CDRH). Although enforcement of requirements related to the Class III medical device designation for allograft heart valves was rescinded due to a decision in late 1994 [8], other federal regulations were published in 1993 and were applicable to a variety of conventional tissue allografts. This federal oversight of human tissues for transplantation advanced further after two specific events. In 1991, there was realization of HIV transmissions from the transplantation of human tissue from one donor reported by the Centers for Disease Control and Prevention (CDC). Soon thereafter, the FDA received reports from US tissue banks of brokers selling unprocessed tissue from improperly screened and tested donors from Russia, eastern Europe, and Central and South America [9]. In response to the concern for public health, the FDA published an Interim Final Rule entitled “Human Tissue Intended for Transplantation” [10]. With this publication, the FDA’s Center for Biologics Evaluation and Research (CBER) was assigned responsibility for oversight of tissue establishments that screen donors, and recover, process, store, and/or distribute tissue for transplantation. This Interim Rule, codified in 21 CFR Part 1270, included minimum requirements for screening and testing tissue donors, and maintaining procedures and records with specific emphasis on preventing the transmission of viral hepatitis and HIV. The American Association of Tissue Banks (AATB) and the Eye Bank Association of America (EBAA) actively promoted communication between industry professionals and CBER to ensure further development of regulations would be effective. Various public workshops and meetings were held and in June 1997 the FDA published a Final Rule and Guidance Document that amended parts of the Interim Rule. These focused on considerations involving the eligibility of deceased donors such as criteria to be used when screening, infectious disease tests that must be performed, plasma dilution evaluation of the blood sample used for testing, and the physical assessment of the donor.

FDA also announced their “Proposed Approach to the Regulation of Cellular and Tissue-based Products” which outlined a tiered, risk-based strategy for regulating traditional tissues as well as new cell/tissue allograft products. This oversight was aimed at the control of contamination and cross-contamination throughout all manufacturing steps. The “Tissue Action Plan” (TAP) was developed to guide this proposal to fruition. Soon after the start of the new millennium, the FDA described a more comprehensive regulatory framework, codified it in 21 CFR Part 1271, and promoted regulations via final rules that encompass registration of tissue establishments and listing of products (2001) [11], donor eligibility requirements (2004) [12], expectations for maintaining Current Good Tissue Practice (2004) [13],

and reporting, inspection, and enforcement regulations. The last of the final rules published in 2004 became effective for cells and tissues recovered from donors after May 25, 2005. The regulations in 21 CFR 1271 describe the scope of the expanded oversight to be applicable to human cells, tissues, and cellular and tissue-based products (HCT/Ps). These are described as conventional tissue (e.g., bone, including demineralized bone, skin, tendons, ligaments, fascia, pericardium, dura mater, cartilage, heart valves, veins/arteries, amniotic membrane), ocular tissue (i.e., corneas, sclera), reproductive tissue (i.e., semen, oocytes, embryos), and hematopoietic stem/progenitor cells (including cells derived from peripheral or cord blood). Federal regulations have matured to include a wide variety of allograft cell/tissue products intended for implantation, transplantation, infusion, or transfer into human recipients, whether sourced from living or deceased donors.

21 CFR 1271 is not applicable to some human-derived therapeutic products, such as solid organs used for transplantation; blood or blood components; minimally manipulated bone marrow; secreted or extracted human products such as milk, collagen, and cell factors; and products derived from or exposed to cells, tissues, or organs from non-human animals. In addition, exemptions include autologous tissue re-implanted within the “same surgical procedure.” A regulatory ladder (tiered, risk-based approach) was created to address nuances if HCT/Ps are combined with other materials or whose use and effect on the body become complicated after further manipulation. In a number of ways, HCT/Ps may be elevated to a higher regulatory scheme that encompasses requirements for medicinal products, specifically those attributable to FDA designation as a “biologic” or a “medical device.”

Australia

In the Therapeutic Goods Act 1989 and subsequent amendments, human organs, tissue, and cellular products, as well as tissue- and cell-based derivatives, are regulated by several different routes. The related Australian Code of Good Manufacturing Practice (GMP) [14] is applicable to human tissue for transplantation when procured, stored, and supplied without deliberate alteration to its biological and mechanical properties (e.g., dura mater, heart valves, skin, corneas, and bone). It was published by the Therapeutic Goods Administration (TGA) in 2000 and adopts GMP expectations for tissue establishments. The quality system requirements include quality objectives, organizational structure, monitoring systems, and management review. It incorporates many quality systems elements from the ISO 9000 series of standards and equally applies these principles for the control of blood products. Similar to the regulatory designations for human tissues and cells in Europe and the Americas, these allografts may be regulated as medicines or therapeutic devices, depending on their biological/mechanical properties or their therapeutic purpose. The regulation of viable human and animal

tissues that undergo processing and modification prior to implantation or infusion to patients have yet to be fully addressed in the current legislation. In July 2002, the Australian Health Ministers supported the TGA for a regulatory framework for human tissues and emerging biological therapies. The ensuing Human Cellular and Tissue therapies (HCT) framework was originally planned as a part of the regulatory partnership between Australia and New Zealand, but its postponement in July 2007 meant the HCT framework was delayed. In July 2009 the Australian Government moved forward independently with this framework, which excludes assisted reproductive tissues and solid organs. Hematopoietic progenitor cells are envisaged to be part of the framework, after a public consultation phase with that profession's stakeholders. Recently, amendments to the Therapeutic Goods Regulations 1990 that create a new regulatory framework for biologicals were passed by Executive Council on March 10, 2011. The biologicals framework commenced on May 31, 2011. After this date, all products within the scope of the framework will need to comply with the requirements made under the new legislation, but a three-year transition period is provided for establishments to come into compliance. Four classes of biologicals have been developed, based upon risk, extent of manipulation applied, and whether use is homologous or not. In this regard, similarities exist with the European and US perspective but a major difference is that the submission of an extensive dossier for products is required for not only Class 3 and 4 biologicals, but also for Class 2. A dossier of information on a product is akin to a "device history file," so requiring this extensive compilation to characterize a Class 2 biological, which is equivalent to a conventional tissue allograft in the USA, is an onerous task for tissue banks. Guidance documents are being developed to assist stakeholders to better understand the TGAs expectations. It is also interesting to note that these biological products (of any class), once reviewed and approved by the TGA, become officially listed on the Australian Registry of Therapeutic Goods (ARTG) and a reimbursement fee is assigned to each one. This is an agreed minimum fee for supplying the product within Australia and must be honored by insurance companies and healthcare providers.

Within the TGA regulation for process control, the quality assurance of the manufactured product is described and encompasses specific requirements for documentation, materials, procedures, conditions, quality control related to sampling, validation of processes to be supported by data, and product release. The glossary contains definitions helpful for the qualification of equipment and validation of processes, prospective and retrospective; and yet, to date, specific guidance is not offered regarding the means to validate the steps used in the processing/manufacture of human tissues. The TGA regularly reviews technical data submitted by tissue establishments that supports the processing steps they use and their claims.

Canada

Continuing with the development of national regulations, in June 2007, Health Canada published “The Safety of Human Cells, Tissues and Organs for Transplantation Regulations” (CTO regulations) [15], with a further supplement which came into force in June 2008. The draft “Guidance Document for Cell, Tissue and Organ Establishments, Safety of Human Cells, Tissues and Organs for Transplantation” [16] was released at this time and finalized in April 2009. The CTO regulations establish safety requirements relating to the processing and handling of CTO products, resulting in improved protection of the health and safety of recipients. These regulations directly reference sections of the General Standard CAN/CSA Z900.1 [17], entitled “Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements,” along with four of the five standards for specific organ and tissue types, thus making them mandatory. Based on the National Standards, the regulations set out basic safety requirements with respect to donor screening, donor testing, collection/retrieval, processing, preservation, packaging, labeling, storage, quarantine, record-keeping, distribution, importation, error, accident and adverse reaction monitoring, reporting, and investigation. Establishments distributing CTOs are required to have a quality assurance system [17] in place that complies with the requirements of the regulations, which enables them to perform their activities effectively. Important components of a quality assurance system are the standard operating procedures (SOPs), which must be kept current and approved by the medical or scientific director.

The prescription of requirements for CTO processing, as defined by regulations in Europe, the USA, and elsewhere, are not clearly elucidated in the federal regulation but are described in the CSA standards for tissues and cells. By definition, the term “processing” (French: “traitement”) means a series of steps, which in other regulations are “manufacturing” phases, such as: donor screening, testing and suitability determination; retrieval; testing/measurements performed on tissue; preparation for use; preservation; quarantine; banking; packaging; and labeling. The CTO regulations/guidance and the CSA standards have not yet defined qualification, validation, or verification, and these terms are attributed to personnel, records, equipment, supplies, labeling, and technical review for tissue release. The section of Process Control in the CSA standards (Z900.1–03) lists requirements for the major components of the operations for a tissue establishment. Updates to these CSA standards are expected during late 2011 or early in the following year.

Brazil

The public health regulations in Brazil are structured under the guidance of Agência Nacional de Vigilância Sanitária (ANVISA) whose mission is to foster health protection by exercising contamination control on the production and

marketing of products and services. Blood, other tissues, cells, and organs are within this oversight and ANVISA works, with state and county systems, to promote sanitation vigilance as a social right/protection. ANVISA was established by law [18] in January 1999 and is designated an autonomous agency operating as an independently administered, financially separate regulatory agency. In the Federal Public Administration, ANVISA has a management contract with the Ministry of Health [19] for their responsibilities to coordinate the National Sanitary Surveillance System (SNVS) [20], the National Program of Blood and Blood Products, and the National Program of Prevention and Control of Hospital Infections.

Specific to tissues, a resolution was enacted in December 2006 and provides for the technical regulations for the functioning of musculoskeletal tissue banks and banking of human skin [21]. It promotes the principles of quality and risk reduction by the adoption of measures outlining critical controls for tissue banking operations and assists with the development of objective guidelines for inspections. The tissue banking profession is fairly young in Brazil but is rapidly developing and, like other tissue establishments located elsewhere, some room for improvement has been identified as a result of inspections by authorities. These regulations are well written, comprehensive, and offer excellent directions for establishing and maintaining quality systems, including requirements for the physical facility, equipment and materials, and operations of the tissue bank. The annex contains sections that are reminiscent of a technical manual and contain good tissue practices garnered from professional standards and international regulations. For instance, some particular requirements relating to processing and packaging include the following:

- It should be performed in a controlled and classified environment.
- Throughout processing the lyophilizer should be maintained in a controlled environment.
- The final package must ensure the moisture content during product life.
- The sterility of tissues should be guaranteed by a complementary validation sterilization process.

By following these and other prescribed mandates, the professionals have a protocol for developing successful systems to provide safe, quality tissues for transplantation. A major reorganization and some revisions to these regulations are planned during 2012.

Singapore

In Singapore, the regulatory control for the processing of human tissue rests with the Licensing and Accreditation Branch of the Ministry of Health. This is implemented through site establishment licenses issued under the Private Hospitals and Medical Clinics Act, and establishments are expected

to duly comply with the formalized “Guidelines For Healthcare Institutions Providing Tissue Banking” [22]. In addition, the Health Sciences Authority (HSA) of Singapore will be implementing the regulatory framework for regulating human cells and tissue-based therapies (CTT) under their current legislation. In line with the regulatory approach undertaken by regulatory agencies in the EU and USA, the HSA intends to adopt a risk-based approach in regulating CTTs. These are viewed as substantially manipulated, for non-homologous use as well as in combination with a drug/biologic/device, and will be subjected to regulatory control similar to pharmaceuticals and biologic medicinal products. These controls include product registration, clinical trial certification, manufacturer’s licensing or GMP certification, and reporting of serious adverse events. In tandem with the regulatory framework applicable to medicinal products, the applicant for product registration for CTTs will be required to submit dossiers, including the product information for chemistry, manufacturing, and control, while the respective manufacturer will be required to conform to the PIC/S GMP guide [23] and its relevant annexes, or equivalent. As a science-based organization recognizing the vibrant development in the field of CTTs, the HSA is committed to closely collaborate with benchmark regulatory agencies and work with stakeholders to fulfill its national responsibility in promoting and advancing public health and safety effectively.

Highlighted above are some brief insights to the history and current status of several national regulations and established systems for ensuring the quality and safety of human tissues and cells. Other countries, for example Korea, India, and Japan, have active work programs for implementing similar controls to improve the quality and safety of human tissues and cells.

Regulations – tissue and cell processing

European Union

For compliance with Directive 2004/23/EC, national regulators are required to authorize the tissue and cell preparation processes performed in tissue establishments. Annex II of Directive 2006/86/EC assists this assessment activity by defining the requirements for the evaluation of donor selection criteria and procurement procedures, the relevant protocols for each step of the process, the quality management criteria, and the final quantitative and qualitative criteria for cells and tissues. Consequently, regulatory oversight of these control systems (i.e., the evaluation of critical processing procedures) is becoming the norm and it can be approached in several ways. Validation of critical processing steps may be based on studies performed by the establishment itself or on data from published studies or, for well-established processing procedures, by a retrospective evaluation of the clinical results

of the tissues or cells supplied by the establishment. Consistency as well as effectiveness of the preparation process in the establishment environment is of particular importance. The quality system should be updated for any significant change to the process and/or after revalidation and qualification programs. A formalized review process is expected to periodically verify that they achieve their intended purpose. As the tissues and cells are native to the human body, with established functionality and proven beneficial purpose – in contrast to medicines or medical devices – the tissue establishment has the duty to demonstrate the preparation process did not render the tissues or cells clinically ineffective or harmful to the recipient.

Annex 1 of Regulation No.1394/2007, for advanced therapy medicinal products, includes a list of processes which are not regarded as “substantial manipulation”. The list includes:

cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation and vitrification.

The exclusion list, subject to modification as technology progresses, is more commonly associated with the processing operations in tissue establishments. Where, for example, “separation,” “concentration,” and/or the “purification” of human cells or tissues (e.g., for the isolation of pancreatic islet cells) is undertaken, it is achieved by the application of process technologies and selective media to maintain the natural state, biological characteristics and native functions of the cells or tissues. The aforementioned processes are viewed as suitable candidates for the use of the “preparation process dossier” (see later section). The technical requirements for the validation of manufacturing processes of advanced therapy medicinal products are specified in a guideline on human cell-based medicinal products [24] from the European Medicines Agency (EMA).

The processing of tissues and cells shall take place in a controlled environment with specified air quality and cleanliness to minimize the risk of contamination, with appropriate measures to prevent cross-contamination. The four classifications (i.e., Grade A, B, C, and D) of environmental standards, with their defined physical and microbiological parameters, are specified in the European Guide to Good Manufacturing Practice for Medicinal Products [25]. Where there is no subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A, with a background environment of at least Grade D, is the normal requirement according to the European Directives. In exceptional circumstances, an alternative standard may be applied where it achieves the quality and safety required for the type of tissue and cells, the process itself, and the proposed human application. Illustrative examples include:

- Where a validated terminal sterilization process has been applied.
- If the expected environment might have a detrimental effect on tissue or cell properties.
- Where the mode/route of application to the recipient has a lower risk of infection transmission than its transplantation.
- Where it is not technically possible to carry out the process in the specified environment.

In all cases the environmental standard applied and its rationale is to be specified within the quality system of the tissue establishment so that it can be scientifically demonstrated to achieve the required standards for quality and safety, taking into account the intended purpose, mode of application, and recipient status.

Advanced therapy medicinal products

The transitional phase for the EU healthcare program of Regulation (EC) No.1394/2007 [26] for advanced therapy medicinal products (ATMPs) started in January 2009 and includes three types of medicinal products for human use: gene therapy, somatic cell therapy, and tissue engineering (e.g., expanded chondrocytes for the repair of damaged cartilage or cultured fibroblasts/endothelial cells for treating skin burns or ulcers). The prerequisite for an ATMP is to ascertain its product characteristics and intended purpose meet the definition for a medicinal product and secondly to review the applicability of Regulation (EC) No.1394/2007. Where these are met, Article 2 of Directive 2004/23/EC stating that “Where such manufactured products are covered by other Directives then it shall apply only to donation, procurement and testing” becomes relevant. For example, tissue engineering is focused towards viable “engineered” human or animal cells and is defined as a product that “contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue”. It subsequently follows the cells or tissues are “engineered” where they fulfill at least one of the following conditions:

- The cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair or replacement are achieved.
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

A process such as “cell culture/expansion” is not included in the list of processes in Annex 1 of the Regulation, implying that it is considered to be substantial manipulation and is therefore “engineering” (e.g., the

expansion of chondrocytes, so the same characteristics, functions or properties are maximally optimized for the reformation of new cartilage). This presumptive approach is consistent with the FDA regulations for “351 products,” where cell culturing/expansion is viewed as “more than minimal manipulation.” In the second case above, separated cells or tissues from a donor site are processed and transplanted into a different site in the recipient where it is intended they perform a different essential function from their natural role in the donor site. For example, isolated stem cells from bone marrow subjected to stimuli (i.e., chemical, enzymatic, or electrical) can in vitro differentiate to a cardiac cell lineage and be transplanted for the repair of myocardial tissue. Conversely, human amniotic membrane functioning as a physical barrier can be processed for ophthalmology applications where the essential function is the same and this is generally not viewed as an ATMP (see Case Study 1.3).

The principles of both regulations, for tissues and cells and ATMPs, overlap with each other. As the regulatory programs for tissue establishments are implemented, there is a parallel initiative for the newer regulations on ATMPs. It is beneficial that the common responsibilities (Box 1.1) at the interface of these work programs are coordinated and mutually compatible, to ensure the timely provision of modern alternative treatments to patients. In early 2012 a European Commission meeting of these health sectors reviewed the common interfaces of both legislative frameworks.

Box 1.1 Common responsibilities at the interface of tissue establishments (TEs) and ATMP manufacturers

- Training/expertise of the specialist inspectors
- The verification system for donation, procurement, and testing requirements
- Coordination of planning site inspections by related sectors
- Mutual recognition of site certificates between the regulators
- Compatibility of the roles and status of the “responsible person” (defined in the Tissue and Cell Directives) and the “qualified person” (defined in GMP for medicinal product manufacture)
- Systems for the long-term storage of quality and traceability-related records
- Reporting of serious adverse events and reactions linked to tissues and cells used in ATMPs to the TE sector
- Verifying coding systems for tissues and cells from the donor to/from the end recipient
- Traceability systems between the intermediaries of TEs and ATMP companies
- Management and control of TE requirements in the clinical investigations of ATMPs
- Defining practical start and end points of quality systems and GMP practices in the two sectors