

Guide to the quality and safety of tissues and cells for human application

2nd Edition

The *Guide to the quality and safety of tissues and cells for human application* is published by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM).

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Director of the publication: Dr S. Keitel

Page layout and cover: EDQM

Cover photo: © Fotolia – everythingpossible

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ISBN 978-92-871-8126-8

© Council of Europe, 2015

Printed at the Council of Europe



Partially funded by the European Union
in the framework of the Health Programme
2008-2013

Foreword

Founded in 1949, the Council of Europe is the oldest and largest of all European institutions and now numbers 47 member states.¹ One of its founding principles is that of increasing co-operation between member states to improve the quality of life for all Europeans. Within this context of intergovernmental co-operation in the field of health, the Council of Europe has consistently selected ethical problems for study. One of the most important of these ethical issues relates to the non-commercialisation of human substances: blood, organs, tissues and cells.

Transplantation activities at the Council of Europe are co-ordinated by the European Directorate for the Quality of Medicines & Health-Care (EDQM). This Directorate is a key European organisation involved in the harmonisation, co-ordination, standardisation,

¹ Albania, Andorra, Armenia, Austria, Azerbaijan, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Republic of Moldova, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, San Marino, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, 'the former Yugoslav Republic of Macedonia', Turkey, Ukraine, United Kingdom.

regulation and quality control of medicines, blood transfusion, organ transplantation, pharmaceuticals, pharmaceutical care, consumer health, cosmetics and food packaging.

Transplant medicine and transplantation have progressed during recent decades in a way nobody would have imagined in the preceding years. As with organs, the demand for some transplantable tissues and cells far outweighs the available supply. This has important consequences because human tissues and cells for human application can save lives or restore essential functions. However, as with all transplanted material of human origin, they carry risks of disease transmission that must be controlled by application of scrupulous donor selection and testing criteria, as well as ensuring that comprehensive quality systems are in place.

The first edition of the *Guide to the quality and safety of tissues and cells for human application* was published in 2013. It collated updated information to provide transplant professionals with a useful overview of the most recent advances in the field as well as technical guidance on ensuring the safety and quality of human tissues and cells applied to patients. To increase safety for recipients of human tissues and cells, it is essential that professionals involved in identifying potential donors, transplant co-ordinators managing the process of donation after death, bone marrow and cord blood collection centres, tissue establishments processing and storing tissues and cells, and inspectors auditing any of the establishments and organisations responsible for human application have easy access to this information. This Guide aims to support professionals on a practical level and improve the rate of successful and safe clinical application of tissues and cells.

This Guide contains the instructions considered to be the ‘minimum standards’ that align with relevant European Union (EU) Directives in the field, and provides assistance for those states outside the EU that consider adopting the EU requirements in their legislation. These standards state ‘what must be done’. However, this Guide goes beyond these standards by providing additional technical advice, based heavily on good manufacturing practice (GMP) guidelines and on

best practices consistent with current scientific knowledge and expert opinion. It describes background information that should be considered in forming policy decisions, as well as in educational initiatives. This additional information explains the ‘why and how’. It also refers to developments that have yet to be incorporated in EU Directives, thereby providing advance information and recommendations regarding technical developments in the field.

Whereas tissue establishments in EU member states are required to comply with legislation derived from EU Directives, this Guide is intended to facilitate ongoing improvements in the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells through education and provision of non-binding recommendations for EU member states and also for non-EU European countries. At any given time, implementation of these recommendations among member states and individual tissue establishments may vary, and alternative procedures, practices and standards of equivalent safety and quality may be in place.

This Guide has been divided into two parts. Part A contains general requirements applicable to all establishments involved in the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells that are not manipulated extensively. Part B contains specific guidelines and requirements for the different tissue and/or cell types. The general guidelines of Part A also apply to tissues and cells that have not been mentioned specifically in Part B of the present edition.

In this second edition, many chapters have been improved, and new and important chapters have been added. Most importantly, the field of assisted reproduction is now addressed in detail in Chapter 25 and the topic of fertility preservation is introduced in Chapter 26. The assisted reproduction field is regulated in the EU together with other types of tissues and cells that are applied to patients by Directive 2004/23/EC and its associated technical directives. This field is also included by the World Health Organization (WHO) in its definition of Medical Products of Human Origin (MPHO), which shares a

common need for robust ethical oversight and for safety and quality measures (requirements associated with their common origin in a human donor). A new working group was established with representatives from authorities and the European Society for Human Reproduction and Embryology (ESHRE) to develop these chapters and to carry out an extensive review of the chapters of Part A to ensure that they adequately address this field. It is notable that the generic chapters on topics such as quality management and donor consent, for instance, required minimal adaptation to address the field of assisted reproduction. The specific aspects of the field are addressed in detail in Chapter 25 in Part B. As a consequence of the inclusion of assisted reproduction in the guide, Chapter 1 (Introduction) has been updated to include important ethical principles that must be respected in the human assisted fertility field.

A very significant enhancement to the Guide has been the development of a chapter (new Chapter 8) dedicated to the principles of microbiological testing of tissue and cell preparations and their processing environments. Development of Chapter 8 was challenging because in the past the topic has been considered in a disjointed manner, with stakeholders involved in the collection or processing of tissues and cells developing their own principles and practices, and regulatory requirements providing minimal technical detail. The authors of this Guide have worked to achieve a practical and scientifically sound approach to this topic by bringing their prior knowledge and experience of microbiological testing in the field of pharmaceutical manufacture to the discussion. We believe that Chapter 8 is a key addition to this edition, recommending (among other features) the testing methods to be applied in the laboratory and, most importantly, outlining the principles that underpin validation of those methods. Some questions were not fully resolved and will be developed further in future editions.

As the fields of donation and transplantation of tissues and cells evolve, new and more sophisticated technologies will provide opportunities to make tissues and cells safer, or their engraftment more effective. Depending on the degree of complexity of the processing or

the manner in which the tissues or cells are applied to the recipient, some of these tissues and cells are classified in the EU as ‘medicinal products’. In many non-EU European countries, this differentiation is not made at a regulatory level, or there is no regulation of the field. Even in EU member states, many tissue establishments are working with tissues or cells that are subsequently sent for manufacture as Advanced Therapy Medicinal Products (ATMP) or are manufacturing those products themselves under the ‘hospital exemption’ allowed by the Regulations on ATMP. Hence, new chapters have been introduced in the Guide to address this field of cell therapy in particular. Chapter 20 provides a didactic overview of the field by describing the different ways in which cells can be expanded, modified or combined with scaffolds to replace damaged or diseased tissues in the recipient. Chapter 22 describes several types of cells (apart from haematopoietic stem cells) that are rapidly becoming important tools in the fight against disease. These chapters do not attempt to classify such cells or tissues under EU or other regulatory definitions. Instead, they inform readers that they must be fully aware of the regulatory classification of the tissues and cells they are working with, follow GMP, and have a marketing authorisation where they are classified as medicinal products. Chapters of this Guide that relate to recruitment and consent of donors, evaluation and testing of donors, as well as procurement of tissues and cells apply in full to the tissues and cells donated for any clinical application.

A new ‘place-holder’, Chapter 23, has been added and provides general principles to be considered if banking adipose tissue, an activity that is showing promise for patients with scarring due to tumour removal or burns. Chapter 24 (Other substances of human origin) introduces several other substances obtained from humans for autologous or allogeneic use: human breast milk, faecal microbiota, teeth/dental pulp, platelet-rich plasma, platelet-rich fibrin and serum eye drops. The regulatory status of these substances in most countries is unclear, but their human origin and the processes applied to procure, process and preserve them are analogous to those that apply for the tissues and cells described in this Guide (particularly in Part A). Hence, they

have been added as a means of providing a generic quality and safety framework for healthcare professionals treating patients with these substances.

Other enhancements to the Guide have been division of the former chapter on identification of potential donors, consent and evaluation into two new, more comprehensive chapters: Chapter 3 (Recruitment of potential donors) and Chapter 4 (Donor evaluation). Chapter 5 (Donor testing) now includes a detailed section that describes principles for validation of screening assays for infectious diseases used for testing blood from deceased donors, and considers differences in test results obtained by various types of testing laboratories (hospital-based versus reference laboratory). Chapter 7 (Processing and storage) has been updated to cover more detailed instructions on the requirements of processing facilities as well as monitoring of such facilities (viable and non-viable particles). The text has also been bolstered with more detailed information on the requirements of the cleaning of facilities, storage and exceptional release. Chapters 9 (Distribution and import/export) and 13 (Traceability) include the new EU requirements for the import and coding of tissues and cells. Finally, all of the chapters have been revised thoroughly to update their contents with the most recent advances in the field.

Throughout this Guide, use of the word ‘must’ indicates mandatory compliance in alignment with EU Directives, whereas use of the word ‘should’ indicates recommended compliance in accordance with good practice. In addition, unless otherwise stated, the guidelines apply only to human tissues and cells intended for transplantation or clinical use (including insemination and fertilisation). Tissues and cells used for ‘basic’ research do not fall under the scope of the present Guide.

Two working groups have contributed to the elaboration of this Guide. Working group TO055 helped to update the first edition and their work was co-ordinated by Deirdre Fehily (Italy) and Esteve Trias (European Association of Tissue Banks [EATB]). Working group TO056 drafted the new chapters on ‘Assisted reproductive technolo-

gies' and 'Fertility preservation', and their work was co-ordinated by Anna Veiga (ESHRE) and Carlos Plancha (Portugal). Names of the experts that participated in both groups can be found in Appendix 14 of the Guide. These experts contributed to different aspects of the book and did a tremendous job in reviewing the literature and extracting knowledge from numerous international guidelines, collaborative projects and diverse publications and Internet websites with the aim of ensuring accessibility to all this information.

In addition, other experts contributed in the discussions on various parts of this Guide and should be acknowledged:

Anna Vilarrodona Serrat (Spain)
Alan Kitchen (United Kingdom)
Alexandra Karström (Sweden)
Anders Lindahl (Sweden)
Anne Rosser (United Kingdom)
Branka Golubic Cepulic (Croatia)
Bronwen Shaw (World Marrow Donors Association)
Carl Jorns (Sweden)
Christian Chabanon (France)
Dagmar Schilling-Leiß (Germany)
Elba Agustí i Rovira (Spain)
Etienne van den Abbeel (Belgium)
Elisa Pianigiani (Italy)
Evi Petrisli (Italy)
Fredrik Huss (Sweden)
Gilbert Verbeken (Belgium)
Iván Miranda Álvarez-Pickman (Spain)
Izabela Uhrynowska-Tyszkiewicz (Poland)
Jaime Tabera Fernández (Spain)
Juan Bueren (Spain)
Jan-Oliver Karo (Germany)
Jürgen Scherer (Germany)
Katarina Le Blanc (Sweden)
Lydia Foeken (World Marrow Donors Association)
Marco Straccia (Spain)

Marjo Schutskoff-Jääskeläinen (Finland)

Nadine Ectors (Belgium)

Olle Korsgren (Sweden)

Òscar Fariñas Barbera (Spain)

Phil Sanders (Spain)

Ramón Farre (Spain)

Raquel Martín Ibáñez (Spain)

Ricardo Pedro Casaroli-Marano (Spain)

Rolf Kiessling (Sweden)

Soeren Ziebe (Denmark)

Ute Sicker (Germany)

Utta Schurig (Germany)

We would also like to thank all the experts that participated in the open consultation and provided extremely useful comments and suggestions.

Special thanks should be given to the European Commission, in particular to Ioana-Raluca Siska, who ensured the current text remained aligned with EU Directives and who made available the results from EU-funded projects.

Several professional associations, in particular the American Association of Tissue Banks (AATB), EATB, ESHRE and the European Society for Blood and Marrow Transplantation (EBMT) should also be thanked for sharing their experience and knowledge.

The drafting and publication of the second edition of the Guide was co-ordinated by Marta López Fraga (Scientific Officer in charge of the Council of Europe European Committee on Organ Transplantation [CD-P-TO]) with the assistance of Ahlem Sanchez, David Crowe and Isabelle Vernay. An extended thank you should also be given to Karl-Heinz Buchheit, Head of the Department of Biological Standardisation, OMCL Network & HealthCare (DBO), and Susanne Keitel, Director of the EDQM.

The entire project has been an exceptional combined effort, with extensive discussions dedicated towards the common goal of increasing the safety, efficacy and quality of donation of tissues and cells, as well

as the testing, processing and storage for clinical application of tissues and cells. The final result is this Guide, which constitutes a common European standard, based on the long-standing expertise and knowledge of the EDQM.

Contents

Foreword	3
PART A. GENERAL REQUIREMENTS	33
Chapter 1 Introduction	35
1.1. Scope and purpose of this guide	35
1.2. Brief history of tissue and cell transplantation and banking ..	39
1.3. European Committee on Organ Transplantation, the European Directorate for the Quality of Medicines & HealthCare and the Council of Europe	43
1.4. Recommendations and regulations in the field	44
1.4.1. Council of Europe	44
1.4.2. World Health Organization	48
1.4.3. European Union	50
1.5. Benefits and risks of human application of tissues and cells ..	55
1.6. Process of donation of tissues and cells and application in humans	58
1.7. Tissue banks, biobanks and tissue establishments	62
1.8. Quality and safety	63
1.9. Ethical issues	65
1.9.1. Consent	66
1.9.2. Conflicts of interest	68
1.9.3. Financial aspects of donation and transplantation	68
1.9.4. Equitable access to transplantation or to assisted reproductive technology treatment	70

1.9.5. Equity in donation	72
1.9.6. Anonymity	73
1.9.7. Transparency.	74
1.10. References	75

Chapter 2 Quality management, risk management and validation.

2.1. Introduction	85
2.2. Applying quality management in donation and banking of tissues and cells.	87
2.3. Personnel and organisation	88
2.3.1. Key personnel	88
2.3.2. Training.	88
2.3.3. Safety issues for healthcare personnel working with tissues and cells for human application	89
2.3.4. Safety issues for tissues or cells handled by personnel with bacterial or viral infections	89
2.4. Premises, equipment and materials.	89
2.4.1. Premises	90
2.4.2. Equipment	91
2.4.3. Materials.	93
2.5. Contractual arrangements.	94
2.6. Documentation and record-keeping	96
2.7. Quality control	98
2.8. Quarantine and release	98
2.9. Validation and qualification	98
2.9.1. Qualification of facilities and equipment	99
2.9.2. General principles of process validation	100
2.9.3. Planning for validation.	101
2.9.4. Validation documentation.	101
2.9.5. Prospective validation.	101
2.10. Change control.	102
2.11. Traceability.	102
2.12. Complaints	103
2.13. Investigation and reporting of non-conformance, adverse events and adverse reactions	103

2.14. Recall	104
2.15. Self-assessment, internal audit and external audit	104
2.16. Quality risk management	105
2.17. Continuity planning	108
2.18. References	108
Chapter 3 Recruitment of potential donors, identification and consent	109
3.1. Introduction	109
3.2. Living donors	110
3.2.1. Donor recruitment	110
3.2.2. Consent/authorisation of donors	113
3.3. The deceased donor	114
3.3.1. Donor detection	115
3.3.2. Consent/authorisation for deceased donation	115
3.4. Data protection and confidentiality	117
Chapter 4 Donor evaluation	119
4.1. Introduction	119
4.2. Donor information	120
4.2.1. Evaluation of medical history (generic- and tissue-specific contraindications)	122
4.2.2. Evaluation of behavioural risk	128
4.3. ‘Hot topics’	131
4.3.1. Malignancy	131
4.3.2. Epidemiological data used to assess sexual-risk behaviours, tattoos, and incarceration	135
4.3.3. Transplantation with xenografts	135
4.4. Physical evaluation of donors	136
4.5. Additional information	138
4.6. Considerations for evaluation of paediatric donors	139
4.7. References	139
Chapter 5 Donor testing	143
5.1. Introduction	143
5.2. General concepts	144
5.3. Quality of donor samples	144

5.3.1. Sample collection (sample type, tubes, labelling, time-limits and handling)	145
5.3.2. Haemodilution assessment.	148
5.4. Testing laboratories.	150
5.5. Tests to be carried out.	151
5.5.1. Additional tests	152
5.5.2. Re-tests of samples from living donors (allogeneic use) ...	154
5.5.3. Testing of autologous samples	154
5.6. Reporting and documentation of test results.	155
5.7. Archived samples	156
5.8. References	156
Chapter 6 Procurement	159
6.1. Introduction	159
6.2. Personnel.	160
6.3. Facilities, equipment and materials	161
6.3.1. Facilities.	161
6.3.2. Equipment and materials	168
6.4. Procedures	169
6.4.1. Temporary storage and transport.	172
6.5. Documentation	173
Chapter 7 Processing and storage	177
7.1. Introduction	177
7.2. Acceptance criteria (receipt at the tissue establishment)	178
7.3. Coding	180
7.4. Processing	181
7.4.1. General	181
7.4.2. Processing methods	183
7.4.3. Processing validation	184
7.4.4. Requirements of processing facilities.	186
7.4.5. Selecting the appropriate air quality for processing	189
7.4.6. Environmental airborne monitoring.	191
7.4.7. Environmental microbiological monitoring.	196
7.4.8. Cleaning	199
7.4.9. Avoiding contamination and cross-contamination.	201

7.5. Quality control	204
7.5.1. General	204
7.5.2. Microbiological control	204
7.6. Packaging and labelling	205
7.7. Storage	205
7.7.1. Methods of storage	205
7.7.2. Expiry date	207
7.7.3. Risk assessment	207
7.7.4. Storage temperature	208
7.7.5. Cross-contamination during storage	208
7.7.6. Quarantine	209
7.8. Release	209
7.8.1. Release procedure	209
7.8.2. Exceptional release	211
7.8.3. Disposal of human tissues and cells	212
7.9. References	212
Chapter 8 Principles of microbiological testing	215
8.1. Introduction	215
8.2. Microbiological examination of donors: blood cultures	216
8.3. General considerations for microbiological control of human tissues and cells	217
8.3.1. Microbiological concepts for the detection of bacteria and fungi	218
8.3.2. Testing for micro-organisms with specific growth requirements	220
8.3.3. Testing for bacterial endotoxins	221
8.3.4. Explanatory notes – microbial controls required for specific processing methods	223
8.4. Microbiological testing	225
8.4.1. Sterility testing of solutions or tissue samples pursuant to <i>Ph. Eur.</i> 2.6.1	225
8.4.2. Microbiological testing using automated culture systems (<i>Ph. Eur.</i> 2.6.27)	227
8.5. Notes on the validation of microbiological methods for the testing of preparations of tissues and cells	229

8.5.1. Growth promotion test	229
8.5.2. Method validation	230
8.5.3. Documentation and interpretation of results	232
8.6. Interpretation of results and actions to be taken.	232
8.7. General considerations for microbiological monitoring of the environment and reagents	234
8.7.1. Incubation of samples	236
8.7.2. Data analyses	236
8.8. References	236
Chapter 9 Distribution and import/export	239
9.1. Introduction	239
9.2. Transport	240
9.3. Allocation	241
9.3.1. Visual examination	241
9.3.2. Medical competence	241
9.3.3. Documentation	241
9.3.4. Recall and return procedures	242
9.4. Import and export.	242
9.4.1. Underlying principles	242
9.4.2. Import.	243
9.4.3. Customs clearance	245
9.4.4. Acceptance at the establishment	246
9.4.5. EU requirements for importing tissues and cells.	246
9.4.6. Export.	247
9.5. International co-operation	248
Chapter 10 Organisations responsible for human application . .	249
10.1. Introduction	249
10.2. Appropriate use	249
10.3. Choosing a supplier of tissues or cells	250
10.4. Receiving tissues or cells from other countries.	253
10.5. Exceptional release	253
10.6. Recipient consent.	254
10.7. Centralised <i>versus</i> decentralised management of tissues and cells	255

10.8. Incoming inspection at the organisation responsible for human application	256
10.9. Package insert/instructions and temporary storage before use	257
10.10. Inspection of the container, documentation and tissues or cells.....	258
10.11. Preparation of tissues or cells before use	258
10.12. Surplus or unused tissues or cells.....	259
10.13. Traceability	259
10.14. Adverse events and adverse reactions	261
10.15. Management of recalls and reviews	262
10.16. References	263
Chapter 11 Computerised systems	265
11.1. Introduction	265
11.2. Planning the implementation of a computerised system. . .	266
11.3. Qualification and testing	267
11.4. Change control	272
11.5. Maintenance of the system.....	272
11.6. Quality assurance	273
11.7. Industry guidance for validation of the computerised system	273
11.8. Regulations governing validation of computerised systems in Good Manufacturing Practices	274
11.9. Infrastructure.....	276
11.10. Failure of the system.....	276
11.11. Electronic signature	276
11.12. Data protection	276
11.13. Archiving.....	277
11.14. References	277
Chapter 12 Packaging and labelling	279
12.1. Introduction	279
12.2. General concepts	280
12.3. Packaging of tissues and cells	281
12.4. Labelling of tissues and cells.....	281

12.5. Sample and documentation labelling	283
12.6. Management of packaging and labelling materials	283
12.7. Primary packaging and labelling for procurement operations	284
12.8. Secondary packaging and labelling for procurement operations	286
12.9. Outer container packaging and labelling for procurement operations	286
12.10. Procurement package insert	287
12.11. Packaging and labelling during processing	288
12.12. Primary packaging and labelling for finished tissues and cells	288
12.13. Secondary packaging and labelling for finished tissues and cells	290
12.14. Outer container packaging and labelling for finished tissues and cells.	290
12.15. Package insert for finished tissues and cells	291
12.16. Customs clearance.	292
12.17. References	293
Chapter 13 Traceability	295
13.1. Introduction	295
13.2. What is traceability?	297
13.3. Which records must be traceable?	299
13.3.1. Records of identification, donor tests and clinical evaluation of the donor	300
13.3.2. Records of procurement of tissues and cells	301
13.3.3. Records of processing of tissues	302
13.3.4. Records of storage and distribution of tissues and cells .	302
13.3.5. Records of end use of tissues and cells	303
13.4. Single European Code for tissues and cells	304
13.4.1. Tools for implementation of the Single European Code .	305
13.4.2. Structure and format of the Single European Code. . . .	306
13.4.3. Application of the Single European Code	307
13.5. References	308

Chapter 14 Biovigilance	311
14.1. Introduction	311
14.2. Management and quality	313
14.2.1. Non-serious adverse events and reactions	314
14.2.2. Complaints	314
14.3. Adverse reactions	315
14.3.1. Detection of adverse reactions	316
14.3.2. Reporting adverse reactions	318
14.3.3. Investigation and assessment of adverse reactions	323
14.4. Adverse events	326
14.4.1. Detection of serious adverse events	326
14.4.2. Serious adverse event reporting	326
14.4.3. Investigation and assessment of adverse events	327
14.5. Vigilance co-ordination	327
14.5.1. Rapid alerts	327
14.6. Vigilance communication	328
14.6.1. ‘No blame’ culture	328
14.6.2. Vigilance experience and feedback	329
14.7. Surveillance for new risks	329
14.8. References	330
 PART B. SPECIFIC REQUIREMENTS	 333
 Chapter 15 Ocular tissue	 335
15.1. Introduction	335
15.2. Donor evaluation	337
15.2.1. Exclusion criteria for cornea donation	337
15.2.2. Exclusion criteria for other types of ocular tissue donation (e.g. sclera, limbal tissue, limbal cells)	338
15.3. Procurement	338
15.3.1. <i>Post mortem</i> time	338
15.3.2. Procurement team	339
15.3.3. Procurement procedure	339
15.3.4. Reconstruction of the donor	340
15.4. Receipt of procured tissue at tissue establishments	340
15.5. Processing and storage	340

15.5.1. Processing facilities	340
15.5.2. Cornea processing methods	341
15.5.3. Cornea storage methods	342
15.5.4. Sclera processing and storage.	343
15.6. Microbiological testing of the storage medium	344
15.7. Quality control and cornea evaluation	344
15.8. Examples of serious adverse reactions and serious adverse events	346
15.9. References	347
Chapter 16 Amniotic membrane	349
16.1. Introduction	349
16.2. Donor evaluation.	350
16.2.1. Specific exclusion criteria	351
16.3. Procurement	351
16.3.1. Procurement facility and procurement team.	351
16.3.2. Storage and transport after procurement.	351
16.4. Processing and storage.	352
16.4.1. Receipt of procured placenta at the tissue establishment .	352
16.4.2. Processing facilities.	353
16.4.3. Processing methods.	354
16.5. Quality control.	356
16.6. Distribution	356
16.7. References	357
Chapter 17 Skin.	359
17.1. Introduction	359
17.2. Skin-specific donor evaluation	361
17.2.1. Skin inspection	361
17.2.2. Skin-specific exclusion criteria.	361
17.2.3. Skin-specific procurement procedures	362
17.2.4. Skin-specific <i>post mortem</i> time	362
17.3. Skin procurement.	362
17.3.1. Skin-specific procurement team.	362
17.3.2. Skin procurement procedure	363
17.3.3. Reconstruction of the skin donor.	363

17.3.4. Procurement documentation	364
17.3.5. Skin transportation to the tissue establishment	364
17.3.6. Receipt of procured skin at the tissue establishment	364
17.4. Skin processing	364
17.4.1. Processing facilities	366
17.4.2. Skin decontamination and preservation	366
17.4.3. Skin graft sizing	367
17.4.4. Glycerol-preserved skin allografts	367
17.4.5. Fresh skin allografts.	367
17.4.6. Cryopreserved skin allografts	368
17.4.7. Lyophilised skin allografts	368
17.4.8. De-epidermised dermis and acellular dermis	368
17.4.9. Sterilisation of skin allografts	369
17.5. Quality control	369
17.5.1. Microbiological testing of skin	369
17.5.2. Skin allograft distribution.	370
17.6. Examples of serious adverse reactions and serious adverse events	370
17.7. References	371
Chapter 18 Cardiovascular tissue	373
18.1. Introduction	373
18.2. Donor evaluation.	375
18.2.1. Contraindications specific for cardiovascular tissue	375
18.3. Procurement	375
18.3.1. Procurement team	375
18.3.2. Procurement procedure	376
18.3.3. Tissue transportation to the tissue establishment.	376
18.3.4. Procurement documentation.	376
18.4. Processing and storage.	376
18.4.1. Decellularisation of cardiovascular tissues	377
18.4.2. Processing facilities.	378
18.5. Cryopreservation and storage in liquid nitrogen	379
18.6. Cardiovascular tissue thawing	379
18.7. Quality control	380
18.8. Cardiovascular allograft distribution	382

18.9. Examples of serious adverse reactions and serious adverse events	383
Chapter 19 Musculoskeletal tissue	385
19.1. Introduction	385
19.2. Donor evaluation requirements	387
19.2.1. Physical evaluation.	387
19.2.2. Specific contraindications for musculoskeletal tissue ...	388
19.2.3. Age limits for donors.	388
19.3. Procurement	388
19.3.1. Time limits for procurement	389
19.3.2. Procurement from deceased donors	389
19.3.3. Reconstruction of the deceased donor	390
19.3.4. Procurement from living donors.	390
19.4. Processing	391
19.4.1. Processing facilities	391
19.4.2. Musculoskeletal graft processing	393
19.4.3. Impact of processing on musculoskeletal allografts	394
19.4.4. Sterilisation or decontamination of musculoskeletal tissues and cells.	395
19.5. Packaging and labelling	397
19.6. Transport and storage.	397
19.6.1. Transport of musculoskeletal tissues	397
19.6.2. Storage of musculoskeletal tissues	398
19.7. Quality control	399
19.8. Examples of serious adverse reactions and serious adverse events	400
19.9. References	401
Chapter 20 General considerations for cell-based therapies	403
20.1. Introduction	403
20.2. EU legal framework	405
20.2.1. Advanced Therapy Medicinal Products Regulation	405
20.2.2. National Competent Authorities	407
20.2.3. Ethics Committees	408
20.3. Processing cells for human application.	409

20.3.1. Special safety considerations when culturing cells	409
20.3.2. Microbiological testing when culturing cells	411
20.3.3. Considerations for quality control	413
20.3.4. Master cell banks and working cell banks	414
20.3.5. Safety considerations when applying cells to patients	415
20.4. Genetic modifications of cells.	416
20.5. Natural scaffolds for clinical use	417
20.5.1. Donor selection and procurement	418
20.5.2. Decellularisation agents	418
20.5.3. Considerations for choosing the appropriate decellularisation agent.	419
20.5.4. Quality controls.	423
20.5.5. Sterilisation of natural scaffolds	423
20.5.6. Packaging and distribution	424
20.6. References	424
Chapter 21 Haematopoietic stem cells	427
21.1. Introduction	427
21.2. Donor evaluation.	429
21.2.1. Specific considerations for paediatric donors	432
21.3. Collection	433
21.3.1. Bone marrow.	434
21.3.2. Peripheral blood	435
21.3.3. Cord blood.	438
21.4. Processing	440
21.4.1. Volume reduction.	441
21.4.2. Red blood cell depletion	442
21.4.3. Plasma removal	442
21.4.4. Cryopreservation, thawing and infusion	442
21.4.5. Cell selected preparations.	444
21.4.6. Depletion of allo-reactive immune effectors.	445
21.4.7. Immunocompetent cells used after haematopoietic stem cell transplantation	446
21.5. Quality control	447
21.5.1. Biological information needed to confirm donor suitability and recruitment.	447

21.5.2. Safety controls	447
21.5.3. Quality controls (including potency assays and markers)	448
21.5.4. Release criteria	449
21.6. Storage	450
21.7. Packaging and labelling	451
21.8. Vigilance and surveillance	451
21.8.1. Serious adverse reactions in the recipient	452
21.8.2. Serious product adverse events/reactions	460
21.8.3. Serious adverse reactions in haematopoietic stem cell donors.	461
21.9. References	462
Chapter 22 Other cells	465
22.1. Introduction	465
22.2. Important notice for tissue establishments and other operators established in the EU.	466
22.3. Allogeneic mononuclear cells (donor lymphocyte infusions)	467
22.3.1. Donor selection	467
22.3.2. Procurement.	467
22.3.3. Processing	468
22.3.4. Quality control.	468
22.3.5. Storage	468
22.3.6. Biovigilance	468
22.4. Virus specific T-cells.	469
22.4.1. Procurement.	469
22.4.2. Processing	469
22.4.3. Quality control.	470
22.4.4. Storage and distribution	471
22.4.5. Biovigilance/pharmacovigilance	471
22.5. Keratinocytes	471
22.5.1. General introduction.	471
22.5.2. Donor selection	473
22.5.3. Procurement	473
22.5.4. Processing and storage	474
22.5.5. Quality controls/release criteria	476

22.5.6. Packaging and distribution	476
22.5.7. Traceability	477
22.5.8. Biovigilance/pharmacovigilance.	477
22.6. Dendritic cells	477
22.6.1. General introduction	477
22.6.2. Donor selection	477
22.6.3. Procurement.	478
22.6.4. Processing and storage.	478
22.6.5. Quality controls/release criteria	478
22.6.6. Packaging and distribution	479
22.6.7. Traceability.	479
22.6.8. Biovigilance/pharmacovigilance	479
22.7. Chondrocytes	479
22.7.1. Donor selection.	480
22.7.2. Procurement.	480
22.7.3. Processing and storage	481
22.7.4. Quality controls/release criteria	482
22.7.5. Packaging and distribution	483
22.7.6. Traceability.	484
22.7.7. Biovigilance/pharmacovigilance	484
22.8. Hepatocytes	484
22.8.1. Donor selection	485
22.8.2. Procurement.	486
22.8.3. Transportation of liver tissue to the processing establishment	486
22.8.4. Processing and storage.	487
22.8.5. Cryopreservation, storage, and thawing of hepatocytes .	487
22.8.6. Quality controls/release criteria	488
22.8.7. Packaging and distribution	489
22.8.8. Traceability.	489
22.8.9. Biovigilance	489
22.9. Natural killer cells.	489
22.9.1. General introduction.	490
22.9.2. Donor selection	491
22.9.3. Procurement.	491

22.9.4. Processing and storage	491
22.9.5. Quality controls/release criteria	492
22.9.6. Packaging and distribution	492
22.9.7. Traceability	492
22.9.8. Biovigilance/Pharmacovigilance	492
22.10. Pancreatic islet cells	493
22.10.1. General introduction.	493
22.10.2. Donor selection	494
22.10.3. Procurement	494
22.10.4. Processing and storage	494
22.10.5. Quality controls/release criteria	494
22.10.6. Packaging and distribution	495
22.10.7. Traceability	495
22.10.8. Biovigilance	495
22.11. Mesenchymal stem cells	495
22.11.1. Donor selection	497
22.11.2. Procurement	498
22.11.3. Processing and storage.	498
22.11.4. Quality controls/release criteria	500
22.11.5. Packaging and distribution.	500
22.11.6. Traceability	500
22.11.7. Biovigilance/pharmacovigilance	500
22.12. Limbal stem cells (ocular surface)	501
22.12.1. General introduction.	501
22.12.2. Donor and tissue selection.	502
22.12.3. Procurement	502
22.12.4. Processing tissue and storage	503
22.12.5. Quality controls and release criteria.	504
22.12.6. Packaging and distribution	504
22.12.7. Traceability	505
22.12.8. Biovigilance/pharmacovigilance	505
22.13. References	505
Chapter 23 Adipose tissue	511

Chapter 24 Other substances of human origin for clinical application 513

24.1. Introduction 513

24.2. Breast milk 514

24.3. Faecal microbiota 516

24.4. Teeth and dental pulp 518

24.5. Platelet-rich plasma and platelet-rich fibrin 518

24.6. Serum eye drops 519

24.7. References 520

Chapter 25 Assisted reproductive technology 525

25.1. Introduction 525

25.2. Consent 528

25.3. Donor evaluation 530

 25.3.1. Evaluation of partner donors 530

 25.3.2. Evaluation of non-partner donors 533

25.4. Testing 535

 25.4.1. Testing in partner donation 535

 25.4.2. Testing in non-partner donation 536

25.5. Collection 537

 25.5.1. Sperm 537

 25.5.2. Oocytes 539

 25.5.3. Ovarian tissue 540

25.6. Processing 540

 25.6.1. Facilities for processing of gametes and embryos 540

 25.6.2. Handling of gametes and embryos 541

 25.6.3. Insemination of oocytes 544

 25.6.4. Assessment of fertilisation 544

 25.6.5. Embryo culture and transfer 545

 25.6.6. Pre-implantation genetic diagnosis and pre-implantation genetic screening 546

 25.6.7. *In vitro* maturation 547

 25.6.8. Processing of samples from seropositive donors 547

25.7. Cryopreservation and storage 548

 25.7.1. Methods for cryopreservation of human gametes and embryos 548

25.8. Storage	550
25.8.1. Storage limits	550
25.8.2. Storage temperature	550
25.8.3. Storage devices	551
25.8.4. Cross-contamination during storage.....	551
25.8.5. Storage safety	552
25.9. Packaging and labelling in assisted reproductive technologies.	552
25.10. Vigilance in assisted reproductive technologies	552
25.10.1. General criteria for reporting serious adverse reactions and events in assisted reproduction technologies	553
25.10.2. Transmission of genetic diseases by assisted reproductive technologies with non-partner donations	555
25.10.3. Examples of serious adverse reactions and events in assisted reproduction technologies	555
25.10.4. Cross-border management of serious adverse reactions and events	556
25.11. Final considerations	556
25.12. References	557
Chapter 26 Fertility preservation.	561
Appendix 1 General reference documents used	565
Appendix 2 Acronyms	573
Appendix 3 Glossary	583
Appendix 4 Sample consent form	609
Appendix 5 Sample donor assessment form.	617
Appendix 6 Sample tissue donor physical assessment form.	651
Appendix 7 Sample haemodilution algorithm	655
Appendix 8 Validation of screening for infectious disease assays for use with blood from deceased donors.	657
Appendix 9 Sample form to assess the suitability of the working environment	663

Appendix 10 Sample donor identification form 665

Appendix 11 Example of a process validation 667

Appendix 12 Adverse reaction or event impact assessment tool . 671

Appendix 13 Summary of data reported in the 2011 EU-wide report of serious adverse reactions and serious adverse events associated with the clinical application of tissues and cells (data reported for 2010) 675

Appendix 14 Members of the *ad hoc* working groups (TO055 and TO056) for the elaboration of the 2nd edition of the Guide to the quality and safety of tissues and cells for human application 679

Appendix 15 Members of the European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO) 687