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

2nd Edition

European Directorate for the Quality of Medicines & HealthCare (EDQM)

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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 adaption 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:

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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.

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