PAS 84:2012

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Cell therapy and regenerative medicine – Glossary

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Foreword

This PAS was commissioned by the UK Department for Business, Innovation and Skills (BIS). Its development was facilitated by BSI Standards Limited and published under licence from The British Standards Institution. It came into effect on 30 March 2012.

Acknowledgement is given to the technical author, Emily Culme-Seymour, and the following organizations that were involved in the development of this vocabulary as members of the Steering Group:

- Anthony Nolan (Alejandro Madrigal)
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Acknowledgement is also given to those organizations and individuals that submitted comments during the public consultation.

This PAS is not to be regarded as a British Standard. It will be withdrawn upon publication of its content in, or as, a British Standard.

The PAS process enables a specification to be rapidly developed in order to fulfil an immediate need in industry. A PAS may be considered for further development as a British Standard, or constitute part of the UK input into the development of a European or International Standard.

Supersession

This PAS supersedes PAS 84:2008, which is withdrawn.

Information about this document

This is a full revision of the PAS and introduces the following principal changes:

- update of existing terms and definitions for accuracy and relevance
- addition of new terms that have appeared within the research, clinical, bioprocessing and regulatory space since the last revision
- update of the annex on regulatory terms to reflect changes in legislation and include regulatory terms used in the USA as well as in the UK and Europe
- addition of an annex on finance terms that are likely to be of use to the cell therapy and regenerative medicine community

Relationship with other publications

This PAS provides a set of terms and definitions that is of relevance to the cell therapy and regenerative medicine industry.

It includes definitions of terms used in:

- PAS 83, *Developing human cells for clinical applications in the European Union and the United States of America – Guide*
- PAS 93, *Characterization of human cells for clinical applications – Guide*

Where possible, an attempt has been made to use terms and definitions that have been defined in existing standards, in particular ASTM F2312-11, *Standard terminology relating to tissue engineered medical products*.

A number of regulations exist that are relevant to the field of cell therapy and regenerative medicine. These regulations contain terms that are defined in some detail. In some instances regulatory definitions have been included verbatim. However, in order for this PAS to achieve its intended objective, more succinct and precise definitions consistent with regulations have been developed.

Presentational conventions

The terms and definition in the PAS are presented in roman (i.e. upright) type.

Commentary, explanation and general informative material is presented in smaller italic type.

When terms defined in this PAS are used in the definition or notes of another term, they are shown in bold type.

Where a term has been given a meaning narrower than its generally accepted meaning, a qualification has been included in angular brackets at the start of the definition denoting the context within which it has been defined, i.e. <…>.

Spelling conforms to *The Shorter Oxford English Dictionary*. If a word has more than one spelling, the first spelling in the dictionary is used.

Feedback

Feedback on the technical content of this PAS can be submitted through the BSI Document Feedback system http://feedback.bsigroup.com.

Any feedback received will be reviewed when developing future revisions of this document.

Contractual and legal considerations

Attention is drawn to the following statutory regulations.

a) European Directive 2001/83/EC relating to medicinal products for human use (and amendments) [1]

b) European Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [2] implemented in the UK by Human Tissue (Quality and Safety for Human Application) Regulations 2007 [3]

c) European Directive 2010/45/EU on standards of quality and safety of human organs intended for transplantation [4]

d) European Regulation No. 1394/2007 on advanced therapy medicinal products [5]

e) Human Fertilisation and Embryology Act 1990 (and amendments) [6]

f) Human Tissue Act 2004 [7]

g) Human Tissue (Scotland) Act 2006 (and amendments) [8]

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

Compliance with a PAS cannot confer immunity from legal obligations.

Ministerial statement

The first edition of this popular glossary was published in 2008. Over the past four years, a great many new terms have appeared. These additions reflect the rapid development of regenerative medicine, including the spinning out of cell therapy as a dominant new therapeutic modality. It is encouraging that the glossary's name has thus been modified in order to reflect the step-change importance of cell therapy, whilst continuing to recognize its linkages with regenerative medicine.

Regenerative medicine, the pursuit of regeneration by drugs, biomaterials, devices and/or cells, originated in the 1980s and today is an expanding multibillion pound industry. Likewise, the emerging cell therapy industry is predicted to grow from £1 billion in global revenue in 2011 to over £3 billion by 2014, with even greater growth expected to follow. These projections will not be achieved unless certain barriers are removed. There is an imperative for all stakeholders – patients, researchers, clinicians, entrepreneurs, manufacturers, press, public and politicians, to share a common language. This signals an urgent need for a universally agreed set of terms and definitions.

The first edition of this glossary started to facilitate this process and has admirably demonstrated its utility in the academic, clinical, business and societal settings. Indeed the demand for the original glossary led to tens of thousands of PDF web downloads, as well as a number of publisher reprints. Given the rapid scientific and technical progress since 2008, it is now time for a new and up to date edition to maintain the breadth and accuracy of the terms in use today.

As a globally acknowledged leader in cell therapy and regenerative medicine, and the pioneer of standardization through The British Standards Institution, the UK is well placed to take responsibility for maintaining this comprehensive glossary. Regularly updating the glossary to accommodate the pace of progress will help to ensure that language is not a barrier to successful clinical translation and commercialization.

As a robust supporter of research, translation and commercialization of cell therapies and regenerative medicine, I would like to warmly congratulate the steering group of international experts responsible for producing this second edition – one sponsored by the UK Government, but intended for global use.

Rt Hon David Willetts MP

Minister of State for Universities and Science

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Introduction

This PAS has been developed to encourage the use of common terms and definitions within the field of cell therapies and regenerative medicine. For the purpose of this PAS:

- cell therapy is a "*therapy in which cells are administered to the body to the benefit of the recipient*"*;* and
- regenerative medicine is a "*process for replacing or regenerating cells, tissues or organs, to restore or establish normal function*".

There has been increasing scrutiny of current standardization and regulations by researchers, manufacturers and the general public as cell therapy products and regenerative medicine products move nearer to commercialization.

UK stakeholders identified a need for standardization to achieve consensus on the terms and definitions used within cell therapies and regenerative medicine. Using the views and opinions of key UK stakeholders, this PAS has been developed to meet this need. The first edition of PAS 84 was published in 2008 and since then a number of developments have taken place in this field. As such, this revision of this PAS has been conducted to introduce changes that reflect these developments.

The aim of this PAS is to provide clear guidance on the meaning of terminology currently used within this field in the UK by industry, regulators, government and academia. Where applicable, terms and definitions have been aligned with existing regulations, codes of practice or standards. The sources of reproduced or adapted terms and definitions are referenced within this PAS.

It is recognized that there are international differences in terminology in current use, such as between the USA and Europe and particularly with regard to regional legislation. In this case, the European legislative or common terms have been used where possible.

It is intended that this document will help UK stakeholders to:

- prepare for legal, commercial and societal issues;
- facilitate a common understanding of the science of cell therapies and regenerative medicine;
- improve communication and understanding of advances in the field;
- demonstrate best practice and product quality; and
- reduce research, development, production and transaction costs.

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1 Scope

This PAS lists terms and definitions:

a) associated with the naming of types of cell therapy and regenerative medicine products; and

b) that describe materials, processes, methodologies and applications within cell therapies and regenerative medicine.

It covers:

i) general terms;

ii) cell and tissue components;

iii) non-cellular components;

iv) cell and tissue procurement;

v) measurement and analysis;

vi) manufacturing and production; and

vii) clinical trials.

Alternative definitions of terms found in regulations relevant to the cell therapy and regenerative medicine industry are covered in Annex A.

Finance terms and definitions relevant to the cell therapy and regenerative medicine industry are covered in Annex B.

2 Terms and definitions

2.1 acceptance criteria
predetermined criteria for acceptance of a test result

NOTE Such criteria can include numerical limits and ranges.

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Part II [9]]

2.2 active implantable medical device
active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

[European Directive 90/385/EEC (and amendments) [10]]

2.3 active medical device
medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity

[European Directive 90/385/EEC (and amendments) [10]]

2.4 active substance
substance or mixture of substances intended to be used in the **manufacture** of a **medicinal product** and that, when used in the production of a medicinal product, becomes a part of the medicinal product that furnishes pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or affects the structure and function of the body

NOTE 1 Also known as active pharmaceutical ingredient (API) and drug substance.

*NOTE 2 See also **cellular active substance**.*

[derived from ICH Harmonised Tripartite Guideline Q7 [11]]

2.5 active surveillance
surveillance ascertaining the number of **adverse events** via a continuous pre-organized process

*NOTE Examples include the follow-up of patients treated with a particular **medicinal product** through a **risk management** programme. In general, it is more feasible to obtain comprehensive data on individual adverse events through active surveillance than through **passive surveillance**.*

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union,* Volume 9A [12]]

2.6 admixed embryo
embryo that contains both human and animal material

*NOTE 1 Also known as **hybrid embryo**.*

*NOTE 2 Examples include an **animal chimera embryo,** a **cytoplasmic hybrid embryo (cybrid)** a **human chimera embryo** and a **transgenic human embryo**.*

NOTE 3 A legal definition of human admixed embryo applicable in the UK is given in Table A.1.

*NOTE 4 See also **permitted embryo**.*

2.7 adult stem cell
stem cell derived from an adult body or fetus

NOTE Also known as somatic stem cell or stromal stem cell.

[derived from the UK Stem Cell Bank's *Code of Practice for the Use of Human Stem Cell Lines* [13]]

2.8 advanced therapy medicinal product
medicinal product for human use that is a **gene therapy medicinal product**, a **somatic cell therapy medicinal product** or **tissue engineered product**

[European Regulation No. 1394/2007 [5]

2.9 adventitious
coming from an external source

2.10 adventitious agent
unintentionally introduced infectious **contaminant**

[derived from ASTM F2312-11]

2.11 adverse event
unexpected occurrence that might have an influence on a patient or **clinical trial subject** who has been administered a **medicinal product,** and that is not necessarily caused by the product

NOTE 1 A legal definition applicable in the EU for clinical trials is given in Table A.1.

NOTE 2 Also known as adverse experience. A legal definition of adverse experience applicable in the USA is given in Table A.1.

*NOTE 3 See also **serious adverse event (SAE)**.*

2.12 adverse event reporting
system for notification to an authority of **adverse events**

NOTE Notification can be made to national regulatory authorities as well as international authorities such as the World Health Organization (WHO).

2.13 adverse reaction
response to a **medicinal product** which is noxious and unintended

NOTE 1 Two legal definitions applicable in the EU are given in Table A.1, the first relating to clinical trials and the second relating to medicinal products for human use.

*NOTE 2 See also **serious adverse reaction (SAR)** and **unexpected adverse reaction (UAR)**.*

2.14 allogeneic
where **donor** and recipient are different individuals

2.15 allograft
allogeneic graft

NOTE Also known as homograft.

2.16 ancillary material
components used during the **manufacture** of a **medicinal product** that are not deliberately present in the medicinal product

*NOTE Examples include **cytokines, growth factors**, monoclonal antibodies, cell-separation devices and media components.*

2.17 animal chimera embryo
admixed embryo created by inserting human cells into an animal embryo

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [14]]

2.18 apoptosis
programmed cell death

*NOTE See also **necrosis**.*

2.19 arm
treatment or patient group in a **randomized trial**

2.20 aseptic technique
manner of handling or processing where the risk of **contamination** with living or dead bacteria, fungi or viruses and other **biological agents** is minimized or prevented

2.21 asymmetric cell division
cell division where each daughter cell has a different cellular fate

2.22 audit
documented, systematic evaluation to determine whether approved policies, **standard operating procedures** or operations have been properly implemented and are being followed

[NetCord-FACT's *International Standards for Cord Blood collection, Processing, and Release for Administration* [15]]

2.23 autograft
autologous graft

2.24 autologous
where **donor** and recipient are the same individual

2.25 baseline
information gathered at the beginning of a study from which variations found in the study are measured

2.26 batch (or lot)
defined quantity of **starting material**, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous

*NOTE To complete certain **manufacturing** steps, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch corresponds to a defined fraction of the production, characterized by its intended homogeneity.*

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Glossary [16]]

2.27 batch (or lot) number
unique combination of numbers, letters and/or symbols that identifies a **batch (or lot)** and from which the production and distribution history can be determined

[European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Glossary [16]]

2.28 bioactive agent
agent that has a biological effect on cells or **tissue**

2.29 bioaesthetics
regenerative medicine-like therapies aimed at **cosmesis** rather than traditional medical alignments

2.30 bioburden
quantity and type of microorganisms present in a **raw material**, **intermediate** or **active substance**

*NOTE Bioburden is considered **contamination** when the quantity of microorganisms has exceeded an accepted level or the microorganisms detected are of an objectionable type.*

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Part II [9]]

2.31 biocompatibility
ability of a material to perform with an appropriate host response in a specific application

[*The Williams Dictionary of Biomaterials* [17]]

2.32 biodistribution
dispersal of **biological agents** or **medicinal products** throughout a human or animal body

2.33 biological agent
microorganism, **cell culture** or human endoparasite, whether or not genetically modified, which can cause infection, allergy, toxicity or otherwise create a hazard to human health

[The Control of Substances Hazardous to Health Regulations 2002 [18]]

2.34 biological medicinal product
product, the **active substance** of which is a **biological substance**

NOTE Also known as biologic.

[European Directive 2001/83/EC (and amendments) [1]]

2.35 biological substance
substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its **quality**, a combination of physicochemical-biological testing together with the production process and its control

[European Directive 2001/83/EC (and amendments) [1]]

2.36 biomarker
molecular indicator of a specific biological property

2.37 biomaterial
material intended to interface with biological systems to evaluate, treat, augment or replace any **tissue**, **organ** or function of the body

[BS EN ISO 10993-6:2009, **3.3**]

2.38 biomolecule
biologically active peptide, protein, carbohydrate, vitamin, lipid or nucleic acid produced by and purified from naturally occurring or recombinant organisms, **tissues** or **cell lines** or synthetic analogs of such molecules

[ASTM F2312-11]

2.39 bioprocessing
activity performed on cells, **tissues** and **organs** other than collection

*NOTE For example, preparation and **preservation** for storage and packaging.*

2.40 bioreactor
device, equipment or apparatus designed to contain structures, both cellular and molecular, that are capable of taking part in a specific biological process and from which the products of the process can be harvested or extracted

[*The Williams Dictionary of Biomaterials* [17]]

2.41 biosimilar
new **biological medicinal product** claimed to be similar in terms of quality, safety and efficacy to a reference **medicinal product** that has been granted a **marketing authorization** in the community

NOTE Also known as similar biological medicinal product.

[derived from the definition of similar biological medicinal product in the European Medicines Agency's *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues* [19]]

2.42 blastocyst
pre-implantation embryo of about 150 cells produced by **cell division** around 144 hours following fertilization

*NOTE 1 The blastocyst is a sphere made up of an outer layer of cells (the **trophoblast**) and the **inner cell mass**.*

*NOTE 2 See also **morula**.*

[derived from the Stem Cell Information *Glossary* [20]]

2.43 blastomere
cell contained within a **morula**

2.44 cancer vaccine
therapy intended to stimulate a primary immune response to **tumour-associated antigens**, with the intention of inducing **tumour** regression

NOTE Also known as cancer immunotherapy.

2.45 cell authenticity
degree to which a population of cells has the correct identity and is free of other cell types

*NOTE The **quality** of the authentication depends on the specificity and sensitivity of the technique used.*

2.46 cell bank
collection of cells of uniform composition stored under defined conditions

NOTE 1 Uniform composition refers to the collection of cells being representative of the original cell culture or cultures from which they are derived.

*NOTE 2 A two-tiered cell banking system consisting of a **master cell bank (MCB)** and **working cell bank (WCB)** is commonly used for **cell lines** that are to be used extensively within a process.*

[derived from ICH Harmonised Tripartite Guideline Q5D [21]]

2.47 cell-based medicinal product (CBMP)
medicinal product containing cells

NOTE These products may be combined with non-cellular components and may include genetically modified human cells.

[derived from the European Medicines Agency's *Guideline on Human Cell-Based Medicinal Products* [22]]

2.48 cell culture
in vitro growth and maintenance of cells

2.49 cell division
process by which a cell divides to form daughter cells

*NOTE See also **asymmetric cell division**.*

2.50 cell expansion
increase in the number of cells by their **proliferation**

2.51 cell line
characterized **cell culture** that has been demonstrated to be phenotypically and genotypically consistent over a specified number of **population doublings**

2.52 cell migration
movement of cells in response to a stimulus

2.53 cell morphology
microscopic study of the form and structure of cells

2.54 cell selection
separation of a homogenous population of cells from a heterogeneous population

2.55 cell surface marker
biomolecule expressed on the surface of a cell and is used to identify cell type

2.56 cell therapy
therapy in which cells are administered to the body to the benefit of the recipient

2.57 cell therapy product
product consisting of cells used for **cell therapy**

2.58 cell viability
measure of a cell's potential for metabolism or multiplication

2.59 cellular active substance
active substance that consists of cells and/or **tissue**

2.60 cellular starting material
starting material that consists of cells and/or **tissue**

2.61 centralized authorization procedure
procedure leading to a **marketing authorization**

*NOTE 1 This procedure is administered by the European Medicines Agency (EMA) in accordance with European Regulation No. 726/2004 [23]. The procedure is mandatory for certain **medicinal products**, including all **advanced therapy medicinal products (ATMPs)**.*

NOTE 2 Also known as centralized procedure.

2.62 chief investigator
investigator who takes overall charge of a multi-centre study

*NOTE See also **clinical investigator** and **principal investigator**.*

2.63 chimera
organism consisting of two or more **tissues** of different genetic composition

*NOTE Conventionally produced by the injection of **embryonic stem cells** into a recipient **blastocyst** or in adults following **haematopoietic stem cell transplantation**.*

2.64 chimerism
condition of being a **chimera**

2.65 cleanroom (or clean facility)
room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary

[BS EN ISO 14644-1:1999, **2.1.1**]

2.66 clinical equivalent
medicinal product that contains essentially an identical amount of an identical **active substance** to that found in another medicinal product, and that provides an identical therapeutic effect to that other medicinal product

NOTE 1 A decision on whether a therapeutic effect is considered identical to another therapeutic effect is determined by assessing the extent to which a symptom or disease is controlled by the medicinal product.

NOTE 2 Also known as therapeutic equivalent.

2.67 clinical follow-up
follow-up of patients conducted by a healthcare professional

*NOTE 1 It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, **adverse reactions** and medical errors.*

*NOTE 2 See also **post-market surveillance**.*

[European Medicines Agency's *Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products* [24]]

2.68 clinical hold
delay of a proposed **clinical trial** or suspension of an ongoing **clinical trial**

NOTE Attention is drawn to the US Code of Federal Regulations, 21CFR312.42(a) [25], which legislated for the use of clinical hold orders by the US Food and Drug Administration (FDA).

2.69 clinical investigator
medical researcher who is responsible for a **clinical trial's protocol**

*NOTE See also **chief investigator** and **principal investigator**.*

2.70 clinical research organization (CRO)
organization that assumes, as an independent contractor with the sponsor of a **clinical trial**, one or more of the obligations of the sponsor with respect to the clinical trial

*NOTE 1 These obligations might include design of a **protocol**, selection or monitoring of investigations, evaluation of reports and preparation of materials to be submitted to a relevant authority.*

*NOTE 2 See also **contract manufacturing organization (CMO)** and **contract research organization (contract RO)**.*

2.71 clinical translation
process of taking a treatment from the laboratory to testing in volunteers

2.72 clinical trial
investigation in human **subjects** intended to discover or verify the **safety** and efficacy of a **therapy**

NOTE Legal definitions applicable in the EU and USA are given in Table A.1.

2.73 clone
genetically identical copy of a cell or organism

2.74 cloning
isolation and production of a genetically identical copy of a cell or organism

*NOTE 1 This can be conducted via **somatic cell nuclear transfer**.*

NOTE 2 This is to be distinguished from molecular or gene cloning, which refers to the identification and copying of a specific gene sequence rather than a whole cell or organism.

2.75 clonogenic cell
single cell able to proliferate into a colony of genetically identical cells

2.76 closed system
system in which a **medicinal product** is not exposed to the immediate room environment during **manufacture**

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, draft Annex 2 [26]]

2.77 colony forming unit (CFU)
macroscopic colony formed after the introduction of one or more microorganisms to microbiological growth media

NOTE One colony forming unit is expressed as 1 CFU.

[US Food And Drug Administration's *Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* [27]]

2.78 combination cell therapy
combination product containing a **cell therapy product**

*NOTE See also **combination product** and **combined advanced therapy medicinal product (combined ATMP)**.*

2.79 combination product
product that is a combination of a **medicinal product** and/or **biological medicinal product** and/or **medical device**

*NOTE See also **combination cell therapy** and **combined advanced therapy medicinal product (combined ATMP)**.*

2.80 combined advanced therapy medicinal product (combined ATMP)
product that incorporates one or more **medical devices** or one or more **active implantable medical device**s and either its cellular or **tissue** part contains viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues is liable to act upon the human body with action that can be considered as primary to that of the devices referred to

*NOTE See also **advanced therapy medicinal product (ATMP), combination cell therapy** and **combination product**.*

[European Regulation No. 1394/2007 [5]]

2.81 comparability
exercise to evaluate the impact of changes to a manufacturing process on the validity of **quality**, non-clinical and/or clinical data relating to a **cell therapy product** or its components

*NOTE The components of a cell therapy product include, for example, cellular populations and **cell banks**.*

2.82 comparable
conclusion that a **medicinal product** has highly similar **quality** attributes before and after manufacturing process changes and that no adverse impact on the **safety** or efficacy, including **immunogenicity**, of the product occurred

NOTE This conclusion can be based on an analysis of quality attributes. In some cases, non-clinical or clinical data might contribute to the conclusion.

[derived from ICH Harmonised Tripartite Guideline Q5E [28]]

2.83 comparative genomic hybridization (CGH)
method for the analysis of copy number changes in the chromosomal DNA content of a cell or **tissue**

2.84 competent authority
person or organization that has the legally delegated or invested authority, capacity, or power to perform a designated function

NOTE This will sometimes be referred to as a national competent authority (NCA), since authorities in different countries have different responsibilities.

2.85 conditioning
<patient care> medical procedure used to prepare a patient for the application of a **medicinal product**

*NOTE Examples include **therapeutic immunosuppression**, destruction of the patient's bone marrow, use of hormones for stimulation or inhibition of certain physiological functions.*

[European Medicines Agency's *Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products* [24]]

2.86 confounding factor
variable that has the potential to interfere with the interpretation of data resulting from a scientific study, technical study or **clinical trial**

2.87 contained use
operation in which **genetically modified organisms** are cultured, stored, used, transported, destroyed or disposed of and for which physical, chemical and/or biological barriers are used to limit their contact with the general population and the environment

[derived from European Directive 90/219/EEC (and amendments) [29]]

2.88 contamination
undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a **raw material**, **intermediate** or **active substance** during production, sampling, packaging or repackaging, storage or transport

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Part II [9]]

2.89 contaminant
impurity of a chemical or microbiological nature, or foreign matter, unintentionally introduced into or onto a **raw material**, **intermediate** or **active substance** during production, sampling, packaging or repackaging, storage or transport

[derived fromthe European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Part II [9]]

2.90 continued process verification
assurance that during routine production a process remains in a **state of control**

[US Food And Drug Administration's *Guidance for Industry – Process Validation: General Principles and Practices* [30]]

2.91 continuous cell line
cell line that appears to have the capacity for indefinite **cell division**

*NOTE See also **finite cell line**.*

2.92 contract manufacturing organization (CMO)
organization performing some aspect of manufacturing on behalf of another party

*NOTE See also **clinical research organization (CRO)** and **contract research organization (contract RO)**.*

2.93 contract research organization (contract RO)
organization that assumes, as an independent contractor with the sponsor of any type of research, one or more of the obligations of the sponsor

*NOTE 1 These obligations might include design of a **protocol**, selection or monitoring of investigations, evaluation of reports and preparation of materials to be submitted to a relevant authority.*

*NOTE 2 See also **contract manufacturing organization (CMO)** and **clinical research organization (CRO)**.*

2.94 control
benchmark against which experimental observations are evaluated

2.95 controlled trial
comparative **clinical trial** involving a **control**

2.96 cord blood
blood isolated from an umbilical cord at birth

2.97 cord blood stem cell
stem cell isolated from **cord blood**

2.98 cord blood transplantation
transfusion of **cord blood**

2.99 cosmesis
preservation, restoration or bestowing of bodily beauty

[*Dorland's Medical Dictionary* [31]]

2.100 cost benefit analysis
form of economic evaluation which attempts to value the consequences of a **therapy** in monetary terms in order to ascertain whether the beneficial consequences of the programme justify the costs

[derived from *Methods for the Economic Evaluation of Health Care Programmes* [32]]

2.101 cross-contamination
unintended presence of a cell or a material with another cell or material

*NOTE This can occur during a cell manufacturing process as a result of the inadvertent switching or mixing of **cell cultures**.*

[derived from ASTM F2312-11]

2.102 cryopreservation
maintenance of the viability of cells, **tissues** and **organs** by the process of **cryoprotection**, cooling and storing at very low temperatures

*NOTE See also **vitrification**.*

2.103 cryoprotectant
agent used to protect cells, **tissues** and **organs** from damage that can occur during cooling and storing at very low temperatures

NOTE 1 An example of damage is intracellular ice crystal formation.

*NOTE 2 See also **cryoprotection**.*

2.104 cryoprotection
protection of cells, **tissues** and **organs** from damage that can occur during cooling and storing at very low temperatures

*NOTE See also **cryoprotectant**.*

2.105 culture medium
nutrient supply used to support the growth and expansion of cells or to maintain **tissue** or **organ** cultures

2.106 cytokine
intercellular signalling **biomolecule**

2.107 cytoplasmic hybrid embryos (cybrid)
admixed embryo created by replacing the nucleus of an animal egg or a cell derived from an animal embryo with a human cell or the nucleus of a human cell

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [14]]

2.108 de-differentiation
regression of a cell to a less specialized **phenotype**

2.109 differentiation
development into a more specialized cell **phenotype**

2.110 defined medium
culture medium in which all components are known

2.111 direct use
donation and use of cells that does not involve storage in a **cell bank**

[derived from European Directive 2006/17/EC [33]]

2.112 DNA profiling
technique to identify an organism from its DNA

NOTE Also known as DNA fingerprinting.

2.113 DNA short tandem repeat profiling (DNA STR profiling)
DNA profiling by recognizing short sequence elements present throughout a DNA molecule

2.114 donation
process of providing human **tissues** or cells with **informed consent**

*NOTE This does not include the donation of **organs** for **transplantation** as this is not part of regenerative medicine.*

2.115 donor
source from which cells or **tissues** are derived for **cell therapy** and **regenerative medicine**

[derived from European Directive 2004/23/EC [2]]

2.116 donor selection
process of selecting **donors** against **eligibility criteria**

2.117 dose
prescribed quantity of a medicine or of a remedial agent

[*Larousse Dictionary of Science and Technology* [34]]

2.118 dose finding study
study in which different groups of patients are given different **doses** of a product to select the best doses for use in later, larger-scale trials

2.119 double-blind trial
randomized trial in which the clinician and patient are unaware of which **arm** of the trial the patient is on

*NOTE 1 See also **single-blind trial**.*

*NOTE 2 Contrasts with **open-label trial**.*

2.120 downstream processing
technologies involved in the recovery and purification of products

*NOTE Contrast with **upstream processing**.*

2.121 efficacy follow-up
systematic collection and collation of data that is designed in a way that enables learning about the efficacy or effectiveness of a **medicinal product**

*NOTE It can include **active surveillance, clinical trials, observational trials** and **passive surveillance**.*

[European Medicines Agency's *Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products* [24]]

2.122 eligibility criteria
predetermined criteria for establishing whether an individual may or may not be entitled to be chosen

NOTE Also known as inclusion and exclusion criteria.

2.123 embryonic stem cell
undifferentiated cell derived from a pre-blastocyst or **blastocyst** that is **pluripotent**

2.124 embryonic stem cell line
cell line consisting of **embryonic stem cells**

2.125 encapsulation
procedure by which biological materials are enclosed within a microscopic or macroscopic semipermeable barrier

[derived from ASTM F2312-11]

2.126 endpoint
overall outcome that a **protocol** is designed to evaluate

2.127 engineered cells and/or tissues
cells or **tissues** that have been subjected to **substantial manipulation**, so that the biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; and that are not intended to be used for the same essential function or functions in the recipient as in the **donor**

NOTE The manipulations listed in Annex I to European Regulation No. 1394/2007 [5], in particular, are not considered as substantial manipulations.

[European Regulation No. 1394/2007 [5]]

2.128 engraftment
process of integration of cellular material into a recipient

2.129 epigenetic
heritable change in the heritable pattern of gene expression that is mediated by mechanisms other than alterations in the primary nucleotide sequence of a gene

NOTE For example, DNA methylation or histone modifications.

[derived from *Epigenetic mechanisms of gene regulation* [35]]

2.130 ethics committee
independent body consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, **safety** and well-being of human **subjects** involved in a study

NOTE 1 Legal definitions applicable in the EU and USA are given in Table A.1.

NOTE 2 A hierarchy of ethical committees exists. The committees are known as the local research ethics committee (LREC), the multi-centre research ethics committee (MREC) and the central office for research ethics committee (COREC).

2.131 ex vivo
outside the living body

2.132 excipient
ingredient added intentionally to an **active substance**, which does not have pharmacological properties in the quantity used

[derived from ICH Harmonised Tripartite Guideline Q1A(R2) [36]]

2.133 extracellular matrix (ECM)
non-cellular matrix surrounding cells

2.134 extracorporeal
situated or occurring outside the body

2.135 false negative
<statistics> erroneously recognized as bad or false

*NOTE Contrasts with **false positive**.*

2.136 false positive
<statistics> erroneously recognized as good or true

NOTE Can be due to a failure in an alerting system or due to an error made in a statistical decision process.

2.137 feeder cell
cell used in co-culture to sustain the viability and desired characteristics of other cells

2.138 fetal stem cell
multipotent stem cell originating from a fetus that has the potential to differentiate into or generate a limited range of specialized cell types

2.139 finite cell line
cell line that can be maintained for a limited number of **population doublings** before it becomes senescent and ultimately loses the ability to divide

*NOTE See also **continuous cell line**.*

2.140 flow cytometry
technique that measures and analyses light scatter and fluorescence from single cells as they flow in a fluid stream through a laser beam

*NOTE This can be used to determine the **phenotype** of single cells.*

2.141 fluorescence activated cell sorting (FACS)
sorting of a heterogeneous mixture of cells into two or more containers, one cell at a time, using the specific light scattering and fluorescent characteristics of each cell

*NOTE See also **magnetic-based cell sorting**.*

[derived from *The Williams Dictionary of Biomaterials* [17]]

2.142 gene expression profile (transcriptome)
spectrum of mRNA levels resulting from gene activity at a given time

2.143 gene therapy
deliberate manipulation of genetic material into cells for therapeutic purpose

*NOTE See also **gene therapy medicinal product**.*

2.144 gene therapy medicinal product
biological medicinal product which contains an **active substance** which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and whose therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence

NOTE 1 This does not include vaccines against infectious diseases.

*NOTE 2 See also **gene therapy**.*

[European Directive 2001/83/EC (and amendments) [1]]

2.145 gene transfer
process of transferring a gene into cells, involving an expression system contained in a delivery system known as a **vector**, which can be of viral as well as non-viral origin

NOTE After gene transfer, genetically modified cells are also termed transduced cells.

[European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, draft Annex 2 [26]]

2.146 genetic locus
specific location of a gene or DNA sequence on a chromosome

2.147 genetically modified organism (GMO)
organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination

[derived from European Directive No. 2001/18/EC (and amendments) [37]]

2.148 genotype
genetic constitution of an individual cell or organism

2.149 Good Cell Culture Practice (GCCP)
guidelines to define minimum standards in cell and **tissue** culture

NOTE Also known as current Good Cell Culture Practice (cGCCP).

2.150 Good Clinical Practice (GCP)
regulations, codes and guidelines covering the conduct of **clinical trials**

NOTE Also known as current Good Clinical Practice (cGCP).

2.151 Good Laboratory Practice (GLP)
regulations, codes and guidelines for laboratories conducting **non-clinical studies**

NOTE Also known as current Good Laboratory Practice (cGLP).

2.152 Good Manufacturing Practice (GMP)
regulations, codes and guidelines for the **manufacture** of **cell therapy products**, **medicinal products**, **medical devices**, diagnostic products, food products and **active substances**

NOTE Also known as current Good Manufacturing Practice (cGMP).

2.153 Good Tissue Practice (GTP)
regulations, codes and guidelines for the **manufacture** of **cell therapy products**

NOTE Also known as current Good Tissue Practice (cGTP).

2.154 graft versus host disease (GVHD)
aggressive immune response caused when T-cells derived from **donor** cells recognize the **tissue** of a recipient

*NOTE This can occur following a **stem cell** or bone marrow **transplantation**.*

2.155 growth factor
naturally occurring protein capable of stimulating cellular **proliferation** and/or **differentiation**

2.156 haemocytometer
glass slide with a chamber for counting cells in a given volume

2.157 haematopoiesis
formation of blood lineages from **haematopoietic stem cells**

2.158 haematopoietic stem cell (HSC)
stem cell that gives rise to all red and white blood cells and platelets

[derived from the Stem Cell Information *Glossary* [20]]

2.159 Hayflick limit
number of divisions a cell can undergo before it stops dividing further

2.160 heterologous use
different use

2.161 heterotopic
different anatomical location

2.162 histocompatibility
measure of the extent to which implanted cells are immunologically matched to the recipient

2.163 histology
microscopic study of the form and structure of **tissues**

2.164 homologous use
same essential function

2.165 homotopic
same anatomical location

NOTE Also known as orthotopic.

2.166 human chimera embryo
admixed embryo created by inserting animal cells into a human embryo

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [14]]

2.167 human leucocyte-associated antigen (HLA)
highly polymorphic molecule required for antigen presentation encoded within the human **major histocompatibility complex**

*NOTE See also **tissue typing**.*

2.168 immobilization
entrapment of materials within, or bound to, a matrix

[derived from ASTM F2312-11]

2.169 immortal
capacity of cells to proliferate indefinitely

2.170 immunocytochemistry
method that uses antibodies to identify, locate and visualize specific molecules in or on the surface of cells

2.171 immunogenicity
extent to which an administered substance provokes an immune response in the recipient

2.172 immunohistochemistry
method that uses antibodies to identify, locate and visualize specific molecules or cell types in **tissue** sections

2.173 immunological rejection
failure of a recipient's body to accept a transplanted **tissue** or **organ** as the result of immunological incompatibility

2.174 immunomodulation
therapeutic strategy aimed at altering the normal course of an immune response, either enhancing it for the purpose of vaccination or suppressing its effects if deleterious

*NOTE This is often used in the case of **allograft** rejection and autoimmunity.*

2.175 immunotherapy
planned intervention in the normal course of a potentially detrimental immune response, intended to solicit an outcome of benefit to an individual

2.176 impurity
component present in a substance that is not the desired substance

2.177 in vitro
within an artificial environment

2.178 in vivo
within the living body

2.179 in-process control
checks performed during processing in order to monitor and if necessary adjust the process to ensure that the product conforms to its **specification**

NOTE 1 Environmental conditions and equipment can, for example, be monitored as part of in-process control.

*NOTE 2 One element of in-process control is **process analytical technology (PAT)**.*

2.180 induced pluripotent stem cell (iPS cell)
human **embryonic stem cell**-like cell that is produced by **reprogramming** a cell to a state of pluripotency

2.181 informed consent
voluntary decision to take part in a **clinical trial** or donate cells or tissues, after being duly informed of the nature, significance, implications and risks associated with the clinical trial or **donation**, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative

NOTE 1 Legal definitions applicable in the EU and USA for clinical trials are given in Table A.1.

NOTE 2 The annex to European Directive 2004/23/EC [2] specifies the information that must be provided to a donor, their relatives or any person granting authorization on behalf of a donor.

NOTE 3 In the UK, detailed advice on when and how consent should be sought, and what information should be given is provided in the Human Tissue Authority Code of practice 1 *[38].*

2.182 inner cell mass (ICM)
cluster of cells inside a **blastocyst**

*NOTE These cells are used to generate **embryonic stem cells**.*

[derived from the Stem Cell Information *Glossary* [20]]

2.183 intermediate
material produced during steps in the processing of an **active substance** that undergoes further molecular change or purification before it becomes an active substance

NOTE Intermediates may or may not be isolated.

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Part II [9]]

2.184 investigational medicinal product (IMP)
pharmaceutical form of an **active substance** or **placebo** being tested or used as a reference in a **clinical trial**

*NOTE 1 This includes products already with a **marketing authorization** but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.*

NOTE 2 Also known in the USA as investigational new drug (IND).

[derived from European Directive 2001/20/EC [39]]

2.185 karyotyping
assessment of the complete set of all chromosomes of a cell that can identify chromosomal abnormalities

2.186 magnetic-based cell sorting
sorting of a heterogeneous mixture of cells via mixing with magnetic beads coated with antibodies against specific cell surface antigens, followed by separation and selection using a column placed in a magnetic field

*NOTE See also **fluorescence activated cell sorting (FACS)**.*

2.187 major histocompatibility complex (MHC)
genetic locus encompassing a family of highly polymorphic genes encoding proteins that regulate immune responses

*NOTE The **human leucocyte-associated antigen (HLA)** is encoded within the human MHC.*

2.188 manufacture
any or all of the steps in the recovery, screening, testing, processing, storage, labelling or packaging of any **cell therapy product**

[derived from ASTM F2312-11]

2.189 marketing authorization
authorization by a relevant authority for a **medicinal product** to be placed on the market

NOTE 1 A new drug application (NDA) is the vehicle by which drug sponsors formally propose that the US Food and Drug Administration approve a new pharmaceutical for sale and marketing in the USA.

NOTE 2 A biologics licence application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce in the USA.

2.190 marrow stromal cell
differentiated progeny from **mesenchymal stem cells**

*NOTE Typically a heterogeneous population including a range of **stromal cells** at different stages of **differentiation** and of different composition or nature including osteoblasts (bone), chondrocytes (cartilage) and adipocytes (fat).*

2.191 master cell bank (MCB)
cell bank prepared from an aliquot of a single pool of cells

*NOTE 1 Generally the pool of cells is prepared from a **clone** under defined conditions.*

*NOTE 2 In a two-tiered cell banking system, the MCB is used to derive the **working cell bank (WCB)**.*

[derived from ICH Harmonised Tripartite Guideline Q5D [21]]

2.192 medical device
instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

[European Directive 93/42/EEC (and amendments) [40]]

2.193 medicinal product
substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

[European Directive 2001/83/EC (and amendments) [1]]

2.194 mesenchymal stem cell
multipotent bone marrow-derived non-**haematopoietic stem cell** with the capacity to generate cells of the stromal lineage

NOTE 1 Examples of cell types that can be derived from mesenchymal stem cells include osteoblasts, chondrocytes and adipocytes.

NOTE 2 These cells are also referred to as mesenchymal stromal stem cells.

2.195 microarray
set of DNA or protein molecules spotted onto a solid matrix for use in multiplex probing of a biological sample to determine gene or **protein expression**, marker pattern or the nucleotide sequence of DNA/RNA

2.196 minimal manipulation
processing that does not alter the relevant biological characteristics of cells or **tissue**

*NOTE Contrasts with **substantial manipulation**.*

[derived from the US Code of Federal Regulations, 21CFR1271.3(f)(2) [41]]

2.197 minor histocompatibility antigen (mH antigen)
naturally polymorphic protein that is recognized as foreign by the immune system of the recipient, potentially contributing to the rejection of a **tissue**

2.198 morula
pre-implantation embryo of about 30 cells produced after cleavage of the **zygote** around 96 hours following fertilization

*NOTE 1 The morula is a sphere of **blastomeres** contained within a glycoprotein membrane (zona pellucida).*

*NOTE 2 See also **blastocyst**.*

2.199 multipotent
having the ability to develop into a limited number of cell types

2.200 mycoplasma
parasitic bacterium without a cell wall, which belongs to the phylum Mollicutes

*NOTE Mycoplasma is a common **contaminant** in **cell culture** and can cause serious deleterious effects on cells. It is resistant to many antibiotics and as such is hard to remove entirely from a cell culture.*

2.201 necrosis
non-programmed cell death

*NOTE See also **apoptosis**.*

2.202 non-clinical study
study performed **in vitro** and/or **in vivo** (in animals) to provide data on an **investigational medicinal product**

*NOTE See also **preclinical study**.*

2.203 non-interventional trial
trial where a **medicinal product** is prescribed in the usual manner in accordance with the terms of the **marketing authorization**

NOTE The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the trial. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

[derived from European Directive 2001/20/EC [39]]

2.204 observational trial
trial to assess biomedical health outcomes in predetermined groups of individuals where the investigator does not assign specific interventions to the individuals

2.205 off-label use
use of a **medicinal product** to treat a separate medical condition to that which it has been approved for

2.206 open-label trial
randomized trial in which both the clinician and patient are aware of which **arm** of the trial the patient is on

*NOTE Contrasts with **single-blind trial** and **double-blind trial**.*

2.207 organ
differentiated part of the human body, formed by different **tissues**, that maintains its structure, vascularization and capacity to develop physiological functions with a significant level of autonomy

NOTE A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularization.

[derived from European Directive 2010/45 [4]]

2.208 orphan drug
medicinal product designed to treat a rare disease

2.209 parallel group
treatment and **control** are allocated to different individuals

2.210 parthenogenesis
development of a female embryo without fertilization from the male

2.211 parthenogenetic stem cell line
stem cell line derived from a one-pronuclear oocyte formed following **parthenogenesis**

*NOTE Derivation of such a line avoids ethical issues associated with the derivation of human **embryonic stem cells** and also enables the development of homologous **cell lines** suitable for **transplantation**.*

2.212 passage
transfer of cells from one **cell culture** environment to another

2.213 passage number
number of times cells have been transferred from one **cell culture** environment to another

2.214 passive surveillance
surveillance conducted by a method that relies on the collection of unsolicited initial patient **safety** information

NOTE 1 Examples include spontaneous reporting schemes, literature monitoring and Internet searches.

*NOTE 2 Contrasts with **active surveillance**.*

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union,* Volume 9A [12]]

2.215 pathogen
disease-producing agent or microorganism

[*Dorland's Pocket Medical Dictionary* [31]]

2.216 performance indicator
measurable value used to quantify **quality** objectives to reflect the performance of an organization, process or system

NOTE Also known as performance metrics.

[derived from ICH Harmonised Tripartite Guideline Q10 [42]]

2.217 permitted embryo
embryo licensed for use **in vitro** fertilization treatment

NOTE 1 The licensing of permitted embryos is covered by the Human Fertilisation and Embryology Act 1990 (and amendments) [6].

*NOTE 2 See also **admixed embryo**.*

2.218 pharmacodynamics
study of the biochemical and physiological effects of **medicinal products** and the mechanisms of their actions

[*Dorland's Pocket Medical Dictionary* [31]]

2.219 pharmacokinetics
study of the fate of drugs in a body

NOTE This includes a mathematical account of their absorption, distribution, metabolism and excretion.

[derived from the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment's *Annual Report 2006* [43]]

2.220 pharmacology
study of the uses, effects and actions of **medicinal products** on living systems

2.221 pharmacovigilance
science relating to the detection, assessment, understanding and prevention of adverse effects from medicines

[derived from the World Health Organization's *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products* [44]]

2.222 phase I trial
clinical trial performed in patients to determine **safety** data

NOTE Preliminary efficacy data can also be obtained from a phase I trial.

2.223 phase II trial
clinical trial performed in patients to ascertain **safety** and efficacy

NOTE This can be further separated into a phase IIa trial and phase IIb, which determine dosing requirements and efficacy respectively.

2.224 phase III trial
clinical trial that involves a large number of patients in different clinical settings to determine **safety** and efficacy

2.225 phase IV trial
post-authorization **clinical trial** using **pharmacovigilance** to determine the long-term **side effects** of **medicinal products**

2.226 phenotype
physical and biological characteristics of a cell or organism as determined by both genetic make-up and environmental influences

2.227 placebo
product or treatment that mimics a **medicinal product** but contains no **active substance**

2.228 placebo controlled trial
controlled trial in which the **control** is a **placebo**

2.229 placing on the market
first making available in return for payment or free of charge a **medicinal product** with a view to distribution and/or use on the market

[derived from European Directive 90/385/EEC (and amendments) [10]]

2.230 plasmid
piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome

NOTE It can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.

[European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, draft Annex 2 [26]]

2.231 plating efficiency
measure of the number of colonies originating from single cells

2.232 pluripotent
having the ability to develop into all cell lineages, except those related to extraembryonic **tissues**

NOTE 1 In humans there are three cell lineages from which all cell types, except extraembryonic tissues (e.g. placenta), are developed. These are the endoderm, mesoderm and ectoderm.

*NOTE 2 Contrasts with **unipotent**.*

2.233 polymerase chain reaction (PCR)
technique for the **in vitro** amplification of a specific target DNA sequence from a background of non-target DNA

2.234 population doubling
measured doubling of cell numbers

2.235 porosity
property of a solid which contains an inherent or induced network of channels and open spaces

NOTE This can be measured by the ratio of the pore (void) volume to the apparent (total) volume of a porous material and is commonly expressed as a percentage.

[ASTM F2312-11]

2.236 post-authorization safety study
study relating to an authorized **medicinal product** conducted with the aim of identifying, characterizing or quantifying a **safety** hazard, confirming the safety profile of the **medicinal product**, or of measuring the effectiveness of **risk management** measures

*NOTE This can be one element in a **phase IV trial**.*

[Directive 2001/83/EC (and amendments) [1]]

2.237 post-market surveillance
practice of monitoring the **safety** or efficacy of a **medicinal product** or **medical device** after it has been released onto the market

*NOTE 2 See also **clinical follow-up**.*

2.238 potency
<medicinal product> quantitative measure of biological activity based on those attributes of a product that are linked to relevant biological properties

[derived from ICH Harmonised Tripartite Guideline Q6B [45]]

<stem cell> extent to which a stem cell can differentiate along distinct cell lineage pathways

*NOTE For example, whether a stem cell is **multipotent** or **pluripotent**.*

2.239 power of study
<statistics> number or percentage that indicates the probability a study will obtain a statistically significant effect

2.240 preclinical study
study performed **in vitro** and/or **in vivo** (in animals) to provide data to support initiation of **clinical trial** phases and/or support **marketing authorization**

*NOTE See also **non-clinical study**.*

2.241 precursor cell
cell at a stage of development immediately prior to terminal **differentiation**

*NOTE See also **progenitor cell** and **somatic cell**.*

2.242 preservation
prevention or retardation of the biological or physical deterioration of cells or **tissues**

*NOTE 1 This can be achieved during cell or **tissue processing**, for example, through the use of chemical agents or alterations in environmental conditions.*

*NOTE 2 See **cryopreservation**.*

[derived from European Directive 2004/23/EC [2]]

2.243 primary cell culture
culture of cells isolated directly from **tissue**

2.244 principal investigator
investigator who takes overall charge at a **clinical trial** centre

*NOTE See **chief investigator** and **clinical investigator**.*

2.245 process analytical technology (PAT)
system for designing, analysing and controlling manufacturing through timely measurements, during processing, of critical **quality** and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

[ICH Harmonised Tripartite Guideline Q8(R2) [46]]

2.246 progenitor cell
cell which is at a more advanced stage of **differentiation** than a **stem cell** but is not yet fully differentiated

*NOTE See also **precursor cell** and **somatic cell**.*

2.247 proliferation
growth of a cell population by **cell division**

2.248 prospective trial
clinical trial that observes outcomes during a trial and relates these to influencing factors

*NOTE 1 Influencing factors include suspected **risk** or protection factors.*

*NOTE 2 Contrast with **retrospective trial**.*

[derived from *The Oxford Dictionary of Statistical Terms* [47]]

2.249 protein expression
translational and post-translational processing of proteins

2.250 protocol
<clinical trial> document that describes the objectives, design, methodology, statistical considerations and organization of a **clinical trial**

NOTE The term protocol refers to the protocol, successive versions of the protocol and protocol amendments.

[derived from European Directive 2001/20/EC [39]]

2.251 provenance
adequate knowledge of the source of a material, cells or reagents used in the derivation of cells in order for a **risk** assessment of **contamination** or infection to be made

NOTE 1 Provenance is essential when a material, cells or reagents are intended for clinical use.

*NOTE 2 Provenance can include knowledge of the medical histories of **donors** of gametes used to derive embryos.*

2.252 purity
level of freedom from **impurities**

2.253 qualification
<manufacturing> confirmation by examination and provision of objective evidence that equipment functions in the manner intended by the manufacturer

NOTE 1 This includes examination of the installation, operation and performance of equipment.

*NOTE 2 See also **validation**.*

2.254 qualified person (QP)
person responsible for certifying that a **batch** of **medicinal product** conforms to requirements prior to release

NOTE European Directive 2001/83/EC [1] specifies requirements for a QP.

2.255 qualified person responsible for pharmacovigilance (QPPV)
person responsible for **pharmacovigilance** for licensed **medicinal products**

NOTE European Directive 2001/83/EC [1] specifies requirements for a QPPV.

2.256 quality
degree to which a set of inherent properties of a product, system or process fulfils requirements

[ICH Harmonised Tripartite Guideline Q9 [48]]

2.257 quality assurance (QA)
total sum of organized arrangements made with the object of ensuring that **medicinal products** are of the **quality** required for their intended use

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union,* Volume 4, Part I, Chapter 1 [49]]

2.258 quality by design (QbD)
systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality **risk management**

[ICH Harmonised Tripartite Guideline Q8(R2) [46]]

2.259 quality control (QC)
process or set of processes or measures used to maintain predefined standards to assure the **quality** of a product

2.260 quality system
documented organizational structure, defined responsibilities, procedures, processes and resources for implementing **quality** management including all activities which contribute to quality, directly or indirectly

[derived from European Directive 2006/17/EC [33]]

2.261 quiescence
stage in a cell cycle when the cell stops dividing

2.262 randomized trial
trial in which participants are randomly (i.e. by chance) assigned to one of two or more treatment **arms** of a **clinical trial**

*NOTE Examples include **double-blind trial, open-label trial** and **single-blind trial**.*

2.263 raw material
starting materials, reagents and solvents intended for use in the production of **intermediates** or an **active substance**

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, Part II [9]]

2.264 real time release testing (RTR testing)
evaluation and ensurance of the **quality** of an in-process product and/or final product based on process data

NOTE Process data typically include a combination of measured material attributes and process controls.

[derived from ICH Harmonised Tripartite Guideline Q8(R2) [46]]

2.265 recall
removal or correction of a marketed product that a relevant authority considers to be in violation of their laws

2.266 regenerative medicine
process of replacing or regenerating human cells, **tissues** or **organs** to restore or establish normal function

[derived from *Regenerative Medicine*, 2008, **3**(1), 1–5 [50]]

2.267 release criteria
predetermined criteria against which a product is assessed to determine its suitability for release

*NOTE These measurements can include identity, **purity**, impurities, sterility, **potency**, **cell viability** and total cell number.*

[derived from the European Medicines Agency's *Guideline on Human Cell-Based Medicinal Products* [22]]

2.268 reproductive cloning
production of identical animals via **cloning**

2.269 reprogramming
<genetics> facilitating the uptake of genes by a cell

*NOTE This is a method frequently used to derive **induced pluripotent stem cells (iPS cells)**.*

2.270 retrospective trial
clinical trial that identifies outcomes from data that has previously been collected and relates these to influencing factors

*NOTE 1 Influencing factors include suspected **risk** or protection factors.*

*NOTE 2 Contrast with **prospective trial**.*

[derived from *The Oxford Dictionary of Statistical Terms* [47]]

2.271 risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999]

*NOTE See also **risk analysis** and **risk management**.*

2.272 risk analysis
systematic use of available information to identify hazards and to estimate the **risks**

NOTE Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.

[ISO/IEC Guide 51:1999]

2.273 risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling **risk**

[BS EN ISO 14971:2009, **2.22**]

*NOTE Attention is drawn to the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 9A [12], which in the context of **pharmacovigalance**, specifically defines:*

*a) a risk management system as a set of **pharmacovigilance** activities and interventions designed to identify, characterize, prevent or minimize risks relating to **medicinal products**, and the assessment of the effectiveness of those interventions;*

b) *EU risk management plan (EU-RMP) as a document that describes a risk management system, which is specific to a particular product; and*

c) *risk minimization as activities used to reduce the probability of an **adverse reaction** occurring or its severity should it occur.*

2.274 safety
freedom from unacceptable **risk**

[ISO/IEC Guide 51:1999]

2.275 safety follow-up
systematic collection and collation of data that is designed in a way that enables learning about the **safety** of a **medicinal product**

*NOTE It can include **active surveillance, clinical trials, observational trials** and **passive surveillance**.*

[European Medicines Agency's *Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products* [24]]

2.276 same surgical procedure
surgical intervention, or series of interventions, related to the same therapeutic goal on an individual under the continuous care of a medical doctor or team of medical doctors for the purpose of obtaining a specific therapeutic effect

2.277 scaffold
support, delivery vehicle or matrix for facilitating the migration, binding or transport of cells or **bioactive agents**

[derived from ASTM F2312-11]

2.278 scale out (or scale horizontally)
increasing production by an increase in the number of units rather than increasing the size of the process

2.279 scale up (or scale vertically)
increasing the size of the process rather than increasing production by an increase in the number of units

2.280 seeding density
number of cells used to initiate or progress a **cell culture**

NOTE Usually expressed as total number of cells per unit area or volume.

2.281 self-renewal
ability to continuously undergo **cell division** where each daughter cell is identical

2.282 senescence
decline or degeneration related to cellular ageing

2.283 sensitivity
<statistics> degree of response to a change in input/components of the test

2.284 serious adverse event (SAE)
untoward occurrence associated with the procurement, testing, processing, storage and distribution of **tissues** and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or that might result in, or prolong, hospitalization or morbidity

NOTE 1 A legal definition of SAE applicable in the EU for clinical trials is given in Table A.1.

*NOTE 2 See also **adverse event**.*

[European Directive 2004/23/EC [2]]

2.285 serious adverse reaction (SAR)
unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization or morbidity

NOTE 1 A legal definition of SAR applicable in the EU for clinical trials is given in Table A.1.

*NOTE 2 See also **adverse reaction** and **unexpected adverse reaction (UAR)**.*

[European Directive 2004/23/EC [2]]

2.286 sham procedure
procedure that is performed as a **control** and that is similar to but omits a key therapeutic element of the treatment or procedure under investigation

2.287 side effect
undesired action or effect resulting from therapeutic treatment

2.288 significance
<statistics> fixed probability of wrongly rejecting the null hypothesis

2.289 single-blind trial
randomized trial in which either the clinician or patient are unaware of which **arm** of the trial the patient is on

*NOTE 1 See also **double-blind trial**.*

*NOTE 2 Contrasts with **open-label trial**.*

2.290 somatic cell
fully differentiated cell from an adult body or fetus

*NOTE 1 These cells can be **autologous, allogeneic** or **xenogeneic somatic cells** that have been manipulated or altered **ex vivo** to be administered in humans to obtain a therapeutic, diagnostic or preventive effects.*

*NOTE 2 See also **progenitor cell** and **precursor cell**.*

[derived from the UK Stem Cell Bank's *Code of Practice for the Use of Human Stem Cell Lines* [13]]

2.291 somatic cell nuclear transfer (SCNT)
technique that combines an enucleated egg (nucleus removed) and the nucleus of a somatic cell to make an embryo

2.292 somatic cell therapy medicinal product
biological medicinal product which contains or consists of cells or **tissues** that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or **tissues** that are not intended to be used for the same essential functions in the recipient and the **donor**; and is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues

NOTE The manipulations listed in Annex I to European Regulation No. 1394/2007 [5], in particular, are not considered as substantial manipulations.

[Directive 2001/83/EC (and amendments) [1]]

2.293 specification
predetermined set of criteria to which a **medicinal product**, **active substance** or **intermediates** thereof, should conform to be considered acceptable for its intended use

[derived from ICH Harmonised Tripartite Guideline Q6B [45]]

2.294 specificity
<statistics> probability of a true negative being correctly identified

*NOTE Contrasts with **false negative**.*

2.295 stability testing
determination of the shelf life of a substance under anticipated storage and in use

*NOTE 1 This includes, for example, assessment of the ability of cells to survive and maintain their **potency**.*

*NOTE 2 This applies to, for example, **raw materials, starting materials, intermediates** and final products.*

[derived from the European Medicines Agency's *Guideline on Human Cell-Based Medicinal Products* [22]]

2.296 standard operating procedure (SOP)
detailed, written instructions to achieve uniformity of the performance of a specific function

[ICH Harmonised Tripartite Guideline E6(R1) [51]]

2.297 starting material
raw material, **intermediate** or **active substance** that is used in the production of an active substance and that is incorporated as a fragment into the structure of the active substance

*NOTE 1 Attention is drawn to European Directive 2001/83/EC (and amendments) [1], Annex 1, Part IV, which requires for **somatic cell therapy medicinal products** and **tissue engineered products** that additional substances (e.g. **scaffolds**, matrices, devices, **biomaterials**, **biomolecules** and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.*

*NOTE 2 See also **cellular starting material**.*

[derived from ICH Harmonised Tripartite Guideline Q7 [11]]

2.298 state of control
condition in which a set of controls consistently provides assurance of continued process performance and product **quality**

[derived from ICH Harmonised Tripartite Guideline Q10 [42]]

2.299 stem cell
cell capable of both **asymmetric cell division** and **self-renewal**, and of providing cells capable of **differentiation**

2.300 stem cell line
cell line consisting of **stem cells**

2.301 sterile
completely absent of any viable microorganisms

NOTE Sterility is determined through a validated process that demonstrates the absence of microorganisms at a specified statistical probability.

2.302 stromal cells
non-haematopoietic cells capable of supporting the growth of blood cells

NOTE Typically derived from bone marrow.

2.303 subject
individual who participates in a **clinical trial** as either a recipient of the **investigational medicinal product** or **control**

[derived from European Directive 2001/20/EC [39]]

2.304 substantial manipulation
manipulation of cells or **tissue** so that biological characteristics, physiological functions or structural properties relevant for the therapeutic application are achieved

NOTE 1 The following manipulations are not considered as substantial manipulations:

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

*NOTE 2 Contrasts with **minimal manipulation**.*

[derived from European Directive 2001/83/EC (and amendments) [1]]

2.305 syngeneic
where **donor** and recipient are genetically identical individuals

NOTE For example, identical twins or animals of a single highly inbred strain.

2.306 therapeutic cloning
production of cells that exactly match the cells of a **donor**

2.307 therapeutic immunosuppression
suppression of the immune response in order to prevent the rejection of grafts or transplants or control autoimmune diseases

2.308 therapy
treatment intended to heal or relieve a disorder

2.309 tissue
aggregation of specialized cells united in the performance of a particular set of functions

[derived from ASTM F2312-11]

2.310 tissue bank
collection of **tissues** stored for research or clinical utility

2.311 tissue engineered product
product that contains or consists of **engineered cells and/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**

[European Regulation No. 1394/2007 [5]]

2.312 tissue engineering
use of a combination of cells, engineering, materials and methods to **manufacture ex vivo** living **tissues** and **organs** that can be implanted to improve or replace biological functions

*NOTE Usually through the use of **scaffolds** for restoration or regeneration of tissues or organs.*

2.313 tissue establishment
establishment where the activities of processing, **preservation**, storage or distribution of human **tissue** and cells are undertaken

*NOTE 1 For example, a **tissue bank** or a unit of a hospital.*

NOTE 2 It might also be responsible for procurement or testing of tissue and cells.

[derived from European Directive 2004/23/EC [2]]

2.314 tissue typing
process of determining the set of **human leucocyte-associated antigens** encoded within an individual's **major histocompatibility complex**

*NOTE This is performed in order to determine the acceptance or rejection of a **tissue** graft prior to **transplantation**.*

2.315 toxicology
study of the potential of materials to harm health by virtue of their effect on biological systems

2.316 totipotent
having the ability to develop into all types of cell including extraembryonic **tissues**

NOTE An example of extraembryonic tissue is placenta.

2.317 traceability
ability to track **tissues** or cells by recording their status at all points from initial collection right through to either **transplantation** or disposal

NOTE Legal definitions applicable in the EU and USA are given in Table A.1.

2.318 transgenic
organism that contains a foreign gene in its normal genetic component

NOTE Such organisms might be produced in order to express biological pharmaceutical materials.

[derived from the European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, draft Annex 2 [26]]

2.319 transgenic human embryo
admixed embryo created by inserting animal genes into an early embryo

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [14]]

2.320 translation
active turning of a basic science discovery into a safe and effective **therapy** deployed in routine clinical practice

2.321 transplantation
process of implanting cells, **tissues** or **organs**

[derived from ASTM F2312-11]

2.322 transplantation tolerance
state of induced immunological acceptance of a graft that would otherwise be rejected

2.323 trophoblast
outer cell layer of a **blastocyst**

NOTE It develops into extraembryonic tissue, such as placenta.

[derived from the Stem Cell Information *Glossary* [20]]

2.324 tumour
swelling of a part of the body caused by an abnormal growth of **tissue** whether benign or malignant

2.325 tumour-associated antigen
protein whose expression is predominantly restricted to a given type of **tumour**

*NOTE This can serve as a target for a **cancer vaccine**.*

2.326 tumorigenicity
tendency of cells to form a **tumour**

2.327 unexpected adverse reaction (UAR)
adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics

*NOTE See also **adverse reaction** and **serious adverse reaction (SAR)**.*

[derived from European Directive 2001/83/EC (and amendments) [1]]

2.328 unipotent
having the ability to develop into only one cell type

*NOTE Contrasts with **pluripotent**.*

2.329 upstream processing
technologies involved in the initial stages of product **manufacture**

*NOTE 1 For example where cells are grown in a **bioreactor**.*

*NOTE 2 Contrasts with **downstream processing**.*

2.330 user requirement brief (URB)
overarching, strategic document describing what outcomes an end user expects from a project as a whole

NOTE 1 It includes a description of the business, as well as the technical, need for a project.

*NOTE 2 It is used, for example, for capital manufacturing projects licensed by a relevant **competent authority**, such as the Medicines and Healthcare products Regulatory Agency (MHRA).*

*NOTE 3 It is underpinned by **user requirement specifications (URSs)**.*

2.331 user requirement specification (URS)
document describing what outcomes an end user expects from an individual component of a project

NOTE 1 Individual components of a project include individual products and systems.

*NOTE 2 It is written in line with the requirements of a **user requirement brief (URB)**.*

2.332 validation
means of establishing documented evidence that provides a high degree of assurance that a specific process, **standard operating procedure**, piece of equipment or environment will consistently produce a product meeting its predetermined **specifications** and **quality** attributes perform according to the intended specified outcomes

NOTE A process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

[European Directive 2006/17/EC [33]]

2.333 vector
agent that can carry a DNA fragment into a host cell

*NOTE If it is used for reproducing the DNA fragment, it is named **cloning** vector. If it is used for expressing the fragment, it is named expression vector.*

2.334 viral vector
vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes

NOTE If the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.

[European Commission's *Eudralex: The Rules Governing Medicinal Products in the European Union*, Volume 4, draft Annex 2 [26]]

2.335 vitrification
form of **cryopreservation** whereby cells, **tissues** or **organs** are converted into a glass-like amorphous state prior to cooling to ultra-low temperatures

2.336 whole bioprocessing
<allogeneic> entire bioprocess from **donor** through to implantation of a **cell therapy**

<autologous> entire bioprocess from patient biopsy through to implantation of a **cell therapy**

2.337 working cell bank (WCB)
cell bank prepared from aliquots of a homogeneous suspension of cells obtained from culturing cells from the **master cell bank**

[derived from ICH Harmonised Tripartite Guideline Q5D [21]]

2.338 xenogeneic
where the **donor** and recipient belong to different species

[derived from ASTM F2312-11]

2.339 xenograft
xenogeneic graft

2.340 xenotransplantation
procedure that involves the **transplantation** or infusion into a human recipient of either cells, **tissues** or **organs** from a non-human animal source, or human body fluids, cells, tissues, or organs that have had **ex vivo** contact with live non-human cells, tissues, or organs

[ASTM F2312-11]

2.341 zygote
fertilized egg

Annex A (informative) Regulatory terms

Table A.1 **Regulatory terms**

Term	Definition	Legislation
adverse event	any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment	European Directive 2001/20/EC [39]
adverse experience	adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: an adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action	US Code of Federal Regulations, 21CFR600.80 [52]
adverse reaction	untoward and unintended responses to an investigational medicinal product related to any dose administered	European Directive 2001/20/EC [39]
	response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function	Directive 2001/83/EC (and amendments) [1]
clinical trial	investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy	European Directive 2001/20/EC [39]
	prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)	US National Institutes of Health *Glossary & Acronym List* [53]

Table A.1 **Regulatory terms** *(continued)*

Term	Definition	Legislation
ethics committee	independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent	European Directive 2001/20/EC [39]
	review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection	US Code of Federal Regulations, 21CFR312.3 [54]
human admixed embryo	a) an embryo created by replacing the nucleus of an animal egg or of an animal cell, or two animal pronuclei, with: 1) two human pronuclei; 2) one nucleus of a human gamete or of any other human cell; or 3) one human gamete or other human cell; b) any other embryo created by using: 1) human gametes and animal gametes; or 2) one human pronucleus and one animal pronucleus; c) a human embryo that has been altered by the introduction of any sequence of nuclear or mitochondrial DNA of an animal into one or more cells of the embryo; d) a human embryo that has been altered by the introduction of one or more animal cells; or e) any embryo not falling within paragraphs (a) to (d) which contains both nuclear or mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal (“animal DNA”) but in which the animal DNA is not predominant	Human Fertilisation and Embryology Act 1990 (and amendments) [6]

Table A.1 **Regulatory terms** *(continued)*

Term	Definition	Legislation
informed consent	decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation	European Directive 2001/20/EC [39]
	person's voluntary agreement, based upon adequate knowledge and understanding, to participate in human subjects research or undergo a medical procedure	US National Institutes of Health *Glossary & Acronym List* [53]
serious adverse event (SAE) or serious adverse reaction (SAR)	untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect	European Directive 2001/20/EC [39]
traceability	ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells	European Directive 2006/17/EC [33]
	establishment and maintenance of procedures for identifying with a control number each unit or batch of finished medical devices and where appropriate components	US Code of Federal Regulations, 21CFR820.65 [55]

Annex B (informative) Finance

B.1 angel investor
specialist, independent investor that typically provides start-up capital to early stage companies

B.2 cash burn rate
measure of how rapidly a company spends its shareholders' capital

B.3 cross licensing
reciprocal agreement between two or more parties that confers rights to access and utilized named intellectual capital

B.4 discount rate
interest rate applied in discounted cash flow analysis to determine the time value of money, accounting for inflation and predicted returns from alternative investments

B.5 discounted cash flow (DCF) analysis
valuation technique that accounts for the time value of money, including inflation and predicted returns from alternative investments

B.6 disruptive technology
innovation that creates a new (and unexpected) market by applying a different set of values

B.7 initial public offering (IPO)
transaction whereby a company offers shares of ownership, or equity, to investors through a market in order to raise capital

NOTE Thereafter, the shares can be publicly traded without any restrictions on ownership.

B.8 internal rate of return (IRR)
discount rate at which the net present value, NPV, of costs, negative cash flows become equal to the NPV, of benefits, positive cash flows, of a given investment

*NOTE In other words, the point at which any profits generated by a company exceed the borrowing costs of capital used to provide the initial investment. Calculated through **discounted cash flow (DCF) analysis**.*

B.9 net present value (NPV)
valuation methodology that analyses discounted cash flows to account for their present and future values

B.10 parallel importing
importing and sale of pharmaceutical products into jurisdictions other than those in which they were initially intended for sale, thus attempting to realize an arbitrage opportunity

B.11 private equity
investment in or acquisition of mature companies

B.12 small and medium sized enterprise (SME)
companies with headcount and either turnover or balance sheet total below certain limits

NOTE 1 A small enterprise is described as having a headcount of below 50 and a turnover of less than or equal to €10 000 000.

NOTE 2 A small enterprise is described as having a headcount of below 250 and a turnover of lower than or equal to €50 000 000.

B.13 venture capital
investment in or acquisition of early stage companies

[US Food And Drug Administration's *Guidance for Industry – Process Validation: General Principles and Practices* [30]]

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Useful websites

- ASTM International
  www.astm.org
- EU pharmaceutical information
  http://ec.europa.eu/health/index_en.htm
- EU legislation information
  http://europa.eu/
- European Medicines Agency (EMA)
  www.ema.europa.eu
- International Society for Cellular Therapy (ISCT)
  www.celltherapysociety.org
- US National Institutes of Health (NIH)
  www.nih.gov
- UK Medicines and Healthcare products Regulatory Agency (MHRA)
  www.mhra.gov.uk
- UK Department of Health
  www.dh.gov.uk
- UK Department of Health/Medical Research Council online clinical trials guide
  www.ct-toolkit.ac.uk
- UK Human Fertilisation and Embryology Authority
  www.hfea.gov.uk

- UK Human Tissue Authority
  www.hta.gov.uk
- UK National Blood Service
  www.blood.co.uk
- UK Stem Cell Bank
  www.ukstemcellbank.org.uk
- US Food and Drug Administration
  www.fda.gov
- The United States Pharmacopeia Convention (USP)
  www.usp.org

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