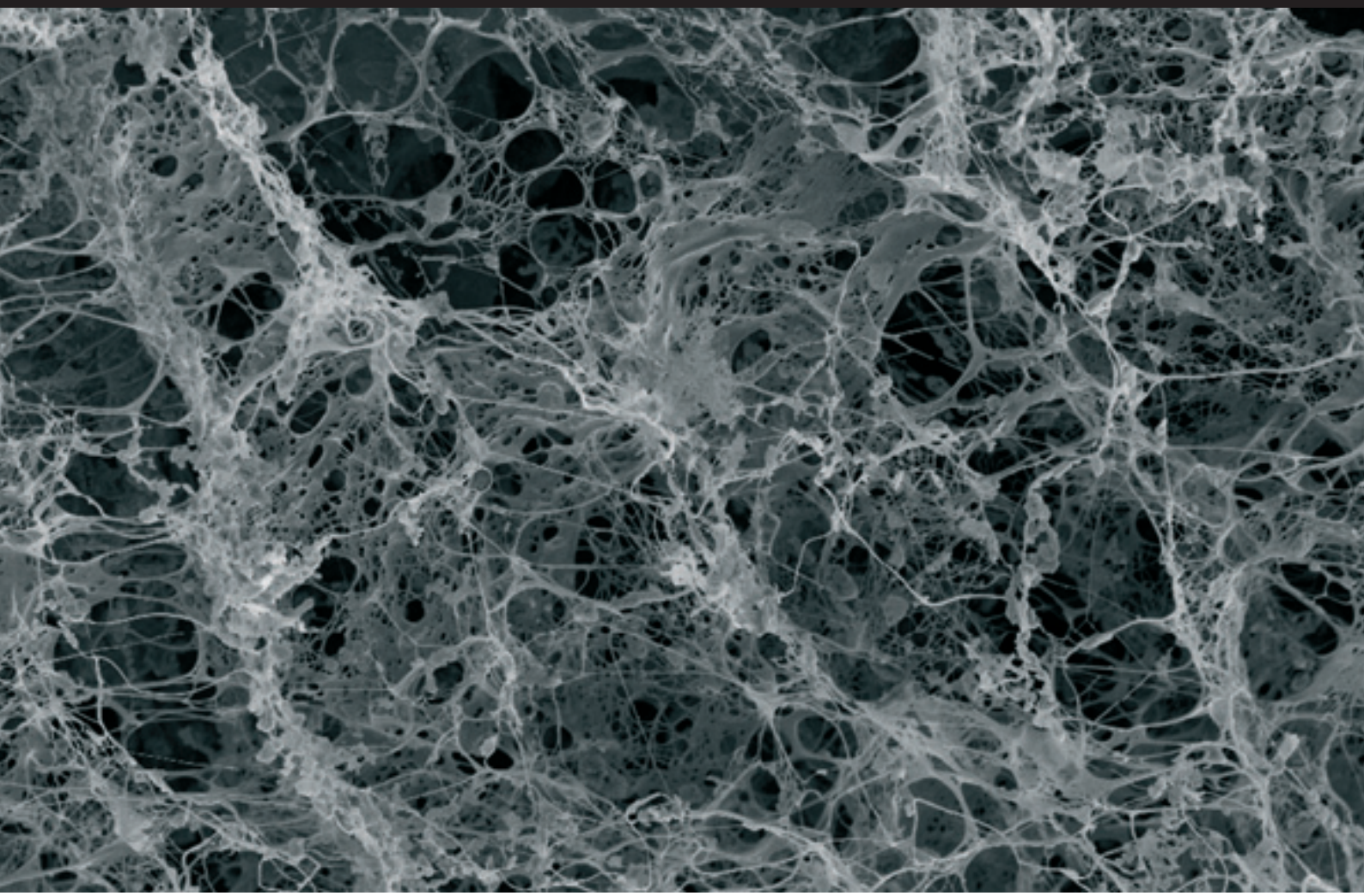
PUBLICLY AVAILABLE SPECIFICATION

PAS 83:2012

Developing human cells for clinical applications in the European Union and the United States of America – Guide



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Foreword

This Publicly Available Specification (PAS 83) was sponsored by the UK Department for Business, Innovation and Skill (BIS) and its development was facilitated by the British Standards Institution (BSI). This Publicly Available Specification came into effect on 1 June 2012.

Acknowledgement is given to the following organizations that were consulted in the development of this specification.

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Acknowledgement is given to Christopher Bravery of Consulting on Advanced Biologicals as the Technical Author for the revision of PAS 83.

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As a guide, this Publicly Available Specification takes the form of guidance and recommendations: it does not contain specified requirements.

The word "should" is used to express recommendations of this Publicly Available Specification. The word "may" is used in the text to express permissibility, e.g. as an alternative to the primary recommendation of the clause. The word "can" is used to express possibility, e.g. a consequence of an action or an event.

Notes are provided throughout the text of this Publicly Available Specification to give references and additional information that are important but do not form part of the recommendations.

Contractual and legal considerations

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

Compliance with a Publicly Available Specification cannot confer immunity from legal obligations.

This Publicly Available Specification is not to be regarded as a British Standard.

Ministerial statement

The first edition of PAS 83 (Guidance on codes of practice, standardised methods and regulations) was published in 2006. Since then, a number of legislative changes have occurred which help to clarify the regulatory framework for cell-based medicinal products in the EU. These changes mean that new cell therapy products will be evaluated by the European Medicines Agency.

However, the commercial success of the UK cell therapy industry does not just rely on developing products to supply domestic and European markets, but also markets further afield. To reflect this need, the scope of this revised PAS has been expanded to cover the United States, and is applicable to other jurisdictions. Routinely updating the guide to accommodate the pace of progress will help to ensure that understanding of regulation and best practices in development is not a barrier to successful clinical translation and commercialisation of cell therapy.

The recently revised *PAS 84* provides a glossary of terms for cell therapy and regenerative medicine, and the newly published *PAS 93* provides a more detailed guide on characterisation of human cells for clinical applications. Together these three documents are designed to support patients, researchers, clinicians, entrepreneurs, manufacturers, press, public and politicians – to share a common language and understanding of how cell therapies are developed and regulated. This will, in turn, contribute significantly to the UK operating as a single, globally competitive cluster, led by the London-based Cell Therapy Catapult Centre.

As a robust supporter of research, translation and commercialisation of cell therapies, 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 for Universities and Science

0 Introduction

0.1 Background and aim of this Publicly Available Specification (PAS)

"a product in which human cells are administered to the body, for the purpose of replacing, repairing, regenerating, or enhancing function of tissues"

The aim of this PAS is to:

- provide an overview of the development and regulation of cell therapy products in the European Union (EU) and the United States of America (US);
- define in the form of a process map the key steps in a cell-based product lifecycle, from cell/tissue procurement through to commercialization and post-launch activities;
- identify legal requirements and guidelines applicable to each stage of the process map, identify which regulations and guidelines are already available in this field and link them to the lifecycle of the product.

The term cell therapy, as defined in PAS 84, *Cell therapy and regenerative medicine – Glossary*, covers any use of cells to benefit a recipient. However, the regulation of cell therapy products is dependent on the degree of manipulation or use. The main purpose of this PAS is to describe the principles of development and regulatory requirements for products regulated in the EU as medicinal products and in the US as biologics. The term cell-based medicinal product (CBMP) is used in this PAS to refer specifically to such products. Due to the overlap in regulatory regimes some of the text on regulation is also applicable to products that are not regulated as medicines or biologics, and many of the principles of development described may also be broadly appropriate.

0.2 Use of this PAS

To this end, a detailed process map highlights the critical stages involved in the product pathway, initiated by the procurement of cells or tissue. Each stage is then accompanied by a set of bullet points informing users of important points of awareness and a list of the accompanying legislative acts and guidance documents supporting the legislation. In the case of the latter, it is intended that these will act as a navigation tool to direct the user to the relevant documents.

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1 Scope

This Publicly Available Specification (PAS) gives guidance by providing a quick reference source, to increase clarity for users on the requirements needed for exploitation of cell therapy products. The main focus of this PAS are cell based medicinal products (CBMPs) that are regulated as advanced therapy medicinal products (ATMP) in the EU and biologics (351 HCT/P) in the US. However, for completeness aspects of minimally manipulated, homologous use products (also known as 361 HCT/P in the US) are also covered.

This PAS will act as a guide to point users in the direction of the relevant EU and US legislation, guidance documents, pharmacopoeial chapters and monographs.

NOTE 1 *Since the implementation of EU Directives varies between Member States it is not possible to provide specific national details of how legislation is enacted around the EU.*

NOTE 2 *Where national differences exist this will be indicated in the text.*

This PAS is intended for use by organizations and individuals with an interest in the development of human cells for clinical applications including academic groups, small and medium sized enterprises (SMEs) and larger industrial manufacturers and the general public.

For researchers new to the field, this PAS will give an appreciation of the level of regulation, guidance and associated quality issues that apply to cell therapy products.

This PAS does not cover:

- solid organ transplantation or blood transfusions;
- blood products (e.g. serum, plasma, erythrocytes and platelets);
- xenogeneic products and xenogeneic feeder cells, although much of the text will be broadly applicable;
- combination products, although the text will still be applicable to the cellular component, other requirements will also apply;
- tissue and cell products regulated in the US as devices (e.g. requiring PMA), although much of the text will be broadly applicable to the cellular component, other requirements will also apply;
- genetically modified cell or tissues products, although the text will still be applicable to the cellular component other requirements will also apply;

but for clarity, their relationship to the overall process map is included where useful.

2 Normative references

The following referenced document is indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

PAS 84, *Cell therapy and regenerative medicine – Glossary*

3 Terms, definitions and abbreviations

3.1 Terms and definitions

For the purposes of PAS 83 the terms and definitions given in PAS 84 apply.

3.2 Abbreviations

The following abbreviations apply.

ATMP Advanced Therapy Medicinal Product

NOTE 1 *This term covers somatic cell therapy medicinal products, tissue engineered products and gene therapy medicinal products. Gene therapy products are not covered in this PAS.*

NOTE 2 *For the purposes of this PAS, the term CBMP is used to cover any ATMP consisting of cells.*

BLA Biologics Licence Application

CAT Committee for Advanced Therapies

CBER Center for Biologics Evaluation and Research (FDA)

CBMP Cell-Based Medicinal Product

NOTE 3 *This term is used to identify cell therapy products that are regulated as medicinal products (ATMP) in the EU or biologics products (351 HCT/P) in the US only.*

CFR Code of Federal Regulations

CHMP Committee for Human Medicinal Products

CJD Creutzfeldt-Jakob Disease

CMC Chemistry, Manufacturing and Controls

NOTE 4 *This term is synonymous with quality in the sense of module 3 of the CTD.*

CoA Certificate of Analysis

CTD Common Technical Document

NOTE 5 *Electronic standards also exist, eCTD.*

CTA Clinical Trials Authorization

CTFG Clinical Trials Facilitation Group

NOTE 6 *This is a working group of the Heads of Medicines Agencies (HMA) within the EU.*

CTGTAC Cellular, Tissue and Gene Therapies Advisory Committee (FDA)

DG Directorate General

NOTE 7 *European Commission, e.g. DG Health.*

DSUR Development Safety Update Report

EC European Commission

EDQM European Directorate for the Quality of Medicines

NOTE 8 *Includes the European Pharmacopoeia.*

EEA European Economic Area

EEC European Economic Community

NOTE 9 *Predecessor of the EU.*

EMA European Medicines Agency

NOTE 10 *Previously called the European Medicines Evaluation Agency (EMEA).*

EOP End of Phase

EPAR European Public Assessment Report

EU European Union

EUDRACT European Union Drug Regulating Authorities Clinical Trials

EUTCD EU Tissues and Cells Directive

FCS Fetal Calf Serum

FDA US Food and Drugs Administration

GCP Good Clinical Practice

NOTE 11 *Also 'current' GCP, cGCP.*

GLP Good Laboratory Practice

GMP Good Manufacturing Practice

NOTE 12 *Also 'current' GMP, cGMP.*

GNA Grounds for Non-Acceptance

GTP Good Tissue Practices

NOTE 13 *Also 'current' GTP, cGTP.*

HBV Hepatitis B Virus

HCT/P Human Cells, Tissues, and Cellular and Tissue-Based Products

NOTE 14 *Also 361 HCT/P, products regulated under GTPs only.*

NOTE 15 *Also 351 HCT/P, products regulated as biologics, requiring a BLA.*

HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IP	Intellectual Property
IRB	Institutional Review Board
ITF	Innovation Task Force (EMA)
MAA	Marketing Authorization Application
MoA	Mechanism of Action
NAT	Nucleic Acid-based Test
NCA	National Competent Authority

NOTE 16 *This is an EU term but its use within this PAS is extended to include equivalent authorities in the US, e.g. FDA.*

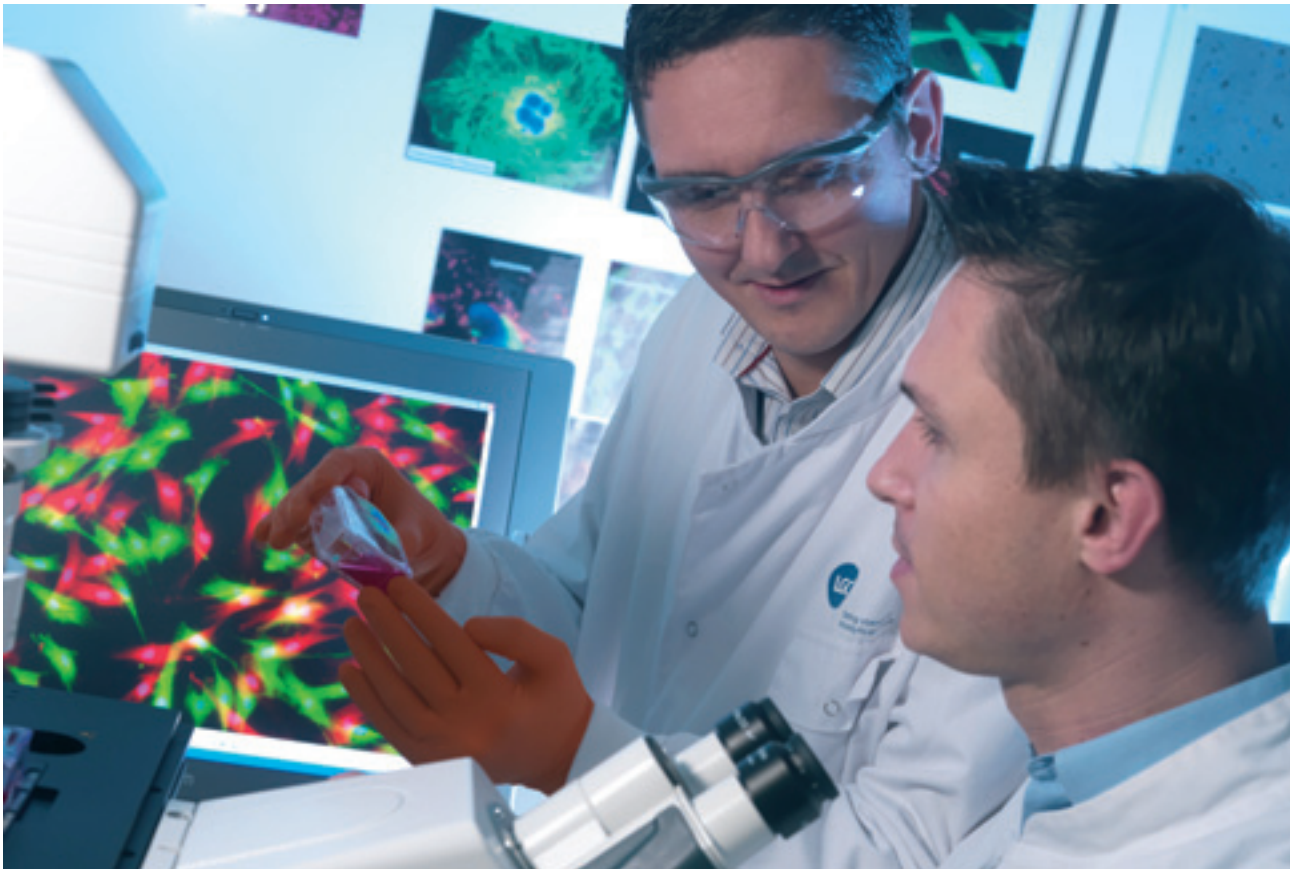
OD	Orphan Drug
OECD	Organisation for Economic Co-operation and Development
PD	Pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PhEur	European Pharmacopoeia

NOTE 17 *Also, EP.*

PHS Act	Public Health Services Act
PK	Pharmacokinetics
PMA	Pre-Market Approval
PSUR	Periodic Safety Update Report
QoS	Quality Overall Summary

NOTE 18 *Part of module 2 of the CTD.*

QP	Qualified Person
SME	Small and Medium Sized Enterprise
SOP	Standard Operating Procedure
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
US	United States of America
USC	United States Code
USP	United States Pharmacopoeia

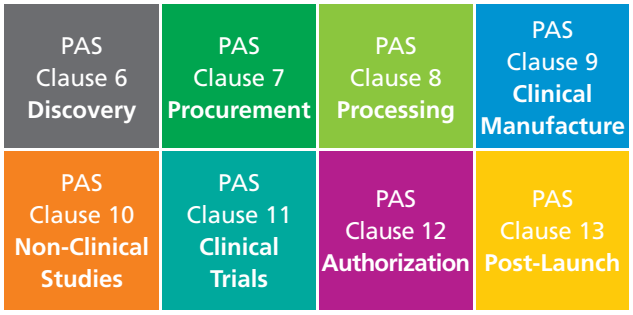


4 The process map

The development of cell therapy products is complex and consequently any attempt to partition activities brings limitations. This PAS separates the development of cell therapy products into eight activities for convenience (see Figure 1) but these are not independent from each other and do not necessarily occur sequentially.

Cell therapy products cross the border between cell transplantation and cell-based medicinal products (CBMPs); this PAS focuses on CBMPs, but includes cell processing for cell transplantation (see Clause **8**). In overview the development of CBMPs can be viewed as similar to other medicinal/biologics products (see Figure 2) even though their characteristics are very different from typical (bio)pharmaceuticals. The most significant differences to this general approach are likely to be the clinical strategy which is unlikely to follow a traditional phase 1, 2, 3 paradigm, and non-clinical development which can pose unique challenges. However, in accordance with harmonized regulatory principles in all ICH regions it is necessary to generate sufficient data as evidence of quality, safety, and efficacy to enter the market.

Figure 1 The process map

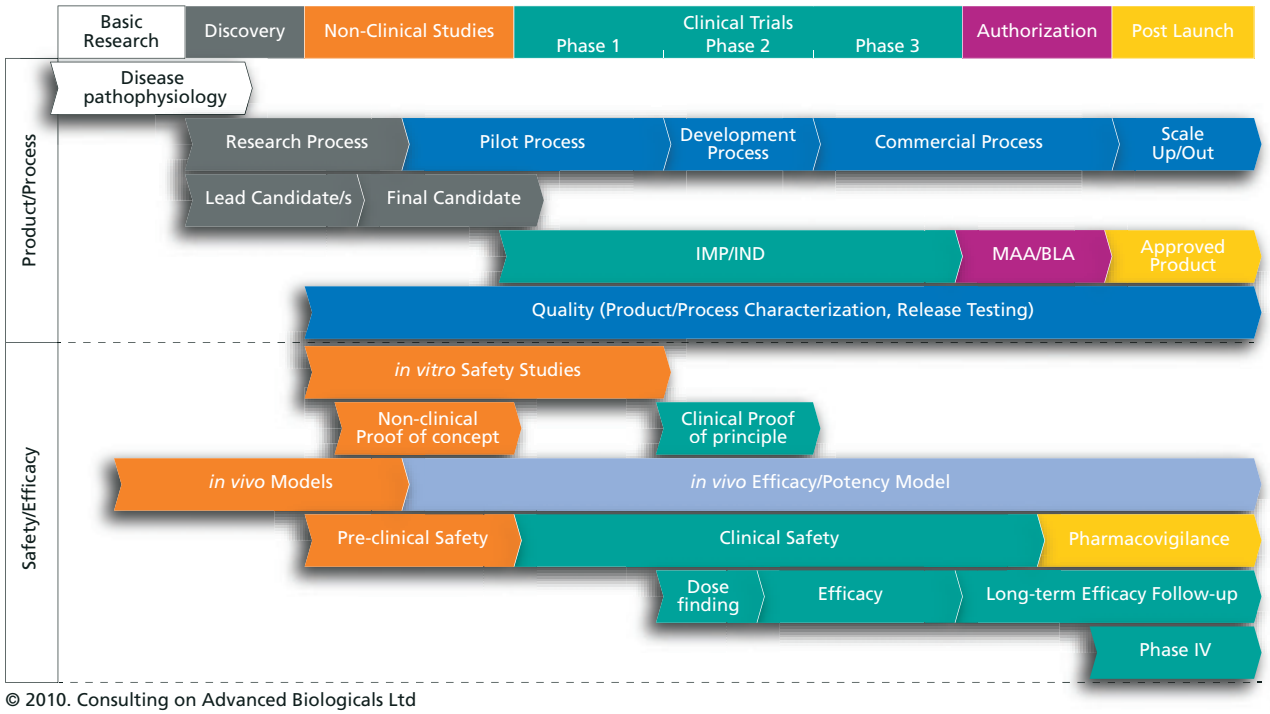


Clauses **6** to **13** discuss the stages of the process map, identifying the legal framework that regulates the activities and identifying available sources of guidance on the EU and US requirements.

Clause **5** provides an overview of the regulatory framework and other information that will assist in developing a regulatory strategy.

NOTE *For the purposes of this PAS the term cell-based medicinal products (CBMPs) is used to cover cell therapy products regulated in the EU as advanced therapy medicinal products (ATMP) and in the US as biologics (351 HCT/P).*

Figure 2 Stages of product development



NOTE *Colours correspond to activities identified within the process map in Figure 1.*

5 Regulation

5.1 Legal basis

The use of human cells and tissues in human therapeutics is highly regulated and in the EU and US this can be divided broadly into two regimes, as given in Table 1.

This PAS focuses on those products that are considered to be medicinal/biologics products, which are subject to both regulatory regimes. Some uses for cell and tissue products are not considered to be medicinal and these will be subject to public health legislation only (see Clause **8**), or in some instances in the US as medical devices.

The rules governing medicinal/biologics products can be implemented through various legal instruments and additional technical guidance is provided by authorities through guidelines and other communications (see Table 2).

The majority of cell therapy products will be classified as medicinal/biologics products and thus require that the developer demonstrates that they are manufactured to an appropriate and consistent quality and are acceptably safe and efficacious. The overall risk/benefit to the proposed patient population is evaluated with respect to the available data on quality, safety and efficacy on a case-by-case basis.

In addition to public health and core pharmaceutical legislation other related legal requirements exist, these are summarized in Figure 3. Although this figure is designed to indicate which legislation applies at which stage, it is important to remember this is an artificial division and requirements may span stages. In particular there is an overlap between the legislation identified for cell processing and that for GMP manufacture. In the US in particular, GTPs apply also to the manufacture of CBMPs and are intended to complement GMP; where these rules conflict, those rules that are more specific to the product should be applied.

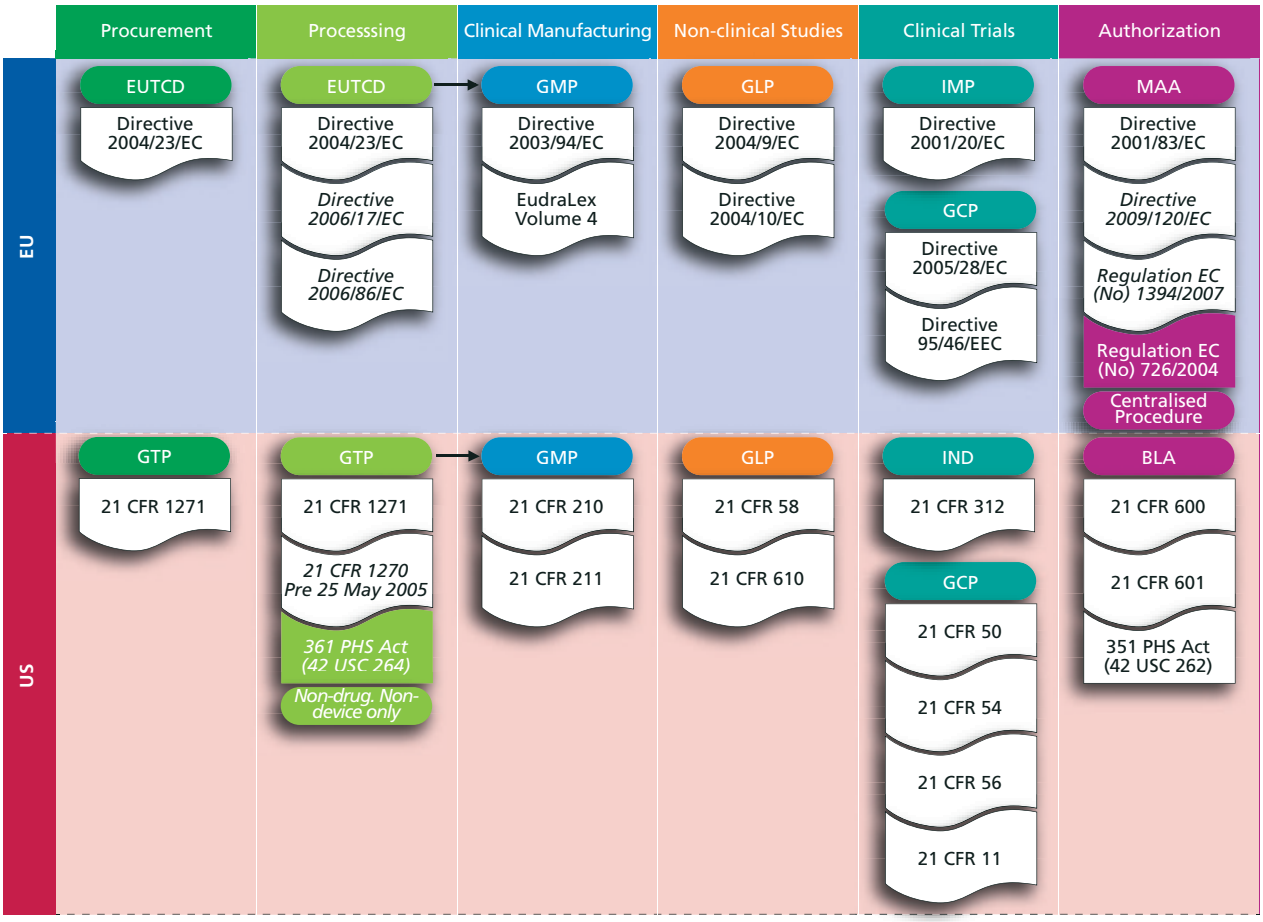
Table 1 Regulatory regimes applicable to CBMPs

	EU	US
Public health legislation	European Tissues and Cells Directive (EUTCD) Directive 2004/23/EC	Good Tissue Practices Section 361 PHS Act [42 USC 264] and 21 CFR 1271[a)]
Pharmaceutical legislation	Medicinal Products Directive 2001/83/EC	Biologics Section 351 PHS Act [42 USC 262] and 21 CFR 1271[a)]
[a)] Tissues or cells procured since 25 May 2005; those procured before this date are subject to 21 CFR 1270.		

Table 2 Legal hierarchy

	EU	US
Regulation / Act	EU Parliament, Council and/or Commission – **obligatory** to the Member States	Federal Government – **legally binding**
Directive / Code	EU Parliament, Council and/or Commission – **has to be adopted in national law** to be effective	Federal Government – **legally binding**
Notice to applicants / Regulatory guidelines	Usually EU Commission – **formal status** and effectively binding	N/A
Guidance	EMA and WPs – **not legally binding** but should be applied	FDA – **not legally binding** but should be applied

Figure 3 Summary of legislation applicable at each stage of development



5.2 Regulatory authorities

5.2.1 EU

Regulation of healthcare products in the EU is based on Directives which instruct Member States to put national legislation in place to achieve the outcome described. Consequently, differences exist in implementations that are out of the scope of this PAS. Each Member State assigns responsibility for regulation to national competent authorities (NCA), and in some instances more than one NCA is involved.

NOTE *For example responsibilities under the EUTCD are generally divided between a NCA responsible for fertility treatment and a NCA for somatic cells. In contrast most Member States have a single NCA for medicines.*

A number of medicinal product categories and indications are mandated to gain market authorization from the EMA, including CBMPs even though the NCA is responsible for facilities licensing and CTAs. The EMA also administers a number of other related procedures; the various roles of the EMA and NCAs in the regulation of CBMPs (and other ATMPs) are summarized in Table 3.

Table 3 Summary of EU regulatory authority responsibilities for CBMPs

	NCA [a]	EMA
Manufacturing (GMP) licence	✔	
EUTCD [b]	✔	
Orphan designation		✔
Innovation Task Force		✔
SME registration		✔
Classification [c]	✔	✔
Certification [d]		✔
Scientific advice	✔	✔
CTA	✔	
MAA		✔
Variations (post MAA)		✔
Pharmacovigilance	✔	✔

Key to Table 3

[a] *National competent authority of the country in which the activity takes place.*

[b] *The NCA for medicines and EUTCD are not necessarily the same, this differs between Member States.*

[c] *The NCA will determine whether the product is a medicinal product, and can provide a national opinion on whether it is an ATMP. The EMA (CAT) will determine whether a medicinal product is an ATMP.*

[d] *Applicable to SMEs developing ATMPs only.*

5.2.1.1 EUTCD

Where a human cell or tissue product is not also a medicinal product the local NCA is solely responsible for licensing in their jurisdiction. Export of human cells or tissues to another EU Member State is allowed, although the receiving Member State may require additional donor testing beyond that defined in the Directives. Likewise importation from other Member States may require additional testing to satisfy the local NCA. In contrast importation from a third country will require evidence that the cells and tissues were procured following equivalent standards to those set out in the EUTCD and as with import from another EU country additional requirements may still be required by the NCA.

Where human cells and tissues are processed and used in a way that is not medicinal, the facilities should be licensed by the local NCA whether or not they are also licensed for the manufacture of medicinal products.

There are a number of other requirements set out in the EUTCD including traceability and adverse events reporting procedures.

5.2.1.2 Medicinal products

Where cells and tissues are used to manufacture medicinal products they should also conform to the EUTCD, but only with respect to donation, procurement and testing. Consequently, a licence from the appropriate NCA under the EUTCD will also be required, which may differ from the NCA responsible for medicines (e.g. Human Tissue Authority and Medicines and Healthcare products Regulatory Agency in the UK). Manufacturing requires GMP which is different from the facilities requirements under the EUTCD. However, the EUTCD does reference some of the requirements of pharmaceutical GMP, such as the standard of air quality during processing of tissues and cells.

Medicinal products based on human cells and tissues are classified as advanced therapy medicinal products (ATMP) in the EU, and can only be authorized for general use by the European Medicines Agency (EMA), although the benefit is that a licence from the EMA is valid for the whole EU. However, the EMA cannot authorize clinical trials; these are the responsibility of the NCAs (see Table 3).

The EMA is an administrative body whose work is conducted through committees and working parties composed of representatives of the NCAs. All licensing opinions are reached by consensus voting with each Member State having a vote.

5.2.2 US

The situation in the US is somewhat simpler in that the FDA are responsible for both aspects of the legislation and where products are considered to be biologics (351 HCT/P) they also authorize clinical trials.

Unlike the EU it is possible for human cells and tissues to be regulated as devices, however, this possibility is outside of the scope of this document and will not be discussed in detail, neither will combination biologics/devices.

Cells and tissues imported into the US for clinical use should conform to GTP requirements, and where they meet the definition of a biologic require authorization (through the BLA route) before they can be marketed.

5.3 Determining the regulatory route

Table 4 provides some key definitions for each region. The definition of a medical device is included since in the US products containing human tissues or cells can be regulated as devices; in the EU they are specifically excluded whether or not the product can otherwise be argued to meet the definition.

The regulatory route is determined by criteria which differ between the EU and US. If products meet the following criteria they are regulated:

EU: solely under the EUTCD [Directive 2004/23/EC] and thus on a national basis;

US: under section 361 of the PHS Act [42 USC 264].

Criteria:

1. Is minimally manipulated – Table 5 provides an example list of manipulations that are not considered substantial for each region.

NOTE *Both regions consider deliberate expansion of cells in culture as more than minimal manipulation.*

2. Intended for homologous use – cells are used for the same essential function in the host as the donor (see Table 5).

3. Not combined with another product/article.

EU: a medical device or an active implantable medical device [Regulation EC (No) 1394/2007].

US: not combined with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function;

or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(a) is for autologous use;

(b) is for allogeneic use in a first-degree or second-degree blood relative; or

(c) is for reproductive use.

[21 CFR 1271.10]

Products that fail one or more of the criteria above are regulated as:

EU: As medicinal products [Directive 2001/83/EC and Regulation EC (No) 1394/2007]. Human tissues and cells (viable or non-viable) cannot be medical devices [Directive 93/42/EEC, article 1.5(f)].

US: Under section 351 of the PHS Act [42 USC 262]. Human cell and tissue products (HCT/P) can be regulated either as a biologic or as a device depending on the primary mode of action.

Table 4 Key legal definitions

	EU	US
Medicinal product Drug	a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or b) 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. [Directive 2001/83/EC, Article 1.2]	a) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official national formulary, or any supplement to any of them; and b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and c) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and d) articles intended for use as a component of any article specified in Clause a), b), or c). [21 USC 321(g)(1)]
Biological MP Biologic product	A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a 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 physico-chemical-biological testing, together with the production process and its control. [Directive 2001/83/EC; Annex I; part 2.1]	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. [42 USC 262(i)]
Medical device	Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: • diagnosis, prevention, monitoring, treatment 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. [Directive 93/42/EEC, article 1.2(a)]	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is: (1) recognized in the official national formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. [21 USC 321(h)]

Table 4 Key legal definitions

	EU	US
Combination product	'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions: • it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and • its cellular or tissue part must contain viable cells or tissues, or • its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.	Combination product includes: (1) A product comprised of two or more regulated components, i.e. drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; [21 CFR 3.2(e)] ***NOTE*** *Additional definitions (2) to (4) have been omitted for simplicity.*

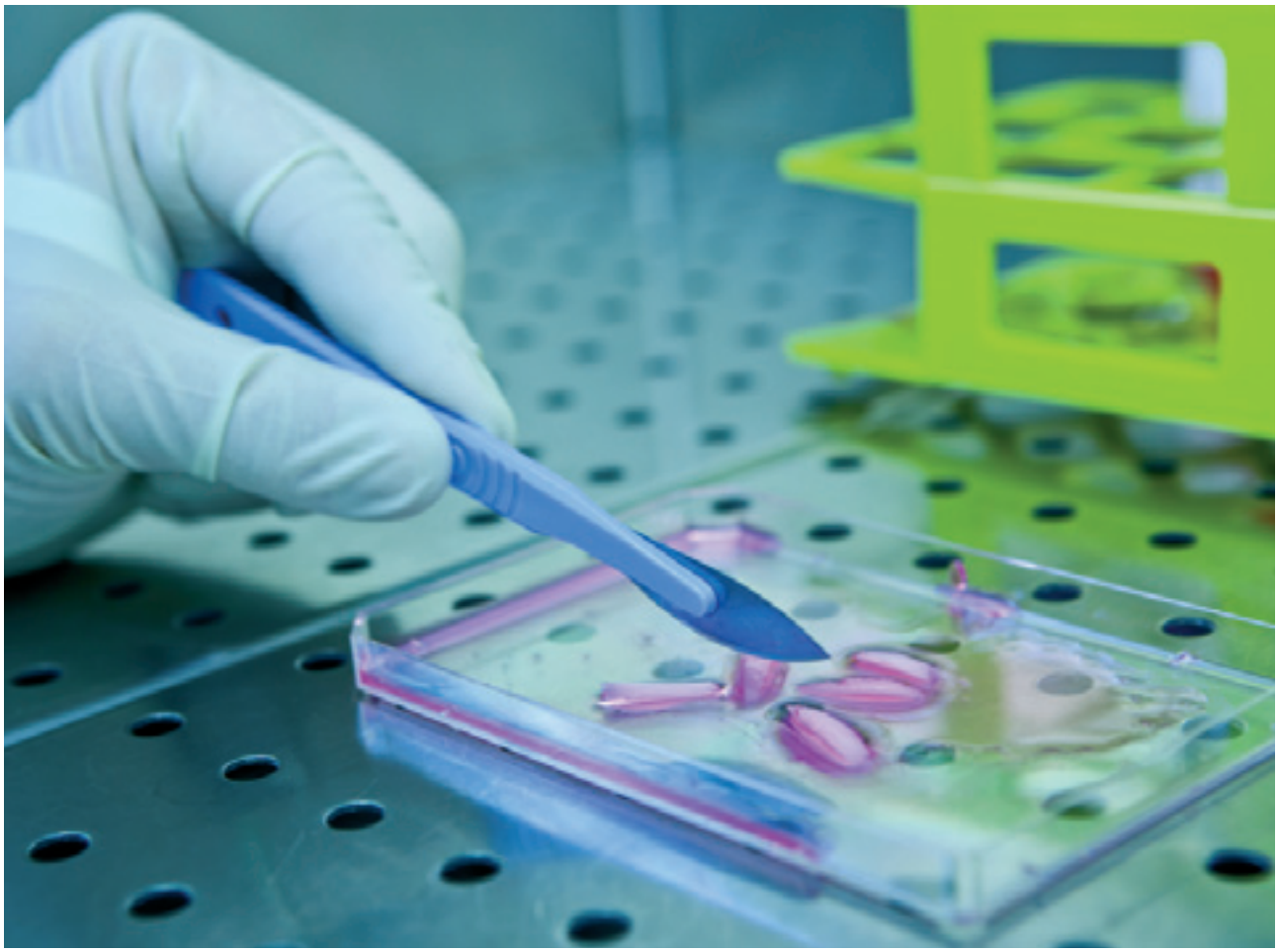


Table 5 Definitions for minimal manipulation and homologous use

	EU	US
Minimal manipulation	Cells or tissues in which the biological characteristics, physiological functions or structural properties relevant for the intended clinical use have not been substantially altered. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations. [Adapted from Directive 2001/83/EC, Annex I, Part IV.2 (Directive 2009/120/EC) and Regulation (EC) No 1394/2007 Article 2(c)] Manipulations referred to in the first indent of Article 2(1)(c): • cutting; • grinding; • shaping; • centrifugation; • soaking in antibiotic or antimicrobial solutions; • sterilization; • irradiation; • cell separation, concentration or purification; • filtering; • lyophilization; • freezing; • cryopreservation; • vitrification. [Regulation (EC) No 1394/2007 Annex I]	(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) For cells or non-structural tissues, processing that does not alter the relevant biological characteristics of cells or tissues. [21 CFR 1271.3(f)] Minimally manipulated include those that have been subjected to the following procedures: • cutting; • grinding; • shaping; • centrifugation; • soaking in antibiotic solution; • sterilization by ethylene oxide treatment or irradiation; • cell separation; • density gradient separation; • lyophilization; • freezing; • cryopreservation; • selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; [Adapted from: 66 Fed Regulation 5447, 5457 (Jan 19, 2001)]
Homologous use	***NOTE*** *The term homologous isn't used in the EU but the same principle is applied with the following wording:* Somatic Cell Therapy: cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. [Directive 2001/83/EC, Annex I, Part IV.2 (Directive 2009/120/EC)] Tissue Engineered Product: not intended to be used for the same essential function or functions in the recipient as in the donor. [Regulation (EC) No 1394/2007 Article 2(c)]	The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. [21 CFR Part 1271.3(c)]

5.4 Regulatory procedures and advice

NOTE 1 *The strategy taken by developers will be influenced by many factors; this section provides general information to assist in this process.*

NOTE 2 *It is also possible to undertake joint scientific advice between the EMA and FDA (see agency websites).*

5.4.1 EU

5.4.1.1 Innovation task force (EMA)

The innovation task force (ITF) is an initiative by the EMA to provide a single first point of contact and allow discussion of early stage products or simply get advice. The ITF can arrange informal briefing meetings with appropriate EU experts as a first informal discussion of new technologies or concepts. If the regulatory situation for your proposed product is unclear they can facilitate a classification.

5.4.1.2 Certification procedure (EMA)

Certification is a non-binding assessment and gap analysis of the quality and non-clinical development of a product to date. The procedure is intended to help products move into the clinic and thus even if clinical data has been generated it is not included in the procedure. This procedure is specifically designed to help small and medium size enterprises (SME) and is only available to registered SMEs.

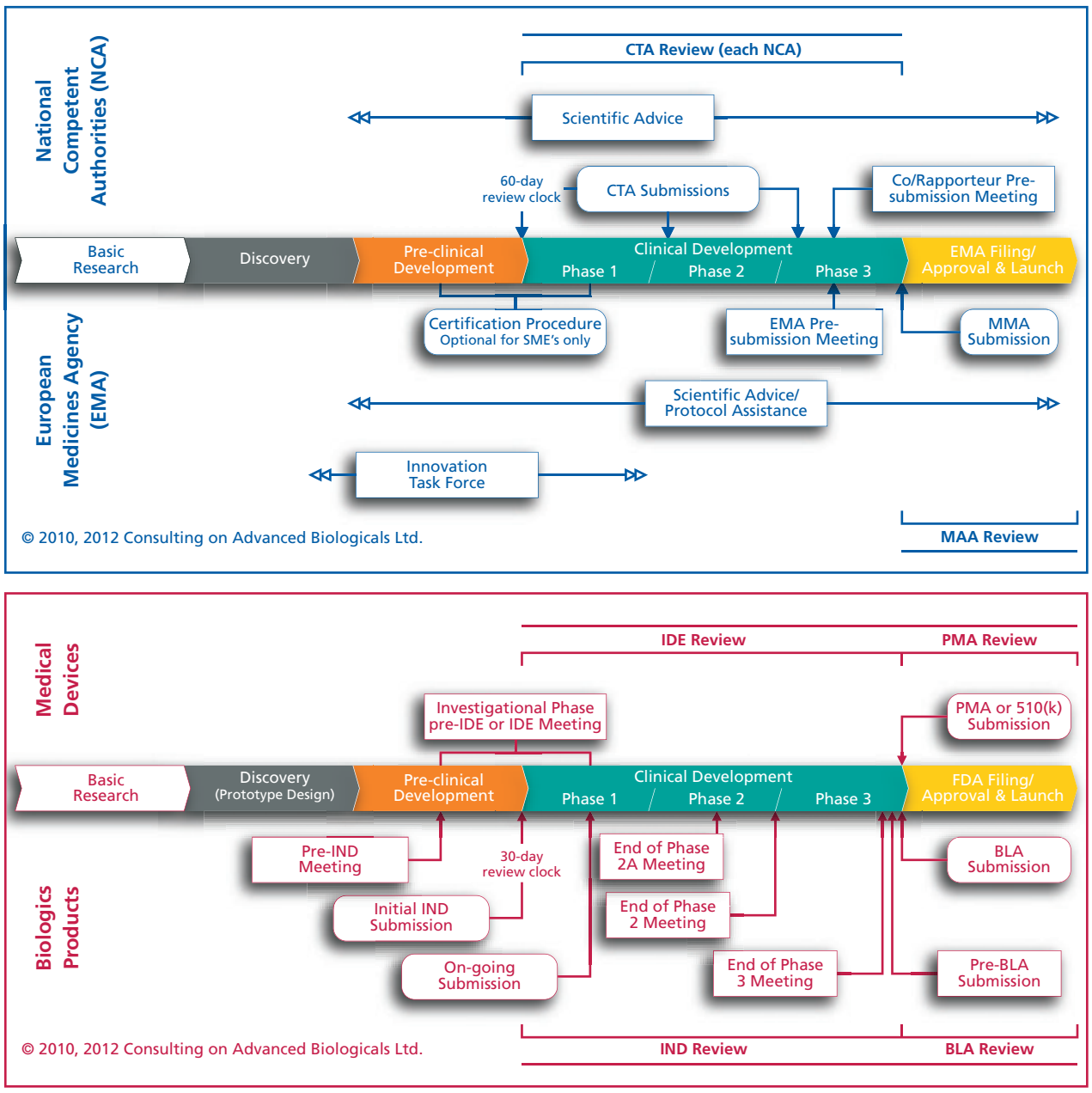
5.4.1.3 Scientific advice (EMA/NCA)

All competent authorities offer regulatory, scientific and procedural advice covering both clinical trials and market authorization. Consequently, there are two options when seeking advice on the development of a CBMP, centralized (EMA), or national (NCAs). Specific questions on the local requirements for a clinical trial can only be addressed by the NCA. Many NCAs will discuss the requirements for market authorization, but since only the EMA can authorize a definitive answer can only be given by them. Furthermore, EMA scientific advice is the consensus view of the representatives of all Member States.

The EMA offer protocol assistance where a product has orphan designation (see **5.5**), which is otherwise identical to scientific advice.

There is no obligation to have meetings with any EU authorities; the decision to do so, timing and objectives are up to the developer.

Figure 4 Overview of regulatory interactions and procedures during product development in the EU (top) and US (bottom)



Adapted from http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

***NOTE** A limited indication of the device route is provided for the US since these routes may be available:*

- *IDE, Investigational device exemption (class III device);*
- *PMA, pre-market approval (class III device);*
- *510(k), substantially equivalent class II device.*

Table 6 FDA meeting types

Type	A	B	C
Confirming of scheduling	14 days	21 days	21 days
Held no later than	30 days	60 days	75 days
Briefing package	2 weeks	4 weeks	4 weeks
Description	Dispute resolution, Clinical holds, Special Protocol Assessment	Pre-IND, EOP1, EOP2, Pre NDA/BLA	Any other than type A or B

Table 7 Comparative overview of agency interactions

	EU		US
	EMA	**NCA**	**FDA**
Early development	ITF briefing meeting	Informal meeting	Pre-pre-IND (type C)
Initial clinical trials	Scientific advice/ Protocol assistance [a)]	Scientific advice	Pre-IND (type B)
Pivotal clinical trials	Scientific advice/ Protocol assistance [a)]	Scientific advice	EOP2 (type B)
Pre-licensing	Pre-submission meeting	N/A [b)]	EOP3/Pre-BLA (type B)
Post-authorization	Scientific advice/ Protocol assistance	N/A [c)]	Post-BLA (type C)
Safety	Scientific advice/ Protocol assistance	Scientific advice	Safety

Key to Table 7

[a)] The specific requirements for the authorization of a trial are a national responsibility and specific issues may also require discussion with the NCA.

[b)] Pre-submission meetings can also be held with the Rapporteurs at the NCA.

[c)] The Rapporteur may agree to a meeting at the NCA.

5.4.2 US

Scientific advice can be sought from the FDA at any time, but certain specific stages in product development are identified (see Figure 4) and defined meetings at these stages are encouraged. Meetings are therefore classified as type A, B or C as shown in Table 6.

5.4.2.1 Pre-Pre-IND meeting

For novel technologies it is possible to enter into early discussion with the FDA, such meetings are commonly referred to as pre-pre-IND meetings, and are type C.

5.4.2.2 Pre-IND meeting

A pre-IND meeting is encouraged for novel technologies and indications, particularly where there is no guidance available.

5.4.2.3 End of phase 2 meeting

Objectives of this type B meeting is to reach agreement on pivotal study designs, and safety and efficacy end points for phase 3 studies and identify other studies that might be necessary before approval.

NOTE *Under special circumstances an end of phase I meeting can occur.*

5.4.2.4 End of phase 3/Pre-BLA meeting

The main objective is to discuss the adequacy of the sponsor's dossier for the submission of a BLA and address other issues specific to the application, including ongoing studies to address paediatric safety and efficacy.

5.5 Orphan Drugs

Both the EU and US offer assistance to companies developing products for rare indications, both refer to these as orphan drugs (OD). Although the definitions and incentives differ (see Table 8) the application form is common to the EMA and FDA and applicants are encouraged, although not required, to submit in parallel.

NOTE *Orphan designated products may also be eligible for accelerated or conditional approval processes (not covered in this PAS).*

Table 8 Overview of main incentives for orphan drug designation

EU	US
EMA Fee reductions [a)] Protocol assistance: the EMA provides protocol assistance (a form of scientific advice) for sponsors intending to develop an orphan-designated medicinal product for marketing authorization Access to the centralized authorization procedure and ten years of market exclusivity once authorized Community and Member State incentives [b)]	Annual grant funding to defray the cost of clinical testing Tax credits for the costs of clinical research Assistance in clinical research study designs Seven-year period of exclusive marketing after an orphan drug is approved Waiver of Prescription Drug User Fee Act (PDUFA) filing fees

Key to Table 8

a) list of fee reductions is available on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102327.pdf

b) An inventory of national incentives is available on the European Commission website: http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

5.6 Common Technical Document (CTD)

In addition to defining the dossier structure for ICH regions, there are also electronic submission standards (eCTD).

Most competent authorities now accept CTD and for many it is now mandatory (e.g. EMA); specific requirements for submissions should be confirmed with the relevant competent authority.

NOTE 1 *The CTD was developed for pharmaceuticals and consequently section headings may not accurately reflect the data required, and not all sections will be applicable.*

The CTD is divided into five sections:

Module 1 – Administrative information;

Module 2 – Summaries (not required for clinical trial dossiers):

- Quality overall summary (QoS);
- Non-clinical summary;
- Clinical summary.

Module 3 – Quality;

NOTE 2 *In US Module 3 is still commonly referred to as chemistry manufacturing and controls (CMC).*

NOTE 3 *This module includes all information on the manufacturing process, process development and process control along with characterization of the product (and any intermediates) along with release specifications. CTD assumes the active substance or substances are manufactured separately from the final drug product, as is more typical for other medicinal products. Most CBMPs involve a continuous manufacturing process and these distinctions cannot be easily applied. Where no distinction is made between the active substance and final product the applicant can decide which sections of the CTD to populate unless clear guidance is available from the relevant competent authority.*

Module 4 – Non-clinical;

Module 5 – Clinical.

Additional granularity can be included within CTD sections to improve clarity.

NOTE 4 *Many competent authorities now require eCTD dossiers which may require specialist software or services to publish.*

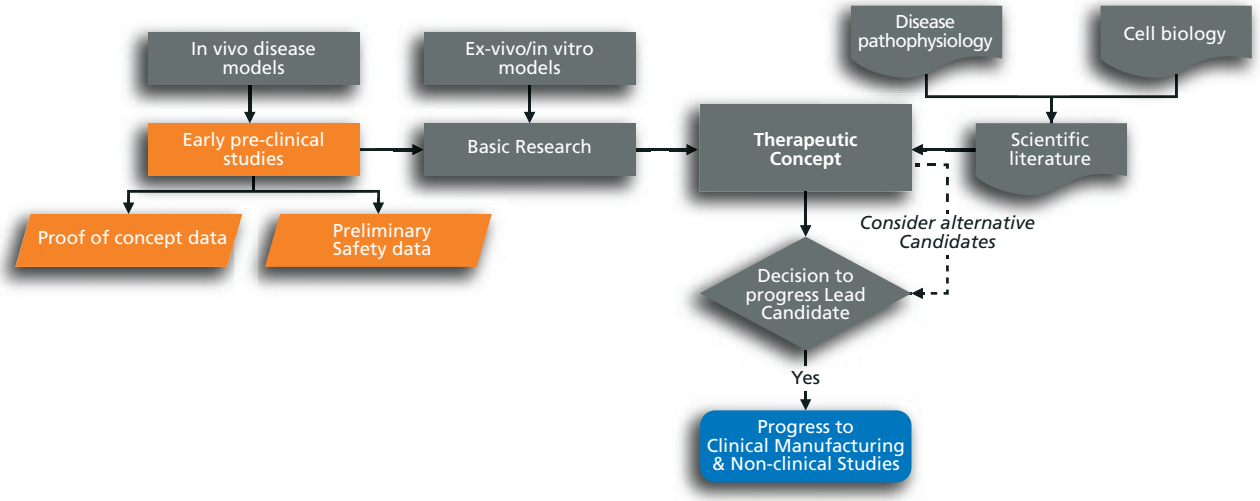
5.7 Summary

	EU	US
Key legislation	See Figure 3	
Key guidance	Check competent authority website for current procedural guidance.	
Web links	EMA website *http://www.ema.europa.eu*	FDA website *http://www.fda.gov*
	Scientific Advice (EMA) *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000057.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229bf*	Biologics Procedures (FDA) *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm*
	Innovation Task Force (EMA) *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800ba1d9*	Small business assistance (FDA) *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm*
	Orphan Drugs (EMA) *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240ce&jsenabled=true*	Orphan Drugs (FDA) *http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm*
	Orphan Drugs (EU Commission) *http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm*	
	List of medicines NCAs *http://www.hma.eu/hdirectory.html*	
	EU Commission, DG Health *http://ec.europa.eu/health/blood_tissues_organs/tissues/index_en.htm*	
	List of EUTCD NCAs *http://www.iss.it/ecet/scie/cont.php?id=85&lang=2&tipo=23*	
	UK Stem Cell Tool Kit *http://www.sc-toolkit.ac.uk*	
Other considerations	Additional local organizational and national rules may apply.	

6 Discovery

6.1 Process map

Figure 5 Discovery



The discovery phase takes ideas from basic research and explores whether these have potential for human therapeutic application (see Figure 5). The discovery phase is outside of the regulatory regimes discussed in this PAS, but subject to other local legal requirements covering issues such as:

- the use of animals in research;
- environmental protection;
- ethical approval.

Public health legislation around donation, procurement and testing of human tissues and cells is not applicable where these tissues and cells are not used for human application; however, it may still be necessary to comply with other local legal requirements and obtain local ethical approval following appropriate local procedures to obtain such material.

Good laboratory practice (GLP) is not mandatory for this stage, but should be applied where possible to ensure data integrity.

Early studies are undertaken with lab-based manufacturing processes with few if any in-process controls or release specifications. As understanding progresses it is important to begin to characterize (see PAS 93) both the early lead product candidate and the process to facilitate later transfer to clinical manufacturing should early proof of concept be achieved for the lead product candidate.

Early non-clinical studies can be considered part of discovery and generally focus on mechanism of action (MoA) in disease models (where available). Difficulties in using human cells and tissues in animals may require homologous models to be developed, or ex vivo approaches. The objective of early nonclinical studies is to reach proof of concept before investing resources in developing a GMP compliant clinical manufacturing process.

NOTE *Homologous models refers to the use of an animal equivalent of a human CBMP in an animal.*

Formal non-clinical safety studies (see non-clinical studies), including proof of concept evidence, should not be performed until a pilot GMP process has been designed and implemented (see clinical manufacturing) since it is necessary to obtain data to support the safety of the actual product and process that will be used in patients.

Results should be written up as study reports that capture the rationale and assumptions since these data will be required for later regulatory submissions.

Ultimately the decision to progress a concept is influenced by many factors including (but not limited to) the intellectual property (IP) situation, business opportunity, health economics, availability of funding in addition to scientific and technical feasibility.

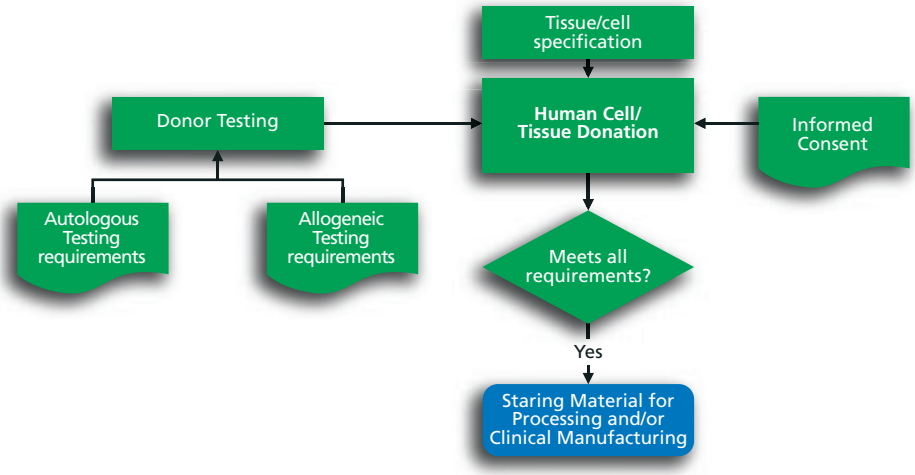
6.2 Summary

	EU	US
Key legislation	**GLP** Directive 2004/9/EC Directive 2004/10/EC	**GLP** 21 CFR 58 21 CFR 610
Key guidance	None specific to this stage	
Web links	OECD *http://www.oecd.org* Links to national websites on GLP *http://www.oecd.org/document/51/0,3746,en_2649_34381_4408051_1_1_1_1,00.html*	
Other considerations	Local organizational and national rules may apply, including ethics consent.	

7 Procurement of human cellular starting material

7.1 Process map

Figure 6 Procurement



The general principles surrounding donation, procurement and testing of human tissues and cells are similar in both the EU and the US. These principles are summarized in **7.2** to **7.4**, and the specific legislation and guidance for each region is provided in **7.5**.

In both the EU and the US cells and tissues removed and returned to the same donor in the same procedure are not subject to the EUTCD/GTP.

Donated tissues and cells that meet the following requirements may either be:

- processed for cell and tissue transplantation (see Clause **8**); or
- manufactured into medicinal/biologic product (see Clause **9**)

NOTE 1 *For the purposes of this document, the term 'processing' is used to distinguish 'processing' of minimally manipulated products (EUTCD/GTP only) from 'manufacturing' of medicinal products/biologics (MAA/BLA).*

NOTE 2 *Clause is not applicable to solid organ transplantation which is subject to different regulation.*

7.2 Donation

The following general principles apply although specific requirements are complex (see NCA website).

A robust quality system should be in place at all facilities where these procedures are executed.

All aspects of good clinical practice (GCP) should be followed where they relate to donation, including:

- donor consent;
- ethics;
- full protocols, including inclusion/exclusion criteria, mandatory screening and donor history;
- donation should be unpaid.

Donor consent should be explicit. The future potential use of the cells harvested and the nature of any analytical tests to be performed should be explained.

A system for notification of adverse events and reactions related to procurement should be in place.

7.3 Procurement

A number of procedures should be in place for post-donation. These include, but are not limited to:

- manipulation/handling methodologies for donated material;
- adequate storage facilities for material following removal;
- appropriate labelling to enable traceability;
- appropriate transportation methods to enable transfer of the material to other establishments;
- a system of tracking donated samples;
- an appropriate system for dealing with the disposal of discarded or 'waste' tissue.

Traceability:

- all donated tissues and cells require an anonymized coding system to ensure traceability from donor to recipient/s;
- traceability records should be maintained for a minimum of:
  - EU: 30 years following use or expiry/disposal;
  - US: 10 years following use or expiry/disposal.

7.4 Testing

NOTE 1 *Clauses to describe the minimum testing requirements for donors; however, additional testing may be required by the NCA depending on the intended use.*

NOTE 2 *Table 9 provides a summary of the current minimum donor testing requirements for each region.*

7.4.1 EU

The EUTCD directs EU Member States as to the minimum requirements for donation, procurement and testing, but allows Member States to impose additional requirements. Consequently, it is necessary to confirm local rules in the country of donation (for a list of EUTCD NCAs, see **7.5**).

7.4.2 US

In the US it should be noted that the current guidance on donor eligibility states EU donors are excluded on the grounds of CJD risk (see **F.1** for a link to guideline on donor eligibility).

Table 9 Donor testing requirements

		HIV-1 [a]	HIV-2 [a]	HBV [a]	HCV [a]	Syphilis	HTLV-I [b]	HTLV-II [b]	Chlamydia trachomatis	Neisseria gonorrhoea
Autologous somatic cells [c]	EU	■	■	■	■	■	■			
	US									
Allogeneic somatic cells	EU	■	■	■	■	■	■			
	US	■	■	■	■	■				
Leukocyte-rich cells and tissues	EU	Category not defined								
	US	■	■	■	■	■	■	■		
Gametes: sexually intimate partner for reproduction [d]	EU									
	US									
Gametes: other donors	EU	■	■	■	■	■	■		■	
	US	■	■	■	■	■			■	■

Key to Table 9

[a] EU: for HIV, HBV and HCV the minimum requirement is to test for antibody (in addition to antigen for HBV), however, some Member States require NAT testing for these viruses, and some require HIV antigen testing.

[b] EU: Testing should be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas.

[c] EU: Testing not required if used directly without processing or storage. Positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and re-implanted, if appropriate isolated storage facilities are available to ensure no risk of cross-contamination with other grafts and/or no risk of contamination with adventitious agents and/or mix-ups.

[d] EU: Unless gametes are to be stored, then testing as unrelated.

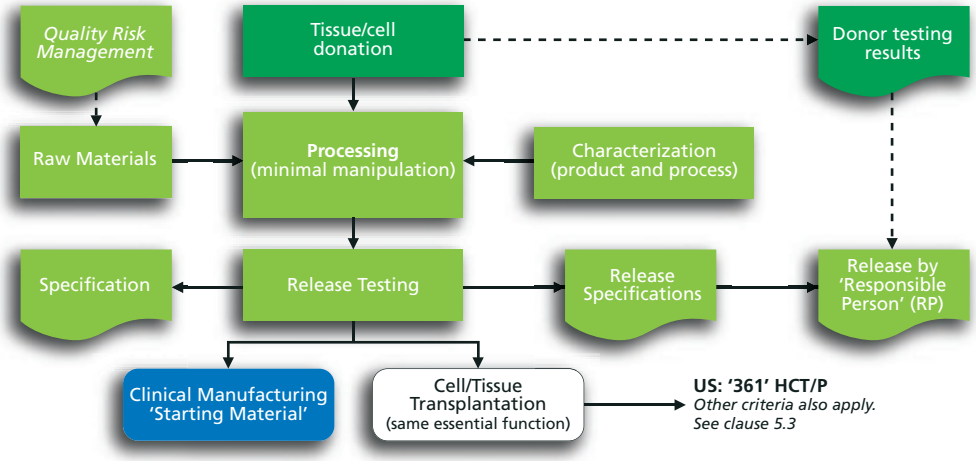
7.5 Summary

	EU	US
Key legislation	**EUTCD** Directive 2004/23/EC	**GTP** 21 CFR 1271
Key guidance	See website of appropriate NCA	See **F.1**
Web links	List of EUTCD NCAs *http://www.iss.it/ecet/scie/cont.php?id=85&lang=2&tipo=23* EU Commission, DG Health *http://ec.europa.eu/health/blood_tissues_organs/tissues/index_en.htm*	FDA website *http://www.fda.gov* Tissue safety and availability *http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/default.htm*
Other considerations	Local organizational rules may apply.	

8 Processing human tissues and cells

8.1 Process map

Figure 7 Processing



Cell and tissue transplants (those not classified as medicinal/biologics products or devices, see **5.3**) may undergo processing steps prior to their clinical use for the same essential function (see **5.3**).

In some instances it may be possible in the EU to undertake initial processing prior to GMP manufacturing.

NOTE *For the purposes of this PAS, the term 'processing' is used to distinguish 'processing' of minimally manipulated products (EUTCD/GTP only) from 'manufacturing' of medicinal products/biologics (MAA/BLA). In some cases it may be possible to process tissues or cells to produce a cellular starting material for the manufacture of CBMPs.*

Donor cells/tissues should be received and processed in licensed facilities (tissue establishment).

Raw materials and processing steps should be selected to minimize risk of contamination.

Suitable characterization should be undertaken appropriate to the intended use.

For processed cells intended for immediate clinical use (or following storage that does not alter their regulatory route) characterization should focus on confirming that the processing step has retained the intended characteristics, and that the product has not been contaminated.

For processed cells intended to be used as starting materials for the manufacture of a medicinal product/drug (or device), the characterization should focus on controlling the quality of the starting material and that it has not been contaminated (Figure 7).

Processing steps should be appropriately qualified or validated, as required by the appropriate competent authority.

Where processed cells will be the starting material for the manufacture of multiple batches of a medicinal product, a cell banking system should be considered. Depending on the anticipated capacity of the bank, a one-tier (working only) or two-tier (master and working) banking system can be utilized. These banks should be prepared under GMP (EU/US) and/or GTP (US) as appropriate.

It is considered good practice to deposit certain cell lines, e.g. human embryonic stem cell lines, into an appropriate national repository, e.g. the UK Stem Cell Bank.

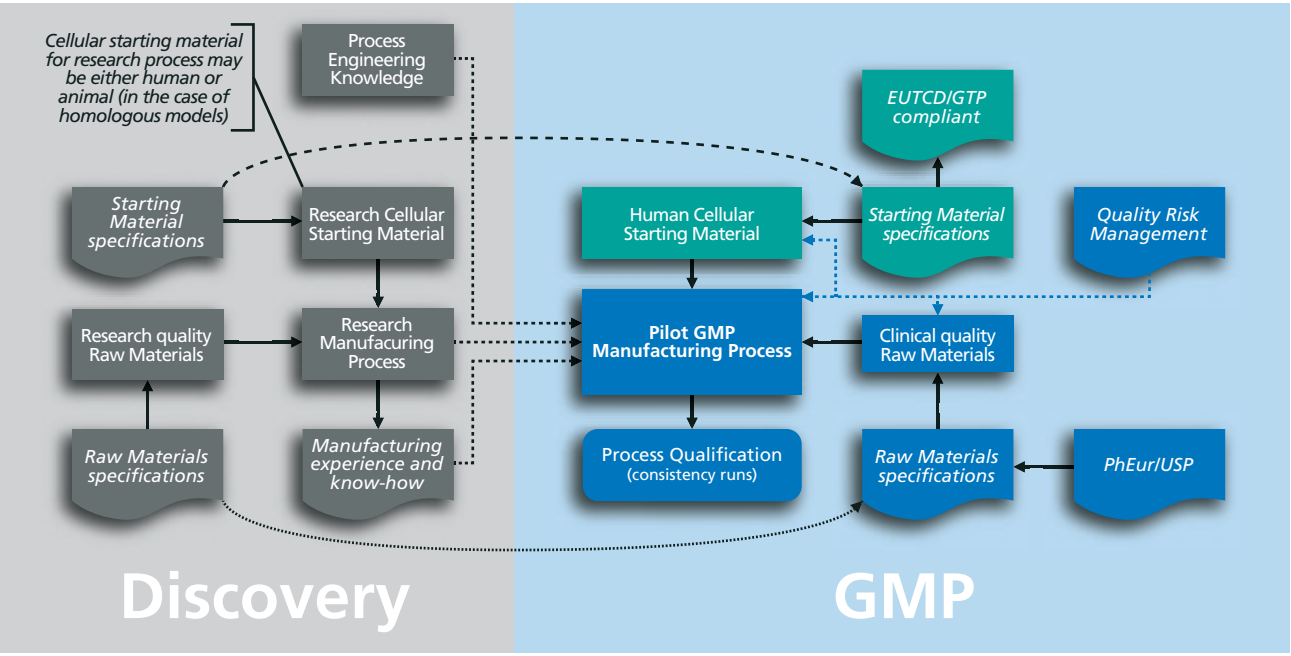
8.2 Summary

	EU	US
Key legislation	**EUTCD** Directive 2004/23/EC Directive 2006/17/EC Directive 2006/86/EC	**GTP** 21 CFR 1271 21 CFR 1270
Key guidance	See website of appropriate NCA	See **F.1**
Web links	List of EUTCD NCAs *http://www.iss.it/ecet/scie/cont.php?id=85&lang=2&tipo=23*	FDA website *http://www.fda.gov*
Other considerations	Local organizational rules may apply.	

9 Clinical manufacture of cell-based medicinal products

9.1 Process map

Figure 8 Overview of process leading to pilot GMP manufacturing process



NOTE *The terms 'research quality' and 'clinical quality' in Figure 8 have no specific meaning but merely indicate that the quality of these materials may need to change between research, non-clinical and clinical development.*

Once the decision has been made to progress to clinical development it is necessary to transfer the discovery process to a GMP environment. In some cases it will be possible to use the same process, in others significant changes may be required (see Figure 8).

In some situations, in particular autologous products, it may be difficult or impossible to get enough donor material to undertake many of the studies described throughout Clause **9**. This may necessitate the use of alternative sources of donor material such as normal living donor (where patient material cannot be collected), cadaveric, or some other related source. In these situations it is recommended to discuss the limitations with the appropriate authorities as early as possible.

9.1.1 Facilities

Facilities should be compliant with appropriate GMP requirements.

EU: The EUTCD applies only to donation, procurement and testing where the cells or tissues will be manufactured into a medicinal product. Unless any of these activities occur at the manufacturing site there is no requirement for tissue establishment registration. However, since national differences exist this should be confirmed with the appropriate NCA.

US: Facilities should also conform to GTP requirements. Where GMP and GTP requirements conflict, the more stringent requirement should be applied.

A product specific quality system including Standard Operating Procedures (SOP) should be defined to allow reproducible test product to be manufactured.

9.1.2 Clinical manufacturing process

The lead candidate developed in the discovery phase will need to be repeatedly produced for use in non-clinical safety testing and clinical trials and accompanying SOPs and procedures developed.

The design of the clinical manufacturing process will depend on knowledge gained from the discovery process along with related published literature, process engineering know-how, and GMP requirements.

The principles of quality risk management (ICH Q9) should be applied to the design and control of the process.

The pilot GMP manufacturing process should be adequately qualified with sufficient consistency runs and as far as possible comparability to the discovery process demonstrated to ensure validity of assumptions.

9.1.3 Selection of starting and raw materials and excipients

Unlike other medicinal/drug products, it is not currently possible to include manufacturing steps to reduce or eliminate adventitious agents, e.g. sterilization, ultrafiltration. It is therefore necessary to undertake a risk assessment on all starting materials, raw materials and excipients that are in direct contact with the cells during manufacture.

The principles of quality risk management (ICH Q9) should be applied to the selection of all materials used in manufacture.

Where possible all materials in direct contact with the cells should themselves be manufactured under GMP or equivalent standards. Where it is not possible it is essential the risk assessment takes this into account.

9.1.3.1 Non-biological materials

Where raw materials are described in a pharmacopoeial monograph they should conform to the monograph (minimum standard).

Where a clinical trial or market authorization is sought in both regions, materials should conform to both USP and PhEur monographs, where applicable.

NOTE *EU: For investigational medicinal products compliance with USP, JP or EU national pharmacopeias is acceptable.*

9.1.3.2 Biological-origin materials

For biological starting materials (e.g. human cells, scaffolds and matrices) and raw materials (e.g. serum, growth factors, enzymes) particular care should be taken to ensure risk is minimized. Alternatives to the use of biological materials should be considered where possible.

The source of all biological materials should be known and tested for appropriate adventitious agents and conform to regional requirements for TSE risk. In particular, bovine material (e.g. FCS) should be given special attention due to TSE risk. Bovine materials should:

EU: have a valid EDQM certificate of suitability;

US: (be) sourced from closed herds in certified TSE-free countries.

Where possible additional risk mitigation measures should be considered, e.g. irradiation.

NOTE *Even where biological materials may not apparently be of animal origin, e.g. bacterially expressed growth factors, the manufacture of those biological materials may involve the use of animal materials, e.g. bovine and porcine heart-brain broth to ferment bacteria.*

Where a cellular starting material or raw material (e.g. feeder cells) originates from a cell bank, the bank should be appropriately characterized and tested for appropriate adventitious agents. Where such materials are of human origin, they should also conform to appropriate legislation covering their donation, procurement and testing (e.g. for tissues and cells or for blood and blood derivatives).

Where cellular starting material is held in a cell banking system, these should be appropriately tested and characterized, and a stability programme initiated. To ensure against catastrophic loss of the cell bank it is common practice to store part of the bank at another site.

9.1.4 Validation

The manufacturing process, including the equipment used, test methods and shipping should be fully validated. Qualification (e.g. consistency runs) of the process and methods is generally acceptable for early clinical studies. The decision on when to undertake full validation is influenced by many factors outside of the manufacturing environment but should be completed before licensing.

As mentioned in **9.1**, in some situations, for instance where donor material is limiting, it may not be possible to undertake all testing on all batches and an alternative approach may be necessary (for example not performing all tests on all validation batches). Where these limitations exist it is recommended to discuss the approach with appropriate regulatory authorities prior to validation.

9.2 Quality/CMC

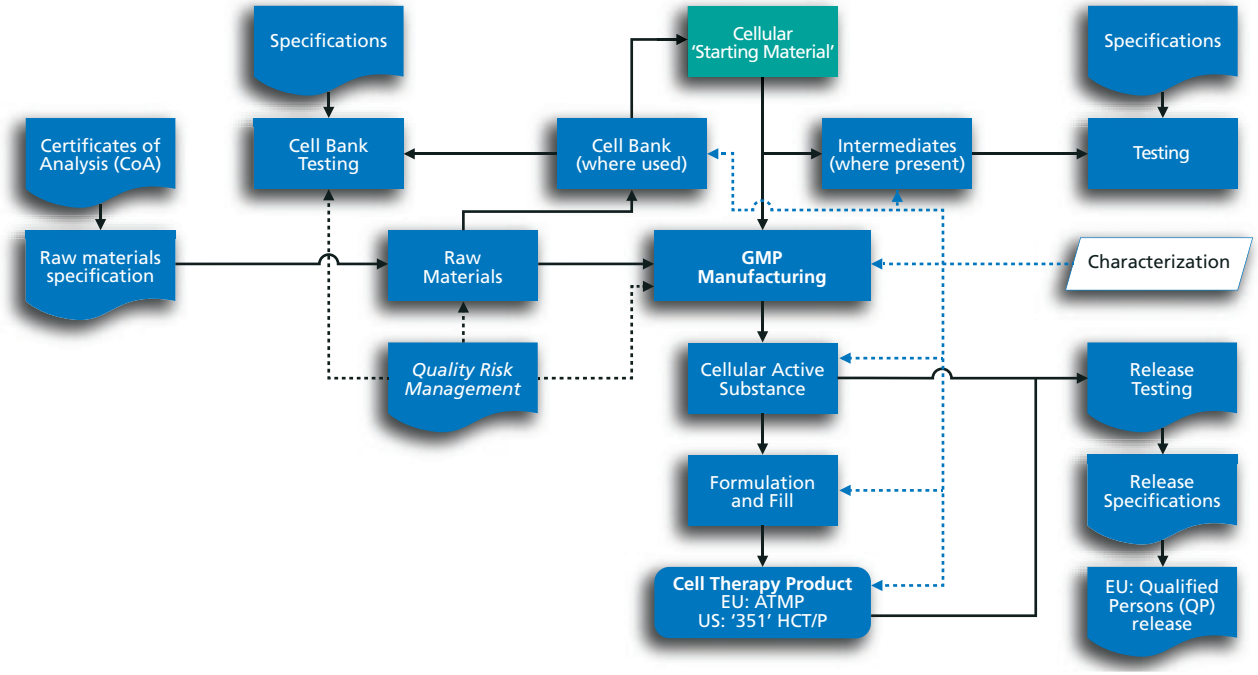
9.2.1 Quality control of materials

The quality of all starting materials, raw materials and excipients should be appropriately defined and controlled. The following characteristics should be considered for each material as appropriate to its purpose and associated risk. Where necessary in-house testing should confirm suitability before acceptance of each batch:

- identity;
- purity;
- impurities (e.g. solvents, metals, host cell proteins);
- contaminants (e.g. bacteria, viruses).

NOTE *See Figure 9.*

Figure 9 Clinical manufacture – quality



9.2.2 Process control

All manufacturing steps should have adequate controls to ensure process consistency.

Limits should be set based on process and product characterization results. Proposed ranges should reflect both the limitations of the method and the criticality of the parameter, and should be supported by data and, where appropriate, validated.

In-process controls, operational parameters and product release specifications should be defined based on all experience to date.

Additional testing outside the preliminary parameters should be considered as part of product and process characterization.

A risk assessment of the overall process should be undertaken and used together with the risk assessments of the materials to confirm appropriate in-process controls, operating parameters, acceptance criteria and release specifications are defined.

9.2.3 Specifications

9.2.3.1 Acceptance criteria

Specifications (usually termed acceptance criteria) should be set for all starting materials, raw materials and excipients used in manufacture. These should aim to define the following:

- identity (appearance and unique identifier);
- purity (of the active substance; e.g. intended cell population);
- impurities:
  - product-related (e.g. dead cells, cell debris, unintended cell types);
  - process-related (e.g. bovine serum, enzyme, antibiotics);
  - contaminants (e.g. bacteria, viruses);
- biological activity (where appropriate, e.g. growth factors, enzymes);
- general quality attributes, e.g. pH, osmolality, appearance.

As a minimum, identity should be confirmed for all raw materials and excipients as described in the appropriate pharmacopeia, or using appropriate in-house methods, before release into the manufacturing facility.

It may be necessary to undertake additional testing, for example:

- for a new supplier as part of supplier qualification;
- where a material is particularly critical;
- where material batch variation is high (e.g. serum);
- where the CoA is insufficient or not provided.

Starting materials, in particular donated human tissues and cells, will usually require more comprehensive acceptance criteria, and usually require these to be tested by the developer since they are not usually supplied with a CoA.

Stability of all materials should be established and appropriate measures introduced to ensure materials are not used beyond their shelf-life.

Where manufacturing intermediates exist (e.g. cell banks, cryopreserved reserve samples) that might be stored prior to the next manufacturing step, these should also be characterized and acceptance criteria set for continuation of manufacturing.

Acceptance criteria for intermediates should address the same general criteria identified above, and also include stability testing to define acceptable limits for storage (or hold steps).

9.2.3.2 Release specifications

Most medicine/drug manufacturing is divided into manufacture of the drug substance and manufacture (formulate and fill) of the drug product, and both steps require separate release specifications. This is reflected in the CTD format used to prepare regulatory submissions. However, for cell therapy products there is usually no clear delineation between manufacture of the drug substance and product and it is usual for only one set of release specifications to be defined. Furthermore, not all test results may be available at release where the shelf-life is short requiring careful risk assessment to ensure product quality is adequately controlled and provisions are in place to deal with non-conforming release specifications that only become available after treatment (e.g. sterility).

Product release specifications should be developed based on characterization (product and process) and include the following criteria:

- identity (appearance and unique identifier);
- purity (of the active substance; e.g. intended cell population);
- impurities:
  - product-related (e.g. dead cells, cell debris, unintended or undesired cell types);
  - process-related (e.g. bovine serum, enzyme, antibiotics);
  - contaminants (e.g. bacteria/sterility, viruses, endotoxin, mycoplasma, viruses);
- potency (relevant biological function);
- general quality attributes (e.g. pH, osmolality, appearance);
- dose/fill/content (e.g. cell number that can be extracted from final vial).

US: the section headed contaminants in the list above is usually separated out under the heading ‘safety’, i.e.:

- safety (freedom from microbial contamination);
  - sterility cultures, endotoxin, mycoplasma, viruses.

Where pharmacopoeial methods exist and are suitable, these should be used. Pharmacopoeial methods do not usually require validation, but require qualification (as defined in pharmacopoeia text).

In-house methods should either be validated or at least sufficiently evaluated and qualified to ensure reliability.

The decision on when to validate test methods lies with the manufacturer, but the impact on data reliability should be considered.

Validation is required by MAA/BLA and may be requested earlier by authorities.

9.2.3.3 Stability

Stability data from product (and any intermediates, e.g. cell bank) manufactured using the current process will be required before clinical trials can commence.

As a general principle only real-time (actual data) stability is accepted by authorities at market authorization; extrapolation (to later time points) of data for biological products is not usually accepted.

For clinical trials some stability data should be available to support the shelf-life claimed for the proposed for the study (i.e. adequate to ensure the product can be delivered to the patient in time) but authorities may allow some extrapolation.

Stability protocols should be consistent with release specifications, but may differ to take account of characteristics that change during storage as long as the data support the proposed specification.

As mentioned in **9.1**, in some situations, for instance where donor material is limiting, it may not be possible to undertake all testing on all batches and an alternative approach may be necessary (for example not performing all tests at all time-points). Where these limitations exist it is recommended to discuss the approach with appropriate regulatory authorities.

Additional stability studies for raw materials, manufacturing intermediates (e.g. cell banks) may be required (see **9.2.3.1**). Other product stability studies are generally required by market authorization including shipping studies and in-use stability.

9.2.4 Reference materials

A 'product reference standard' should be established where possible:

EU: "*A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterized*"

NOTE *A detailed explanation of reference materials is beyond the scope of this PAS, please refer to ICH Q6B and national guidelines for further explanation.*

9.2.5 Test methods

Data reliability is dependent on the test methods used; whether they are accurate, precise, specific, and repeatable.

Where appropriate pharmacopoeial methods exist, these should be used unless they are not suitable; some tests may be mandatory.

All test methods should be adequately qualified to confirm their suitability for use.

Test methods used for in-process controls, acceptance and release testing should be validated by MAA/BLA.

The decision on when to fully validate will depend on many factors, but the impact on data integrity should be considered along with the need to understand accuracy, precision, specificity and repeatability.

9.3 Process development

Ideally the manufacturing process and test methodologies should be fixed before starting clinical trials and never be changed; however, inevitably changes are required.

Whenever changes are made it is essential they are introduced in a controlled manner and comparability established to the previous process, to ensure that manufacturing still yields the desired product.

Failure to demonstrate comparability between manufacturing processes will result in the product from individual processes being considered different and consequently studies using products from different manufacturing processes will no longer support each other.

Figure 10 Clinical manufacture – process development

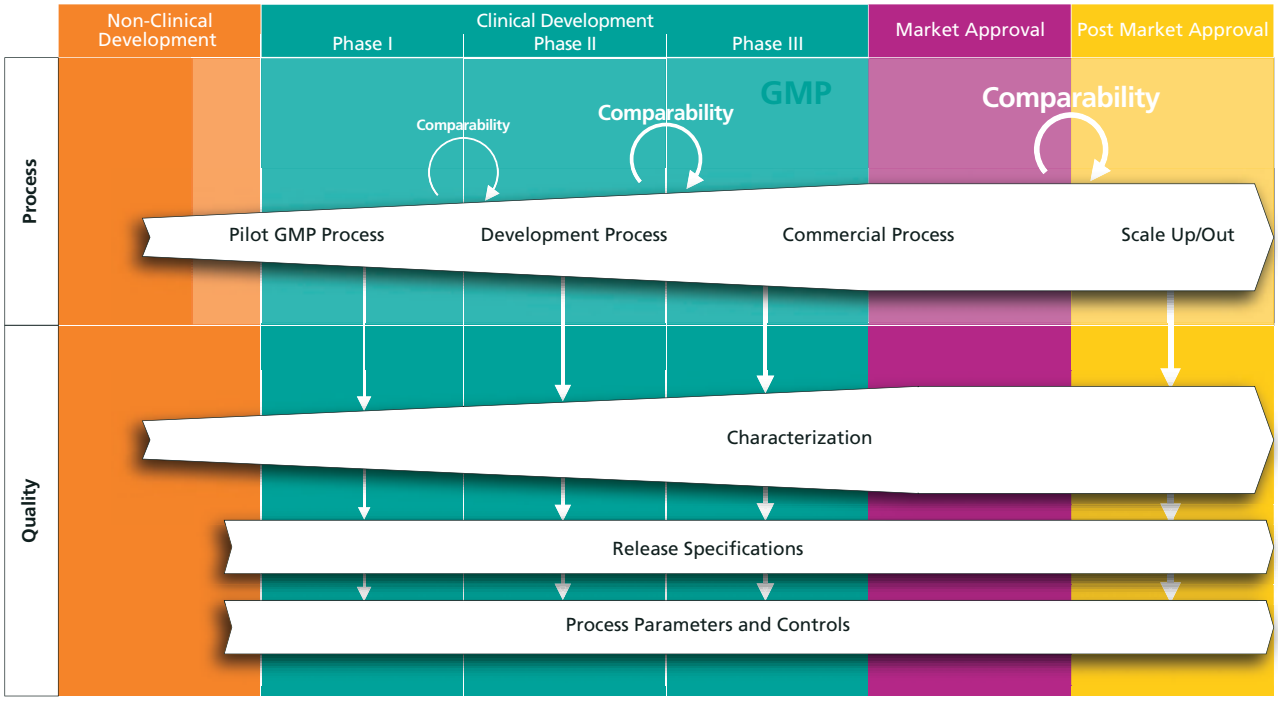


Figure 10 shows a situation where the pilot GMP process used for non-clinical and first-in-man studies is modified before continuing to phase 2 (e.g. change to excipients to improve stability, materials changes) and changed again before pivotal studies (e.g. to achieve commercial scale manufacture). It also includes post-authorization changes that can result from the need to change the supplier of key materials, implement improved safety measures (e.g. remove bovine serum) or change the manufacturing scale/site.

9.3.1 Process characterization

In addition to characterizing the product, it is also necessary to characterize the process including intermediates, for example it is necessary to demonstrate that cells retain their critical characteristics before and after cryopreservation steps.

Process parameters should be investigated to understand whether they are critical to product quality and what the tolerances are. Such parameters may include:

- time/duration (e.g. maximum/minimum duration of process steps, hold times for intermediates);
- temperature (all steps);
- pH;
- cell density/confluence;
- cell population doublings/passages;
- population doubling time (i.e. rate of growth);
- concentration (e.g. enzymes, growth factors);
- osmolality (excipients).

Where these parameters are found to be 'critical' to final product quality they should be adequately controlled.

Non-critical parameters may still be useful to monitor process performance.

9.3.2 Process parameters

This clause should be read in conjunction with **9.2.2**.

Process parameters after a manufacturing change may no longer be valid, or may require different specifications.

Sufficient characterization is required to confirm the existing parameters are still valid, or establish new parameters or ranges.

9.3.3 Process control

This clause should be read in conjunction with **9.2.3**.

In-process controls may no longer be valid, or may require different specifications.

Sufficient characterization is required to confirm in-process tests are still valid, confirm existing or establish new specifications, or introduce new test methods and specifications.

9.3.4 Comparability

Whenever changes are made, however small, it is necessary to prepare a comparability protocol that ensures adequate data on the process before and after change are collected to confirm the active substance is unaltered and the overall product quality is not impaired and where the objective of the change was to improve quality (e.g. remove an impurity) that the change was successful.

The extent of data required will depend on the nature of the change, and cannot easily be generalized. All but minor changes will require data beyond the existing in-process controls, acceptance criteria and release specifications.

Significant changes will require additional extended characterization which may even need to go beyond quality/CMC to include non-clinical (e.g. disease model) or clinical evaluation.

NOTE *The importance of characterization and its relationship to comparability are explored further in PAS 93.*

Stability is also an important characteristic of any product and should normally be included as part of comparability.

Adequate numbers of batches should be run to ensure data are reliable.

Where at all possible samples from each process should be tested at the same time, where this is not possible, the results from test method validation should be considered when reaching conclusions.

The in-house product reference standard (where available) should be included in the analysis.

The final comparability data should leave little scientific doubt that the quality attributes of the pre-change and post-change product are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the CBMP.

9.3.5 Test method changes

During development it is often desirable or necessary to modify methods (e.g. improve precision) or introduce a different (orthogonal) method of measurement for that characteristic.

To ensure data continuity over time, it is essential to directly compare methods before and after the change to ensure the impact of that change is understood.

It may be necessary to run the old and new test in parallel for a period of time to ensure equivalent results are achieved in-use. This may be particularly important when orthogonal methods are introduced for the same characteristic, and for key assays such as potency.

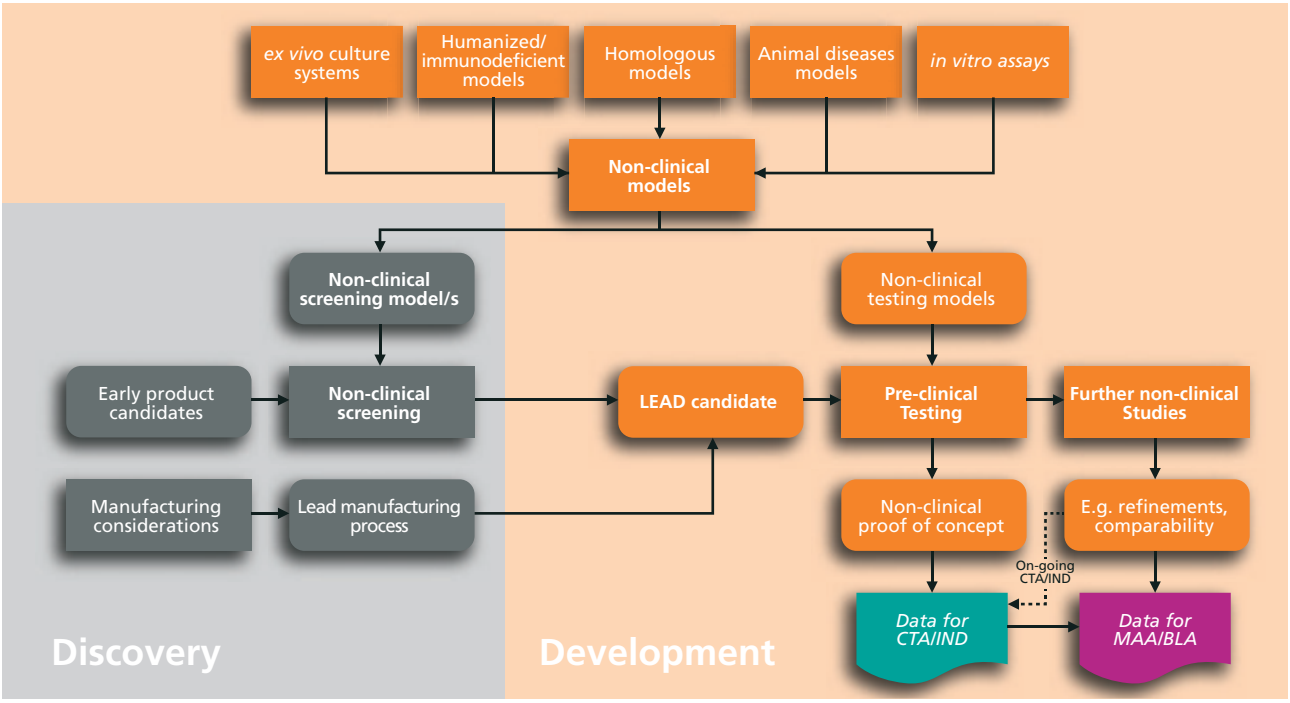
9.4 Summary

	EU	**US**
Key legislation	**GMP** Directive 2003/94/EC	**GMP** 21 CFR 210 21 CFR 211
Key guidance	Eudralex Volume 4 Eudralex Volume 4, Annex 13 – Manufacture of Investigational Medicinal Products ICH, see **B.1**, **E.1** EMA, see **B.2**, **E.2** PhEur, see Annex A	*See web links* FDA, see **B.3**, **E.3** USP, see Annex A
Web links	EMA website *http://www.ema.europa.eu* Eudralex (EU Commission) *http://ec.europa.eu/health/documents/eudralex/index_en.htm* EDQM (PhEur) website *http://www.edqm.eu* ICH website *http://www.ich.org*	FDA website *http://www.fda.gov* CMC and GMP guidance *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm217665.htm* USP website *http://www.usp.org*
Other considerations	Additional local organizational and national rules may apply.	

10 Non-clinical studies for cell-based medicinal products

10.1 Process map

Figure 11 Non-clinical studies



Early product candidates should be manufactured under conditions appropriate to ensure resulting studies are relevant. For example, product containing high levels of endotoxin may alter the characteristics of the cells and lead to both direct and indirect confounding physiological effects in animal studies.

Where research grade materials are used, consideration should be given to the availability of alternatives that are suitable for clinical use (see Clause **9**). The use of good quality materials in early development will reduce the risk of substitution problems when developing the GMP manufacturing process.

Product candidates and processes should be appropriately characterized and the extent of characterization should increase as the lead candidate is refined.

NOTE *The importance of characterization is discussed in PAS 93.*

10.2 Objectives of non-clinical testing

Studies should be conducted to provide data on the following:

- safety (toxicity, including immunogenicity);
- tolerance (local, systemic);
- biodistribution;
- persistence (duration of exposure);
- in vivo proliferation and differentiation;
- tumorigenicity;
- reproducibility;
- biological activity (potency) in vivo and/or in vitro;
- dose definition;
- route of administration and schedule;
- study duration to monitor for toxicity.

NOTE *1 Genotoxicity studies are not conducted for CBMPs unless there is a reason for concern, e.g. in relation to an excipient.*

Key studies should be designed to ensure clear end point criteria and robust predefined analyses.

Key studies should be GLP compliant where possible; lack of compliance should be well documented and explained.

***NOTE** 2 Attention is drawn to national laws relating to animal welfare.*

10.2.1 Early candidates

The actual testing applied to early product candidates will be dependent on the product and indication and availability of suitable test systems, but should aim to understand which cells or cell characteristics have therapeutic value.

Early studies with product and process candidates should aim to identify the key characteristics for further study.

Studies with early candidates should provide scientific justification for the selection of the lead candidate.

10.2.2 Lead candidate

Once a lead candidate is identified, a full non-clinical testing programme should be developed which may require input from regulatory authorities to ensure buy-in and provide quantitative evidence to support the proposed human doses from both an efficacy and safety perspective for the proposed route of administration and indication.

Non-clinical data should where possible demonstrate proof of concept and provide evidence for the mechanism of action.

10.2.3 Ongoing non-clinical studies

As the product is further developed it may be necessary to repeat studies or undertake new studies to:

- support comparability following changes in manufacturing, formulation, or product administration;
- confirm the validity of new analytical methods, e.g. potency assays;
- provide further evidence and understanding of the mechanism of action;
- complete or extend safety testing;
- undertake safety testing of novel excipients.

10.3 Non-clinical models

Traditional pharmaceutical non-clinical animal studies pose significant challenges when applied to CBMPs because of molecular incompatibility and immune rejection in xenogeneic human-animal combinations.

Without non-clinical data it is difficult or impossible to evaluate the potential safety of the proposed initial clinical trials and consequently options should be explored that could yield evidence of safety, including:

- the use of immunodeficient or immunosuppressed animals;
- the use of homologous model(s);
- the use of transgenic or humanized animals;
- the use of ex vivo culture systems;
- the use of in vitro assay systems;
- the use of non-invasive whole animal/patient modelling systems (e.g. MRI/CT imaging).

***NOTE** Large animals may be required to develop complex surgical procedures which would be technically difficult or impossible in small species.*

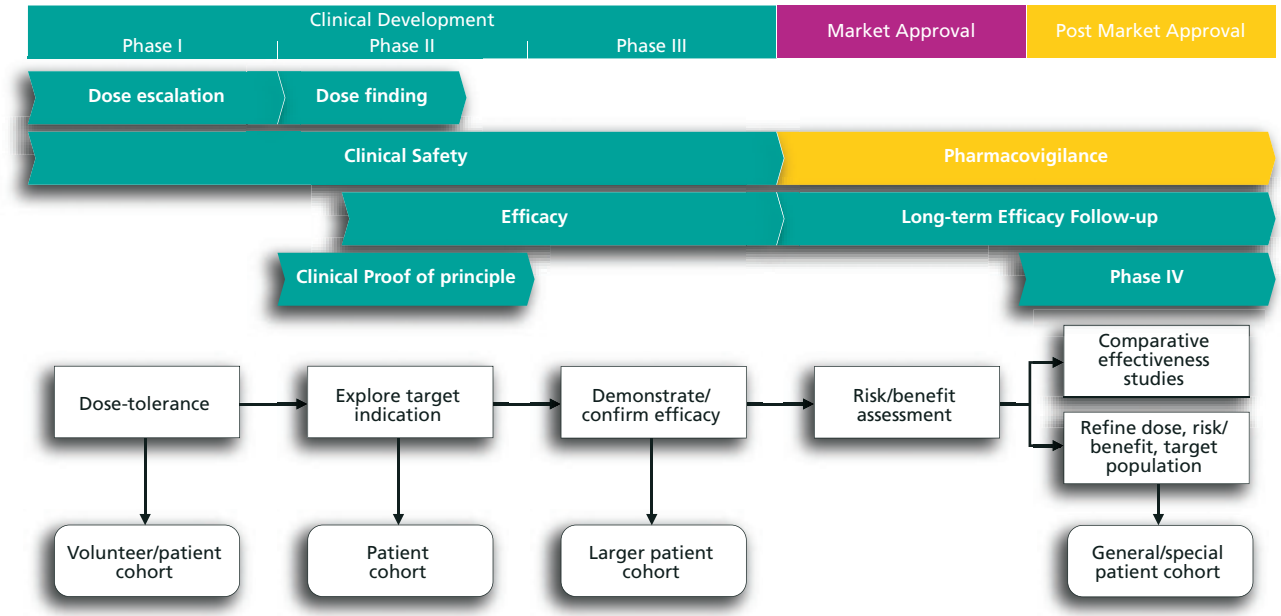
10.4 Summary

	EU	US
Key legislation	**GLP** Directive 2004/9/EC Directive 2004/10/EC	**GLP** 21 CFR 58 21 CFR 610
Key guidance	ICH, see **C.1**, **E.1**	
	EMA, see **C.2**, **E.2**	FDA, see **C.3**, **E.3**
Web links	EMA website *http://www.ema.europa.eu*	FDA website *http://www.fda.gov*
	ICH website – *http://www.ich.org*	
	OECD – *http://www.oecd.org*	
	Links to national websites on GLP *http://www.oecd.org/document/51/0,3746,en_2649_34381_4408051_1_1_1_1,00.html*	
Other considerations	Local organizational and national rules may apply, including ethics consent.	

11 Clinical trials with cell-based medicinal products

11.1 Process map

Figure 12 Clinical trials



11.2 Trial designs

Good clinical practice (GCP) is necessary for all clinical trials. Clearly defined clinical end point measures and success criteria should be established, and statistical considerations made for phase 2 and 3 trials.

A clear protocol section for storage and manipulation of cell-based products in the operating theatre is required, and training may be required.

Special attention should be paid to informed patient consent. Additional issues include, but are not limited to:

- ethics of cell therapy treatment;
- patient awareness of outcome of phase I trials (safety and effect but not necessarily direct therapeutic benefit);
- a need to track patients long-term post treatment (a robust secure database is required);
- anonymous traceability to donor;
- traceability of recipient, donor and materials to manufacturing records.

Clinical trials should aim to confirm non-clinical studies, including (but not limited to):

- safety (toxicity, including immunogenicity);
- tolerance (local, systemic);
- biodistribution;
- persistence (duration of exposure);
- in vivo proliferation and (de)differentiation;
- tumorigenicity;
- reproducibility;
- efficacy;
- dose definition;
- route of administration and schedule.

Where delivery of the CBMP is complex (e.g. surgery) clinical staff should be adequately trained and the potential impact of delivery technique taken into account.

Both the EMA and FDA have rules to encourage the development of products for paediatric populations; these should be taken into consideration when developing an overall clinical strategy.

Table 10 provides the classification of trials proposed by ICH which approximate the studies generally performed for phases 1-4.

NOTE *Phase 4 is post-marketing trials.*

Table 10 An approach to classifying clinical studies according to objective (ICH E8)

Type of study	Objective of study	Study examples
Human pharmacology	• Assess tolerance • Define/describe PK1and PD2 • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies
Therapeutic exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, end points, methodologies	• Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological end points or clinical measures • Dose-response exploration studies
Therapeutic confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Adequate, and well-controlled studies to establish efficacy • Randomized parallel dose-response studies • Clinical safety studies • Studies of mortality/morbidity outcomes • Large simple trials • Comparative studies
Therapeutic use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional end points • Large simple trials • Pharmacoeconomic studies

11.3 Clinical trial authorization (CTA) in the EU

A clinical trial authorization (CTA) should be obtained from the NCA of each Member State for each clinical trial, including those on healthy volunteers, prior to commencing the study.

Ethics approval should be sought from a national ethics committee for each trial before commencing.

An investigational medicinal product dossier (IMPD) in CTD format and clinical protocol should be prepared (see **5.6**).

An investigator's brochure (IB) should be prepared with appropriate background on available product safety and efficacy data.

The system is designed to allow a CTA and ethics review to occur in parallel in no more than 60 days, however procedural differences exist nationally (see NCA website).

NOTE 1 *There are exceptions to the standard 60 days, certain higher risk products (including CBMPs) may have their review extended to a maximum of 90 days at the discretion of the NCA, with the possibility of a further extension of 90 days for external consultation.*

Where the NCA has serious concerns they will issue grounds for non-acceptance (GNA) and these issues are required to be addressed before the end of the procedure, or the CTA will be refused. Since not all NCAs allow clock-stops there may be limited time within the 60 day procedure to address these concerns.

Once authorized, any amendments to the IMPD or clinical protocol will require prior agreement with the NCA.

NOTE 2 *The EU the Clinical Trials Facilitation Group (CTFG) is piloting a voluntary harmonization procedure (VHP) for multi-centre trials with sites in at least three Member States.*[1)] *This new procedure has been shown to significantly reduce approval times for multi-EU trials.*

11.4 Investigational new drug (IND) application in the US

An Investigational New Drug (IND) application should be filed with the FDA prior to commencing a clinical study. The IND application should include detailed descriptions of previous clinical experience, preclinical studies, manufacturing and testing, and the clinical trial plan. The FDA has 30 days in which to review the IND application and indicate any objections or concerns. If by the end of this period the IND has not been placed on hold, it is considered allowed and the clinical trial may proceed.

Institutional Review Board (IRB) approval should be obtained from the IRB for each clinical site.

The IND should be in CTD format (see **5.6**) and include the clinical protocol.

An investigator's brochure (IB) should be prepared, except in the case of investigator-sponsored INDs.

Table 11 Key differences between a CTA (EU) and IND (US)

CTA	IND
NCA input through optional scientific advice procedure as required	Interactive process, with pre- and post-submission meetings at FDA
Protocol based	Product/indication based
Either written approval or allowance, in 60 days [a)]	Allowed, not approved if not placed on hold within 30 days.
Have EUDRACT number for trial before filing	Number assigned to IND at filing
Lifetime: should close 90 days after last visit	Lifetime: until "not open", variable
Dossier to NCA and Ethics Committee [b)]	Dossier to FDA only [b)]
Amendments require NCA approval within 35 days	Amendments are notified
EU facility manufacturing licence required	US facility manufacturing licence not required
Additional documents may be required by different NCAs	Annual reports to FDA

[a)] *Note, for first-in-man trials this is shortened to 30 days unless the product falls in a high risk category when it may be increased to 90 days.*

[b)] *Ethics committees/IRB may require additional documents.*

[1)] See Heads of Medicines Agency website (http://www.hma.eu/).

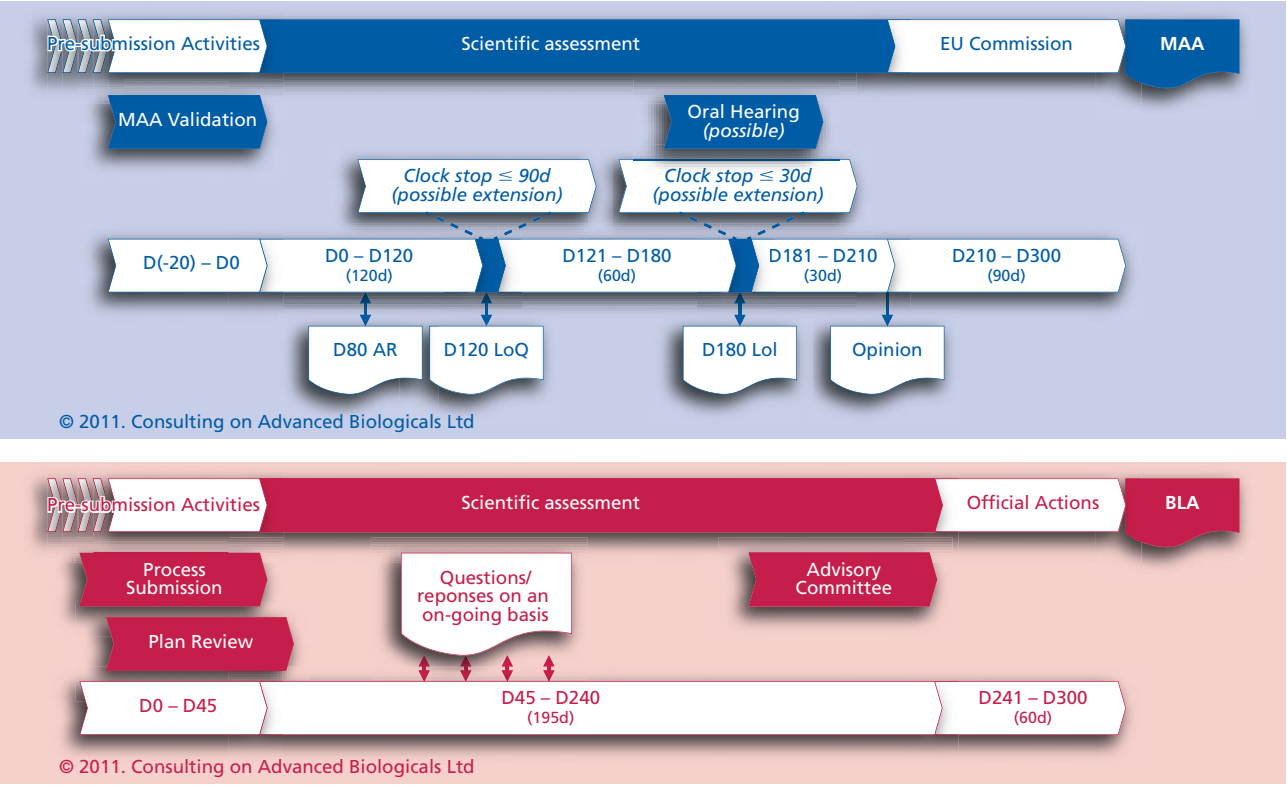
11.5 Summary

	EU	**US**
Key legislation	**Clinical Trials Directive** Directive 2001/20/EC	**IND** 21 CFR 312
	GCP Directive 2005/28/EC Directive 95/46/EEC	**GCP** 21 CFR 50 21 CFR 54 21 CFR 56 21 CFR 11
Key guidance	ICH, see **D.1**, **E.1**	
	EMA, see **D.2**, **E.2**	FDA, see **D.3**, **E.3**
	Eudralex Volume 10 – Clinical trials	
	Eudralex Volume 4, Annex 13 – Manufacture of Investigational Medicinal Products	
	See also NCA website for national guidelines	
Web links	EMA website *http://www.ema.europa.eu*	FDA website *http://www.fda.gov*
	Eudralex *http://ec.europa.eu/health/documents/eudralex/index_en.htm*	IND process (FDA, CBER) *http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/default.htm*
	Heads of Medicines Agencies website *http://www.hma.eu*	
	List of medicines NCAs *http://www.hma.eu/hdirectory.html*	
	Clinical Trials Facilitation Group *http://www.hma.eu/78.html*	
Other considerations	Additional local organizational and national rules may apply.	

12 Authorization of cell-based medicinal products

12.1 Process map

Figure 13 High level overview of MAA (EMA) and BLA (FDA) processes



NOTE *AR – assessment report;*
LoI – list of outstanding issues;
LoQ – list of questions.

CBMPs require marketing authorization before marketing.

Dossiers are required to be in CTD format and many competent authorities now accept eCTD submission (see **5.6**).

The summaries in Module 2 of the CTD should be prepared by appropriate experts.

NOTE *1 Differences exist between regions as to the scope of the summaries.*

NOTE *2 Attention is drawn to advertising and marketing legal requirements.*

NOTE *3 Packaging, distribution and wholesale selling also require national licensing.*

Both the EMA and FDA also have fast-track procedures to authorize products when related to an urgent unmet clinical need.

Both the EMA and FDA have rules to encourage the development of products for paediatric populations, these should be considered well ahead of submission.

12.2 EU

Marketing authorization for ATMPs in the EU can only be obtained through the EMA centralized procedure [Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007]. Applications should be in CTD format (see **5.6**) and may be submitted in full eCTD format.

Licences are valid throughout the EU and EEA, except where "national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells" exists.

CBMPs (being ATMPs) are assessed by the Committee for Advanced Therapies (CAT) at the EMA.

Two committee members are assigned as Rapporteurs (Rapporteur and Co-Rapporteur) who will assemble two assessment teams, generally drawn from their own NCA.

All standard EU medicines licensing procedures take 210 days of assessment time, but clock stops at day 120 and day 180 allow applicants time to respond to questions.

Initial assessment reports from the Rapporteurs are provided at day 80 for reference followed by the official consolidated report and list of questions at day 120.

Following the day 120 report a pre-authorization GMP inspection will be undertaken and may include an on-site visit by members of the assessment teams.

A final list of outstanding issues is provided at day 180 which may involve written responses and/or oral hearings.

Following a 'positive opinion' the EU Commission takes around 3 months to issue a licence.

A European public assessment report (EPAR) is published on the EMA website after the procedure is complete whether for a positive opinion, negative opinion or withdrawal.

12.3 US

US marketing approval under section 351 of the PHS Act [42 USC 262] requires submission of a BLA to the FDA in accordance with 21 CFR 601. Applications may be submitted in CTD format (see **5.6**).

An FDA review committee first evaluates the BLA for completeness. Significant deficiencies should be communicated to the applicant within 74 days. If the BLA is considered insufficient to permit a meaningful review, a Refuse to File letter is issued. If the BLA appears complete, the FDA review committee undertakes a complete review, which may include requests for additional information. When the BLA review has been completed, the FDA conducts a site inspection of the manufacturing facility, and obtains advice from the FDA Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC). The FDA review committee meets to discuss outstanding issues, agreements and commitments developed in the course of the BLA-related interactions with the applicant, and to reach a determination regarding disposition of the BLA.

If the BLA is considered not ready for approval, the FDA provides a complete response letter itemizing all deficiencies in the application that should be corrected prior to approval. If recommended for approval, the FDA issues a Summary of Basis for Approval (SBA), an approval letter itemizing all agreements and commitments accompanying the approval, and the biologics licence.

Redacted documents related to the procedure are made available on the FDA website following approval.

12.4 Summary

	EU	US
Key legislation	**MAA** Directive 2001/83/EC Directive 2009/120/EC Regulation (EC) No 1394/2007 Regulation (EC) No 726/2004	**BLA** 21 CFR 600 21 CFR 601 351 PHS Act (42 USC 262)
Key guidance	ICH, see **E.1** (CTD) Eudralex Volume 2 – Notice to Applicants,	*See FDA website*
Web links	EMA website *http://www.ema.europa.eu* Eudralex *http://ec.europa.eu/health/documents/eudralex/index_en.htm*	FDA website *http://www.fda.gov* BLA process (FDA, CBER) *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm*
Other considerations	Rules apply to encourage the development of products for paediatric populations, see competent authority website. Fast-track procedures exist for urgent unmet clinical needs. Procedures are available to appeal where market authorization is not granted.	

13 Post-launch considerations

13.1 Process map

Stored and updated information should include complete traceability of:

- patients;
- products;
- starting materials.

The data storage should be compatible with requirements laid down with regards to donation, procurement and testing (Clause **10**), and include the following, but is not limited to:

- patient information (to follow up with any adverse event recording and reporting);
- risk management;
- aspects of data protection, confidentiality and anonymity of both donor and recipient;
- patient registry.

There should be a continual QA/QC aspect of manufacture related to the ongoing GMP for product production.

Both regions are replacing annual update reporting with development safety update reports (DSURs).

NOTE *In the EU the initial MA requires renewal after 5 years.*

13.2 Pharmacovigilance

Pharmacovigilance covers:

- reporting of any adverse reactions;
- periodic safety update reports (PSURs);
- post-authorization safety studies.

Pharmacovigilance for cell therapy products is relatively early in development. Given currently limited understanding of the long-term effects of treatment with cell-based therapies, patient registries can be expected to be encouraged or required following product approval.

13.3 Post-market licence changes

Necessary changes to the commercial manufacturing process (e.g. materials changes, scale-up, improvements and new manufacturing facilities) should be carefully managed.

The relevant competent authority should be informed and in most cases pre-approval will be required before the commercial process can be changed.

The extent of the data required depends on the change and the nature of the product, but the objective is to confirm the proposed process change does not alter the quality, safety and efficacy of the final product.

Small changes (e.g. change in raw material specification) can usually be confirmed with test batch data, larger changes (e.g. new isolation process) may require non-clinical or even clinical data to confirm comparability (see also **9.3**).

13.3.1 EU

EU: 'Variations' to a market authorization are defined as:

- type 1A – mostly administrative;
- type 1B – very minor quality changes;
- type II – most manufacturing changes;
- line extensions – generally to include new indications and consequently clinical data only.

13.3.2 US

FDA requirements for making a change to an approved product are described in 21 CFR 601.12. Changes may include product labelling, manufacturing process, quality controls, equipment, facilities, or the product itself.

The FDA should be informed in advance about any such changes, and the manufacturer will be expected to demonstrate that the proposed change has no adverse effect on product safety or effectiveness. Changes, or supplements to the BLA are reported as:

- Annual report (AR) – minimal potential for adverse effect on safety or effectiveness;
- changes being effected in 30 days supplement (CBE30) – moderate potential impact on product safety or effectiveness;
- prior approval supplement (PAS) – substantial potential product impact.

13.4 Summary

	EU	US
Key legislation	**MAA** Directive 2001/83/EC (Directive 2009/53/EC)	**BLA** 21 CFR 601.12
Key guidance	Eudralex Volume 6	*See FDA website*
Web links	ICH E2F (DSUR)) see **E.1**	
	EMA website *http://www.ema.europa.eu*	FDA website *http://www.fda.gov*
	Eudralex *http://ec.europa.eu/health/documents/eudralex/index_en.htm*	Biologics guidance *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*
Other considerations	Market authorization may include conditions or commitments to provide additional data in a particular time frame. Post-marketing studies may be required for reimbursement purposes or to meet conditions of approval. Competent authorities will re-inspect GMP facilities from time to time. Competent authorities may undertake pharmacovigilance inspections. EU: Initial market authorization is for 5 years. Licensed products that are not marketed within a certain timeframe may have their market authorization withdrawn.	

Annex A (informative)
Pharmacopoeia chapters and monographs

Table A.1 PhEur and USP chapters and monographs relevant to CBMPs

PhEur			USP	
Code	**Title/Code**	**Title**	**Code**	**Title**
Adventitious Agents			**Adventitious Agents**	
<02>	<02>	Methodos of Analysis	<61>	Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
	<02.06>	Biological Test	<62>	Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms
	<02.06.01>	Sterility	<63>	Mycoplasma Tests
	<02.06.02>	Mycoplasmas	<71>	Sterility Tests
	<02.06.08>	Pyrogens	<85>	Bacterial Endotoxins Test
	<02.06.12>	Microbiological examination of non-sterile products: microbial enumeration tests	<151>	Pyrogen Test
	<02.06.13>	Microbiological examination of non-sterile products- test for specified micro-organisms	<161>	Transfusion and Infusion Assemblies and Similar Devices
	<02.06.14>	Bacterial Endotoxins	<1050>	Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
	<02.06.27>	Microbiological control of cellular products	<1116>	Microbiological Evaluation of Clean Rooms and other Controlled Environments
<05>	General Texts		<1208>	Sterility Testing – Validation of Isolator Systems
	<05.01.01>	Methods of Preparation of Sterile Products	<1211>	Sterilization and Sterility Assurance of Compendial Articles
	<05.01.06>	Alternative Methods for the Control of Microbial Quality	<1223>	Validation of Alternative Microbiological Methods
	<05.01.07>	Viral Safety	<1227>	Validation of Microbial Recovery from Pharmacopeial Articles
	<05.01.09>	Guidelines for using the test for sterility	<1237>	Virology Test Methods
	<05.01.10>	Guidelines for using the test for bacterial endotoxins		
	<05.02.08>	Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products		
<06>	General Monographs			
	<1483>	Products with risk of transmitting agents of animal spongiform encephalopathy		
Product Issues			**Product Issues**	
<02>	Methodos of Analysis		<381>	Elastomeric Closures for Injections
	<02.09.05>	Uniformity of mass of single-dose preparations	<660>	Containers – Glass
	<02.09.06>	Uniformity of content of single-dose preparations	<661>	Containers – Plastic
	<02.09>	Pharmaceutical technical procedures	<1046>	Cellular and Tissue-Based Products
	<02.09.17>	Test for Extractable Volume of Parenteral Preparations	<1086>	Impurities in Official Articles
	<02.09.19>	Particulate contamination- sub-visible particles	<1121>	Nomenclature
	<02.09.20>	Particulate contamination- visible particles	<1151>	Pharmaceutical Dosage Forms
<05>	General Texts			
	<05.02>	General Texts on Biological Products		
	<05.02.01>	Terminology used in monographs on biological products		
	<05.10>	Control of Impurities in Substances for Pharmaceutical Use		
<03>	Materials and Containers			
	<03.01>	Materials Used for the Manufacture of Containers		
	<03.02>	Containers		
<07>	Dosage Form			
	<0520>	Parenteral preparations		
<06>	General Monographs			
	<2034>	Substances for pharmaceutical use		

Table A.1 PhEur and USP chapters and monographs relevant to CBMPs

PhEur			USP	
Code	**Title/Code**	**Title**	**Code**	**Title**
Production Issues			**Production Issues**	
<05>	General Texts		<1>	Injections
	<05.01.01>	Methods of Preparation of Sterile Products	<90>	Fetal Bovine Serum-Quality Attributes and Functionality Tests
	<05.01.06>	Alternative Methods for the Control of Microbial Quality	<92>	Growth Factors and Cytokines used in Cell Therapy Manufacturing
	<05.02>	General texts on Biological Products	<797>	Pharmaceutical Compounding-Sterile Preparations
	<05.02>	Injections	<1024>	Bovine Serum
	<05.15>	Functionality-related characteristics of excipients	<1041>	Biologics
<02>	Methods of Analysis		<1043>	Ancillary Materials for Cell, Gene and Tissue Products
	<02.01>	Apparatus	<1045>	Biotechnology-Derived Articles
	<02.02.34>	Thermal Analysis	<1046>	Cellular and Tissue-Based Products
	<02.02.44>	Total organic carbon in water for pharmaceutical use	<1074>	Excipient Biological Safety Evaluation Guidelines
	Monographs		<1180>	Human Plasma
	<0169>	Water for Injections	<1231>	
	<1927>	Highly Purified Water		
	<0008>	Purified Water		
	<2262>	Bovine Serum		
Characterization			**Characterization**	
<02>	Methods of analysis		<11>	USP Reference Standards
	<02.02>	Physical and Physicochemical Methods	<111>	Design and Analysis of Biological assays
	<02.02.03>	Potentiometric determination of pH	<785>	Osmolality and Osmolarity
	<02.02.08>	Viscosity	<788>	Particulate Matter in Injections
	<02.02.35>	Osmolality	<791>	pH
	<02.06>	Biological Tests	<881>	Tensile Strength
	<02.07>	Biological Assays	<911>	Viscosity
	<02.07.01>	Immunochemical Methods	<1027>	Flow Cytometry
	<02.07.23>	Numeration of CD34 CD45 plus Cells in Haematopoietic Products	<1046>	Cellular and Tissue-Based Products
	<02.07.24>	Flow cytometry	<1045>	Biotechnology-Derived Articles – Tests
	<02.07.28>	Colony-forming Cell Assay for Human Haematopoietic Progenitor Cells	<1049>	Quality Of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
	<02.07.29>	Nucleated Cell Count and Viability		
<05>	General Texts			
	<05.03>	Statistical Analysis of Results of Biological Assays and Tests		
	<05.12>	Reference Standards		
			Equipment	
			<16>	Automated Methods of Analysis
			<21>	Thermometers
			<31>	Volumetric Apparatus
			<41>	Weights and Balances
			<1051>	Cleaning Glass Apparatus
			<1058>	Analytical Instrument Qualification
			<1072>	Disinfectants and Antiseptics
			<1118>	Monitoring Devices-Time, Temperature, and Humidity
			<1251>	Weighing on an Analytical Balance
			Biocompatibility	
			<87>	Biological Reactivity Tests, in vitro
			<88>	Biological Reactivity Tests, in vivo
			<1031>	The Biocompatibility of Materials Used in Drug Containers, Medical Devices and Implants
			<1184>	Sensitization Testing

NOTE 1 *Similar chapters/monographs are aligned, although direct equivalents are not common.*

Annex B (informative)
Quality (CMC) guidelines

B.1 ICH quality (CMC) guidelines

Title	Source
ICH Q1A: *Stability testing of new drug substances and products*	http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html
ICH Q1B: *Photostability testing of new drug substances and products*	
ICH Q1D: *Bracketing and matrixing designs for stability testing of drug substances and drug products*	
ICH Q1E: *Evaluation of stability data*	
ICH Q2: *Validation of analytical procedures: Text and methodology*	
ICH Q3A: *Impurities in new drug substances*	
ICH Q3B: *Impurities in new drug products*	
ICH Q5A: *Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin*	
ICH Q5B: *Quality of biotechnological products: analysis of the expression construct in cells used for production of r-DNA derived protein products*	
ICH Q5C: *Quality of biotechnological products: stability testing of biotechnological/biological products*	
ICH Q5D: *Derivation and characterisation of cell substrates used for production of biotechnological/biological products*	
ICH Q5E: *Comparability of biotechnological/biological products subject to changes in their manufacturing process*	
ICH Q6B: *Specifications: Test procedures and acceptance criteria for biotechnological/ biological products*	
ICH Q7: *Good manufacturing practice guide for active pharmaceutical ingredients*	
ICH Q8: *Pharmaceutical development*	
ICH Q9: *Quality risk management*	
ICH Q10: *Pharmaceutical quality system*	

B.2 EMA quality (CMC) guidelines

Title	Source
Testing	
Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003814.pdf
Tests on samples of biological origin	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003498.pdf
Guideline on real time release testing (formerly guideline on parametric release) DRAFT	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500075028.pdf
Adventitious agents	
Guideline on virus safety evaluation of biotechnological investigational medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003795.pdf
Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003798.pdf
First cases of BSE in USA and Canada: Risk assessment of ruminant materials originating from USA and Canada	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003697.pdf
CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108069.pdf
Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:073:0001:0018:EN:PDF
Materials	
Note for guidance on the use of bovine serum in the manufacture of human biological medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003675.pdf
Explanatory note: Gelatin for use in pharmaceuticals	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003721.pdf
Position statement on the use of tumourigenic cells of human origin for the production of biological and biotechnological medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003294.pdf
Use of transgenic animals in the manufacture of biological medicinal products for human use	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003458.pdf

B.2 EMA quality (CMC) guidelines

Title	Source
Concept paper on the need to revise the guideline	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003454.pdf
Excipients in the label and package leaflet of medicinal products for human use	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf
Note for guidance on limitations to the use of ethylene oxide in the manufacture of medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002915.pdf
Note for guidance on quality of water for pharmaceutical use	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003394.pdf
Reflection paper on water for injection prepared by reverse osmosis	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003403.pdf
Comparability	
Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: Quality issues ***NOTE*** *Superseded by ICH Q5*E.	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003573.pdf
Miscellaneous	
Note for guidance on development pharmaceutics	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003533.pdf
Development pharmaceutics for biotechnological and biological products – Annex to note for guidance on development pharmaceutics	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003603.pdf
Requirements for quality documentation concerning biological investigational medicinal products in clinical trials DRAFT	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500075559.pdf
GMP	
Volume 4, Annex 2: Manufacture of biological medicinal products for human use	http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/anx02en200408_en.pdf
Volume 4, Annex 2: Manufacture of biological medicinal substances and products for human use DRAFT	http://ec.europa.eu/health/documents/latest_news/gmp_annex2_03-2010.pdf
Volume 4, Annex 13: Investigational medicinal products	http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf

B.3 FDA CMC (quality) guidelines

Title	Source
Testing	
DRAFT Guidance for Industry: Analytical procedures and methods validation – Chemistry, manufacturing, and controls documentation	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122858.pdf
DRAFT Guidance for Industry: Comparability protocols – Protein drug products and biological products – Chemistry, manufacturing, and controls information	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070262.pdf
Demonstration of comparability of human biological products, including therapeutic biotechnology-derived products	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm
Submitting samples and analytical data for methods validation	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm123124.htm
Guideline for validation of limulus amebocyte lysate test as an end-product endotoxin test for human and animal parenteral drugs, biological products, and medical devices	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080966.pdf
Guidance for Industry: Potency tests for cellular and gene therapy products	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf
Adventitious agents	
Testing HCT/P donors for relevant communicable disease agents and diseases	http://www.fda.gov/biologicsbloodvaccines/safetyavailability/tissuesafety/ucm095440.htm
Nucleic Acid Testing (NAT) for human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV): Testing, product disposition, and donor deferral and re-entry	http://www.fda.gov/downloads/biologicsblood%20vaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm210270.pdf
Draft Guidance for Industry: Use of serological tests to reduce the risk of transmission of trypanosoma cruzi infection in whole blood and blood components for transfusion and human cells, tissues, and cellular and tissue-based product (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm126098.pdf
Validation of growth-based rapid microbiological methods for sterility testing of cellular and gene therapy products	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078696.pdf

B.3 FDA CMC (quality) guidelines

Title	Source
Use of nucleic acid tests to reduce the risk of transmission of West Nile virus from donors of whole blood and blood components intended for transfusion and donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078614.pdf
Guidance for Industry: Availability of licensed donor screening tests labelled for use with cadaveric blood specimens	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091395.pdf
Testing HCT/P donors: specific requirements	http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm151757.htm
Materials	
Biological product deviations	http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/biologicalproductdeviations/default.htm
Guidance for Industry: Monoclonal antibodies used as reagents in drug manufacturing	http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm080417.pdf
Guidance for Industry: Container closure systems for packaging human drugs and biologics	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf
Guidance for Industry: The sourcing and processing of gelatin to reduce the potential risk posed by bovine spongiform encephalopathy (BSE) in FDA-regulated products for human use	http://www.fda.gov/RegulatoryInformation/Guidances/ucm125182.htm
Clinical trials	
Guidance for Industry: INDs for phase 2 and phase 3 studies chemistry, manufacturing, and controls information	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf
Guidance for FDA reviewers and sponsors: Content and review of chemistry, manufacturing, and control (CMC) information for human somatic cell therapy investigational new drug applications (INDs)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092705.pdf
Miscellaneous	
Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091694.pdf

B.3 FDA CMC (quality) guidelines

Title	Source
Guidance for the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM169060.txt
Guidance for Industry: Class II special controls guidance document: Cord blood processing system and storage container	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091730.pdf
GMP	
Current good manufacturing practice for phase 1 investigational drugs	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf
Guidance for Industry: Sterile drug products produced by aseptic processing – Current good manufacturing practice	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

Annex C (informative)
Safety (non-clinical) guidelines

C.1 ICH safety (non-clinical) guidelines

Title	Source
ICH S3A: *Note for guidance on toxicokinetics: The assessment of systemic exposure in toxicity studies*	http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html
ICH S4A: *Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)*	
ICH S6: *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*	
ICH S7A: *Safety pharmacology studies for human pharmaceuticals*	
ICH S3A: *Note for guidance on toxicokinetics: The assessment of systemic exposure in toxicity studies*	

C.2 EMA safety (non-clinical) guidelines

Title	Source
Toxicity	
Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity'	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094590.pdf
Guideline on repeated dose toxicity	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079536.pdf
Note for guidance on non-clinical local tolerance testing of medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003315.pdf
Guideline on evaluation of control samples for non-clinical safety studies: checking for contamination with the test substance	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003974.pdf
Note for guidance on photosafety testing	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003353.pdf
Q&A	http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/04/WC500105109.pdf

C.2 EMA safety (non-clinical) guidelines

Title	Source
Tumourigenicity	
Guideline on the limits of genotoxic impurities	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf
Note for guidance on carcinogenic potential	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003258.pdf
Clinical trials	
Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf
Miscellaneous	
Guideline on environmental risk assessment of medicinal products for human use	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf
Replacement of animal studies by in-vitro models	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003354.pdf

C.3 FDA safety (non-clinical) guidelines

Title	Source
Toxicity	
DRAFT Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf
Clinical trials	
Nonclinical safety evaluation of drug or biologic combinations	http://www.fda.gov/OHRMS/DOCKETS/98fr/05d-0004-gdl0002.pdf
DRAFT Guidance for Industry and FDA Staff: Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf
Miscellaneous	
Animal Models – Essential elements to address efficacy under the animal rule	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078923.pdf
Human cell & tissue products (HCT/P) adverse reaction reporting	http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/ucm152576.htm

Annex D (informative)
Efficacy (clinical) guidelines

D.1 ICH efficacy (clinical) guidelines

Title	Source
ICH E2A: *Clinical safety data management: definitions and standards for expedited reporting*	http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
ICH E2B: *Clinical safety data management data elements for transmission of individual case safety reports*	
ICH E2C: *Clinical safety data management: Periodic safety update reports for marketed drugs*	
ICH E2D: *Post-approval safety data management: definitions and standards for expedited reporting*	
ICH E2F: *Pharmacovigilance planning*	
ICH E2F: *Development safety update report*	
ICH E3: *Structure and content of clinical study reports*	
ICH E4: *Dose-response information to support drug registration*	
ICH E5: *Ethnic factors in the acceptability of foreign clinical data*	
ICH E6: *Good clinical practice: Consolidated guideline*	
ICH E7: *Studies in support of special populations: Geriatrics*	
ICH E8: *General considerations for clinical trials*	
ICH E9: *Statistical principles for clinical trials*	
ICH E10: *Choice of control group and related issues in clinical trials*	
ICH E11: *Clinical investigation of medicinal products in the pediatric population*	
ICH E15: *Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories*	

D.2 EMA efficacy (clinical) guidelines

Title	Source
Clinical trials	
Clinical trials in small populations	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf
Inclusion of appendices to clinical study reports in marketing authorisation applications	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003638.pdf
Note for guidance on coordinating investigator signature of clinical study reports	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf
Points to consider concerning end points in clinical studies with haematopoietic growth factors for mobilisation of autologous stem cells	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003733.pdf
Data analysis	
Choice of a non-inferiority margin	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf
Points to consider on multiplicity issues in clinical trials	http://home.att.ne.jp/red/akihiro/emea/090899en.pdf
Points to consider on application with 1. Meta-analyses; 2. One pivotal study	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf
Extrapolation of results from clinical studies conducted outside Europe to the EU population	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003583.pdf
Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf
Points to consider on switching between superiority and non-inferiority	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf
Points to consider on adjustment for baseline covariates	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003639.pdf
Guideline on missing data in confirmatory clinical trials	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003642.pdf
Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products	http://www.ispor.org/workpaper/EMEA-HRQL-Guidance.pdf
Data Monitoring Committees	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf

D.2 EMA efficacy (clinical) guidelines

Title	Source
Concept paper on the need for a guideline on the use of subgroup analyses in randomised controlled trials	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090116.pdf
GCP	
Detailed guidelines on good clinical practice specific to advanced therapy medicinal products	http://ec.europa.eu/health/files/eudralex/vol-10/2009_11_03_guideline.pdf
Q&A	http://ec.europa.eu/health/files/eudralex/vol-10/final_03-2011.pdf
Clinical trials	
Clinical trials in small populations	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf
Inclusion of appendices to clinical study reports in marketing authorisation applications	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003638.pdf
Note for guidance on coordinating investigator signature of clinical study reports	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf
Points to consider concerning end points in clinical studies with haematopoietic growth factors for mobilisation of autologous stem cells	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003733.pdf
Data analysis	
Choice of a non-inferiority margin	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf
Points to consider on multiplicity issues in clinical trials	http://home.att.ne.jp/red/akihiro/emea/090899en.pdf

D.3 FDA efficacy (clinical) guidelines

Title	Source
Clinical trials	
Collection of Race and Ethnicity Data in Clinical Trials	http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126396.pdf
Recruiting Study Subjects – Information Sheet	http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm
Drug Study Designs – Information Sheet	http://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm
MedWatch form FDA 3500A: Mandatory reporting of adverse reactions related to human cells, tissues, and cellular and tissue-based products (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm062583.pdf
Guidance for Industry: cGMP for phase 1 investigational drugs	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf
Data analysis	
Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm201790.pdf
Evaluation of Gender Differences in Clinical Investigations – Information Sheet	http://www.fda.gov/RegulatoryInformation/Guidances/ucm126552.htm
Computerized Systems Used in Clinical Trials	http://www.fda.gov/regulatoryinformation/guidances/ucm126402.htm
Draft Guidance for Industry Non-Inferiority Clinical Trials	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf
Clinical trials	
Collection of Race and Ethnicity Data in Clinical Trials	http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126396.pdf
Recruiting Study Subjects – Information Sheet	http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm
Drug Study Designs – Information Sheet	http://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm

Annex E (informative)
Multi-disciplinary guidelines

E.1 ICH multi-disciplinary guidelines

Title	Source
ICH M1: *Medical terminology*	http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html
ICH M3: *Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals*	
ICH M4: *The Common technical document*	

E.2 EMA multi-disciplinary guidelines

Title	Source
ATMP	
Guideline on human cell-based medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003894.pdf
Reflection paper on stem cell-based medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf
Concept paper on the development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500069264.pdf
Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004223.pdf
Guideline on xenogeneic cell-based medicinal products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500016936.pdf
Miscellaneous	
Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development (Draft)	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094445.pdf
Reflection Paper on pharmacogenomic samples, testing and data handling	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf
Guideline on the limits of genotoxic impurities	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf

E.2 EMA multi-disciplinary guidelines

Title	Source
Comparability	
Guideline on comparability of medicinal products containing biotechnology -derived proteins as active substance: non-clinical and clinical issues	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003937.pdf

E.3 FDA multi-disciplinary guidelines

Title	Source
HCT/P	
Considerations for allogeneic pancreatic islet cell products	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM182441.pdf
Draft Guidance for Industry and FDA Staff – Investigational new drug applications (INDs) for minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indications	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187146.pdf
Minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indications	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf
Guidance for Industry: Preparation of IDEs and INDs for products intended to repair or replace knee cartilage	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM288011.pdf
Guidance for Industry: Cellular therapy for cardiac disease	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM164345.pdf
Points to Consider in the collection, processing, and testing of ex-vivo activated mononuclear leukocytes for administration to humans	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM062770.pdf

E.3 FDA multi-disciplinary guidelines

Title	Source
Miscellaneous	
Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM085439.pdf
Guidance for Human Somatic Cell Therapy and Gene Therapy	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm081670.pdf
Early Development Considerations for Innovative Combination Products	http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126054.pdf
Points to Consider in the manufacture and testing of therapeutic products for human use derived from transgenic animals	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153306.pdf
Comparability	
Demonstration of comparability of human biological products, including therapeutic biotechnology-derived products	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm

Annex F (informative)
FDA tissue guidance

F.1 FDA tissue guidance

Title	Source
Adventitious agents	
Guidance for Industry: Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf
Guidance for Industry: Certain human cells, tissues, and cellular and tissue-based products (HCT/Ps) recovered from donors who were tested for communicable diseases using pooled specimens or diagnostic tests	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm062596.pdf
Guidance for Industry: Class II special controls guidance document: cord blood processing system and storage container	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091730.pdf
DRAFT Guidance for Industry: Use of serological tests to reduce the risk of transmission of trypanosoma cruzi infection in whole blood and blood components for transfusion and human cells, tissues, and cellular and tissue-based products	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm126098.pdf
Guidance for Industry: Screening and testing of donors of human tissue intended for transplantation	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM188251.pdf
Miscellaneous	
DRAFT Guidance for Industry: Current good tissue practice (cGTP) and additional requirements for manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091408.pdf
Guidance for Industry: Regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps) – Small entity compliance guide	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm062592.pdf

F.1 FDA tissue guidance

Title	Source
Guidance for Industry: Preparation of IDEs and INDs for products intended to repair or replace knee cartilage	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM288011.pdf
Guidance for Industry: Recommendations for obtaining a labeling claim for communicable disease donor screening tests using cadaveric blood specimens from donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091374.pdf
Draft Guidance for Industry: Minimally manipulated, unrelated, allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution in patients with hematological malignancies	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091744.pdf
Guidance for Industry and FDA staff: Minimal manipulation of structural tissue jurisdictional update	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM085439.pdf
Guidance for Industry: Compliance with 21 CFR part 1271.150(c)(1) – Manufacturing arrangements	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091694.pdf
Guidance for Industry: MedWatch form FDA 3500A: Mandatory reporting of adverse reactions related to human cells, tissues, and cellular and tissue-based products (HCT/Ps)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm062583.pdf
Guidance for Industry: Validation of procedures for processing of human tissues intended for transplantation	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM085526.pdf
Guidance for Industry: Availability of licensed donor screening tests labeled for use with cadaveric blood specimens	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091395.pdf

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Standards publications

PAS 93:2011, *Characterization of human cells for clinical applications – Guide*

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