Annex I of Directive 2001/83/EC[1], do apply. Conventional excipients should also be characterised with respect to their combination with cells.

Information on the choice of excipients, their properties, their characteristics and the design and testing of a final scaffold/matrix should be provided in the dossier as part of the development pharmaceutics.

Should the finished product contain components that act to modify the delivery or ensure the local retention of cells after administration, the scientific rationale should be provided and supported by adequate development data. The evaluation of individual non-cellular components is required although aspects of this evaluation may be incorporated into studies designed to assess the product as a whole. Where the safety of a non-cellular component has previously been established for other applications, for example in support of the approval of a particular material for a medical device or medicinal product application, elements of that evaluation may be applicable to an evaluation of its safety and suitability when used in a cell-based medicinal product, if justified.

The relevance of the structural and functional characteristics of the non-cellular components in a combination product should be discussed. Interaction of the cellular component and any additional non-cellular components with the device should be evaluated and the development and characteristics of the combined product as a whole should be presented.

Tissue differentiation and functionality are highly dependent on the local environment and thus on the choice of biomaterials and cell signalling biomolecules (e.g. growth factors). Therefore, studies should be carried out to verify critical aspects of the character and performance of biomaterials and other non-cellular components used in the CBMP, for example biocompatibility and mechanical strength.

In particular, to confirm that the properties of a biomaterial permit the growth and proper function of the tissue/cells with which it is in contact and support the overall performance of the product, assurance should be provided in relation to the following:

- absence of components or leachables that might be toxic to cell growth and/or to the intended performance;
- characterisation of features (e.g. topography, surface chemistry, strength) critical to structural support, optimisation of viability and cellular growth or other functional characteristics;
- biocompatibility of the structural material with the cells or tissues to confirm that the system maintains the desired cell differentiation, functionality and genotype during production and until use;
- release kinetics and/or rate of degradation of any bioactive molecules, to verify that they are appropriate for the achievement of the intended effect.

To establish biocompatibility, it is necessary to specify the nature of biological responses that a biomaterial is required to elicit from the host tissue or cell-based components, and to provide evidence that the desired tissue response is achieved in a relevant model.

The stability of the non-cellular components should be assessed in the presence and absence of cellular components in order to determine whether the non-cellular component undergoes degradation, or physico-chemical alterations (e.g. aggregation, oxidation) that may impact on the quality of the product by affecting cellular behaviour and survival. The effect of the cellular component or of the surrounding tissues on the degradation (rate and, if appropriate, products) or stability of the structural component should be assessed, considering also the effect of the non-cellular components throughout the expected lifetime of the product. The general principles that are applied to the biological evaluation of medical devices can also be applied to the evaluation of biomaterials intended for use in CBMP. Such an evaluation involves a programme of characterisation, testing and review of existing data to assess the potential for an adverse biological reaction to occur as a result of exposure to the biomaterial. These principles are set out in international standard ISO 10993 Part 1[33]. Other parts of the ISO 10993 series of standards specify methods that may be relevant to the assessment of material characteristics, biological safety and degradation of biomaterials used in cell-based medicinal

products. Additional studies (e.g. cell adhesion studies, growth studies) may be necessary to demonstrate aspects of biocompatibility specific to cell-based applications.

3. Final Product

Once the "formulation", i.e. the delivery system of a combined product has been established, the parameters for determining the role of constituents and appropriateness of composition should be presented within a justification of the composition of the product.

The key parameters for performance testing of the completed product should be justified in relation to the development data and the final quality requirements. It may be appropriate that *in vitro* and *in vivo* testing of the formulation/delivery system/combined product during development are included.

4.2.7 Traceability

A system allowing complete traceability of the patient as well as the product and its starting materials is essential to monitor the safety and efficacy of cell-based medicinal products. The establishment and maintenance of that system should be done in a way to ensure coherence and compatibility with traceability and vigilance requirements laid down in Directive 2004/23/EC[4] and in Directives 2006/17/EC[5] and 2006/86/EC[6] and Art. 15 of the Regulation (EC) No 1394/2007[2].

Article 15 of the Regulation (EC) No 1394/2007[2] defines a two tiered system connecting the required traceability from cell donation and procurement (Dir 2004/23/EC) to the manufacturer and user (hospital or practice). This means that anonymity can be guaranteed. At the tissue establishment there has to be a link between the donor and the donation. At the manufacturing side, there has to be a link between donation and product and at the hospital/practice side there has to be a link between the product and the recipient. The systems should allow full traceability from the donor to the recipient through anonymous coding systems. Manufacturers should establish their coding systems in a rational way, building from the coding system of the tissue establishment, and designing it to facilitate the tracing of the donation to the product and to the patient. Bar coding and peeling labelling systems could be suitable tools for the purpose of patient management.

4.2.8 Comparability

Development of a cell-based medicinal product may encompass changes in the manufacturing process that might have an impact on the final product. Given the complex and dynamic nature of CBMP it is particularly important that all stages of development are fully evaluated and tracked within the dossier. This is especially significant once clinical studies have commenced. Data on the behaviour and characteristics of developmental prototypes should be retained as it could provide background information relevant to the evaluation of the final product. During the pivotal clinical studies changes should not be introduced to the manufacturing process and the final product.

Materials used in the clinical studies should be sufficiently characterised in order to allow the demonstration of consistency in the production. The manufacturers should consider the critical parameters drawn from the characterisation of their product to establish the analytical tools necessary for the required comparability studies throughout development. Comparability studies with the product resulting from those changes should be performed in relation to clinical trial batches that were used. Appropriate guidance can be found in ICH Q5E Comparability of Biotechnological/Biological Products[34] and related guidance documents.

Whenever comparability at the analytical and/or non-clinical level cannot be established, it must be demonstrated by clinical data.

4.3 Non-clinical development

The scrutiny applied during non-clinical testing should take into account the nature of the Cell-based medicinal product (CBMP) and be proportional to the risk expected to be associated with clinical use.

The variability of cell-based medicinal products should be reflected in the non-clinical studies. Conventional requirements as detailed in Module 4 for pharmacological and toxicological testing of medicinal products may not always be appropriate. Any deviation from these requirements shall be justified. If cells in a CBMP have been genetically modified, non-clinical development must be performed in compliance with guidance available on gene transfer medicinal products[23].

The objectives of the non-clinical studies are to demonstrate proof-of-principle, define the pharmacological and toxicological effects predictive of the human response, not only prior to initiation of clinical trials, but also throughout clinical development. The goals of these studies include the following: to provide information to select safe doses for clinical trials, to provide information to support the route of administration and the application schedule, to provide information to support the duration of exposure and the duration of the follow-up time to detect adverse reactions, to identify target organs for toxicity and parameters to monitor in patients receiving these therapies.

The non-clinical studies should be performed in relevant animal models. If relevant animal models cannot be developed, *in vitro* studies may replace animal studies. The rationale underpinning the non-clinical development and the criteria used to choose a specific animal model must be justified. Expression level of biologically active molecules, the route of administration and the dosages tested should reflect the intended clinical use in humans

The recommendations of the ICH S6 Guideline[35] should be considered. The number of animals, their genders, the frequency and duration of monitoring should be appropriate to detect possible adverse effects.

The safety and suitability of all structural components for their intended function must be demonstrated, taking into account their physical, mechanical, chemical and biological properties. (See section 4.2.6 Development pharmaceutics).

4.3.1. Pharmacology

Primary pharmacodynamics

Non-clinical studies should be adequate to demonstrate the proof of principle of the CBMP. The principal effects should be identified in non-clinical studies in a suitable model *in vitro* or *in vivo*.

Reasonably justified markers of biological activity should be used to adequately identify the pharmacodynamic action of the CBMP in the host.

If the intended use of the CBMP is, for example, to restore the function of deficient cells/tissue (tissue regeneration), functional tests should be implemented to demonstrate that function is restored. If the intended use is, for example, adoptive immunotherapy in cancer patients, the biological effect should be supported by data describing the immunologic action of the CBMP.

The chosen animal model may include immunocompromised, knockout or transgenic animals. Homologous models may be advantageous, since the *in vivo* behaviour of the applied cells or tissue in heterologous models could be altered due to species-specific mismatches. Homologous models should be considered for the study of stem cell differentiation. *In vitro* studies, addressing cell and tissue morphology, proliferation, phenotype, heterogeneity and the level of differentiation may be part of the primary pharmacodynamic analyses.

If possible, studies should be conducted in order to determine the minimal or optimal effective amount of CBMP that is needed to achieve the desired effect.

Secondary pharmacology

Potential undesirable physiological effects of human CBMP including their bioactive products should be investigated in an appropriate animal model. Cells may migrate from their intended location and, after a systemic administration, may home to other organs beside the intended location. Also, somatic cells may secrete additional biologically active molecules besides the protein of interest. Also, the protein(s) of interest can have additional targets beside the desired one.

Safety pharmacology

Safety pharmacology should be considered on a case-by-case basis depending on the characteristics of the CBMP. Cells may secrete pharmacologically active substances resulting in CNS, cardiac, respiratory, renal or gastrointestinal dysfunctions. Alternatively, cells by themselves could be envisaged to induce such consequences for example stem cells or muscle cells transplanted to infarcted regions of the heart.

For further guidance see ICH S7A Guideline[36] when applicable.

Kinetics, migration and persistence

Conventional ADME studies are usually not relevant for human CBMP. However, studies should be carried out to demonstrate tissue distribution, viability, trafficking, growth, phenotype and any alteration of phenotype due to factors in the new environment.

Cells may migrate within the host, thus presenting clinical concerns regarding adverse reactions deriving from displaced, possibly differentiating cells. This should be evaluated in animals using appropriate methods for specific identification of the cells.

Regarding biodistribution, the use of small animals allows meticulous cell detection, which will be practically more difficult in larger animals.

For human CBMP producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules and the survival and the functional stability of the cells at target sites should be studied.

Interactions

The interaction of the applied cells or surrounding tissue with the non-cellular structural components and other bioactive molecules as well as the integration of the CBMP with the surrounding tissue should be monitored.

4.3.2. Toxicology

The need for toxicological studies depends on the product. However, as conventional study designs may not be appropriate, the scientific justification for the models used, or the omission of studies, shall be provided.

Toxicity may evolve, for example, due to unknown cellular alterations developing during the manufacturing process such as altered excretion patterns and *in vivo* behaviour due to differentiation of the cells. Other potential factors that may induce toxicity include the allogeneic use of the product, the presence of components that are used in the manufacturing process or are part of a structural component, or proliferation of the applied cells in an unwanted quantity or in an unwanted location.

Conventional toxicology studies might nevertheless be required, for example for complex regimens where CBMP are combined with other medicinal products or treatments such as adjuvants/cytokines or irradiation, respectively. The need for drug interaction studies is dependent on the intended use and the type of the cell-based product and should be discussed.

The induction of an immune response against the cells themselves and/or towards cell-derived pharmacologically active substances might modulate the efficacy of the CBMP. Therefore, the possible immunogenicity of a CBMP should be considered. For guidance on immunogenicity of excreted substances see ICH S6 Guideline[35].

Auto-immunity should be considered when cells are used for immunotherapy purposes, e.g. cancer immunotherapeutic products.

Single and repeated dose toxicity studies

Toxicity studies should be performed in relevant animal models. If the human cells are not immediately rejected, the studies may be combined with safety pharmacology, local tolerance, or proof of concept and efficacy studies. Sufficiently characterized analogous animal-derived cells may be used for some allogeneic CBMP when not immediately rejected.

The duration of observations in such studies might be much longer than in standard single dose studies, since the cells are supposed to function for long times, or induce long term effects, which should be reflected in the design of these studies. The route and dosing regimen should reflect the intended clinical use. Repeated dose toxicity studies are only relevant if the clinical use includes multiple dosings.

Local tolerance studies

Local tolerance studies may be required in an appropriate species. Most often, local tolerance, tissue compatibility and tolerance to excreted substances can be evaluated in single or repeated dose toxicity studies.

Other toxicity studies

The risk of inducing tumourigenesis due to neoplastic transformation of host cells and cells from the CBMP should be considered, as appropriate, on a case-by-case basis. Conventional carcinogenicity studies may not be feasible. Tumourigenesis studies should preferably be performed with cells that are at the limit of routine cell culturing or even beyond that limit. Tissues found to contain applied cells or expressed products during the biodistribution studies should also be analysed with special emphasis during tumourigenicity studies.

Genotoxicity studies are not considered necessary for human CBMP, unless the nature of any expressed product indicates an interaction directly with DNA or other chromosomal material.

The need for reproductive studies is dependent on the CBMP and should be considered on a case-by-case basis.

4.4 Clinical development

4.4.1 General aspects

In general, when a Cell-based medicinal product (CBMP) enters the clinical development phase, the same requirements as for other medicinal products apply. The clinical development plan should include pharmacodynamic studies, pharmacokinetic studies, mechanism of action studies, dose finding studies and randomised clinical trials in accordance to the Directive 2001/20/EC[37] and to the existing general guidances and specific guidances for the condition evaluated.

Due to specific biologic characteristics of CBMP, alternative approaches to Phase I to Phase III clinical trials might be required and acceptable for clinical development, if justified. The relevant non-clinical studies, previous clinical experience of the treated pathology, and initial clinical studies could be applied for demonstration of the "proof of principle" and the choice of clinically meaningful endpoints for safety and efficacy evaluation. European scientific advice is strongly recommended in case of uncertainties in rationale of CBMP development at the earliest phase.

CBMP might require administration through specific surgical procedures, method of administration or the presence of concomitant treatments to obtain the intended therapeutic effect. The biological effects of CBMP are highly dependent on the *in vivo* environment, and may be influenced by the replacement process or the immune reaction either from the patient or from the cell-based product. These requirements coming from the clinical development should be taken into account for the final use of these products. Their standardisation and optimisation should be an integral part of the clinical development studies. The therapeutic procedure as a whole, including the method of administration and required concomitant medication, such as immunosuppressive regimens need to be investigated and described in the product information, notably in the Summary of Product Characteristics (SPC).

4.4.2 Pharmacodynamics

Even if the mechanism of action is not understood in detail, the main effects of the CBMP should be known. When the purpose of the CBMP is to correct the function of deficient or destroyed cell/tissue, then functional tests should be implemented. If the intended use of the CBMP is to restore/replace cell/tissues, with an expected lifelong functionality, structural/histological assays may be potential pharmacodynamic markers. Suitable pharmacodynamic markers, such as defined by microscopic, histological, imaging techniques or enzymatic activities, could be used.

When CBMP includes a non cellular component, the combination should be assessed clinically for compatibility, degradation rate and functionality.

4.4.3 Pharmacokinetics

Conventional ADME studies are usually not relevant for human CBMP. Study requirements, possible methodologies and their feasibility shall be discussed, attention being paid to monitoring of viability, proliferation/differentiation, body distribution / migration and functionality during the intended viability of the products.

If multiple (repeated) administrations of the CBMP are considered, the schedule should be discussed in view of the expected in vivo life span of the CBMP.

4.4.4 Dose finding studies

The selection of the dose should be based on the findings obtained in the quality and the non-clinical development of the product and it should be linked with the potency of product. Even though the dosage for cell-based product might be determined by individual characteristics of the intended

patients (i.e. cell mass density per body weight/ volume of missing tissue/ missing surface), the dose to be tested in the confirmatory trial should be supported by the evidence provided by the phase I/II studies.

Phase I/II studies should be designed to identify a Minimal Effective Dose, defined as the lowest dose to obtain the intended effect or an Optimal Effective Dose Range, defined as the largest dose range required to obtain the intended effect based on the clinical results for efficacy and tolerability. If possible, also the Safe Maximal Dose, defined as the maximal dose which could be administered on the basis of clinical safety studies without acceptable adverse effects, should be investigated.

4.4.5 Clinical Efficacy

Clinical efficacy studies should be adequate to demonstrate efficacy in the target patient population using clinically meaningful endpoints, to demonstrate an appropriate dose-schedule that results in the optimal therapeutic effect, to evaluate the duration of therapeutic effect of the administered product and to allow a benefit – risk assessment taking into account the existing therapeutic alternatives for the target population. Confirmatory studies should be, as stated before, in accordance to the existing general guidelines and specific guidelines for the condition evaluated.

Deviations from these will need a justification. For example, the fact that the nature and the mechanism of action of the CBMP may be entirely novel does not mean necessarily that the therapeutic benefit should be measured by different endpoints from those recommended in the current disease-specific guidelines (e.g. medicines vs. cell implants for Parkinson's disease).

For new therapeutic applications of CBMP where limited guidance exists, consultation of regulatory authorities on the clinical development plan, including the confirmatory studies, is highly recommended.

The use of previously validated or generally accepted surrogate endpoints is possible provided that a correlation-between clinical meaningfully endpoints and efficacy can be established. Sometimes, the desired clinical endpoint, such as prevention of arthrosis, can be observed only after a long follow up. In such cases, the marketing authorisation can be based on surrogate markers. If the efficacy is dependent on the long-term persistence of the product, a long-term follow up plan of the patients should be provided. Thus, the use of novel meaningful endpoints, clinical or other, is acceptable if justified.

4.4.6 Clinical Safety

The safety database should be able to detect common adverse events. The size of the database might be decided also in the light of previous clinical experience with similar products.

The risk of the therapeutic procedure as a whole, e.g. the required surgical procedures to administer the CBMP or the use of immunosuppressive therapy, shall be evaluated and used to justify the clinical studies and the choice of the target patient population

All safety issues arising from the preclinical development should be addressed, especially in the absence of an animal model of the treated disease or in the presence of physiologic differences limiting the predictive value of homologous animal model.

Particular attention should be paid to those biological processes including immune response, infections, malignant transformation and concomitant treatment during development and post-marketing phase of cell-based medicinal products.

For products with expected long term viability, patient follow-up is required in order to confirm long term efficacy and safety issue related to the product.

Clinical safety studies on repeated administrations should be performed as required by the risk analysis. The definition of Maximal Safe Dose should take into account also the possibility of repeated administration.

4.4.7 Pharmacovigilance and Risk Management Plan

The routine pharmacovigilance and traceability of the product should be described in the EU Risk Management Plan (RMP) as described in Guideline on risk management systems for medicinal products for human use[7]. CBMP may need special long-term studies to monitor specific safety issues, including loss of efficacy.

The long-term safety issues, such as infections, immunogenicity/immunosuppression and malignant transformation as well as the *in vivo* durability of the associated medical device/biomaterial component should be addressed in the RMP. Special pharmacoepidemiological studies may be needed. The specific requirements are linked to the biologic characteristics of the cell-based product. Traceability in the donor-product-recipient axis, or of the product-recipient for autologous products, is required in all circumstances as described in Directive 2004/23/EC[4] and in Regulation (EC) No. 2007/1394/EC on Advanced Therapy Medicinal Products[2].

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[5] Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE RISK-BASED APPROACH ACCORDING TO ANNEX I, PART IV OF DIR. 2001/83/EC APPLIED TO ADVANCED THERAPY MEDICINAL PRODUCTS

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1. INTRODUCTION

The aim of the risk-based approach as defined in Annex I, part IV of Dir. 2001/83/EC is to determine the extent of data required for Marketing Authorisation Application (MAA) for an advanced therapy medicinal product (ATMP). The risk-based approach is based on the identification of risk factors inherent to the nature of the ATMP in question and associated with its quality, safety and efficacy. The risk-based approach as defined in Annex I, part IV of Dir. 2001/83/EC should be distinguished from Risk Management, and the benefit / risk assessment in the context of a marketing authorization evaluation. The risk-based approach, when applied to the development program should be described and justified in Module 2 of the Marketing Authorisation Application dossier.

The risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells, the manufacturing process, and the biological characteristics of used vectors, the properties of protein expression, non-cellular components and the specific therapeutic use of the ATMP. Thus the manufacturing process including in-process testing and batch release testing should be adequate to limit the risk of the ATMP. Nonclinical and clinical testing should further address the identified risk factors.

2. PROBLEM STATEMENT

The guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) and the Note for Guidance on gene transfer medicinal products (CPMP/BWP/3088/99) addressed the manufacturing and quality control as well as non-clinical and clinical development of respectively cell-based medicinal products (which includes somatic cell therapy medicinal products and tissue engineered products) and gene therapy medicinal products. Revision of Annex I part IV of Directive 2001/83/EC, which followed the entry into force of Regulation (EC) No. 1394/2007 for ATMPs, introduced the concept of the risk-based approach. However, no detailed guidance on the practical application of the risk-based approach and the consequences for the product development are available so far. Moreover, there is a necessity to familiarise the stakeholders, future applicants, National Competent Authorities as well as consumer with this concept.

This concept paper is intended to provide the background and rationale of the guideline on the risk-based approach and shall describe the approach and content of the future guideline.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The use of ATMPs may be associated with certain risks, which are linked to several risk factor related to the Quality, biological activity and administration of the ATMP. Individual risk factors shall be discussed in order to enable a conclusion on the overall risk of the ATMP.

A non-exhaustive list of risk factors for cell-based and gene therapy medicinal products is given below:

Cell based medicinal products:

Risk factors, e.g.

- The cells used including cell source, cell type and differentiation status
- All aspects of the manufacturing process including manipulation
- The non-cellular components
- The specific therapeutic use including mode of administration, duration of exposure

The risk factors may be linked with risks such as

- Unwanted immune responses as target or effector cell
- Genetic instability and tumorigenicity of the cells used
- The transmission of viruses and adventitious agents
- Undesired immunogenic, pyrogenic or toxicological reactions by non-cellular components
- Unintended biological responses of the product

Gene therapy medicinal products:

Risk factors, e.g.

- Potential for and extent of chromosomal integration of a vector
- Capacity of a vector/ gene for latency/ reactivation
- Capacity of a vector for inadvertent replication after complementation by viruses causing escape from latency and reactivation and eventually leading to mobilisation
- Replication incompetence or competence of a vector
- Potential for recombination or re-assortment
- Altered expression of (a) host gene(s)
- Transgene expressed and its duration
- Biodistribution
- Potential for shedding and transmission

The risk factors may be linked with risks such as

- Unwanted immune responses
- Tumorigenicity
- Infection
- Unintended biological responses of the product

4. RECOMMENDATION

The CPWP and GTWP recommend drafting a guideline on the application of the risk-based approach for ATMPs. It is proposed that the guideline has two separate sections on aspects specific to cell-based medicinal products and gene therapy medicinal products, respectively. Furthermore aspects regarding combined ATMPs will be addressed.

The guideline is intended to provide an approach on how to identify and describe the risks of an ATMP in the MAA dossier. It is not the intention to provide a rigid classification system of different risks but rather to exemplify the concept by using several examples with different risk profiles (i.e. a genetically modified stem cell product of allogeneic and/or xenogeneic nature or an autologous cell-based product of locally administered differentiated cells).

It is foreseen that the application of the risk-based approach shall follow the following basic steps:

1) **Risk Identification of the ATMP:**

The Applicant is asked to propose a systematic process for the identification and discussion of risks to the quality, safety and efficacy of an ATMP. The risk shall be based on individual risk factors, such as the ones listed above. The Applicant's conclusion on the degree of risk should be thoroughly justified on the basis of scientific data underpinning identified risk factors.

2) **Consequences for the extent of data in the MAA dossier:**

Based on the identification and discussion of the risk of an ATMP, the Applicant should justify the extent of quality, non-clinical and clinical data presented for Marketing Authorisation Application and provide an overview of the implement in the MAA dossier. The extent of data shall take into account the technical requirements for ATMPs as described in Annex I, part IV of Dir. 2001/83/EC. Depending on the risk of the product certain chapters may be emphasised and complemented with additional data, where necessary, or limited when appropriately justified on the basis of the risk.

In order to address these risks, certain minimisation activities need to be conducted and measures implemented during the product lifecycle.

The approach described in this guideline should enable the applicant to establish an adequate development strategy for an ATMP, including but not limited to adequate in-process controls, setting of specifications, non-clinical data and clinical data requirement. These issues will also be illustrated by examples of products with different risk profiles.

Within the MAA dossier, the risk-based approach shall be placed into Module 2 of the Common Technical Document as a supplement to the quality, nonclinical and clinical overall summaries. Further guidance to applicants on the practical aspects of the chapter on the risk-based approach will be provided in the guideline.

5. PROPOSED TIMETABLE

It is anticipated that a draft guideline will be available within 12-18 months after adoption of the concept paper and will be released for 6 months external consultation, before finalization within a further 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The development of a guideline on the risk based approach will be led by CPWP and GTWP (1 common coordinating drafting group) in collaboration with BWP (consulted for quality aspects), with SWP (consulted for non-clinical aspects), with PhVWP (consulted on the complementarity of this approach with the risk analysis and risk management activities in place), and in compliance with directions given by the CAT. Other relevant working parties and relevant scientific committees e.g. PDCO and CHMP and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. The relevant working parties will discuss draft versions at or in the margin of their regular meetings.
Based on the multidisciplinary nature of this revision, it is considered that a minimum of two dedicated face-to-face drafting group meeting will be necessary.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline on the application of the risk-based approach is expected to clarify the process (analysis, methodology, and presentation) of the determination of the extent of data requirements needed for marketing authorisation application of an ATMP. The guideline is also intended to help regulators in the assessment of the MAA dossier. It may contribute to streamline the development, enabling the applicant to establish an adequate development strategy and ultimately marketing authorisation of applications of ATMP via the centralised procedure.

8. INTERESTED PARTIES

Pharmaceutical industry and academic or other developers of ATMPs, academic networks and learned societies involved in the area.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products
- Commission Directive Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.
- Guideline on Human Cell-based Medicinal Products (EMEA/CHMP/410869/2006)
- Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99)
- Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/149995/2008)

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4)(a) thereof,

Having regard to the proposal from the Commission [1],

Having regard to the opinion of the European Economic and Social Committee [2],

Following consultation of the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty [3],

Whereas:

(1) The transplantation of human tissues and cells is a strongly expanding field of medicine offering great opportunities for the treatment of as yet incurable diseases. The quality and safety of these substances should be ensured, particularly in order to prevent the transmission of diseases.

(2) The availability of human tissues and cells used for therapeutic purposes is dependent on Community citizens who are prepared to donate them. In order to safeguard public health and to prevent the transmission of infectious diseases by these tissues and cells, all safety measures need to be taken during their donation, procurement, testing, processing, preservation, storage, distribution and use.

(3) It is necessary to promote information and awareness campaigns at national and European level on the donation of tissues, cells and organs based on the theme 'we are all potential donors'. The aim of these campaigns should be to help European citizens decide to become donors during their lifetime and let their families or legal representatives know their wishes. As there is a need to ensure the availability of tissues and cells for medical treatments, Member States should promote the donation of tissues and cells, including haematopoietic progenitors, of high quality and safety, thereby also increasing self-sufficiency in the Community.

(4) There is an urgent need for a unified framework in order to ensure high standards of quality and safety with respect to the procurement, testing, processing, storage and distribution of tissues and cells across the Community and to facilitate exchanges thereof for patients receiving this type of therapy each year. It is essential, therefore, that Community provisions ensure that human tissues and cells, whatever their intended use, are of comparable quality and safety. The establishment of such standards, therefore, will help to reassure the public that human tissues and cells that are procured in another Member State, nonetheless carry the same guarantees as those in their own country.

(5) As tissue and cell therapy is a field in which an intensive worldwide exchange is taking place, it is desirable to have worldwide standards. The Community should therefore endeavour to promote the highest possible level of protection to safeguard public health regarding quality and safety of tissues and cells. The Commission should include in its report to the European Parliament and to the Council information on the progress made in this respect.

(6) Tissues and cells intended to be used for industrially manufactured products, including medical devices, should be covered by this Directive only as far as donation, procurement and testing are concerned, where the processing, preservation, storage and distribution are regulated by other Community legislation. The further manufacturing steps are covered by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [4].

(7) This Directive should apply to tissues and cells including haematopoietic peripheral blood, umbilical-cord (blood) and bone-marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells and adult and embryonic stem cells.

(8) This Directive excludes blood and blood products (other than haematopoietic progenitor cells) and human organs, as well as organs, tissues, or cells of animal origin. Blood and blood products are currently regulated by

[1] OJ C 227 E, 24.9.2002, p. 505.
[2] OJ C 85, 8.4.2003, p. 44.
[3] Opinion of the European Parliament of 10 April 2003 (not yet published in the Official Journal), Council common position of 22 July 2003 (OJ C 240 E, 7.10.2003, p. 3), position of the European Parliament of 16 December 2003 (not yet published in the Official Journal) and decision of the Council of 2 March 2004.

[4] OJ L 311, 28.11.2001, p. 67. Directive as last amended by Commission Directive 2003/63/EC (OJ L 159, 27.6.2003, p. 46).

Directives 2001/83/EC and 2000/70/EC [1], Recommendation 98/463/EC [2] and Directive 2002/98/EC [3]. Tissues and cells used as an autologous graft (tissues removed and transplanted back to the same individual), within the same surgical procedure and without being subjected to any banking process, are also excluded from this Directive. The quality and safety considerations associated with this process are completely different.

(9) The use of organs to some extent raises the same issues as the use of tissues and cells, though there are serious differences, and the two subjects should therefore not be covered by one directive.

(10) This Directive covers tissues and cells intended for human applications, including human tissues and cells used for the preparation of cosmetic products. However, in view of the risk of transmission of communicable diseases, the use of human cells, tissues and products in cosmetic products is prohibited by Commission Directive 95/34/EC of 10 July 1995 adapting to technical progress Annexes II, III, VI and VII to Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products [4].

(11) This Directive does not cover research using human tissues and cells, such as when used for purposes other than application to the human body, e.g. *in vitro* research or in animal models. Only those cells and tissues that in clinical trials are applied to the human body should comply with the quality and safety standards laid down in this Directive.

(12) This Directive should not interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells. If, however, any particular use of such cells is authorised in a Member State, this Directive will require the application of all provisions necessary to protect public health, given the specific risks of these cells based on the scientific knowledge and their particular nature, and guarantee respect for fundamental rights. Moreover, this Directive should not interfere with provisions of Member States defining the legal term 'person' or 'individual'.

(13) The donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications should comply with high standards of quality and safety in order to ensure a high level of health protection in the Community. This Directive should establish standards for each one of the steps in the human tissues and cells application process.

(14) The clinical use of tissues and cells of human origin for human application may be constrained by limited availability. Therefore it would be desirable that the criteria for access to such tissues and cells are defined in a transparent manner, on the basis of an objective evaluation of medical needs.

(15) It is necessary to increase confidence among the Member States in the quality and safety of donated tissues and cells, in the health protection of living donors and respect for deceased donors and in the safety of the application process.

(16) Tissues and cells used for allogeneic therapeutic purposes can be procured from both living and deceased donors. In order to ensure that the health status of a living donor is not affected by the donation, a prior medical examination should be required. The dignity of the deceased donor should be respected, notably through the reconstruction of the donor's body, so that it is as similar as possible to its original anatomical shape.

(17) The use of tissues and cells for application in the human body can cause diseases and unwanted effects. Most of these can be prevented by careful donor evaluation and the testing of each donation in accordance with rules established and updated according to the best available scientific advice.

(18) As a matter of principle, tissue and cell application programmes should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient. Member States are urged to take steps to encourage a strong public and non-profit sector involvement in the provision of tissue and cell application services and the related research and development.

(19) Voluntary and unpaid tissue and cell donations are a factor which may contribute to high safety standards for tissues and cells and therefore to the protection of human health.

(20) Any establishment may also be accredited as a tissue and cell establishment, provided it complies with the standards.

[1] Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivates of human blood or human plasma (OJ L 313, 13.12.2000, p. 22).

[2] Council Recommendation of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community (OJ L 203, 21.7.1998, p. 14).

[3] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components (OJ L 33, 8.2.2003, p. 30).

[4] OJ L 167, 18.7.1995, p. 19.

(21) With due regard to the principle of transparency, all tissue establishments accredited, designated, authorised or licensed under the provisions of this Directive, including those manufacturing products from human tissues and cells, whether subject or not to other Community legislation, should have access to relevant tissues and cells procured in accordance with the provisions of this Directive, without prejudice to the provisions in force in Member States on the use of tissues and cells.

(22) This Directive respects the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union [1] and takes into account as appropriate the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine. Neither the Charter nor the Convention makes express provision for harmonisation or prevents Member States from introducing more stringent requirements in their legislation.

(23) All necessary measures need to be taken in order to provide prospective donors of tissues and cells with assurances regarding the confidentiality of any health-related information provided to the authorised personnel, the results of tests on their donations, as well as any future traceability of their donation.

(24) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data [2] applies to personal data processed in application of this Directive. Article 8 of that directive prohibits in principle the processing of data concerning health. Limited exemptions to this prohibition principle are laid down. Directive 95/46/EC also provides for the controller to implement appropriate technical and organisational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access and against all other unlawful forms of processing.

(25) An accreditation system for tissue establishments and a system for notification of adverse events and reactions linked to the procurement, testing, processing, preservation, storage and distribution of human tissues and cells should be established in the Member States.

(26) Member States should organise inspections and control measures, to be carried out by officials representing the competent authority, to ensure that tissue establishments comply with the provisions of this Directive. Member States should ensure that the officials involved in inspections and control measures are appropriately qualified and receive adequate training.

(27) Personnel directly involved in the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells should be appropriately qualified and provided with timely and relevant training. The provisions laid down in this Directive as regards training should be applicable without prejudice to existing Community legislation on the recognition of professional qualifications.

(28) An adequate system to ensure the traceability of human tissues and cells should be established. This would also make it possible to verify compliance with quality and safety standards. Traceability should be enforced through accurate substance, donor, recipient, tissue establishment and laboratory identification procedures as well as record maintenance and an appropriate labelling system.

(29) As a general principle, the identity of the recipient(s) should not be disclosed to the donor or his/her family and vice versa, without prejudice to legislation in force in Member States on the conditions of disclosure, which could authorise in exceptional cases, notably in the case of gametes donation, the lifting of donor anonymity.

(30) In order to increase the effective implementation of the provisions adopted in accordance with this Directive, it is appropriate to provide for penalties to be applied by Member States.

(31) Since the objective of this Directive, namely to set high standards of quality and safety for human tissues and cells throughout the Community, cannot be sufficiently achieved by the Member States and can therefore, by reason of scale and effects, be better achieved at Community level, the Community may adopt measures in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty. In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve that objective.

(32) It is necessary that the best possible scientific advice is available to the Community in relation to the safety of tissues and cells; in particular in order to assist the Commission in adapting the provisions of this Directive to scientific and technical progress in the light of the rapid advance in biotechnology knowledge and practice in the field of human tissues and cells.

[1] OJ C 364, 18.12.2000, p. 1.
[2] OJ L 281, 23.11.1995, p. 31. Directive as amended by Regulation (EC) No 1882/2003 (OJ L 284, 31.10.2003, p. 1).

(33) The opinions of the Scientific Committee for Medicinal Products and Medical Devices and that of the European Group on Ethics in Science and New Technologies have been taken into account, as well as international experience in this field, and will be sought in the future whenever necessary.

(34) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1],

HAVE ADOPTED THIS DIRECTIVE:

CHAPTER I

GENERAL PROVISIONS

Article 1

Objective

This Directive lays down standards of quality and safety for human tissues and cells intended for human applications, in order to ensure a high level of protection of human health.

Article 2

Scope

1. This Directive shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications.

Where such manufactured products are covered by other directives, this Directive shall apply only to donation, procurement and testing.

2. This Directive shall not apply to:

(a) tissues and cells used as an autologous graft within the same surgical procedure;

(b) blood and blood components as defined by Directive 2002/98/EC;

(c) organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body.

[1] OJ L 184, 17.7.1999, p. 23.

Article 3

Definitions

For the purposes of this Directive:

(a) 'cells' means individual human cells or a collection of human cells when not bound by any form of connective tissue;

(b) 'tissue' means all constituent parts of the human body formed by cells;

(c) 'donor' means every human source, whether living or deceased, of human cells or tissues;

(d) 'donation' means donating human tissues or cells intended for human applications;

(e) 'organ' means a differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with an important level of autonomy;

(f) 'procurement' means a process by which tissue or cells are made available;

(g) 'processing' means all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications;

(h) 'preservation' means the use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues;

(i) 'quarantine' means the status of retrieved tissue or cells, or tissue isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection;

(j) 'storage' means maintaining the product under appropriate controlled conditions until distribution;

(k) 'distribution' means transportation and delivery of tissues or cells intended for human applications;

(l) 'human application' means the use of tissues or cells on or in a human recipient and extracorporal applications;

(m) 'serious adverse event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity;

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

(o) 'tissue establishment' means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;

(p) 'allogeneic use' means cells or tissues removed from one person and applied to another;

(q) 'autologous use' means cells or tissues removed from and applied in the same person.

Article 4

Implementation

1. Member States shall designate the competent authority or authorities responsible for implementing the requirements of this Directive.

2. This Directive shall not prevent a Member State from maintaining or introducing more stringent protective measures, provided that they comply with the provisions of the Treaty.

In particular, a Member State may introduce requirements for voluntary unpaid donation, which include the prohibition or restriction of imports of human tissues and cells, to ensure a high level of health protection, provided that the conditions of the Treaty are met.

3. This Directive does not affect the decisions of the Member States prohibiting the donation, procurement, testing, processing, preservation, storage, distribution or use of any specific type of human tissues or cells or cells from any specified source, including where those decisions also concern imports of the same type of human tissues or cells.

4. In carrying out the activities covered by this Directive, the Commission may have recourse to technical and/or administrative assistance to the mutual benefit of the Commission and of the beneficiaries, relating to identification, preparation, management, monitoring, audit and control, as well as to support expenditure.

CHAPTER II

OBLIGATIONS ON MEMBER STATES' AUTHORITIES

Article 5

Supervision of human tissue and cell procurement

1. Member States shall ensure that tissue and cell procurement and testing are carried out by persons with appropriate training and experience and that they take place in conditions accredited, designated, authorised or licensed for that purpose by the competent authority or authorities.

2. The competent authority or authorities shall take all necessary measures to ensure that tissue and cell procurement complies with the requirements referred to in Article 28(b), (e) and (f). The tests required for donors shall be carried out by a qualified laboratory accredited, designated, authorised or licensed by the competent authority or authorities.

Article 6

Accreditation, designation, authorisation or licensing of tissue establishments and tissue and cell preparation processes

1. Member States shall ensure that all tissue establishments where activities of testing, processing, preservation, storage or distribution of human tissues and cells intended for human applications are undertaken have been accredited, designated, authorised or licensed by a competent authority for the purpose of those activities.

2. The competent authority or authorities, having verified that the tissue establishment complies with the requirements referred to in Article 28(a), shall accredit, designate, authorise or license the tissue establishment and indicate which activities it may undertake and which conditions apply. It or they shall authorise the tissue and cell preparation processes which the tissue establishment may carry out in accordance with the requirements referred to in Article 28(g). Agreements between tissue establishments and third parties, as referred to in Article 24, shall be examined within the framework of this procedure.

3. The tissue establishment shall not undertake any substantial changes to its activities without the prior written approval of the competent authority or authorities.

4. The competent authority or authorities may suspend or revoke the accreditation, designation, authorisation or licensing of a tissue establishment or of a tissue or cell preparation process if inspections or control measures demonstrate that such an establishment or process does not comply with the requirements of this Directive.

5. Some specified tissues and cells, which will be determined in accordance with the requirements referred to in Article 28(i), may, with the agreement of the competent authority or authorities, be distributed directly for immediate transplantation to the recipient as long as the supplier is provided with an accreditation, designation, authorisation or licence for this activity.

Article 7

Inspections and control measures

1. Member States shall ensure that the competent authority or authorities organise inspections and that tissue establishments carry out appropriate control measures in order to ensure compliance with the requirements of this Directive.