4. in Article 6(1), the first subparagraph shall be replaced by the following:

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1394/2007.'

Article 29

Transitional period

1. Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

2. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.

3. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in paragraphs 1 and 2 of this Article.

Article 30

Entry into force

This Regulation shall enter into force on the 20th day following its publication in the *Official Journal of the European Union.*

It shall apply from 30 December 2008.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Strasbourg, 13 November 2007.

For the European Parliament
The President
H.-G. PÖTTERING

For the Council
The President
M. LOBO ANTUNES

ANNEX I

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.

ANNEX II

Summary of product characteristics referred to in Article 10

1. Name of the medicinal product.

2. Composition of the product:

2.1. general description of the product, if necessary with explanatory drawings and pictures,

2.2. qualitative and quantitative composition in terms of the active substances and other constituents of the product, knowledge of which is essential for proper use, administration or implantation of the product. Where the product contains cells or tissues, a detailed description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin, shall be provided,

For a list of excipients, see point 6.1.

3. Pharmaceutical form.

4. Clinical particulars:

4.1. therapeutic indications,

4.2. posology and detailed instructions for use, application, implantation or administration for adults and, where necessary, for children or other special populations, if necessary with explanatory drawings and pictures,

4.3. contra-indications,

4.4. special warnings and precautions for use, including any special precautions to be taken by persons handling such products and administering them to or implanting them in patients, together with any precautions to be taken by the patient,

4.5. interaction with other medicinal products and other forms of interactions,

4.6. use during pregnancy and lactation,

4.7. effects on ability to drive and to use machines,

4.8. undesirable effects,

4.9. overdose (symptoms, emergency procedures).

5. Pharmacological properties:

5.1. pharmacodynamic properties,

5.2. pharmacokinetic properties,

5.3. preclinical safety data.

6. Quality particulars:

6.1. list of excipients, including preservative systems,

6.2. incompatibilities,

6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

6.4. special precautions for storage,

6.5. nature and contents of container and special equipment for use, administration or implantation, if necessary with explanatory drawings and pictures,

6.6. special precautions and instructions for handling and disposal of a used advanced therapy medicinal product or waste materials derived from such product, if appropriate and, if necessary, with explanatory drawings and pictures.

7. Marketing authorisation holder.

8. Marketing authorisation number(s).

9. Date of the first authorisation or renewal of the authorisation.

10. Date of revision of the text.

ANNEX III

Labelling of outer/immediate packaging referred to in Article 11

(a) The name of the medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults; the international non-proprietary name (INN) shall be included, or, if the product has no INN, the common name;

(b) A description of the active substance(s) expressed qualitatively and quantitatively, including, where the product contains cells or tissues, the statement 'This product contains cells of human/animal [as appropriate{] origin' together with a short description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin;

(c) The pharmaceutical form and, if applicable, the contents by weight, by volume or by number of doses of the product;

(d) A list of excipients, including preservative systems;

(e) The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, space shall be provided for the prescribed dose to be indicated;

(f) A special warning that the medicinal product must be stored out of the reach and sight of children;

(g) Any special warning necessary for the particular medicinal product;

(h) The expiry date in clear terms (month and year; and day if applicable);

(i) Special storage precautions, if any;

(j) Specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;

(k) The name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him;

(l) Marketing authorisation number(s);

(m) The manufacturer's batch number and the unique donation and product codes referred to in Article 8(2) of Directive 2004/23/EC;

(n) In the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement 'For autologous use only'.

ANNEX IV

Package leaflet referred to in Article 13

(a) For the identification of the advanced therapy medicinal product:

(i) the name of the advanced therapy medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults. The common name shall be included;

(ii) the therapeutic group or type of activity in terms easily understandable for the patient;

(iii) where the product contains cells or tissues, a description of those cells or tissues and of their specific origin, including the species of animal in cases of non-human origin;

(iv) where the product contains medical devices or active implantable medical devices, a description of those devices and their specific origin;

(b) The therapeutic indications;

(c) A list of information which is necessary before the medicinal product is taken or used, including:

(i) contra-indications;

(ii) appropriate precautions for use;

(iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;

(iv) special warnings;

(v) if appropriate, possible effects on the ability to drive vehicles or to operate machinery;

(vi) the excipients, knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65 of Directive 2001/83/EC.

The list shall also take into account the particular condition of certain categories of users, such as children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions;

(d) The necessary and usual instructions for proper use, and in particular:

(i) the posology;

(ii) the method of use, application, administration or implantation and, if necessary, the route of administration;

and, as appropriate, depending on the nature of the product:

(iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;

(iv) the duration of treatment, where it should be limited;

(v) the action to be taken in case of an overdose (such as symptoms, emergency procedures);

(vi) information on what to do when one or more doses have not been taken;

(vii) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;

(e) A description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly asked to communicate any adverse reaction which is not mentioned in the package leaflet to his doctor or pharmacist;

(f) A reference to the expiry date indicated on the label, with:

(i) a warning against using the product after that date;

(ii) where appropriate, special storage precautions;

(iii) if necessary, a warning concerning certain visible signs of deterioration;

(iv) the full qualitative and quantitative composition;

(v) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;

(vi) the name and address of the manufacturer;

(g) The date on which the package leaflet was last revised.

European Medicines Agency

London, 11 January 2007
Doc. Ref. EMEA/CHMP/410869/2006

COMMITTEE FOR HUMAN MEDICINAL PRODUCT (CHMP)

DRAFT

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

DRAFT AGREED BY CPWP AND BWP	December 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	25 January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2007

This guideline replaces guideline CPMP/BWP/41450/98 Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products.

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KEYWORDS	Human cell-based medicinal products, quality and manufacturing aspects, Non-clinical development, Clinical development.

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

This guideline is replacing the existing CPMP Points to Consider on somatic cell therapy products. It takes into account the current legislation (including the Directive 2004/23/EC on Tissues and Cells and the technical directives drawn from it) and the heterogeneity of human cell-based products, including combination products. A risk analysis approach can be used by the applicants to justify the development and evaluation plans and can be a basis for the preparation of a risk management plan.

In the quality and manufacturing section, guidance is provided on the criteria and testing of all starting materials, on the design and validation of the manufacturing process, on characterisation of the human cell-based medicinal products, on quality control aspects, on the development programme, traceability and biovigilance and on comparability issues. Guidance specific to the matrix/device/scaffold component in combination products is provided.

The guideline acknowledges that conventional non-clinical pharmacology and toxicology studies may not be appropriate for cell-based medicinal products. Therefore the guideline addresses what non-clinical studies are relevant to demonstrate proof-of-principle, define the pharmacological and toxicological effects predictive of the human response.

The clinical development of human cell-based medicinal products might be associated with special problems. Guidance is therefore provided on the conduct of pharmacodyanamic/pharmacokinetic studies, dose finding and clinical efficacy and safety studies. Special consideration should be given to pharmacovigilance aspects and the risk management plan for these products.

1. INTRODUCTION (background)

Rapid development in the fields of biology, biotechnology and medicine has led to development of new treatments and highly innovative medicinal products, including medicinal products containing viable cells. These new cell-based medicinal products have a high potential in the treatment of various diseases where there is a high unmet medical need.

Human cell-based medicinal products are heterogeneous with regard to the origin and type of the cells and to the complexity of the product. Cells may be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells exerting a specific defined physiological function. Cells may be of autologous or allogeneic origin. In addition, the cells may also be genetically modified. The cells may be used alone or associated with biomolecules, chemical substances and combined with structural materials that alone might be classified as medical devices (combination products).

2. SCOPE

This multidisciplinary guideline will address development, manufacturing and quality control as well as non-clinical and clinical development of cell-based medicinal products. This guideline is intended for products entering the MA procedure. However, the principles laid down in the guideline should be taken into consideration of applicants entering into the clinical trials.

Cell-based medicinal products (CBMP) discussed in this document have the following characteristics:

- They contain viable human cells[1] of allogeneic or autologous origin undergoing a manufacturing process;
- They may be combined with non-cellular components;
- The cells might be genetically modified.

Although this document does not cover non-viable cells and cellular fragments originating from human cells, the underlying scientific principles may be applicable. This guideline does not cover cell-based medicinal product containing xenogeneic cells.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and part 4 of the Annex I to Directive 2001/83[2] as amended.

Also, procurement and testing of cells from human origin must comply with overarching Directive 2004/23/EC[3] and technical directives drawn from it.

4. MAIN GUIDELINE TEXT

4.1 Risk analysis

The risk posed by the administration of a cell-based medicinal product is highly dependent on the origin of the cells, the manufacturing process, the non-cellular components and on the specific therapeutic use. The variety of cell-based medicinal products can lead to very different levels of risks for the patients, the medical personnel or the general population. This heterogeneity means that the development plans and evaluation requirements need to be adjusted according to a multifactorial risk analysis.

An initial risk analysis may be performed based on existing knowledge of the type of product and its intended use. This should be updated by the applicant throughout the product life cycle as data are collected to further characterise the risk. The risk analysis should be used to justify the product development and evaluation plans and as a basis for the preparation of a risk management plan in accordance with the EMEA guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005). In particular, the results of the risk analysis should be used:

- to identify risk factors associated with the quality and safety of the product
- to determine the extent and focus of the data required during non-clinical and clinical development;
- to establish the need for risk minimisation activities,
- to determine the post market risk management activities to be specified in the pharmacovigilance plan.

The following general risk criteria can be used in the estimation of the overall risk of the product:

- origin (autologous-allogeneic);
- ability to proliferate and differentiate;
- ability to initiate an immune response (as target or effector);
- level of cell manipulation (in vitro/ex vivo expansion/activation/genetic manipulation);
- mode of administration (ex vivo perfusion, local, systemic);
- duration of exposure (short to permanent);
- combination product (cells + bioactive molecules or structural materials)
- availability of clinical data on or experience with similar products.

4.2 Quality and manufacturing aspects

This part of the guideline describes activities by manufacturers after receipt of cells from tissue establishments.

Cell-based medicinal products (CBMP) often involve cell samples of limited amount, mostly to be used in a patient-specific manner. This will raise specific issues pertaining to quality control testing designs for each product under examination. Since this document covers a large variety of CBMP,

processes involved can vary from very simple to highly complex. Therefore, for certain cell-based medicinal products, the starting material, the active substance and the finished product can be closely related or nearly identical. Consequently some requirements listed below could be inadequate for the product in question and in that case only relevant sections and items should be addressed.

4.2.1 Starting and raw materials

Since the manufacturing process of CBMP usually does not include terminal sterilisation, stringent purification steps and viral removal or inactivation steps, acceptance criteria for all materials, especially those derived from human or animal origin, should be adequately defined according to the intended use.

1. Cells

The active substance of a CBMP can be defined as viable cells after manipulation with or without other starting materials, i.e. the non-cellular components (e.g. matrix, device) and/or other materials and reagents (e.g. growth factors, serum).

Donated cellular material from single or pooled donors, once processed (see 4.2.2.1) may be:

- A single primary cell isolate used directly for cell-based product;
- Primary cells cultured for a few passages before being used for the CBMP;
- Cells based on a well-defined cell bank system consisting of a master cell bank and a working cell bank.

An adequately controlled cell storage system should be established to allow proper storage, retrieval and supply of cells without any alteration of their intended final characteristics. The cells should be stored under controlled and optimal conditions, to ensure cell viability, density, purity, sterility and function. Identity should be verified by relevant genotypic and phenotypic markers and the proportion of cells bearing these identity markers evaluated as an indicator of a homogeneous population.

1.1 Cells from primary origin

The quality criteria for the sourcing must meet the requirements of Directive 2006/17/EC[4].

Procedures and standards employed for the selection of appropriate donors and the exclusion of high-risk or otherwise unsuitable candidates should be clearly delineated and justified. If it is necessary to pool cells from different donors, consideration should be given to the possibility that pooling of allogeneic cell populations may increase the risk of undesired immunological responses in the recipient and compromise its therapeutic activity. In addition, pooling of cells from different donors may increase the risk of disease transmission. Depending on the nature of the source of the cells and tissues, other risk factors, e.g. previous radiation exposure, should be also considered and appropriate testing should be performed.

On receipt of the cells for use in a medicinal product, a specific virological screening programme should be in place, adapted to the type of cells, with validated assays capable of detecting human infectious agents with appropriate sensitivity. The starting materials should also be screened by direct culture for bacteria, fungi and mycoplasma. When cells intentially originate from non-healthy tissues (e.g. tumour tissues) , the product specific acceptance criteria should be defined according to the intended use.

Quality parameters aimed at the definition of acceptance criteria for a given organ or tissues should be set, taking into consideration shipment and storage conditions.

In the case of autologous donation, the testing regimen of the starting material should be justified taking into account the autologous use.

1.2. Banking system for established cell lines

Where cell lines are used, a well characterised Master Cell Bank (MCB) and Working Cell Bank (WCB) should be established. Cell banking and characterisation and testing of the established cell banks should comply with the ICH guideline Q5D[5].

2. Other materials and reagents

Various materials are needed for collection, selection, culture or even genetic or phenotypic modification of cells, such as other cells, enzymes, antibodies, cytokines, sera and antibiotics. Exposure to such materials can also compromise the quality, safety and efficacy of the final product. As a consequence, each substance used in the procedure should be clearly specified and evaluated as to its suitability for the intended use. The sterility, absence of contaminating agents and low endotoxin level of these products should be ensured. Materials, including cells that function as support for growth and adhesion in the form of a neo-organ or immuno-isolator should be evaluated and/or validated as to their suitability for the intended use.

Quality of biologically active additives in culture media such as growth factors, cytokines and antibodies, should be documented with respect to identity, purity, sterility and biological activity and absence of adventitious agents. It is recommended to avoid use of reagents with sensitisation potential.

For viral safety aspects, information stated in Eudralex vol. 2B[6], should be taken into consideration. The principles laid down in the general text of the European Pharmacopoeia on viral safety should be followed for every substance of animal origin that participates in the production.

Where appropriate, the Note for Guidance on the "Production and quality control of medicinal products derived by recombinant DNA technology"[7] and the Note for Guidance on the "Production and quality control of Monoclonal Antibodies"[8] should be taken into account.

When the products have a marketing authorisation, are CE marked or mentioned in a pharmacopoeia, appropriate references may be given.

The following information must be added for materials of human or animal origin:

2.1 Human derived materials

Reagents of human origin (e.g. albumin, immunoglobulins) should be evaluated for their suitability in a manner identical to that employed for plasma-derived products as recommended in the CPMP Note for guidance on plasma-derived medicinal products[9]. Measures should be taken to reduce the risk of transmissible spongiform encephalophaties according to the relevant European legislation and guidelines. The use of synthetic media is recommended. If serum is required in the culture media, the use of serum isolated from the same individual who donated the cells is preferred, where possible, to alternate allogeneic serum.

2.2. Animal derived material

Where cells or tissues of animal origin are used e.g. as supportive cells, the guidance given in "Points to consider on Xenogeneic Cell Therapy Medicinal Products"[10] should be followed.

Animal derived reagents may harbour infectious agents and may increase undesirable immunological responses in the recipient. When applicable, the use of animal reagents should be avoided and replaced by non animal derived reagents of defined composition.

The use of bovine, ovine or caprine derived agents should conform to the CPMP and CVMP Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products[11].

When bovine serum is used, the recommendations of the Note for Guidance on the "Use of Bovine Serum in the Manufacture of Human Biological Medicinal Product"[12] should be followed. The use of irradiated sera and/or alternative synthetic media is encouraged and should be considered.

For viral safety testing of materials of other animal species, the table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines[13] and Note for Guidance on Production and Quality Control of Animal Immunoglobulins and Immunesera for Human use[14] should be consulted.

3. Special considerations

3.1. Special recommendations for the starting materials of combined Gene Therapy / Cell Therapy products

When the cells in the active substance are genetically modified, the "Note for Guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products"[15] should be followed, which gives details on the quality control, characterisation and preclinical testing of gene transfer vectors. Cell populations which are transformed should be assayed for appropriate and reproducible expression of the newly acquired characteristics. Special attention should be paid on the level of expression and quality of the gene product(s) produced by the cells. As far as applicable and practicable, the new characteristics should be quantified and controlled.

3.2. Special recommendations for matrix/device/scaffold components of combination products

Cell-based medicinal products may incorporate structural components which are medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Directive 93/42/EEC[16] concerning medical devices and Directive 90/385/EEC[17] on the approximation of the laws of the Member States relating to active implantable medical devices, respectively. Furthermore, if the device part has been evaluated by a Notified Body, the assessment report together with all relevant information of the device should be provided for evaluation. Cell-based medicinal products may also incorporate structural components which are not identical to, or used in the same way as in a medical device. All structural components should be fully characterised and evaluated for their suitability for the intended use (See sections on Characterisation and Development Pharmaceutics).

Any matrices, fibres, beads, or other materials that are used in addition or combined to the cells should be described and their function underpinned by means of chemical, biological, physical (e.g. structure and degradation) and mechanical properties. Inclusion of additional bioactive molecules should also be described and their impact should be evaluated.

Additional product specific information of suitability of the matrix/device/scaffold of the cell-based product for the intended use should be provided.

4.2.2 Manufacturing process

The manufacture of cell-based medicinal products should be carefully designed and validated to ensure product consistency. The consistency specifications should be defined and justified.

The manufacturing area should be physically separated from the area where biological fluids, tissues or organs are collected/procured. If diverse tissues and cellular products are collected, processed and stored in the same manufacturing area there is an increased risk of cross contamination during each step of the procedure, e.g. via processing equipment or in storage containers such a liquid nitrogen tanks, and therefore, adequate control measures to prevent cross-contamination should be put in place.

Equipment and premises used for manufacturing of CBMP should be suitable and validated for aseptic production. It is recommended that dedicated, product-specific or single-use equipment are used in the

production, whenever possible. If the same equipment is used for production of e.g. multiple autologous products, sanitation and sterilisation procedures should be described and validated.

A detailed description of the manufacture of the active substance and of the finished product should be provided. The type of manipulation(s) required for cell processing and the physiological function of the cells shall be described. A flow diagram of the entire process starting from biological fluid/tissue/organ or from cell banks should be prepared indicating critical steps and intermediate products (e.g. intermediate cell batches), as well as operating parameters, in-process controls and acceptance criteria. Manufacture of combined medicinal products consisting of cells and matrices/devices/scaffolds, require additional consideration regarding the cell-matrix/scaffold interactions and quality issues raised there from. Attention should be paid on biodegradable materials which may possess the potential for environmental changes (e.g. raising pH) for the cells during the manufacture or after administration.

Information on procedures used to transport material during the manufacturing process of the product, including transportation and storage conditions and holding times, should be provided.

1. Cell preparation procedures

All cell preparation procedures should be justified in terms of their intended purpose.

Inappropriate handling and improper processing of cells/tissues must be avoided as they can impair or destroy the integrity and/or function of the cells and thus result in therapeutic failure. Microbiological control is a pivotal aspect of process control and quality evaluation of all cell preparations. Monitoring of in vitro cell culturing should include tests for the absence of adventitious agents, at selected stages of the production. The culture should be examined for any microbial contamination in accordance with the culturing procedure and growth characteristics of the cells.

After appropriate controls have been performed/implemented, the biological fluid/tissue /organ can undergo one or more of the following steps:

1.1. Organ/tissue dissociation

The procedure to obtain the cells from the organ/tissue has to be described (type of enzyme, media, etc.) and validated. Consideration should be given to the degree of disruption applied to the tissue in order to preserve functional integrity of the cellular preparation and minimize cell-derived impurities in the product (cell debris, cross contamination of other cell types). Special consideration should be given to reagent-derived adventitious agents.

1.2. Isolation of the cell population of interest

Any procedure used to isolate and / or purify the cell population of interest should be described. Its effectiveness should be addressed in relation to the intended use and the method(s) should be validated.

1.3. Cell culture

During in vitro cell culture, consideration should be given to ensure optimal growth and manipulation of the isolated cells. The processing steps should be properly designed to preserve the integrity and control the function of the cells. The procedures for any manipulation should be documented in detail and closely monitored according to specific process controls. Duration of cell culture and maximum number of cell passages should be clearly specified and/or validated. The relevant genotypic and phenotypic traits of the primary cell cultures, of the established cell lines and the derived cell clones should be defined and their stability with respect to culture longevity determined. Consistency/repeatability of the cell culture process should be demonstrated and the culture conditions including the media and the duration should be optimised with respect to the intended clinical function of the cells.

Special consideration should be given to the growth potential of cells in response to growth factors since cell subpopulations may gain a growth advantage under defined in vitro culturing conditions.

1.4. Cell modification

Various treatments (physical, chemical or genetic) can be applied to cells. The method used to modify the cells should be fully described. In the case of genetic modification of cells, requirements set up in the Note for guidance on Quality, preclinical and clinical aspects of gene transfer medicinal products[15] should be followed.

1.5. Cells cultured in or on a matrix/device/scaffold

If the cells are grown directly inside or on a matrix/device/scaffold, the quality of the combined product relies predominantly on the properly controlled manufacturing process. For such products, the cell culture process has to be thoroughly validated and the effect of the device on the cell growth, function and integrity has to be taken into account.

2. In-process controls

The manufacturing process needs to be controlled by several in-process controls at the level of critical steps or intermediate products. Intermediate cell products are products that can be isolated during the process; specifications of these products should be established in order to assure the reproducibility of the process and the homogeneity of the final product. Tests and acceptance criteria should be described. If storage occurs, it is necessary to validate storage conditions (e.g. time, temperature).

3. Batch definition

The purpose of the batch definition is to ensure consistency and traceability. A clear definition of a production batch from cell sourcing to labelling of final container should be provided (i.e. size, number of cell passages/cell duplications, pooling strategies, batch numbering system). In the autologous setting, the manufactured product should be viewed as a batch.

4. Container and closure system

A description of the container closure system should be provided. Compatibility with the product should be demonstrated. It should be indicated if the container closure has a CE marking under the Medicinal Devices Directive 93/42/CEE[16]. Information on the sterilisation procedures of the container and the closure should be provided.

4.2.3 Characterisation

The characterisation of a CBMP should encompass all the components present in the finished product. Characterisation may prove particularly challenging for products containing cells together with matrices, scaffolds and innovative devices. Characterisation data are likely to be necessary for single components as well as the combined final product. Characterisation data could encompass data obtained throughout the development and/or manufacturing process. It should be noted that in a combined product the characteristics of both the cellular and the non-cellular components may be altered by the process of integration.

An extensive characterisation of the cellular component should be established in terms of identity, purity, potency and suitability for the intended use, unless justified.

The expected biological function of a CBMP encompasses complex interactions that may range from a biochemical, metabolic or immunological action to the structural replacement of damaged tissue or organ. Therefore, the requirements for a complete characterisation of the active substance in terms of biological function could be very taxing. Moreover the specific mechanism of action is often difficult

to pinpoint to specific molecular entity but it is more dependent on the functionality of the cellular components acting in a "tissue-like" fashion as a whole. Therefore, when considering the extent of characterisation, the following issues should be taken into account: i) autologous cells vs. allogeneic cells, ii) extensively or minimally manipulated in vitro, iii) immunologically active or neutral, iv) proliferative capacity of the cells, v) cell-like or tissue-like organisation and dynamic interactions amongst cells and with the structural component, vi) intended use.

Non-cellular components should be characterised in the context of their required function in the finished product. This includes structural components designed to support the cellular components such as scaffolds or membranes which should be identified and characterised in chemical and physical terms such as porosity, density, microscopic structure and particular size according to the type of substances and intended use according to EN/ISO 10993-18[18] and EN/ISO 10993-19[19].

The characterisation should be designed to allow setting up the routine controls that will be applied for release of the active substance and finished product as well as those to be performed at several steps of the process to guarantee batch consistency.

If biologically active molecules are present as components of the cell-based products, these have to be described fully and their interaction with the other components of the product and the surrounding tissues after administration should be characterised. This should involve an appropriate range of *in vitro* and where necessary *in vivo* methods.

1. Identity

1.1. Cellular Component

The identity of the cellular components, depending on the cell population and origin, should be characterised in terms of phenotypic and genotypic profiles.

When addressing the phenotype of the cells, relevant markers should be used. These markers may be based on gene expression, antigen presentation, biochemical activity, response to exogenous stimuli, capability to produce biologically active or otherwise measurable molecules, etc. For adherent cells, morphological analysis may be a useful tool in conjunction with other tests.

Where applicable, a description of the procedures which could lead to a modification of the characteristic of the product, including adhesion, absorption, degradation, presentation of components of the culture media, should be provided.

For cellular components of allogeneic origin, identity should include histocompatibility markers and/or genetic markers with specific reference to the intended use.

1.2. Non-cellular Component

All non-cellular components should be fully characterised as such and identity parameters established.

Should the finished product contain a distinct active substance in addition to the cellular component, then that active substance should be characterised with respect to identity in accordance to relevant CHMP guidelines, depending on the nature of the active substance, whether it be of chemical or biological origin.

Structural components designed to support the cellular components such as scaffolds or membranes should be identified and characterised with respect to their composition and structural characteristics.

1.3. Combined Products

In a combined product the active substance may be formed by the integration of cellular and non-cellular components to form a single entity. In such a case the identity of both the cellular and the non-cellular components may be altered by the process of combination. Consequently a distinct way to define identity should be established for the combination.

2. Cell purity

The cellular population of interest could contain other cells that are of different lineages or differentiation stage from the required population or with cells unrelated to the intended population.

Where a specific cell type is required for the indication, the unwanted cells should be defined and their amount in the final product should be controlled by appropriate specifications, i.e. acceptance criteria for the amounts of contaminating cells should be set.

In cases, where the desired biological activity and efficacy of the product requires a complex mixture of cells, the cell mixture needs to be characterised and its composition needs to be controlled by appropriate in-process controls and release testing.

Irrespective to cell type, the cell population can be contaminated with non-viable cells. Since cell viability is an important parameter for product integrity and directly correlated to the biologic activity, the ratio between non-viable and viable cells should be determined and specifications should be set.

3. Impurities

3.1. Product or process-related

During the production of a CBMP, variable amounts of impurities, product- and process-related, may be introduced into the final product. Any reagents known to be harmful in humans should be analysed in the final product (or in individual components if otherwise not possible) and acceptance criteria should be set. The specification limits should be justified by levels detected in batches used for toxicological and/or clinical studies.

Any material capable to introduce degradation products into the product during the production and/or after administration, e.g. biodegradable materials, should be thoroughly characterised in this respect and the impact of the degradation products to the cell component(s) should be addressed.

If genetically modified cells are used in the product, any additional proteins expressed from the vector, e.g. antibiotic resistance factors, selection markers etc., should be analysed and their presence in the product should be justified.

3.2 Adventitious agents

A critical aspect is to establish that CBMP are free from adventitious microbial agents (viruses, mycoplasma, bacteria, fungi). The contamination could originate from the starting or raw materials (see above), or adventitiously introduced during the manufacturing process. A risk assessment should be performed to evaluate the possibility of reactivation of cryptic (integrated, quiescent) forms of adventitious agents. A thorough testing for the absence of bacteria, fungi and mycoplasma shall be performed at the level of finished product. These tests should be performed with the current methodologies described in the European pharmacopoeia (Ph. Eur.)

Although CBMP are excluded from the scope of the ICH Q5A Guideline on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Product Derived From Cell Lines in of human or animal origin[20], applicants may consult this guideline.

4. Potency

According to the ICH guideline 6QB[21], potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties

The assay demonstrating the biological activity should be based on the intended biological effect which should ideally be related to the clinical response.

Preferably, a suitable potency assay should be in place already when material for the first clinical trial is produced and it should be validated prior to pivotal clinical trials unless otherwise justified. Lot

release and shelf life specifications for potency should be determined and amended during product development, as appropriate. It is strongly recommended that the development of a suitable potency assay be started as soon as possible.

Basically, two types of potency assays can be envisioned: 1) *in vitro* assays using cell systems and 2) *in vivo* assays using animal models. Major cellular functions as viability, self renewal, death and differentiation are pivotal to the quality, function and sustainability of the CBMP and must be monitored constantly using surrogate markers and appropriate technology (e.g. gene expression profiles by microarrays, flow cytometric immunofluorescent analysis, cell cloning, PCR and many others). In vivo assays for potency may also be useful especially when experimental animal models are available.

Reference is made to the Guideline on "Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer"[22]. Although this guideline focuses on cell-based immunotherapy medicinal products, the principles, including on reference preparations, apply for all CBMP.

4.1 Tissue repair and regeneration

An *in vivo* test can either be performed in an animal model mimicking the intended clinical tissue repair/ regeneration or can otherwise be based on the mode of action (e.g. an ectopic model). The potency assay should be performed by using a validated number of cells and when possible quantified against a qualified reference preparation. The potency should be defined as the required time to obtain a predefined effect (e.g. restoration of function or repair of anatomical structure) or the potency is calculated from the measured effect in a defined time period. An *in vitro* assay can be based on the expression of markers that have been demonstrated to be directly or indirectly (surrogate markers) correlated to the intended biological activity, such as cell surface markers, activation markers, expression pattern of specific genes. Also a physiological response under defined conditions such as differentiation in specific cell types and/or secretion of tissue specific proteins (e.g. extracellular matrix components) can be used as a basic principle for a potency test.

4.2. Metabolic or pharmacological activity

Cells contained in a CBMP can be chemically treated or genetically modified *in vitro* to express certain desirable proteins like growth factors, cell surface antigens or other molecules in order to sustain the biological response as long as needed in the new microenvironment. Therefore, the potency assays to be developed should be able to assess the activity-related aspects of the active substance that may be composed not entirely of intact viable cells but also of other components.

If the intended biological function of the CBMP is mainly based on the capacity of cells to secrete specific molecule(s) e.g. to repair a metabolic disorder, to promote growth, to release a metabolite, then its potency assay will be based on the detection of the active molecule(s) produced and the biological activity expected. This will be easily carried out by conventional reliable qualitative and quantitative analytical methods (protein analysis, nucleic acid identification, HPLC chromatography etc.). The same molecule can be also assessed for function in animal model systems assuming that the active substance is released from the cell-based medicinal product into biological fluids (plasma, CSF, urine or interstitial fluid).

4.3. Immunotherapy

Potency assays of cell-based medicinal products intended for immunotherapeutic use will be based on complex immune mechanisms which may be complicated by multi-antigen formulations and inherent variability of the starting material. Special guidance for cell-based immunotherapy medicinal products is provided in Guideline on "Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer"[22].

5. Tumourigenicity

The tumourigenicity of CBMP differs from the classical pharmaceutics as the transformation can also happen in the cellular component of the product and not only in the treated individual. Thus, the

cellular components should be evaluated for their tumourigenic potential by analysing e.g. proliferative capacity, dependence on the exogenous stimuli, response to apoptosis stimuli and genomic modification.

Karyology and tumourigenicity testing of cells derived from a cell culture / cell banking system may be required. Reference is made to the ICH Q5D[23] and to Ph. Eur. Monograph on vaccines for human use, Section 5.2.3. Cell substrates for the production of vaccines for human use[24]

4.2.4 Quality control

For proper quality control, the active substance and/or the final product should be subjected to release testing, whenever possible. If justified, it would be acceptable to have reduced testing at one level provided an exhaustive control is performed at the other.

All release testing should be performed using methods validated at the latest at the time of submission of an application.

1. Release criteria

The release specifications of the active substance and finished product should be selected on the basis of parameters defined during the characterisation studies. Selection of tests is product-specific and has to be defined by the manufacturer.

Specifications for release testing should include identity, purity, impurities, sterility, potency, cell viability and total cell number. If the structure is an essential characteristic of the product, the structural characteristics of the active substance or finished product shall be defined and justified. In case the primary function of the CBMP is the excretion of specific proteins, specifications regarding these excreted proteins should be set.

If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process tests, this needs to be justified. In these cases an adequate quality control has to rise from the manufacturing process, supported by the results of the clinical studies. These exceptions may include the following:

- Some release tests might not be feasible on the combined components of the active substance/ finished product for technical reasons.

- A complete release testing cannot be finalised before the product is administered to the recipient due to time restrictions (e.g. in case of autologous products, which are administered immediately after completion of the production and initial testing). However, a critical set of essential tests that can be performed in the limited time prior to clinical use must be defined and justified. Whenever feasible, retention samples should be stored for future analysis.

- The amount of available product is limited to the clinically necessary dose (e.g. due to very limited cell numbers at collection or low proliferation rates). The release of the product should be justified by the validation of the cell manipulation process and the in-process controls.

2. Stability testing

A shelf life for the cells under specified storage conditions shall be determined for the following materials: i) all intermediates, ii) components of the combined CBMP, iii) the active substance, iv) the finished product. Furthermore, a valid in-use shelf life (after opening from the transport container) should be assigned to the CBMP. This should be supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity. All storage conditions including temperature range should be determined and supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity. If relevant, appropriate methods for freezing and thawing should be documented.