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DRAFT

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

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

Comments should be provided using this template to patrick.celis@emea.europa.eu

Fax +44 20 7418 8545

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

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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.

Due to the complex nature of the active substance of a CBMP, stability must be assessed for both the cellular as well as the non-cellular component separately and together as a finished product in the final packaging, whenever possible.

3. Special quality requirements for cell therapy products containing cells modified by gene therapy

If cells in a CBMP have been genetically modified, quality control must be performed in compliance with guidance available on gene transfer medicinal products[15]. This should include characterisation of the vector used to modify the cells, a description of the modification, and quality control tests on the modified cells that address issues pertaining to the transfected gene(s) of interest, such as integrity, expression, genetic stability and copy number. A suitable assay that addresses the newly acquired biological function following transfection should be established and carried out. This information is in addition to control of the cells according to the guidance presented elsewhere in this document.

4. Special quality requirements for combination products

Specifications for structural components of the product shall be defined. Impurities and degradation product that originate from the structural component (matrix, scaffold, device) shall be described and specifications for the relevant impurities should be set. Testing of the structural/mechanical properties and biological activity with reference to the anticipated conditions for use and potential for degradation may be difficult to conduct as part of release testing. Thus, it is anticipated that these parameters could be explored through proper testing of raw materials and characterisation studies of the final product. In extremely limiting conditions (e.g. for autologous products with small cell numbers), the analysis of structural/functional characteristics of a combination product may necessitate the development of a model product composed of same non-cellular components combined with cell component(s) of equal characteristics but with proven availability.

4.2.5 Validation of the manufacturing process

The entire manufacturing process, including e.g. cell harvesting, cell manipulation processes, maximum number of cell passages, combination with other components of the product, filling, packaging etc., should be validated. Combined CBMP can either correspond to a combination of active substances forming a final product, or in some cases, the supportive structures can be considered as excipients or devices, or a mixed situation. In any case, the combination should be consistently produced.

It should be demonstrated that each step of the manufacturing process of active substance, supportive components and final product is well controlled. The selection and acceptance criteria of the operational parameters and the in-process controls should be justified. Putative variability, related to starting materials and biological processes, should be taken into account in the validation. Furthermore, aseptic processing should be validated and critical points of the manufacturing process should be defined..

Any preservation steps, holding periods and/or transportations of the active substance, supportive structures or intermediate products during the manufacturing process should be validated.

In case of limited sample sizes (e.g. autologous preparations for one single administration), it is recommended that a more extensive validation is performed with cell preparations of comparable characteristics but available in sufficient amounts for validation purposes. It is recommended that validation of such manufacturing process is performed on a regular basis, depending on the product characteristics, for adventitious agents, identity, potency, viability, purity/impurities and other product specific parameters.

4.2.6 Development Pharmaceutics

The general principles set out in Note for Guidance on Development Pharmaceutics for Biotechnological/Biological Products[25] can be applied to human CBMP, but the potential complexity of composition and the dynamic nature of a product containing living cells will result in very specialised pharmaceutical and biopharmaceutical requirements for each development programme from individual cell components to the final product.

1. Cellular Components

The development programme should address how the formulation of a cell population to form a final product will impact on the characteristics of that cell population. This impact should be addressed from the point of view of the biological/therapeutic function, the maintenance and the protection of the cell population.

Stability of cellular component is the most critical for the CBMP and must be assessed by the ability of cells to survive, and maintain the genotype and phenotype needed for the intended functions (regeneration, repair or replacement). Cell viability can be easily assessed in culture by employing widely applied assays. However, detection of possible changes in cellular nature that may influence the intended function, can be feasible by analysis of cellular surface antigens, proteomics and functional genomics analysis (e.g. microassay for gene expression profile, flow cytometry etc.). The ability of cells to continue to produce or express products should be evaluated as part of the stability programme. Such stability studies should be carried out as long as the defined period of validity requires.

2. Non-Cellular Components

A CBMP may contain non-cellular components, such as biomaterials, bioactive molecules, proteins or chemical entities. These may supply structural support, suitable environment for growth, biological signalling or other functions. They may also be used during the *ex vivo* manipulation process.

In the context of a CBMP, excipients can be defined as any additive which does not itself exert a specific therapeutic affect but which acts as a stabiliser, a protective barrier or a structural support to form the “formulated” finished product. Some excipients may act in a similar way as those found in traditional biological medicinal products. In such cases a discussion of their characteristics with respect to justification of their inclusion and explanation of their function within the finished product should be provided.

The choice of structural materials their properties, their characteristics and how the final scaffold/matrix was designed and tested 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 retention of the cells after administration, the design of that aspect of the product should be discussed in terms of its scientific development.

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. For example when a cellular components is combined with a structural component reference to an assessment of a medical device by a Notified Body may be relevant. In such cases, justification for the applicability of the data obtained or the results of the previous evaluation should be provided.

A discussion of the structural and functional characteristics of the non-cellular components of a combination product should be provided. Interaction of the cellular component and any additional

non-cellular components with the device should be fully 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 a toxic response;
- characterisation of features (e.g. topography, surface chemistry, strength) critical to structural support, optimisation of viability and cellular growth or other functional characteristics;
- compatibility of the biomaterial with the tissues with which it is in contact (i.e. biocompatibility) to confirm that the system maintains the desired tissue differentiation, functionality and genotype during production and use;
- release kinetics of any bioactive molecules, to verify that they are appropriate for the achievement of the intended effect;
- the influence of the nature and rate of degradation on critical mechanical and structural properties of the product.

The biological effects of all non-cellular structural or functional components and the presence and, if appropriate, the biological effects of any leachable chemicals or degradation products should be established by an appropriate toxicological evaluation. To establish biocompatibility, it is necessary to specify the nature of biological response 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, 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, together with the effect of the non-cellular components on the long-term efficacy of the product. The continuing ability of the non-cellular components to promote the desired tissue response and support the function of the CBMP over its intended lifespan, or until a steady state has been established, should be assessed, taking into account factors identified as relevant in the non-clinical evaluation of biological activity and which can be verified through clinical study.

The effect of degradation of any structural biomaterial should be assessed to verify that the required and specified mechanical properties are maintained for as long as is necessary for the intended functioning 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[26]. 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", delivery system of combined product has been established, the parameters for determining role of constituents and appropriateness of composition should be presented as 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 is included.

The choice of packaging materials should be discussed as part of the development pharmaceutics and additional data may be required if the packaging components play an additional role in the maintenance of administration of the product.

4.2.7 Traceability and biovigilance

A system allowing complete traceability of the patient as well as the product and its starting materials is essential to monitor the safety of cell-based medicinal products. The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC and in Directives 2006/17/EC and 2006/86/EC[27].

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.

Batches used in the clinical studies should be sufficiently well characterised in order to allow a demonstration of consistency between the batches. During the pivotal clinical studies changes should not be introduced to the manufacturing process and the final product. The companies are expected to draw from the critical parameters 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[28] 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 be proportional to the risk expected to be associated with clinical use. Conventional requirements as detailed in Directive 2001/83/EC 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 cell-based medicinal product (CBMP) have been genetically modified, non-clinical development must be performed in compliance with guidance available on gene transfer medicinal products[16].

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. The rationale underpinning the non-clinical development, and the criteria used to choose a specific animal model must be justified. The inherent variability of some cell-based medicinal products should be reflected in the non-clinical studies.

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 Document on the safety of biotechnology-derived pharmaceuticals should be considered. The number of animals, the genders and 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 regeneration), functional tests should be implemented to demonstrate that function is restored. If the intended use is, for example, adoptive immunotherapy or vaccination in cancer patients, immune assays that capture the immunologic effect of the CBMP should be used.

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 cell-based medicinal product that is needed to achieve the desired effect. In addition to cell numbers or concentrations, emphasis must be laid on the required specific characteristics (e.g. differentiation stage and heterogeneity) of the applied cells or tissues.

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 Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00) 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 and persistence, 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 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

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. In the case of autologous CBMP, the use of homologous models may be considered.

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, 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 CBMP enters the clinical development phase the same principles as for other medicinal products apply. The clinical development plan should include pharmacodynamic studies, pharmacokinetic studies, mechanism of action studies, dose finding studies and RCTs in accordance to the existing general guidance's and specific guidance's for the condition evaluated.

While a deviation from Phase I to Phase III clinical trials progression is acceptable, it needs to be justified by the specificity of CBMP, the non-clinical studies, previous clinical experience and the treated pathology. In such cases, the initial clinical studies may be adequate to demonstrate the "proof of principle" for CBMP and pharmacodynamic parameters (related to efficacy) should be obtained in these studies.

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, needs 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 always known 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 deficient or destroyed 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 considered.

When CBMP includes a non cellular component, this component 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 current system for the definition of dose for pharmaceuticals is not easily applicable to medicinal products containing cells. These products are often used as a single administration with the dosage defined by individual characteristics of the intended patient, such as body weight (i.e. cells/kg. of body weight), volume of missing tissue (i.e. bone defect reconstruction/ regeneration), or surface (i.e. skin replacement).

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, it should be individuated also the Safe Maximal Dose, defined as the maximal dose which could be administered on the basis of clinical safety studies without adverse effects.

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 guidance's and specific guidance's 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 were limited guidance exists, consultation of regulatory authorities on the clinical development plan, including the confirmatory studies, is recommended.

The use of previously validated or generally accepted surrogate end points is possible provided that a correlation between clinical 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 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.

A risk assessment of the therapeutic procedure as a whole, e.g. the required surgical procedures inherent to the application of the cell based product or the use of immunosuppressive therapy, should be performed and used to justify the clinical studies and the choice of the target population.

All the safety issue 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.

Adverse events of CBMPs may be linked to various biological processes, such as immune response, infections and malignant transformation or concomitant treatment that should be addressed during the development and post-marketing phases.

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.

Repeated administration may be associated to new or accumulated adverse effects.

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 (EMEA/CHMP/96268/2005 of 14 November 2005). CBMP may need special long-term studies to monitor specific safety issues, including lack of efficacy.

The long-term safety issues, such as infections, immunogenicity/immunosuppression and malignant transformation as well as the 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 the Directive 2004/23/EC of the European Parliament and of the Council *on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells* and in the (draft) Regulation for Advance Therapy Medicinal Products.

REFERENCES (scientific and / or legal)

[1] Ph. Eur. General Text *Nucleated cell count and viability* (2.7.29) [published in PharmEuropa 18.1 (January 2006, ref. PA/PH/Exp CTP/T (05) 28 ANP)].

[2]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.

[3] 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.

[4] 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.

[5] ICH Q5D, Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products

[6] Eudralex Vol. 2 B, Notice To Applicant, part II-V : virological documentation

[7] EMEA/CHMP Note for Guidance on Production and quality control of medicinal products derived by recombinant DNA technology CPMP/BWP/xx

[8] EMEA/CHMP Note for Guidance on Production and quality control of Monoclonal Antibodies CPMP/BWP/xx

[9] EMEA/CPMP Note for guidance on plasma-derived medicinal products (CPWP/BWP/269/95, rev.3)

[10] EMEA/CHMP Points to consider on Xenogeneic Cell Therapy Medicinal Products (CPMP/1199/02)

[11] EMEA/CPMP/CVMP Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 rev.2)

[12] EMEA/CHMP Note for Guidance on Use of Bovine Serum in the Manufacture of Human Biological Medicinal Product (CPMP/BWP/1793/02)

[13] Eudralex Vol. 7Blm10a 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

[14] Note for Guidance on Production and Quality Control of Animal Immunoglobulins and Immunosera for Human use, CPMP/BWP/3354/99

[15] EMEA/CHMP Note for Guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)

[16] Directive 93/42/EEC

[17] Directive 90/385/EEC

[18] EN/ISO 10993-18:2005 Biological evaluation of medical devices- Part 18: Chemical characterization of materials

[19] EN/ISO 10993-19:2006 Biological evaluation of medical devices- Part 19: Physico-chemical, morphological and topographical characterization of materials

[20] ICH Q5A Guideline on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Product Derived From Cell Lines in of human or animal origin

[21] ICH Q6B Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. CPMP/ICH/365/96

[22] CHMP guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer. EMEA/CHMP/410869/2006

[23] ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products (CPMP/ICH/294/65

[24] Ph. Eur. Monograph on vaccines for human use, Section 5.2.3. Cell substrates for the production of vaccines for human use

[25] Note for Guidance on Development Pharmaceutics for Biotechnological and Biological Products CPMP/BWP/328/99

[26] EN/ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing

[27] Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

[28] ICH Q 5 E, Comparability of Biotechnological/Biological Products