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.

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