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DRAFT

GUIDELINE ON POTENCY TESTING OF CELL BASED IMMUNOTHERAPY MEDICINAL PRODUCTS FOR THE TREATMENT OF CANCER

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GUIDELINE ON POTENCY TESTING OF CELL BASED IMMUNOTHERAPY MEDICINAL PRODUCTS FOR THE TREATMENT OF CANCER

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1. EXECUTIVE SUMMARY

Licensed biological medicinal products must meet specifications for appearance, identity, purity, biological activity and/or quantity of the drug substance. Determining the biological activity of cell based immunotherapy products is not easy since the active ingredient is usually composed of whole cells and the activity of these products can generally not be attributed to one specific cell characteristic. The potency (i.e., the quantitative measure of biological activity) of cell based immunotherapy products can be measured using *in vivo* or *in vitro* tests. An appropriately validated potency assay should be based on the intended biological effect and ideally related to the clinical response. Surrogates for potency may be developed to demonstrate biological activity of the test sample. Development and validation of such assays for cell based immunotherapy products need special considerations. This document represents CHMP's current thinking on these issues.

2. INTRODUCTION (background)

Cell based immunotherapy aims at treating patients by stimulating their immune system using autologous or allogeneic cells. Immunotherapy of cancer is based on an immune response targeted against tumour-specific/tumour associated antigen(s), leading to destruction of malignant cells. The targeting of interactions between the immune system and the tumour constitute a complex approach of which the precise mechanism of action is often not fully understood.

In the scientific literature, cell based immunotherapy products for the treatment of cancer are sometimes called cell based tumour vaccines or cancer vaccines.

Assessment of the biological properties constitutes an essential step in establishing a complete characterisation profile of a biological medicinal product. Due to their complexity, cell based immunotherapy products cannot be fully characterised like products derived by recombinant DNA techniques. Nevertheless, as for any biological medicinal product, the biological activity is an important characteristic and needs to be determined for cell based immunotherapy products.

According to the ICH guideline[1] the biological activity describes the specific ability or capacity of a product to achieve a defined biological effect. Potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties.

Current guidance on cell therapy based medicinal products is found in CPMP Points to consider (PtC) on the manufacture and quality control of human somatic cell therapy medicinal products (CPMP/BWP/41450/98). According to this PtC, the final cell therapy product should be subjected to quality control and lot release testing as well as to tests to evaluate the shelf-life of the product. This should include a potency assay, which should be properly validated. However, specific guidance related to the development and validation of such assays is not available.

This document intends to provide further guidance on specific requirements related to the development and validation of potency assays for cell based immunotherapy products. Other existing guidelines related to testing may be relevant and should be consulted[1,2].

3. SCOPE

This guidance document covers cell based immunotherapy products from autologous or allogeneic origin, consisting of e.g. whole tumour cells, tumour cell lysates, or dendritic cells, all intended to induce tumour-specific cytotoxity although the immunological pathway may differ between products. Tumour-specific cells intended for adoptive transfer (i.e. passive immunisation strategies) are also included, for example ex-vivo primed T-cells.

The cells may be chemically treated or genetically modified *in vitro* to immortalize them or to express certain gene products like growth factors or tumour antigens. If the medicinal product is to be

considered as a gene therapy medicinal product[3], further guidance can be found in the Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products[4].

4. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and Part I: Standardised marketing authorisation dossier requirements as well as Part IV: Advanced therapy medicinal products of the Annex I to Directive 2001/83/CE as amended.

5. ASPECTS TO POTENCY TESTING OF CELL BASED IMMUNOTHERAPY PRODUCTS

Appropriately designed potency assays provide an accurate, reliable and consistent demonstration of the biological activity of the active ingredient. Determining the biological activity of cell based immunotherapy products is not easy since the active ingredient is usually composed of whole cells and the activity of these products can generally not be attributed to one specific cell characteristic. Potency assays for immunotherapy products will be based on complex immune mechanisms which are often poorly or incompletely understood and which may be complicated by multi-antigen formulations and inherent variability of the starting material.

Nevertheless, to assure a consistent functional activity of the medicinal product in the recipient, the potency of the product within justified limits should be demonstrated by a bioassay based on the intended biological effect and ideally related to the clinical response. To establish the intended biological effect, a proper understanding of the biology of these cells is necessitated. Therefore, phenotypic and functional properties of the cells should be extensively characterised. Based on these characteristics and the mode of action established in non-clinical studies the concept of the analytical assay should be deduced. It is generally acknowledged that cellular immunity plays a key role in the immunological destruction of tumours. Therefore, several assays under development have been based on this principle. Induction of a non-relevant immune response (e.g. an antibody response that is not relevant as regards to the intended biological effect) in animals following administration of the medicinal product is generally not accepted as a (surrogate) measurement of potency.

Ideally, one single properly developed and validated assay is sufficient to cover both characterisation issues and batch release testing. However, different kinds of assays may be needed depending on the purpose of the assay, e.g. to characterise the active substance, to validate the production process, to show batch-to-batch consistency, and to determine the stability during shelf life.

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 phase III 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.

A potency assay is an extremely valuable tool to provide assurance of unaltered biological characteristics of the product throughout the development of the product. This is especially important when changes to the manufacturing process are introduced after production of material for non-clinical studies or pivotal clinical studies.

Potency of cell based immunotherapy products can be measured in a number of different assays including *in vivo* and *in vitro* test systems.

5.1 In vivo (animal) potency testing

The development of a relevant biological *in vivo* potency assays for cell based immunotherapy products may be hampered by the lack of a relevant animal model due to the inherent immunological differences between man and animals. However, relevant animal models should be fully explored. For example, animals which are transgenic for human major histocompatibility antigens can be used to

present human antigens to the immune system of these animals. Also, immuno-compromised animals (e.g. athymic mice) could be used to determine the functional response of adoptively transferred human T cells as the measurement of potency.

In addition to the lack of suitable (transgenic) animal models, it is acknowledged that such assays very often suffer from wide inherent biological variability. *In vivo* potency testing may also be particularly lengthy to perform and as such may not be practical for lot release. Nevertheless, they could effectively be applied as a product characterisation tool, e.g. after introduction of a process change or any other change that may impact the quality of the medicinal product.

As for any animal based potency assay, suitable conditions for conducting *in vivo* animal testing should be set after appropriate validation. Some principles outlined in current available guidance for biological assays of prophylactic vaccines and their statistical analysis may be useful (e.g. Ph.Eur. 2.7 & 5.3.6).

5.2 In vitro potency testing

With *in vitro* assays, a biochemical or physiological response can be measured at the cellular level. Such assays may be suitable to assess the biological activity on a routine basis, i.e. for monitoring product consistency in batch release testing. Measurable parameters are, for example, *in vitro* lysis of target cells by tumour-specific (CD8) T-cells, *in-vitro* cytokine production by specific cells, e.g. lymphocytes in response to the product, and co-stimulatory capacity of dendritic cells (DCs).

Surrogates for potency may be developed to demonstrate biological activity of the test sample provided that a correlation between the surrogate and the intended biological activity has been demonstrated. Surrogate analysis may comprise different kind of tests including determination of cell surface markers, activation markers, secretion of factors, expression of a single gene product or protein expression pattern. The possibilities of using combinations of certain parameters (e.g. viability, cell surface marker expression) could be envisaged.

If the mechanism of action of the medicinal product can be clearly attributed to specific cell surface antigens (tumour-specific antigens, tumour-associated antigens), the potency assay could be based on quantification of these antigens by suitable methods (e.g. Flow Cytometry Analysis). However, special consideration should be given to the validation of non-standard methods if used for batch release testing.

5.3 Viable cell count

One of the requirements included in Directive 2003/63/EC (Annex I, part IV) is that human somatic cell therapy medicinal products are made of a defined number (pool) of viable cells. Cell viability is an important parameter of product integrity and may be used as an in-process control after manipulation of certain cell characteristics e.g. up-regulation of cell surface expression of specific antigens after cytokine treatment. Cell viability should not be used on its own as a potency indicator and it is only meaningful when used to express an intended biological effect.

5.4 Autologous cell based products

For cell based immunotherapy products comprised of autologous cells, sample and time constraints may hamper complete batch control testing at release. In addition, there may be an inherent variability within the sourced autologous cell population, which cannot be fully rectified by the manufacturing process. In this case the use of variable cell populations may be clinically justified. This variability in cell characteristics could pose difficulties in validation of the potency assay and in assigning acceptance limits for potency.

Nevertheless, whenever a manipulation generates a more homogeneous subpopulation, the development of an appropriate (surrogate) potency assay should be fully explored, which could

effectively be applied either as a characterisation tool or batch release test, or both. In this situation, the absence of a suitable potency assay is not accepted without proper justification, as this will pose difficulties in demonstrating production consistency of autologous cell preparations after changes in manufacture or product composition have been implemented.

5.5 Reference preparation

In general, potency assays on biological medicinal products rely heavily on the use of reference preparations with an established potency. Most likely, no international reference preparation will be available for highly specific cell based immunotherapy products and it may be difficult to generate such preparations for autologous products. 'In-house' reference materials should be characterised in terms of their composition, purity and biological activity as thoroughly as possible by physical-chemical-biological methods. The in-house reference material should preferably be clinically qualified or shown to be comparable to materials shown to be efficacious in clinical trials.

5.6 Adjuvant containing immunotherapy products

There may be cases, where immunotherapy products will require an adjuvant to raise their low immunogenicity. However, it should be kept in mind that these adjuvants may exert activities that may interfere with the intended potency assay. For example, Mycobacterium bovis (bacillus Calmette-Guerin - BCG)[5] is a commonly used adjuvant but one of the BCG activities is associated with activation of monocytes/macrophages[6]. When the adjuvant may interfere with the specific biological activity of the product measured in the potency assay, special consideration should be given to this issue during assay development.

DEFINITIONS

Biological activity:

The specific ability or capacity of the product to achieve a defined biological effect.

Potency:

The measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product, which is linked to the relevant biological properties.

191 **REFERENCES (scientific and / or legal)**

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[2] ICH Topic Q5C, Step 4 Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. CHMP/ICH/138/95 – Adopted Dec. 95.

[3] EU Commission Directive 2003/63/EC, Annex I, Part IV: Advanced Therapy Medicinal Products

[4] EMEA/CHMP Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products. CPMP/BWP/3088/99

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