European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON POTENCY TESTING OF CELL BASED IMMUNOTHERAPY MEDICINAL PRODUCTS FOR THE TREATMENT OF CANCER

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Giuseppe Vicari and John Petricciani dated 17.04.07	Italy/FDA
2	Onyvax Ltd. dated 17.05.07	UK

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
Overall, this is a reasonable first draft; but it could be improved by taking into consideration the points expressed in the following two recent publications: 1. Hinz T, et al. Manufacturing and quality control of cell-based tumour vaccines: a scientific and a regulatory perspective. J. Immunother., 29, 472-476, 2006. 2. Petricciani J, et al. Potency assays for therapeutic live whole cell cancer vaccines. Biologicals 35,107-113, 2007.
It is important to keep in mind that the two major purposes of a potency assay are to determine if: a) the amount of one or more selected antigens is sufficient to induce a clinically meaningful immune response (based on clinical Phase 3 data); and b) the amount of one or more selected antigens in the vaccine consistent from batch-to-batch.
SPECIFIC COMMENTS ON TEXT

1. EXECUTIVE SUMMARY

Line no. + para no.	**Comment and Rationale**	**Outcome**
1. Executive summary Line 36	The identification of the 'intended biological effect' of a complex product such as cells can be very difficult, primarily because the intended effect may not be easily defined within a complex system such as a fully functioning immune system which is yet to be fully characterised itself. Also, the biological effects are often multifactorial, interacting with one another as limited by current knowledge within the immunology field. In addition, the current technologies and assays available are often unsuitable to be used in a validated setting, even following extensive assay development, as they are designed to be utilised as research tools. Suggested text to read: '*potency assay should be based on a <u>defined</u> biological effect and ideally related to a clinical response*.'	The sentence was amended as follows: "*An appropriately validated potency assay should be based on ~~the intended~~ <u>a defined</u> biological effect ~~and ideally related to the clinical response~~ <u>as close as possible to the mechanism(s) of action/clinical response</u>*".

2. INTRODUCTION

Line no. + para no.	**Comment and Rationale**	**Outcome**

2. Introduction Line 45	There are very probably multiple mechanisms of action. *Proposed Text:… which the precise mechanisms of action are often not fully understood.*	The proposal has been accepted and text amended as follows: *":…the precise mechanisms of action ~~is~~ are often not fully understood".*
3. SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
3. Scope Line 67	Cell lysates are quite different from whole cells. While there is some overlap with whole cells in the points that should be considered, cell lysates should be addressed separately. Proposed to delete "*tumour cell lysate"*.	The proposal has been accepted and the section has been amended as follows: "*This guidance document covers viable cell ~~based immunotherapy~~ products for cancer-immunotherapy from autologous or allogeneic origin, consisting of e.g. whole tumour cells~~, tumour cell lysates,~~ or autologous dendritic cells loaded with tumour antigens, 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. Some principles outlined in this document may also be applicable to tumour cell lysates."*
3. Scope Line 67	Dendritic cells themselves are not appropriate examples. Clarification should be made. Proposed text: …*autologous dendritic cells loaded with tumour antigens.*	The proposal has been accepted (see text above).
5. ASPECTS TO POTENCY TESTING OF CELL BASED IMMUNOTHERAPY PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5. Aspects to potency testing of cell based immunotherapy products	Suggested text to change 'active ingredient' to '*either active biological ingredient, final product, or both '*; we feel this clarification will assist with our comments regarding Section 5.6.	The sentence has been clarified as follows: "*Appropriately designed potency assays provide an accurate, reliable and consistent demonstration of the biological activity of the active ingredient either at the level of drug substance and/or drug product*". The following text has also been added: "*In principle the results of a potency assay should provide assurance that*

Line 82		*the amount of the active ingredient is sufficient to induce a meaningful response and that the amount is consistent from batch to batch. As such, the potency assay should be able to detect clinically meaningful changes in the amount of active ingredient in a human dose of a product".*
5. Aspects to potency testing of cell based immunotherapy products Lines 88-90	This section seems to mandate a bioassay while rejecting an antibody response in animals. We agree that during clinical development it is important to have a bioassay being run in parallel with another potency assay such as quantitative antigen expression, so that if at the end of Phase 3 there are no clinically meaningful immune responses to the selected antigens, the bioassay can be used for lot release. However, if clinically meaningful immune responses are demonstrated to selected antigens, the bioassay can be reserved for comparability studies (as part of the characterization of the product after a manufacturing change has been introduced). Replace the entire sentence with: "*Nevertheless, to assure a consistent functional activity of the medicinal product in the recipient, it is desirable to have a bioassay being run in parallel with another potency assay such as the quantitative measure of antigen expression and viable cell count".*	The section has been amended as follows (revision in line with comment on line 36): "*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~~ a defined biological effect ~~and ideally related to the clinical response~~ as close as possible to the mechanism(s) of action/clinical response*". A new paragraph was also introduced in the same section (see below outcome of comment to lines 93): "*The mechanisms of action may be more complex involving both a cellular and humoral immune response. Assays based on antibody formation against selected antigens or assay based on quantitative antigen expression could thus be considered as well. However, the results of the pivotal studies should ultimately support the chosen assay*". In addition, a new paragraph was introduced which is recommending the parallel developed of different potency assays (line 119-121): *"It may be prudent to develop in parallel different potency assays most suitable for their intended use. These may comprise for example functional bioassays or, where justified, assays based on quantitative antigen expression."*
5. Aspects to potency testing of cell based immunotherapy products Line 90	Suggested text to substitute 'intended' to '*relevant*' for both entries, based on discussion given for Line 36 above.	Text has been amended as follows (in line with comment on line 36): "*….by a bioassay based on ~~the intended~~ a defined biological effect ~~and ideally related to the clinical response~~ as close as possible to the mechanism(s) of action/clinical response*".
5. Aspects to potency testing of cell based	Identification of a single mode of action in a pre-clinical model is extremely challenging, considering not only the complexity of the product (cells), but also the multifactorial interaction with the	Text amended as follows: "*Based on these characteristics and the mode(s) of actions established in*

immunotherapy products Line 93	immune system, which itself is still clearly far from understood. Often, the modes of action are interactive e.g. CD4+T cells interact with both CD8+ T cells and B cells to give a cytotoxic and antibody anti-tumour response respectively. Results from pre-clinical systems will also only indicate what could be expected in the clinic. Suggested text to read '*Based on these characteristics and the* mode*(s) of actions indicated in non-clinical studies the concept of the analytical assay should be deduced*.'	*non-clinical studies the concept of the analytical assay should be deduced. One or more antigens may be selected that are linked to the defined mechanisms of action".* The following sentence has also been added to this section: "*The mechanisms of action may be more complex involving both a cellular and humoral immune response. Assays based on antibody formation against selected antigens or assay based on quantitative antigen expression could thus be considered as well. However, the results of the pivotal studies should ultimately support the chosen assay*".
5. Aspects to potency testing of cell based immunotherapy products 96-98, para 5	This section seems to indicate that there must be a correlation between an antibody response and efficacy in animals in order for the potency assay to be considered acceptable. There are several problems with this statement. First (as mentioned below), there are significant problems associated with the use of animal models. Secondly, and of equal importance is the point that while it may not be possible to make direct correlations between specific antibody responses and efficacy, such responses can nevertheless be useful measures of potency (see Ref 2). Delete the sentence: "*Induction of a non-relevant……measurement of potency"*.	Whilst demonstration of a direct correlation between a specific antibody response and efficacy is not always possible, at least a correlation between such a response with the defined biological effect is normally expected. The sentence has not been deleted but amended as follows (in line with a different comment to line 98, see below): "*Induction of a non-relevant immune response (e.g. an antibody response that is not relevant as regards to the ~~intended~~ defined biological effect) in animals following administration of the medicinal product is generally not accepted as a ~~(surrogate)~~ measurement of potency*".
5. Aspects to potency testing of cell based immunotherapy products Line 98	Following the description for 'surrogate potency assay' given in Lines 137 to 142, we agree with the current description in Line 98 that a non-relevant antibody response is unsuitable to be used as a potency assay. However, we suggest that such an assay could be used as a surrogate potency assay if the correct correlation was determined as described currently in Lines 137 to 142. Suggested text to read "*medicinal product is generally not accepted as a measurement of potency"*.	Proposed text accepted (see above).
5. Aspects to potency testing of cell based immunotherapy	This section states that the potency assay must be validated prior to Phase 3. It should be sufficient to have qualified the assay by the time Phase 3 starts, and to work on validation during Phase 3.	Section has been revised maintaining the term "*validated*" because the potency assay should indeed be validated (not qualified) ahead of Phase III studies.

products Line 104	Proposed text:….*it should be qualified prior to Phase 3*…..	
5.1 IN VIVO (ANIMAL) POTENCY TESTING		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5.1 In vivo (animal) potency testing Line 117	This section seems to be giving mixed messages. On the one hand, it says (line 117) that animal models should be fully explored; then in lines 122-124, the significant problems of animal models is acknowledged. The use of animal models should not be encouraged both for reasons of animal use, and the impracticality of using them for lot release even if they could be validated (which is doubtful). Replace lines 115-126 with: *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. In addition to the lack of suitable animal models, it is acknowledged that such assays very often suffer from wide inherent biological viability. In vivo potency testing may also be particularly lengthy to perform and as such may not be practical for lot release. Nevertheless, they might be useful as a product characterization tool, e.g., after the introduction of a process change or any other change that may impact the quality of the medicinal product. 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) might be used to determine the functional response of adoptively transferred human T-cells as the measurement of potency.*	Section has been revised as follows taking into account the proposed text: *"An in vivo potency assay is a useful tool to verify the biological activity of the active ingredient. However, 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. In addition to the lack of suitable animal models, it is acknowledged that such assays very often suffer from wide inherent biological viability. In vivo potency testing may also be particularly lengthy to perform and as such may not be practical for lot release. However, the use of relevant animal models should be fully explored for their applicability for routinely performed assays. Moreover, they might be useful as a product characterization tool, e.g., after the introduction of a process change or any other change that may impact the quality of the medicinal product. 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) might be used to determine the functional response of adoptively transferred human T-cells as the measurement of potency".*
5.1 In vivo	We agree that in vivo assays can have validity as a suitable	The section has been revised to clarify (see text above).

(animal) potency testing Line 117	potency assay. However, these assays are not applicable to all cases, for the reasons given in the current text. Suggested text to read '*However, relevant animal models should be fully explored <u>if appropriate.</u>*'	
5.2 IN VITRO POTENCY TESTING		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5.2 In vitro potency testing Line 138	We agree with the concept written in the draft Guideline of surrogate assays for potency. We suggest that the correlation should be between the surrogate potency assay and the '*defined biological effect*, and not the surrogate and the 'intended biological activity' as is currently written due to our reasoning discussed above for Line 36. Suggested text to read '*provided that a correlation between the surrogate and the <u>defined</u> biological effect has been demonstrated*.' Perhaps a separate section for Surrogate Assays would be appropriate to facilitate reader clarity as they could be either in vivo or in vitro assays?	Section amended as follows: *"<u>Where a direct measure of potency is not possible</u>, surrogates for potency may be developed <u>to</u> ~~demonstrate~~ <u>verify</u> biological activity of the test sample provided that a correlation between the surrogate and the ~~intended~~ <u>defined</u> biological activity has been demonstrated".*
5.2 In vitro potency testing Line 143-147	We agree with the concept of using cell markers either as a direct measure of potency, or as a surrogate measure. However, we feel that the current draft of the text does not distinguish between the two. For example, for the use of markers as a surrogate, the marker should be *correlated* to the defined biological effect, and may not actually induce the 'mechanism of action' as is currently suggested in the text. Conversely, cell markers which are known to be the active substance could be directly measured to determine potency. Also, tumour-specific or tumour–associated antigens are not exclusively cell surface antigens, as is currently written. Internal cell proteins may also be predictive, and could easily be measured through either intracellular FACS staining or proteomic tools.	Section 5.2 has been revised as follows: *"If the mechanism of action of the medicinal product can be clearly <u>related</u> ~~attributed~~ to specific ~~cell surface~~ antigens (i.e., 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		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5.3 Viable cell count Line 153-4	It is unclear what the last sentence of this section means. Replace with: *Cell viability may be an important element of the potency of cell based products. However, it should be linked with other measures of potency that demonstrate the potential for biological activity of the product, such as quantitative antigen expression and a bioassay.*	The following paragraph has been added to the section: "*Cell viability may <u>also</u> be an important element of the potency of cell based products. However, it should be linked with other measures of potency that demonstrate the potential for biological activity of the product, such as quantitative antigen expression <u>or biological activity as measured in the</u> bioassay*".
5.4 AUTOLOGOUS CELL BASED PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5.4 Autologous cell based products Line 163	We agree with the use of potency assay to validate autologous production processes as is currently written. To clarify, we suggest the text to read 'the development of an appropriate potency assay or *surrogate assay* should be fully explored, which could'.	The proposal has not been accepted because an appropriate potency assay could be based on surrogate markers. The text has been changed to prevent misunderstanding of text '(surrogate)' as an alternative to potency assay. "*…the development of an appropriate potency assay should be fully explored, which could effectively be applied either as a characterisation tool or batch release test, or both*".
5.6 ADJUVANT CONTAINING IMMUNOTHERAPY PRODUCTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
5.6 Adjuvant containing immunotherapy products Line 177-183	We agree that adjuvants are often used in conjunction with immunotherapy products and vaccines to improve efficacy. However, depending on the type of product, there are two broad approaches often utilised clinically, and we feel it would be beneficial to make a distinction between the two: 1. Adjuvant is combined with the active biological substance to constitute the final product prior to quality release from manufacture and distribution to clinic. Depending on the process, a suitable potency assay(s) may be used to control	The section has been modified as follows: *"<u>Where the adjuvant is combined with the active cellular moiety prior to performing the potency assay, and</u> the adjuvant may interfere with the specific biological activity ~~of the product measured in the potency assay~~, special considerations<u></u> should be given to this issue during assay development."* <u>*Compounds that are given separately and/or at a different time point in order to pre-condition the immune system and that may be needed for*</u>

	bulk biological substance release, bulk adjuvant release and final release of drug product. The defined biological effect measured at each stage may be different. 2. Adjuvant manufactured and released separately from final cell product which has no adjuvant when released from manufacturer. Adjuvant and cell product combined immediately prior to clinical administration. A relevant potency assay, which may measure independent defined biological effects, shall be used to release both adjuvant and product prior to extemporaneous combination in the clinic. We feel it is both unfeasible and unnecessary to perform an additional potency assay on the combined agents, shown to be of the correct potency, when they have been combined extemporaneously, if appropriate toxicology and clinical development data has confirmed the safety of the combination in advance.	*biological activity, are not considered to be adjuvants. As such, those compounds are outside the scope of this specific section."*