EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 March 2011
EMA/CAT/134694/2011
Patient Health Protection

Report from CAT-Interested Parties Focus Groups (CAT-IPs FG) on non-clinical development of ATMPs

9th February 2011 - 9:00 -13:00 (UK time)

Chair: Christian Schneider

Item	Draft agenda/Summary of discussions
1.	**Introduction of participants** (see list of participants at the end of the document)
2.	**Scope of CAT-IPs FGs and objective of the meeting** A summary document (EMA/CAT/769749/2010) explaining scope, role, composition, duration of the CAT-IPs FG was distributed to all participant.
3.	**Brainstorming:** **a) Non-clinical development of somatic cell therapy medicinal products and tissue engineered products** - Review of existing labelling techniques that can be used in biodistribution studies with cell-based medicinal products; - Conduct of toxicology and biodistribution studies for cell therapy products, especially products that are not injected but are transplanted (such as regenerative medicine combined products, cells and scaffolds) Presentation by EuropaBio **b) Non-clinical development of combined ATMPs** Presentation by Eucomed **c) Non-clinical development of gene therapy medicinal products** **d) Topics suggested in previous Interested Parties hearings/other items suggested by participants:**

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	- Relevant animal models for non-clinical studies - Pre-clinical data needed when clinical data exist - Clarification of the value of *in vitro* experiments within the ATMP preclinical development programmes and their contribution to meeting with the global EU's wish to reduce animal experimentation (3R concept: replacement, reduction and refinement)
4.	**Wrap-up:** The following summary emerged from the discussions as a collection of significant points highlighted by interested parties to be reported to CAT. A number of correspondent actions were also proposed that could be further explored. <u>Summary of discussions</u> At the start of the meeting, it was highlighted that CAT-IPs FGs aim at improving CAT's interaction with interested parties and propose shared solutions on some of the issues previously identified in general hearings with Interested Parties. Therefore the outcome of the meeting will be reported to CAT and the stakeholders for further considerations. It was agreed by all participants that all considerations made during the meeting on the non-clinical development of ATMPs may not be applicable for specific products. It was stressed that advice of non-clinical development for individual products can only be given in the context of scientific advice procedures. • Non-clinical studies and animal models suggested in guidance documents should not be performed for formal fulfilment of guidance, but rather be scrutinised before commencing them as regards their relevance and the shortcomings they may have. A tailored approach may be applicable to different categories of ATMPs, taking into account also a risk-based approach (RBA) which determines the level of non-clinical studies to be performed. The application of the 3Rs in the development of ATMPs should be also explored. • CAT should explore the possibility of setting up a platform to share information with stakeholders on trends in non-clinical development of ATMPs. This could be achieved by extracting the principles of what was advised from scientific advice procedures as regards choice of animal models, etc.. It was stressed that this would have to be strictly anonymous, based on the confidentiality of the information. • CAT representatives stressed the importance for developers to establish an early, continuous dialogue with the European Medicines Agency (EMA) on the developments of their products: ITF briefing meetings have been proven to be a successful format and represent a soft landing zone for first exchange on scientific issues, including non-clinical development. This can result in future scientific advice on specific questions. ATMP certification is also an important incentive offered to Small and Medium Enterprises (SMEs) that can be used as a 'gap analysis' to verify whether the data generated are in line with what is expected for the Marketing Authorisation Application (MAA). It would be important for CAT to track whether the National Competent Authorities (NCAs) are, when evaluating clinical trial authorisations at a national level, following or

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	deviating from the conclusions given in the ATMP certificates. A pre-submission meeting is encouraged for ATMP certification applications: this is a valuable opportunity for companies to discuss the data to be submitted hence increasing the probability of a positive outcome. The CAT representatives stressed that certification is an important incentive for SMEs, which could serve as an important milestone in early development. • CAT should reflect, when non-clinical studies are requested, on how far the experience from similar products and, if available, previous clinical experience can be taken into account. Dermal products combined with scaffolds were given as an example of long-established products in clinical use: it was discussed whether non-clinical data generated with similar products could be used to justify the lack of non-clinical studies and how these previous data can impact on the analysis of the risk of such products. It was clarified that developers do not request the establishment of a different standard to the evaluation of ATMPs legally on the EU market, but recognition of the long-standing use of these products by applying a rational, scientific, tailored approach for the request of non-clinical studies in these ATMPs. It was identified that such reference would rather be based on science (e.g. discussing results from published papers) than based on a reference to a regulatory-related file (such as an MAA) (i.e. this framework is different from the submission of an abridged application for marketing authorisation). The risk-based approach concept that is inscribed in the legislation for ATMPs offers the opportunity to use experience / data from 'similar' products to justify absence of studies with the product under review. Further guidance is currently under development by the CAT Working Parties. • It was highlighted that in view of the progress in the field the use of smart *in-vitro* testing may in certain cases potentially complement or even substitute animal studies. In any case such approaches can constitute an important add-on to animal testing. • Without prejudice of the specific considerations that need to be applied to each ATMP, some general considerations were made on the choice of animal models for ATMP non-clinical studies. These considerations distinguished between proof of concept (POC) and toxicology: - POC: a homologous model may be preferred, potentially combined with toxicology endpoints to maximise outcome of information. - Toxicology: it may also be necessary to test the actual medicinal product in species normally used if relevant. - The safety assessment of ATMPs was discussed in relation to the non-clinical testing in animals. It was identified that the non-clinical testing of ATMPs is more often meant to generate signals or hazards (qualitative approach) rather than be informative on risk assessment (quantitative approach) due to the limitation of the animal models (e.g. homologous models are only considered appropriate for hazard identifications and not for formal risk estimations). - The driving forces that warrant the use of either homologous or heterologous animal models (i.e.; animal models, tissues, etc.) are dependent on the envisaged scenarios and the expected outcomes - As regards choice of large animal models, it was identified that the request for such models would be driven by the actual need for such data, and based on

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	the availability of a relevant setting. An important element here would not only be the product itself and its characteristics, but also the route of administration that may not be feasibly tested in a small animal species. The application of the principles of the 3Rs should also be considered. - The determination of relevance of animal models in gene therapy may, in general, be easier as one can for example study the expression of the gene etc. as a proof that there is pharmacological action. - The use of emerging specialised animal models with small animal species, as a substitute for large animal models, should be considered. • Concerning the duration of non-clinical studies, it was stressed that, in some cases, short-term toxicity may be more informative than long-term toxicity. Likewise, long-term non-clinical studies involving large animal models may not be systematically called for. The question on how long the long-term study should last is dependent on the long term expected effect. Notwithstanding the translation of effects observed in animal to human, a life-long follow-up might be difficult to put into practice with large animals which have a longer life expectancy than small animals. • Dose finding: - There are scenarios in which a reduction in the number of doses to be tested in animals may be explored, but this would then have to be balanced against the potential need for additional data in the clinical setting. - In combined tissue engineered products, dose finding studies may often be neither feasible nor informative as the selected dose is determined by the number of cells that would cover the medical device part of the product. - Non-clinical testing of doses should distinguish between POC and safety endpoints. For example, a different dose may have to be tested for demonstrating an efficacious dose as compared to establishing a maximum safe dose. This may have an impact on efforts towards limiting the dose ranges to be tested. • With regards to pre-existing clinical data, such data/information may be useful for the assessment of the marketing authorisation application of these products and may partly compensate for non-clinical data. The level of non-clinical data needed will depend on the quality and the source of the clinical data in addition to the availability of a relevant animal model. The normal hierarchy of evidence-based medicine should, as a starting point, be applied. • Determination of risk for ATMPs: The categorisation in high risk and low risk products should be avoided as it may be misleading and put an unnecessary "stamp" on a given product and thus result in an ambiguous perception of the product. The attribution of risk is multi-factorial and differential (e.g. a product can have high risk for tumour formation but low risk for immunomodulation). It would be useful to identify area of risks for risk assessment. It was confirmed that the clinical context is an important factor in the overall risk-benefit assessment (e.g. unmet medical need). • Combined ATMPs: - It would be worthwhile exploring emerging specific animal models such as

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	those presented by EUCOMED. - When considering the non-clinical requirement for combined ATMPs, CAT was invited to review the non-clinical testing performed on the device part as part of the medical device essential requirements (i.e. relevant ISO standards) and any other pertinent standards that deal with risk management. The comparison of criteria used to evaluate the medical device part of combined ATMP would avoid repetitions of studies already performed. - It was stressed that several combined ATMPs may use the same scaffold; therefore it is expected that, unless there are specific concerns, certain non-clinical studies may not have to be requested again, especially if an identical scaffold is used in a next generation of product, provided that there is appropriate scientific justification. - As regards development of a risk-based approach strategy, it may be useful to explore principles for risk assessment in the field of medical devices, where experience has already been gained in the past years. • Gene therapy medicinal products: it was highlighted that most of the considerations made were also applicable to gene therapy medicinal products in general. However, specific additional elements will be raised by ESGCT at future meetings. **Proposed actions:** • CAT, in cooperation with the Scientific Advice Working Party (SAWP), to explore generation of a living document tracking the experience gained with scientific advice on non-clinical questions for ATMPs. This document will provide CAT with an overview on the advice given, products types evaluated, POC models recommended, toxicology models agreed and, where used, disease models. As a second phase it will be determined if common elements can be extrapolated and transformed into mock-up case studies to be shared with stakeholders. • To ensure that assessors in the NCAs have a consistent approach for the evaluation/request of non-clinical studies. CAT to include discussions on non-clinical development in ATMP assessors' training courses. • Risk-based approach: - CAT Working Parties and other CAT members to work on scenarios with different types of risks to be potentially included in the upcoming guideline. - CAT to identify areas of risk relevant to ATMPs (e.g. tumorigenicity, immunosuppression/immunomodulation, immunogenicity) to inform the discussions on the risk-based approach. - Stakeholders to collect data on risks that have been already identified (e.g. tumorigenicity for embryonic stem cell products, insertional mutagenesis in gene therapy products) and on possible scenarios to address these issues in non-clinical studies, and to report back to CAT to inform the Committee's discussions. • To raise awareness of CAT on significant innovative approaches in non-clinical development (e.g. emerging animal models, new labelling techniques in biodistribution). This can be achieved, for example, by presenting these findings to CAT as scientific lectures given by relevant researchers. • Further reflection could be: whether small animal models can substitute the need

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	for large animal models and determination of the duration of such studies when using large animal models (i.e.; a life-long follow-up in large animal models might be difficult to put in practice). • To consider existing ISO standards used for medical devices to compare and gain experience on the risk-based approach used in the medical device field and see how certain elements can be used in the risk based approach used for ATMPs. **Conclusions:** The summary of the discussions held and the proposed actions will be reported to CAT in February for endorsement. It was agreed that such focus group meetings, with more specific content, are a helpful addition to the usual meetings of the CAT with interested parties. The next meeting will be held when significant progress has been made on the majority of the proposed actions (not earlier than April 2011). The Chair thanked all participants for the fruitful discussions and closed the meeting.

LIST OF PARTICIPANTS	
Christian Schneider	CAT Chair
Romaldas Maciulaitis	CAT member
Jean-Hugues Trouvin (apologies received)	CAT member
Henrik Tang Vestergaard	CAT WP expert
Carla Herberts	CAT WP expert
Beatriz Silva Lima (apologies received)	CAT member
Lucia D'Apote	CAT Secretariat
Patrick Celis	CAT Secretariat
Jean-Marc Vidal (partial attendance)	EMA Secretariat
Decebal Bora	EUROPABIO
Dario Pirovano	EUCOMED
Stefan Platz	EBE
Medhi Gasmi	ESGCT
Alicia J. El Haj	TERMIS