



**This is a pre- or post-print of an article published in
Vestergaard, H.T., Apote, L.D., Schneider, C.K.,
Herberts, C.**

**The evolution of nonclinical regulatory science: Advanced
therapy medicinal products as a paradigm
(2013) Molecular Therapy, 21 (9), pp. 1644-1648.**

The evolution of non-clinical regulatory science: Advanced Therapy Medicinal Products as a paradigm

Henrik Tang Vestergaard¹, Lucia D'Apote², Christian K Schneider^{1,2,3}, and Carla Herberts⁴

¹) Danish Health and Medicines Authority, Copenhagen, Denmark, and Committee for Advanced Therapies (CAT), European Medicines Agency, London, UK

²) European Medicines Agency, London, UK

³) Twincore Centre for Experimental and Clinical Infection Research, Hannover, Germany

⁴) Medicines Evaluation Board, Utrecht, The Netherlands, and Cell-based Medicinal Products Working Party (CPWP) of the Committee for Advanced Therapies (CAT), European Medicines Agency, London, UK

Advanced therapy medicinal products (ATMPs) comprise gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (CTMPs) and tissue-engineered products (TEPs). Moreover, so-called Combined ATMPs incorporate one or more medical devices as an integral part of the product. Due to their complexity and innovative nature, ATMPs pose new scientific and regulatory challenges to both developers and regulators (Ref. 1). Many developers of such products request scientific advice from the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA). We have repeatedly been asked to analyze the scientific advice provided by the CHMP with regards to the identification of common principles that might be useful to share with product developers. Here we analyze comprehensively the scientific advice provided by the CHMP following implementation of the 2009 legislation on ATMPs where the Committee for Advanced Therapies (CAT) plays an integral role. This analysis allowed us to conclude that for these innovative medicines, a classical guideline-based approach is insufficient due to the complexity of the products. Regulators must employ a more tailored approach that includes principles of risk identification and mitigation. In the current analysis, we focus on the translational aspects of ATMPs (i.e., non-clinical issues) since these are a direct measure of developmental complexity of innovative treatments and often constitute a bottleneck for ATMP development.

ATMPs constitute pharmaceuticals with a high level of complexity linked to their composition, development, manufacturing, characterisation and/or administration. Such products can serve as a paradigm for any innovative medicinal product or personalized

medicine due to their high specificity, particularly with regards to how regulators provide guidance to accommodate the needs of stakeholders. The current regulatory framework was implemented in the European Community in 2009 (Ref. 2). Central to this regulatory framework for ATMPs was the establishment of a multidisciplinary expert scientific committee, termed the CAT. The CAT is highly integrated into the EMA procedure for CHMP scientific advice. In addition to the well-established procedures for European Medicines Agency (EMA) scientific advice and protocol assistance (Ref. 3, 4), classification and certification procedures have been established (Ref. 5-8) to facilitate discussions with developers. The CAT has published several guidelines for ATMPs in order to facilitate development of this complex class of therapy (Ref. 9). However, due to the broad spectrum of ATMPs with regard to structure and mechanism of action, such general guidance can be difficult to translate into product-specific requirements. These difficulties can be substantial for sponsors developing ATMPs, considering that the major stakeholders in Europe are academia, charities and small companies, which often have limited financial resources or regulatory expertise when compared to “big” pharmaceutical companies (Ref. 10).

Overview of the Non-clinical Scientific Advices on ATMPs

The data set

During the first 3 years following the inauguration of the CAT, the CHMP/CAT provided scientific advice on 54 different ATMPs. Recommendations relating to non-clinical development were provided for 31 products covering 11 GTMPs, 13 CTMPs and 8 TEPs (Fig. 1A). Advice related to the non-clinical development of combined ATMPs was provided in only three cases. For approximately half of the products, oral discussion between the Company and various members of the Scientific Advice Working Party (SAWP) and/or the CAT was deemed necessary before a written response could be finalised owing to uncertainty in the information required by the sponsor or when dealing with innovative products for which there was little regulatory precedence. The aim of these meetings was to discuss the product more generally so that SAWP/CAT would be in a better position to provide final written advice. The relatively high incidence of oral discussion meetings reflects the importance of active dialogue between regulators and developers of innovative products because of their complexity and/or the relative inexperience of the developers and regulators with these types of products.

Gene therapy medicinal products (GTMPs)

The majority of the GTMPs for which the CHMP/CAT provided scientific advice consisted of a viral vector whereas only a few products consisted of genetically modified cells (GMOs) either of human or bacterial origin. The majority of the products used either a replication incompetent adeno-associated viral vector or a lentiviral vector (Fig. 1B). Other products

included genetically modified organisms (with an integrated transgene), retroviral vectors, and replication competent adenoviral vectors, amongst others.

Cell-based Medicinal Products (CBMPs)

For somatic CBMPs, the CHMP/CAT provided scientific advice on products consisting of human cells of either allogeneic or autologous origin (Fig. 1C). No advice on the use of xenogeneic medicinal products was requested. The TEPs for which the CHMP/CAT provided scientific advices were mainly autologous (Fig. 1D). Scientific advice was given on a single allogeneic TEP and a single chimeric product comprising both allogeneic and autologous cells. Considering the similarities in the recommendations given by the CHMP relating to the non-clinical development of CBMPs and TEPs, we have combined the discussion on these medicinal products.

General considerations for all types of ATMPs

The most common issues concerned strategies for evaluation of general toxicity and biodistribution (Table 1), including the need for a full non-clinical testing program. The establishment of proof-of-concept/principle and evaluation of tumourigenicity were more often discussed for somatic cell therapy products than for GTMPs. The CHMP/CAT recognised that conventional non-clinical safety testing was not always feasible for ATMPs owing to their complexity. Generally, animal testing was only considered necessary if the data generated were likely to provide meaningful conclusions, i.e., identification of a potential hazard or a potential risk for human health based on extrapolation from animal data. Known species differences needed to be taken into account for the evaluation of the animal studies. In a few cases (mostly GTMPs), it was advised that if a hazard was already identified (e.g., based on theoretical considerations, *in silico/in vitro* testing, and/or findings observed in the proof-of-concept studies) and it could be scientifically and ethically justified that animal testing would not further substantiate the risk, animal testing was deemed unjustified. It was then recommended to take appropriate measures clinically in order to mitigate the risk.

The lack of standalone toxicity testing was considered acceptable in cases where sufficient safety information could be obtained from the proof-of-concept studies. In such cases, it was recommended that the safety assessment be complemented with a discussion of potential risks/hazards in line with recommendations laid out in the guideline on the risk-based approach (Ref. 11). Furthermore, it was acknowledged that GLP compliance of safety studies might not be feasible for these specific types of product (e.g., due to the need for specialised treatment procedures such as cell transplantation). However, in several cases the CHMP/CAT emphasized that the lack of GLP compliance needed to be sufficiently justified and that GLP principles should be applied as much as possible (i.e., requirements for documentation of all data/procedures/specimens, a complete study report

etc.) This implies that peer-reviewed scientific publications may not alone substitute for GLP compliant safety studies.

The CHMP/CAT considered that the lack of specific safety pharmacology and genotoxicity testing was generally accepted for these types of product. Reproductive toxicity studies were only required in cases where there was a potential for (fetal) exposure. In addition, reproductive toxicity studies were not deemed necessary if there was scientific evidence demonstrating a lack of exposure to the reproductive organs. Furthermore, reproductive studies were in some cases waived based on the intended patient population as is the case for all medicinal products (e.g. for women not of child-bearing potential after menopause), or when evaluation of reproductive organs in the general toxicity study/studies revealed no indication of toxicity. Conventional carcinogenicity testing was usually not considered feasible and/or appropriate for risk assessment, while other means were considered more relevant to assess the potential hazard of tumourigenicity (see below under CBMP). The testing of three different lots of the product was generally agreed to be sufficient for addressing specific toxicity endpoints either *in vitro* or *in vivo*. Additional animal testing was suggested in cases where the CHMP/CAT perceived the need for additional safety evaluation of excipients, scaffold, or impurities (e.g., remains of raw materials used for production), etc.

In most cases, comments were made on the duration of the safety and/or biodistribution studies. The proposed study duration was often considered too short, but no general recommendation can be distilled with regards to the optimal duration of such studies, and a case-by-case approach therefore must be employed. However, it is clear that product specific characteristics, such as the persistence, behaviour and fate of the product *in vivo* and the expected duration of clinical exposure or effectiveness, were taken into account when deciding on the appropriate duration of the studies.

Full GMP was not required for manufacturing batches of product not intended for human use. Hence, non-clinical safety testing could use non-GMP material as long as comparability can be shown with clinical batches. Nevertheless, the CHMP strongly recommended that biodistribution and preferably also toxicity studies be performed with the product intended for clinical use. When using a homologous animal model, it was recommended to use a comparable manufacturing process and to adequately characterise the product. It was recognised that a comparability analysis can be very challenging for ATMPs, as it requires a clear understanding of which product characteristics influence its safety and efficacy, and how changes in the manufacturing process could affect these characteristics. Hence, engineering batches should be controlled for identity (e.g., cell composition), potency (e.g., protein expression efficiency and viral vector infection efficiency) and purity (e.g., impurity profile) to ensure consistency with GMP batches for clinical use.

Gene therapy medicinal products: A paradigm for highly species-specific innovative medicinal products

For GTMPs, the relevance of the animal model used for biodistribution and toxicity studies requires justification with respect to the pharmacologic activity of the gene product(s) and the tissue tropism of the viral vector. Furthermore, the expression of human protein(s) might induce immunogenicity in animals. In such cases, it might be advisable to perform animal testing using a vector encoding the animal homolog. The homology and pharmacological properties of the human and animal protein(s) should be investigated so as to interpret clinical relevance of the nonclinical findings.

Tissue specificity should be addressed using human and animal cells to establish vector tropism. Moreover, safety investigations are not limited to viral vectors and must be performed for medical products consisting of GMOs (ie genetically modified cells) unless alternative strategies can demonstrate that gene transfer from the GMO to host cells does not occur. Such safety testing strategies could include evaluation of bystander cell transduction during co-culturing of the GMO with an immortalised cell line highly permissive to infections caused by the applied viral vector.

Duration of the biodistribution study must be sufficient to cover the persistence of the viral vector. If this is not possible, it was recommended that the duration be sufficiently long to establish the clearance profile of the vector. For GMOs, the clearance of cells, expression cassette and gene product(s) must be demonstrated. Dissemination of the viral vector to non-targeted tissues or organs should be investigated by analysing the presence of viral vector DNA in a range of tissues and fluids. The organs listed in the guideline on repeated dose toxicity (Ref. 12) should be covered unless excluded by a scientifically valid justification. Limitations on the sensitivity of the methods used should be considered. The necessity for evaluation of germline transmission can be based on biodistribution data. In several cases, the CHMP advised that IV administration be used as a "worst-case" scenario for studying biodistribution. Hence, designing an appropriate biodistribution study appears to be a complicated task, especially when biodistribution is combined with proof-of-concept and/or toxicity testing.

Dosing up to 10 times the clinical dose was considered sufficient for toxicity testing, but was not always considered feasible. Furthermore, exposure may be influenced by immunogenicity towards the gene product(s) or viral vector/GMO. The use of disease or homologous models for toxicity testing was generally encouraged by the CHMP. Alternative strategies for evaluation of tumourigenicity included *in silico*, *in vitro* and *in vivo* testing. Similar assays are recommended for the evaluation of CBMPs. Target and non-target cells/tissues may need to be evaluated for signs of tumourigenicity depending on the results from the biodistribution study.

Cell-based medicinal products: A paradigm for highly complex and fragile innovative medicinal products

Differences between species is the major challenge for the use of animal models for non-clinical assessment of human cell-based medicinal products. Human cells will inevitably be rejected in an immunocompetent animal whereas the translation of *in vivo* behavior of the human cell-based product in immune compromised animals is complicated because the fate and activity of the cells is influenced by interactions with tissues and cells of the animal model, which may or may not be functional). Indeed, the choice of animal model was one of the most discussed subjects for CBMP. In general, there was a preference to employ a homologous animal model using allogeneic or autologous animal cells mimicking the human situation. It was also noted that the non-clinical study design should mimic the clinical setting as much as possible (e.g., the age of the animals, the site or route of administration, surgical procedure, etc.). This approach was reflected in recommendations on the use of large animal models as these were only suggested when anatomical differences limited the relevance of small animal models and/or resulted in practical difficulties such as the inability to use the clinical route of application.

The use of homologous models was also encouraged for biodistribution studies. It was stressed in several cases that a lack of biodistribution should not be assumed but shown. Hence, biodistribution studies could seldom be waived. It was recognized that biodistribution studies can be technically challenging, but this does not immediately relieve the need for data on the distribution of the cells. In cases of local administration, careful examination of the site of administration for signs of migration/invasion and draining lymph nodes for ectopic tissue formation may be sufficient. In one case, the need for biodistribution studies was waived because systemic exposure was part of the aim of treatment and the cells were administered intravenously.

Inclusion of safety/toxicity endpoints in the proof-of-concept studies was a widely accepted approach, thus reducing the total number of animals and maximising the information obtained from the study. Thus, safety data can be obtained in a homologous animal model. However for specific endpoints, in particular those focusing on the tumorigenic potential of the CBMP, testing of the clinical (human) product was recommended rather than using homologous animal cells.

For tumourigenicity testing, an approach combining *in vitro* studies with an *in vivo* study was often suggested. In the recommendations, no clear preference for a specific *in vitro* test could be found, but a combination of several *in vitro* tests was always proposed by the companies and agreed to by CHMP/CAT. The proposed *in vitro* studies included evaluation of growth characteristics (e.g., growth rate and anchorage-independent growth), cytogenetics (e.g., karyotyping), cell differentiation, functionality of cell-cycle regulation genes (e.g., expression and functionality of oncogenes and tumour suppressor genes), telomerase activity, or senescence (e.g., transduction leading to immortalisation or

transformation). It was generally recommended to perform at least some of these tests with cells that were cultured beyond the routine limit of cell culturing used for manufacturing of the product. In cases where cells were only minimally manipulated or for which sufficient clinical experience was available, the lack of an *in vivo* tumourigenicity study was accepted. When an *in vivo* study was required, it generally involved a study in immunodeficient animals and it was recommended that the route of administration should mimic the clinical setting if feasible and that the duration of the follow-up period should depend on the persistency of the cells in the immunocompromised animal. This recommendation implies that some knowledge of biodistribution and persistence of the cells in the immunodeficient animal model is required.

In addition to the choice of animal model, one issue that was relatively frequently discussed for CBMP was the possibility of applying for Marketing Authorisation (MA) with a reduced non-clinical package. In these cases, CHMP/CAT agreed to forego requirement for non-clinical studies or omission of certain data (e.g., long-term follow-up) when clinical data of sufficient quality was available for a safety assessment of the product, e.g. for some chondrocyte products for which long clinical experience existed. For proof of concept studies, it appears that literature data can support, at least partially, an application for MA. However, it was suggested that the relevance and similarities of the published product should be discussed for the CBMP.

Discussion

Our analysis of the advice provided by the CHMP/CAT suggests that both regulators and developers must accept limitations inherent in the models available today, and that gaps will have to be filled with complementary approaches. An approach whereby product specific risk factors are used to evaluate the individual risks associated with the product (see Ref. 11) and enriched with a knowledge-based rational approach might be the way forward for these innovative products. This is reflected in the trend towards the use of tailored models that are specifically designed to answer particular safety concerns, so as to complement the combined proof-of-concept/safety studies rather than a scheme that separates pharmacology and safety studies from classical general toxicology studies that aim to assess all concerns comprehensively. These specific approaches should nonetheless ensure a maximum gain of information with the minimum use of animal testing. Importantly, tailored approaches are not only limited to advanced medicinal products, but also to biopharmaceuticals such as highly species-specific monoclonal antibodies, and apply even for small molecules such as thrombopoietin receptor agonists (Ref. 13). The approach will also depend on the stage of development: We observed a shift in the way regulators evaluate non-clinical data depending on the developmental stage, shifting from proof-of-concept ("does the product work and does it work safely enough?") in early development towards safety when assessing proposals from a Marketing Authorisation Perspective ("does the product show findings that require confirmation with/from clinical data?").

Based on our analysis, we believe that published regulatory guidance is only a starting point for development, and that regulators are willing to accept a more tailored scientific approach to Sponsors' proposals. This message is highly relevant because of the uncertainty amongst academic and industry stakeholders with regards to regulatory acceptance of more tailored scientific approaches beyond the relevant guidance documents for innovative product classes. This approach shifts regulation increasingly away from a classical "tick-box" approach and is an absolute prerequisite for regulators to fulfill their future responsibilities to not only oversee development but to facilitate it. Overall we recognize that there is a need for increased and early interactions and open dialogue with all stakeholders (developers, manufacturers, regulators, doctors and patients) to cope with the scientific and regulatory challenges posed by these innovative products. The CAT has organised several focus groups in order to interact with interested parties, enrich the scientific discussion, and (where possible) propose shared solutions to specific issues (Ref. 14, 15, one of them being non-clinical development of ATMPs (Ref. 16-18). Furthermore developers are encouraged to seek scientific advice early in development to discuss their product and the extent and type of quality, non-clinical and clinical data needed for further development and, hopefully, in the end a Marketing Authorisation.

We conclude that the "case-by-case" approach, often quoted from regulators, for translation of innovative drug developments from bench to bedside is not necessarily a negative, as often voiced by stakeholders wishing to receive boilerplate outlines from regulators. We consider rather that a more tailored approach allows for sufficient flexibility. Regulators are open to novel developments in translational medicine and are ready to develop their recommendations as the field continues to evolve.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

References

- 1) Committee for Advanced Therapies (CAT); CAT Scientific Secretariat, Schneider CK et al: Challenges with advanced therapy medicinal products and how to meet them. *Nat Rev Drug Disc.* 2010 9 (3): 195-201.

- 2) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union, L 324/121 of 10 December 2007.
- 3) European Medicines Agency (2013): Scientific Advice and Protocol Assistance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9
- 4) European Medicines Agency (2006): New framework for scientific advice & protocol assistance EMEA/267187/2005/ Rev. 1. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004245.pdf
- 5) European Medicines Agency (EMA) (2010): Procedural Advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation (EC) No 1394/2007 (EMA/CAT/99623/2009). http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf
- 6) European Medicines Agency (EMA) (2012): Reflection paper on classification of advanced therapy medicinal products EMA/CAT/600280/2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136422.pdf
- 7) European Medicines Agency (2010): EMA/CAT/486831/2008/corr. Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070031.pdf
- 8) European Medicines Agency (2010): Procedural advice on the certification of quality and nonclinical data for small and medium sized enterprises developing advanced therapy medicinal products EMA/CAT/418458/2008/corr. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500070030.pdf
- 9) European Medicines Agency (EMA) (2013): Scientific Guidelines for Advanced Therapies. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&mid=WC0b01ac05800862bd
- 10) Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medicinal products in europe: evidence that regulators must be proactive. *Mol Ther.* 2012 Mar;20(3):479-82.
- 11) European Medicines Agency (EMA) (2013): Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products EMA/CAT/CPWP/686637/2011.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf

- 12) European Medicines Agency (2000): CPMP/SWP/1042/99. Guideline on repeated dose toxicity.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003102.pdf
- 13) Erickson-Miller CL, DeLorme E, Tian SS, Hopson CB, Stark K, Giampa L, Valoret EI, Duffy KJ, Luengo JL, Rosen J, Miller SG, Dillon SB, Lamb P. Discovery and characterization of a selective, nonpeptidyl thrombopoietin receptor agonist. *Exp Hematol.* 2005 Jan;33(1):85-93.
- 14) European Medicines Agency (2011): Report from CAT-IPs Focus group on incentives for Academia, hospitals, charities (EMA/CAT/889316/2011).
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136435.pdf
- 15) European Medicines Agency (2011): Report from CAT-Interested Parties Focus Groups (CAT-IPs FG) on system to navigate guidelines for ATMPs (EMA/CAT/463795/2011).
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109209.pdf
- 16) European Medicines Agency (2011): 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) (EMA/CAT/134694/2011).
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/03/WC500103895.pdf
- 17) European Medicines Agency (2012): Activities proposed by CAT-IP Focus group on non-clinical development of ATMPs EMA/CAT/654949/2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/12/WC500136436.pdf
- 18) European Medicines Agency (2012): Report from CAT-Interested Parties Focus Groups (CAT-IPs FG) on non-clinical development of ATMPs 11th October 2012 (EMA/CAT/716942/2012).
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136434.pdf

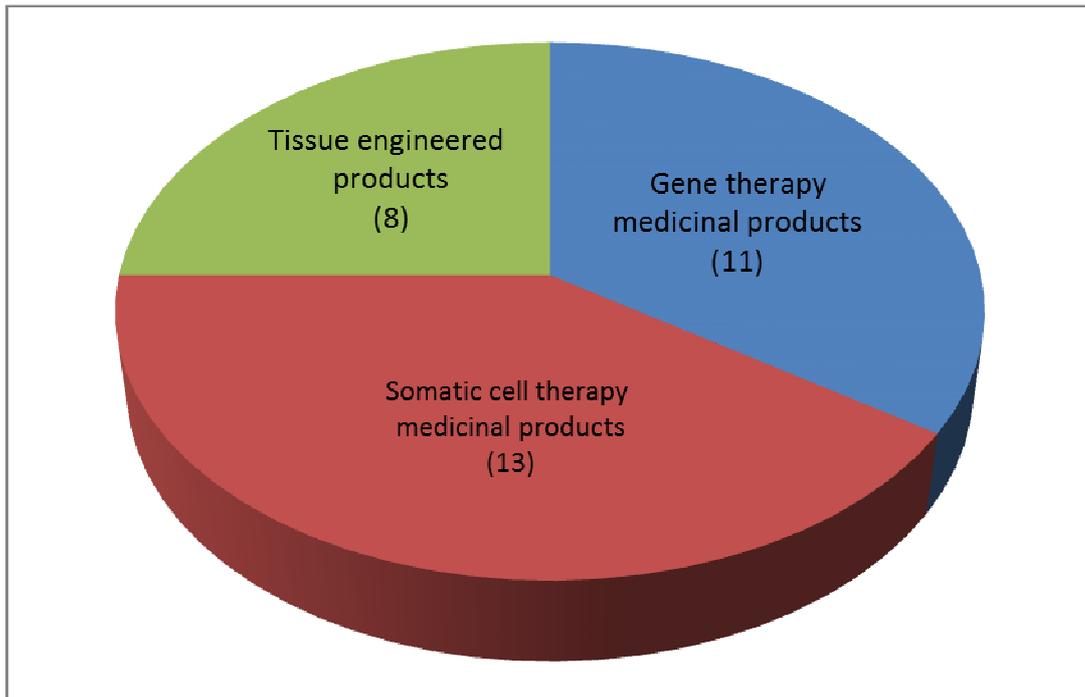
Tables and Figures

Table 1: The number of times in which specific issues were discussed in the EMA Scientific Advice Procedure for ATMPs based on the type of product with their relative frequency between brackets.

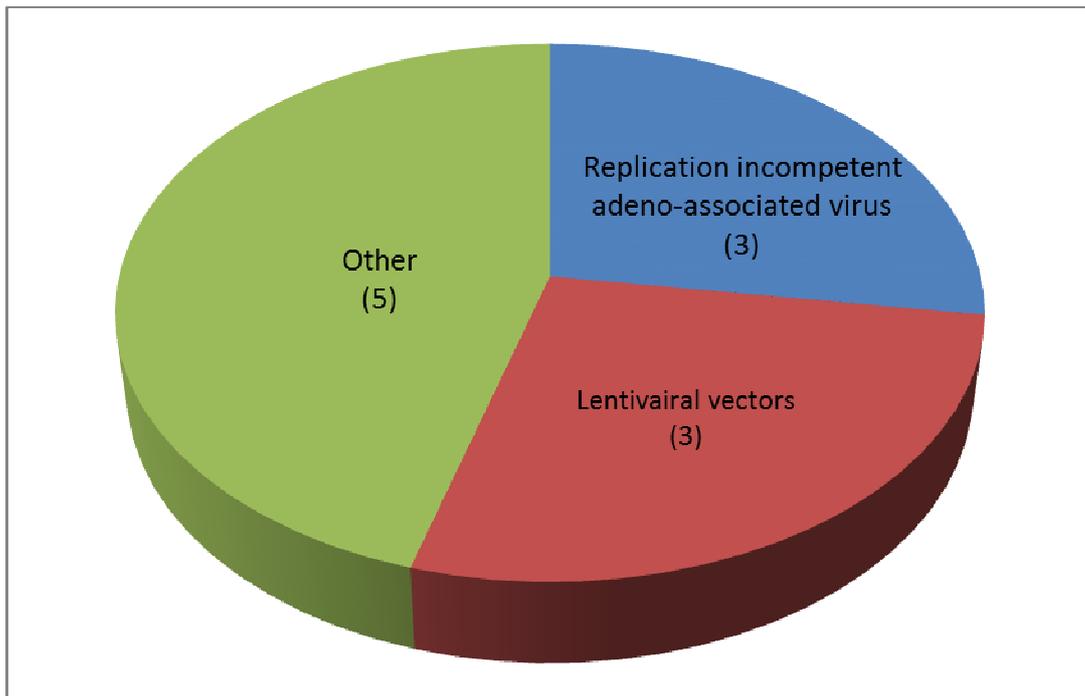
Topic for discussion	N (%)	
	GTMP	CBMP
Proof of concept/principle	4 (36)	16 (76)
Biodistribution	8 (72)	17 (81)
General Toxicity	8 (72)	15 (71)
Tumourigenicity	3 (27)	17 (81)
Reduced non-clinical package	6 (55)	12 (57)

Figure 1: Overview of ATMPs for which scientific advice was provided with the number of products between brackets. Differentiation of the scientific advices based on product type (A), Type of GTMPs (B), and Origin of the cells for CBMP (C) and for TEP (D).

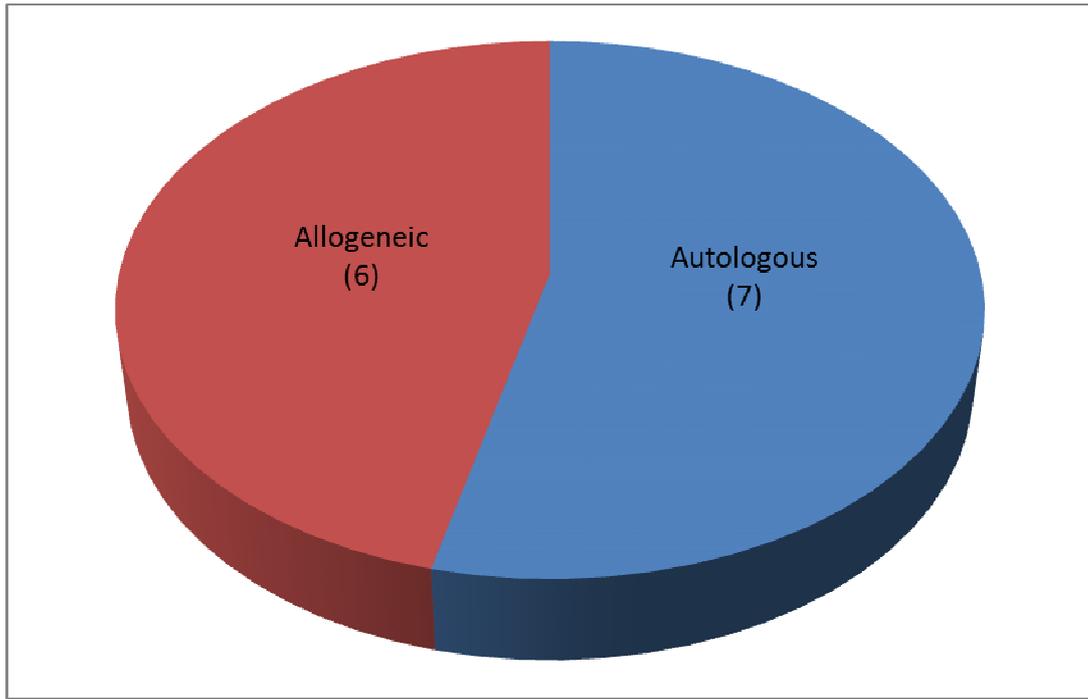
A)



B)



C)



D)

