Quality

To help developers of gene therapy medicinal products (GTMPs) and cell-based medicinal products (CBMPs) navigate the most important quality-related regulatory requirements

Questions to be answered during the development of the product	**What to do** (if not applicable, justification required)	**What you should know** to overcome common challenges
Is the development of the potency assay on schedule?	Perform a potency assay study	• The potency assay has to relate to the mechanism of action and correlate to the clinical outcomes. • The chosen potency assays should provide an accurate, reliable and consistent demonstration of the biological activity of the product and also be able to detect sub-potent batches. • The measure for potency should not be a surrogate marker, but should verify the target (e.g. tumour cells/antigens) or the outcome (e.g. tumour cell death) of the immune response that should be elicited by the product in vivo. Surrogate assays may only be acceptable if the relationship between the measured factor and product activity is firmly established. • The potency assay should normally encompass an evaluation of the efficiency of gene transfer (e.g. infectivity) and the level of expression of the therapeutic sequence or its direct activity. • The potency test should be ready before the pivotal clinical trial and described, justified and validated at the time of the marketing authorisation application. • The relevance of the potency assay, read-out, and acceptance criteria should be in accordance to ICH Q2 (R1) and further supported by (clinical) data to corroborate that the assay will identify sub-potent batches. • Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014); Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (EMEA/CHMP/BWP/271475/2006).
Are the products comparable across all studies? Will future changes in the manufacturing process (including upscaling) or product be needed?	Consider a comparability exercise Describe control strategy of materials and manufacturing process	• The product must be comparable across all studies. Therefore, the product has to be produced consistently and with reproducible quality, also after upscaling production capacity. Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018). • If the ATMP is produced at multiple manufacturing sites, comparability of the product has to be proven by data. Even if the same equipment, materials, procedures, QC-tests, etc. are used. • Be consistent in techniques and procedures to obtain tissue/cells and evaluate and validate these techniques and procedures in clinical trials. European Pharmacopoeia general chapter 5.2.12 (raw materials of biological origin for the production of GTMPs and CBMPs), Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014). • Changes in vector design should preferably be limited to early development phase. Reflection paper on design modifications of gene therapy medicinal products during development (EMA/CAT/GTWP/44236/2009). • In confirmatory trials the product should be based on a mature manufacturing process as close to final as possible before confirmatory trials. Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018). • Relevant guidelines: Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018); ICH Q5E Comparability of biotechnological/biological products (CPMP/ICH/5721/03); Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019); Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014).
What is the location of the manufacturing site?	Ensure the manufacturer adhere to the European GMP regulations Read the rules that apply to importing products into the EU after production outside EU	• Different rules apply to importing products into the EU before and after marketing authorisation. • Guidelines: New guidelines on good manufacturing practices for advanced therapies; Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country (EMA/354272/2019).
Have you started preparing the marketing authorisation dossier?	Define the active drug substance and the final drug product and determine if it is a new active substance Identify raw materials and starting materials Check the community register of orphan medicinal products to see if a similar medicinal product for the same therapeutic indication has been granted market exclusivity protection	• A risk assessment in line with ICH Q5A should be documented for any raw materials and to starting materials of biological origin. In addition, where materials of ruminant origin are used in generation of cell banks or during routine production, compliance with the relevant transmissible spongiform encephalopathy (TSE) note for guidance is required, or the guideline on use of bovine serum should be consulted. • It is recommended to use a combination of measures to ensure viral safety of **GTMP**s, including viral clearance studies to determine reduction factors of relevant steps, where appropriate. European Pharmacopoeia general chapter 5.14 'Gene transfer medicinal products for human use' and 5.1.7 'Viral safety', Guideline on the quality, non-clinical, and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014). • A traceability system should be in place that enables bidirectional tracking of cells/tissues contained in ATMPs from donor to recipient and vice versa. Check Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. • If the product can be used without being frozen prior to administration and after freezing and thawing, the stability data of both the fresh product and post-thaw product has to be available. • Considering that a commercial kit is not under the control of the manufacturer and there may be supply problems or substantial changes may be made to the kit in the future, there should be control measures in place to ensure proper performance of each new lot of the test kit. • The analytical methods for release of drug substance and/or drug product should be validated in line with ICH Q2 (R1). • Relevant guidelines: Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018); Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006); Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014).

What you should know

Additional information applicable to all the above objectives

- Guidelines relevant for advanced therapy medicinal products

Your checklist

- [ ] Develop and validate a potency assay
- [ ] Check the GMP regulations for importing products into the EU
- [ ] Map the development of the manufacturing process and ensure the products across all studies are comparable
- [ ] Explore what is needed in the authorisation dossier
- [ ] Define the active drug substance and final drug product
- [ ] Identify raw materials and starting materials
- [ ] Check the Community register of orphan medicinal products to see if a similar medicinal product for the same therapeutic indication has been granted market exclusivity protection
- [ ] Develop a traceability system that enables bidirectional tracking of cells/tissues contained in ATMPs

Regulatory support

ATMP certification: this procedure aims to identify any potential issues of quality and non-clinical data. For more information see Certification procedures for micro-, small- and medium-sized enterprises (SMEs)

ATMP classification: it is to determine if the product meets the scientific criteria ATMPs and consequently to clarify the applicable regulatory framework, development path and scientificregulatory guidance to be followed. For more information see Advance therapy classification

ITF: the innovation task force (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences. It was set up to provide a forum for early dialogue with applicants on innovative aspects in medicines development. For more information see Innovation in medicines

Orphan designation: medicines for rare disease are termed orphan medicines. Sponsors of designated orphan medicines can benefit from incentives. For more information see Orphan designation: Overview

Orphan similarity: check the Community register of orphan medicinal products to see if a similar medicinal product for the same therapeutic indication has been granted market exclusivity protection. For more information see Applying for marketing authorisation: orphan medicines

PRIME status: it allows support for the development of medicines that target an unmet medical need. For more information see PRIME: priority medicines

Scientific advice and protocol assistance: developers can be advised on the most appropriate way to generate robust evidence on a medicine's benefits and risks. During the non-clinical development phase and prior to the start of the clinical phase. For more information see Scientific advice and protocol assistance

SME status: the micro, small and medium-sized enterprise (SME) status can be used to benefit from regulatory and administrative assistance, and fee incentives. It is recommended to register as soon as possible. For more information see Supporting SMEs