EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ATMP Development Challenges – from Scientific Advice to Marketing Authorisation

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Background

- High number of Major Objections (MO) raised during the initial marketing authorisation applications (MAA) for ATMPs resulting in:
  - long clock stop extensions;
  - withdrawals (MO impossible to solve as development of the product has already been carried out (e.g. quality issues can influence the S&E results obtained);

- Many ATMP developers come for SA but they often do not ask the key questions which would prevent them from having these controversial points being raised during the assessment of the initial MAA.

Common Aims for ATMP developers and Regulators

- To conduct efficient product development

- To increase MA success for ATMPs (no MO leading to a negative outcome)

- To get innovative medicines approved quickly for patients

- To inform ATMPs developers about the pitfalls so that same mistakes do not happen

Spin-off potential to the ATMP developers:

- to identify potential for adaptive pathways initiatives

- to improve availability of parallel HTA & EMA advice

To inform ATMPs developers about the pitfalls

Analysis on:

- Major Objections (MO) raised during the initial MAA on the past 14 applications
- Common questions raised during Scientific/Protocol Advice (SA/PA)

Finding: concerns were grouped with the following clusters:

- Defining the ATMPs
- Ensuring consistency
- Aiming for a safe product
- Proving efficacy

Defining the ATMP

- Active substance - impacts on new active substance claim, similarity for orphans
- Finished product - impacts on QP release
- Device (choice of device, biocompatibility)
- Carefully select raw materials - impacts on cell characteristics
- Dose
- Indication, target population and treatment duration

Ensure consistency

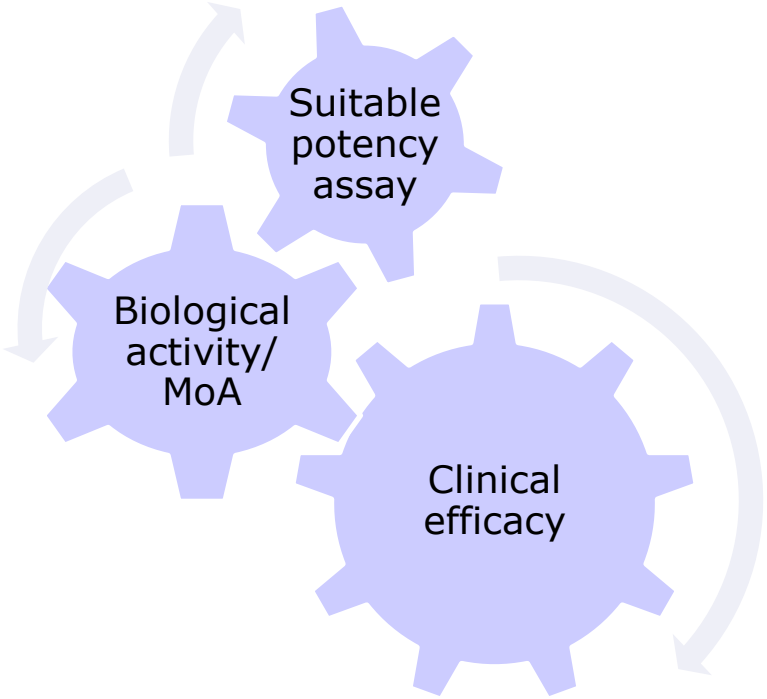
- In the procedures and techniques for the starting materials (e.g. biopsies)
- In the manufacturing process (change may lead to comparability exercise)
- ATMP should be administered in a reproducible way - to achieve this developers should:
  - Gather data during clinical trials (e.g. checklist for physicians)
  - To become Risk minimisation measures (e.g. educational materials for physicians)

Aiming for a safe product

- Impurities / identity test / characterisation
- Compatibility with the primary packaging
- Importance of biodistribution studies (choice of animal model), evaluating the tumourogenicity risk
- Shedding studies, GMO aspects to consider
- Enough re-assurance for first-in-human clinical trial

Proving efficacy: building evidence

- Potency assay - correlates with clinical efficacy
- Choice and/or change of endpoints, choice of comparator, patient selection criteria
- Statistical impact of limited number of patients in clinical trials
- Dose finding
- Justification of indication and population



Proving efficacy- strategy of the data package

- Randomised clinical trials expected
- Other data could be provided (e.g. supportive data, patient files, post-marketing data) if:
  - Adequate methodology guarantees unbiased interpretation of the data
  - Evidence and provision of data coming from AE reporting

Discuss with Regulators

Cell based and Gene therapy guidelines

Guidelines relevant for advanced-therapy medicinal products

The European Medicines Agency develops scientific guidelines to help pharmaceutical companies and individuals to prepare marketing-authorisation applications for human medicines. This page lists relevant guidelines for applicants for advanced-therapy medicinal products.

All of the below listed guidelines are available on the Agency's scientific guidelines pages as well as in the European Pharmacopoeia database and are listed because of their relevance to:

- Gene therapy medicinal products
- Cell-therapy and tissue engineering

Gene therapy medicinal products

Web page	Relevant guidelines
Gene therapy	▸ The **overarching guideline** for human gene therapy medicinal products is the Note for guidance on the quality, non-clinical and clinical aspects of gene transfer medicinal products (CHMP/GTWP/671639/2008) ▸ **Questions and answers** on gene therapy (EMA/CHMP/GTWP/212377/08) available under the Gene Therapy Guidelines, ▸ Guideline on scientific requirements for the **environmental risk assessment** of gene therapy medicinal products (CHMP/GTWP/125491/06) ▸ Reflection paper on **design modifications** of gene therapy medicinal products **during development** (EMA/CAT/GTWP/44236/2009)

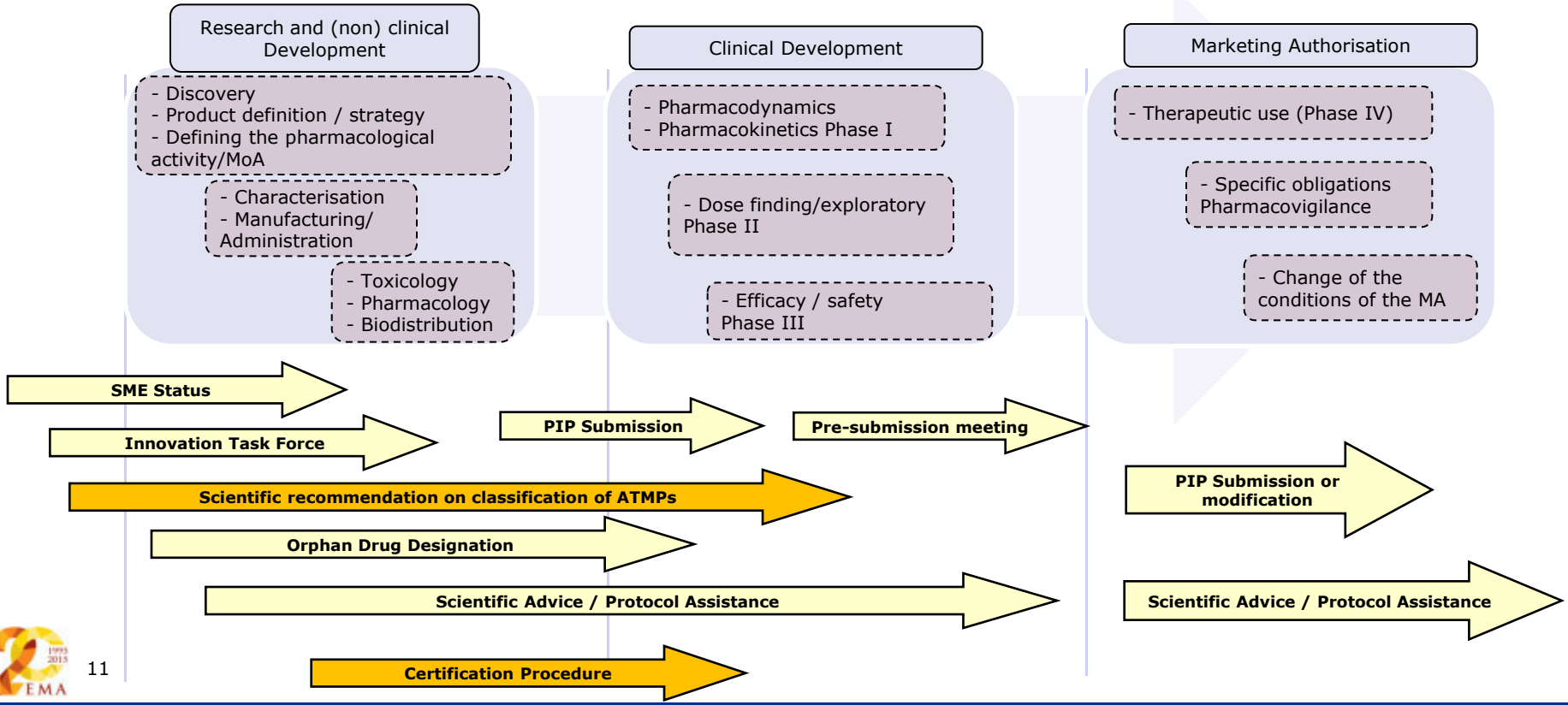
Cell-therapy and tissue engineering

Web page	Relevant guidelines
Cell-therapy and tissue engineering	▸ The **overarching guideline for human cell- based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)** ▸ Reflection paper on **stem cell-based medicinal products** (EMA/CAT/571134/2009) ▸ Reflection paper on in-vitro cultured **chondrocyte** containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009) ▸ Guideline on **xenogeneic cell-based medicinal products** (EMEA/CHMP/CPWP/83508/2009) ▸ Guideline on potency testing of **cell based immunotherapy medicinal** products for the treatment of cancer (CHMP/BWP/271475/06) ▸ Reflection paper **on clinical aspects related to tissue engineered products** (EMA/CAT/573420/2009)

Take home messages

- Quality concerns of ATMPs will often influence the obtained clinical safety and efficacy results of the product
- Integrated Quality, Non-Clinical and Clinical development - a risk based approach
- Strategy on product definition should be well defined – any change could lead to the provision of comparability data
- Discuss with Regulators as early as possible

Interactions with the Agency



Thank you for your attention

Further information

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