Trends & Challenges in ATMP manufacturing

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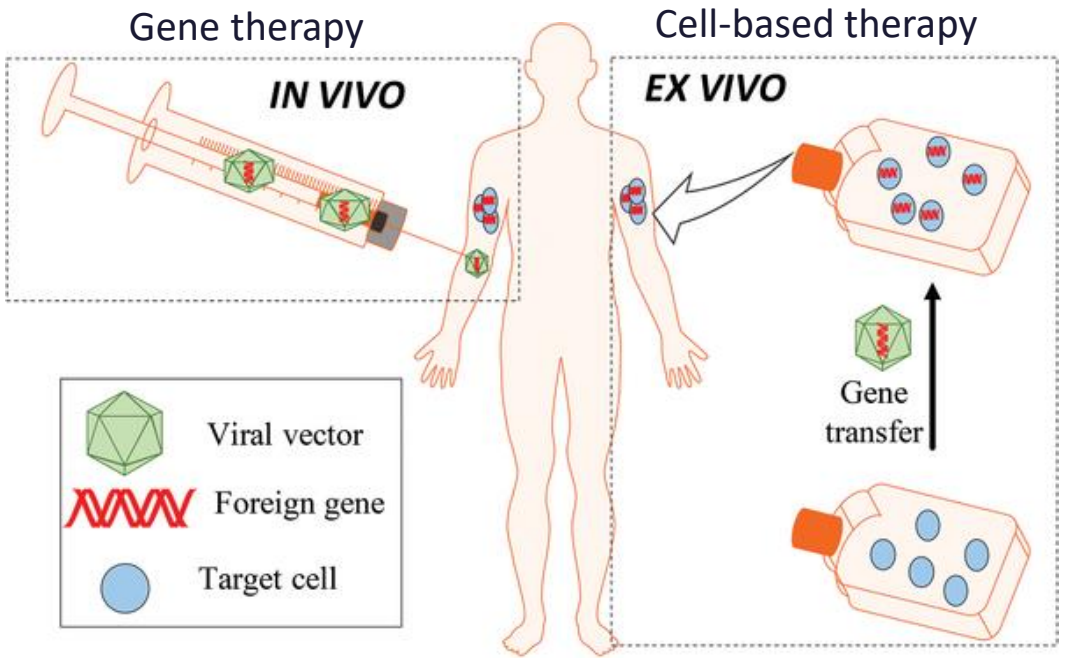
12-12-2024

PROGRESS

Introduction

Advanced Therapy Medicinal Products (ATMP) include:

- Gene therapy products e.g. AAV-based products
- Cell-based and "*substantially manipulated*" products e.g. CAR-T products



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Development of ATMPs

- Bringing a research procedure for preparing a candidate medicinal product to the clinic
- Considering product **quality, safety and efficacy**
- Entering an **highly regulated environment**
  - Compliance with Good Manufacturing Practice for ATMP
  - Compliance with regulatory guidances and pharmacopoeia
- Regulators understand that ATMP are special

EUROPEAN
COMMISSION

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

Document History	
Adoption by the European Commission	22 November 2017
Date for coming into operation	ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

These Guidelines are specific to ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference thereto is made in these Guidelines.

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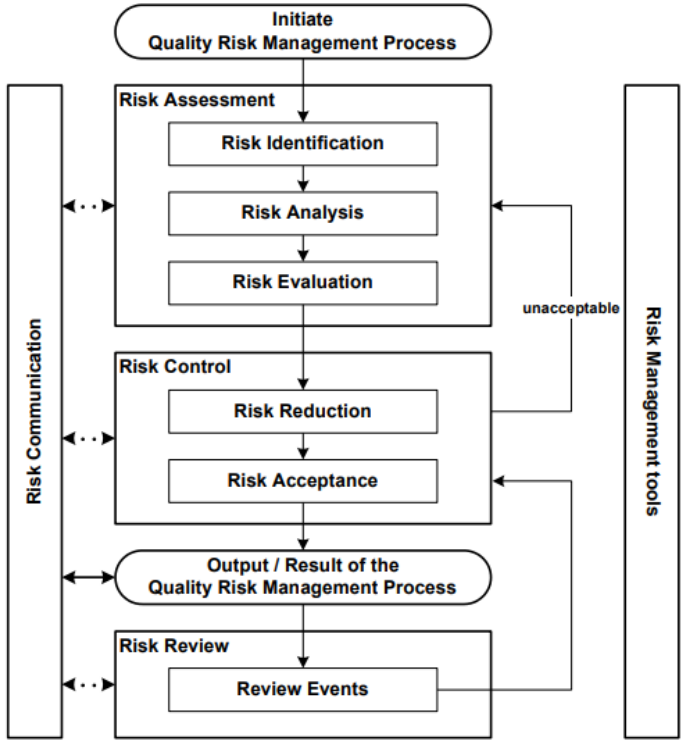
Development of ATMPs

Learning Development/Regulatory language:

- Considering product **attributes** (“outputs”) of the developed ATMP
  - E.g. the quality attribute purity: e.g. microbial contamination
- **Risk-based approaches** (“RBA”) are encouraged for ATMP
- Various risk assessment tools can be used; see ICH Q9 guideline
- RBA is the basis for designing suitable **control strategies** e.g. microbial control strategy
- For each product attribute a specific control strategy can be established
- It is understood that for early clinical development **process and product knowledge** is limited

Figure 1. Overview of a typical quality risk management process



ICH Q9 guideline

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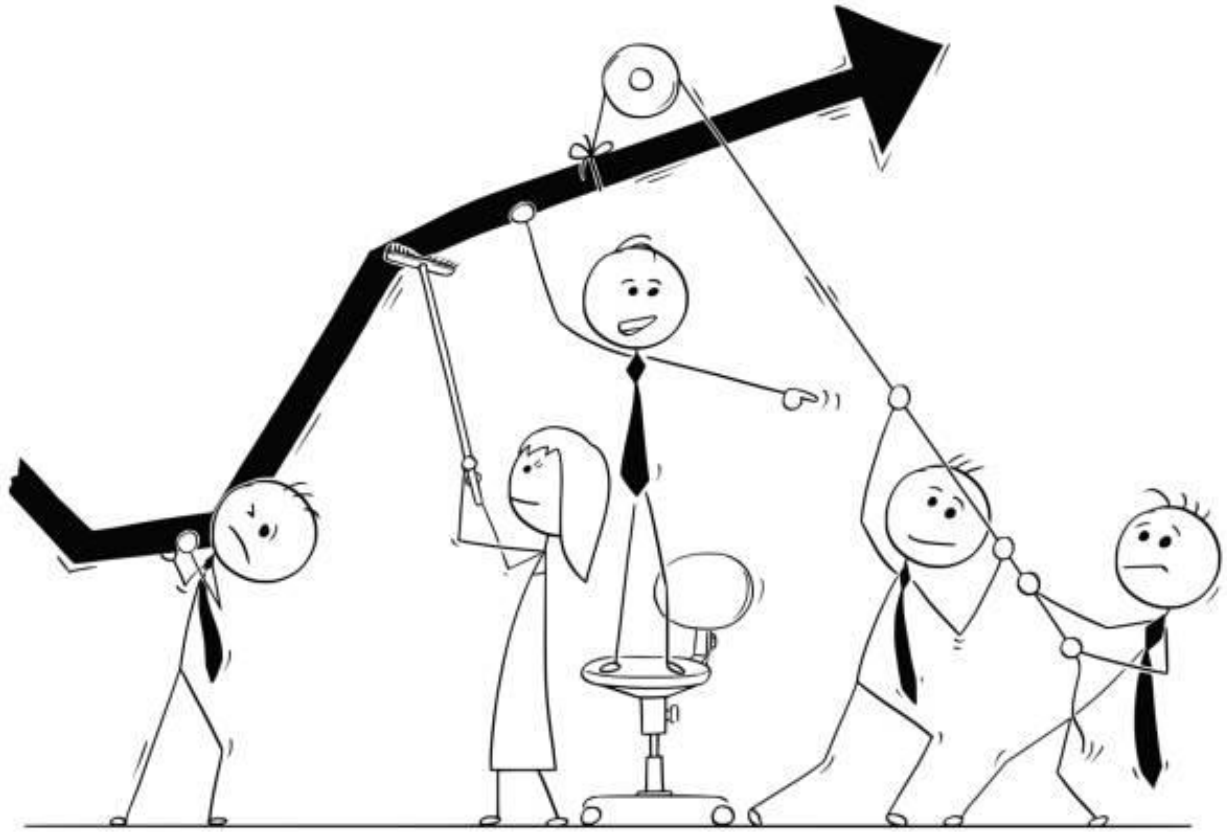
Development of ATMP: Tips

- Get **development expertise** on board i.e. in your own organization
- Select **suitable partner** (CDMO; internal or external) for production of clinical ATMP material
- Typically three candidate CDMO should be compared for quality, timing and cost
- Assure the CDMO has a GMP-license for production of clinical ATMP material
- **Tech transfer** from research process to GMP process needs substantial investments in time and money
- The CDMO may use a platform for production of clinical ATMP material e.g. particular equipment
- **Communication** with CDMO is key and needs careful consideration
- Face-to-face meetings with the CDMO and wittnessing of production are essential



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Development of ATMPs: Process Design

- Test donor of cells / patient for blood-born viruses and bacteria
- Minimize use of raw materials from animal or human origin
  - If such materials cannot be replaced, use gamma-irradiated quality
- Use *qualified* viral vectors including testing for viral contaminants
- Design processes such to minimize risk for microbial contamination
  - E.g. aim for using closed systems for manufacturing
- Run processes in *qualified* clean rooms using *qualified* equipment
- *Qualify* operators for aseptic techniques and apply health policy

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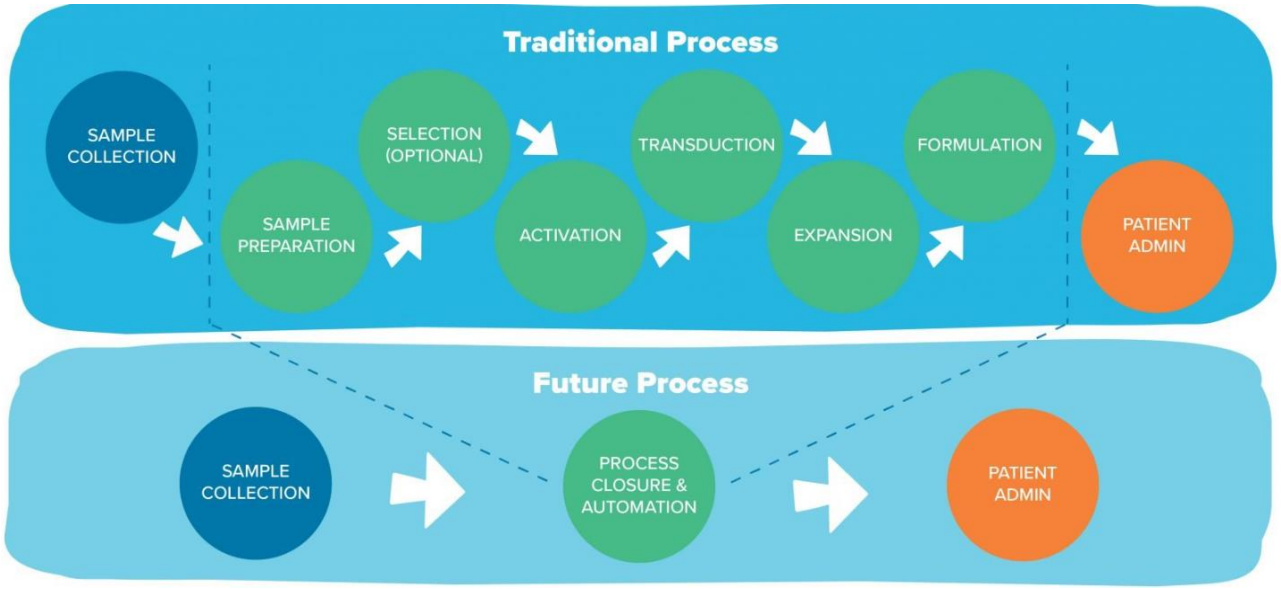
Development of ATMP: Process Development

- Define process steps
- Explore relevant process parameters for each process step
- Set target ranges for relevent process parameters
- Assess effect of batch-to-batch variation of raw and starting materials
- Study impact of hold steps on product quality
- Select suitable excipients for final product formulation, controlling pH and osmolality
- Evaluate compatibility of contact materials e.g. final container



Ref: CRB Insights

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Development of ATMPs: Analytical Development

- Design sampling plan for raw materials, starting material, in process controls and final product
- Select tests for samples collected; for early development more samples tested than for routine production
- Use suitable samples volumes e.g. not more than 10% of the volume of the final product
- Use rapid tests to allow batch release immediately after production of final product
- Validate selected test methods prior to GMP manufacturing
- Set specifications smart: tight where needed; wide where possible
- Initiate stability studies, including in use stability studies
- Initiate product characterization studies

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Development of ATMP: Facilities and Equipment

- Facility options:
  - In house clean room facilities
  - Rental clean room facilites; using your own operators
  - CDMO; fully outsourced
- Equipment:
  - Use closed systems
  - Use standard equipment were possible

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Development of ATMP: Summary

- Development of ATMP follows the same path as development of other biologics, with its unique challenges
- Regulators understand these challenges and allow some flexibility in particular for early development
- When moving from the research stage to development stage, the development team should be supplemented with development experts keeping oversight on the development of the ATMP
- The process as developed on the research bench needs to be transferred to a GMP production facility
- A suitable partner for GMP production should be carefully selected
- A risk based approach is encouraged for designing suitable control strategies for the production of ATMP
- Control of starting and raw materials for microbial and viral contamination is critical
- Closed systems are preferred for controlling microbial contamination risk during production of ATMP
- Effective and efficient analytical and process development are critical for successful ATMP development

Thank you for your attention

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