



# ATMPs - New concepts and the existing regulatory framework

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## My personal take ...

ATMPs are not unique in **ALL** of their challenges and issues,

however,

ATMPs are unique in that **MANY** challenges and issues apply to them **IN COMBINATION**

## What do I mean by that ...

Fundamental concepts apply as for any medicinal product  
(quality, safety, efficacy)  
but,

Because of the novelty and complexity of (some of) the products,  
the demonstration of adherence to these concepts might need  
different approaches

→ Guidance through principles rather than prescriptive details

# „Pitching“ your novel ATMP product

## Product Requirement Document (PRD)

*PRD as organized list of product attributes and features created .. to establish consensus about product design requirements (performance, safety, quality)*

- With innovative concepts, the introduction of the scientific background and potential quality control parameters represents the „pitch“ that directs the quality review
- Advisable to incorporate sections of the PRD into the quality documentation – not least to provide assurance that there actually IS directed development
- Provide a discussion on how the fundamental requirements of quality can be satisfied with the given product, and where challenges exist  
e.g. how can consistent manufacturing be insured, leading to a safe product

# Novel products/technologies

## When and how to approach the regulators

### ■ What do I need an answer on?

- Early guidance
- Procedural questions
- Generate awareness on an approach/product
- General development path
- Conduct of early clinical trials
- Design of pivotal clinical trials

### ■ Who can provide support?

#### **NCA**

- Innovation office
- Scientific advice (simultaneous SA)

#### **EMA**

- Innovation Task Force (ITF) meetings
- Scientific advice and protocol assistance (FDA, HTA, biosimilars)
- Qualification of novel methodologies
- PRIME scheme

# Product development

## Challenges in the context of ATMP manufacturing

- Scarcity of starting material/product – *maximize information generated*
- Donor variability – *explore range*
- Limited batch size – *Manufacturing strategy*
- Adequate product control with minimal material – *Characterization vs Specifications*
- Individualized products – *validation challenges*
- Definition of potency and establishing (surrogate) potency assays – *how and when?*
- Strategies for comparability demonstration – *prepare early*
- Combination with medical devices – *legislative interface, control of the product*
- Transport logistics – *non-frozen cell-based products, QP release*
- Single treatment expected – *impact on the patients' future options*

# Strategic thinking

## Simple truths

- Your trial results can only be considered as reproducible, if the investigational product is sufficiently characterized
- If your trial is supposed to provide pivotal data, the IMP in this trial needs to be mature → Insufficient quality control jeopardizes the use of the data for MAA
- If you want to accelerate your development, you need to accelerate your manufacturing process development and product characterization
- Getting a clinical trial approved  $\neq$  generating relevant evidence for a MAA
- Where treatment prevents patients from receiving similar products in the future the impact should be considered (indications)



# Clinical trials

## .. and product development

- In case of rare diseases it is to be anticipated that even the first clinical data will be relevant for MAA → prepare well for the first-in-man study
  - Adequate analytics should be in place to define your product, manage process changes and link outcomes to a particular product profile
  - The better the mechanism of action is clarified, the better the product can be controlled (potency assay)
  - Consider and explore the impact/variability of starting material
  - Evaluate the impact of raw materials
  - Preclinical data need to link to the product administered

# Automated manufacturing

## Advances in technology

- Automation is increasingly incorporated in manufacturing processes and is either used for distinct steps or the entire manufacturing process
- Parameters that used to be reflected in the SOPs and quality documentation are now programmed into the software, which raises various questions, for example ...
  - Information presentation for review
  - How to demonstrate comparability
- Automation facilitates decentralization and manufacture by „anyone“ → implications for product control and patient safety need to be discussed

# Leveraging existing data

## For clinical trial submissions

- ATMPs are biologics and that excludes generic concepts →
  - Data need to be product-specific
  - Published data with other developments have generally limited value for quality
- Earlier in-house data are, of course, relevant and can be leveraged e.g. vector backbones and other shared aspects of products → justification needed
- „Red line“ of data generation, e.g. comparability between manufacturing processes needs to be ensured
- In the EU, the master file concept is not applicable for biologic products

# Device combinations in the context of ATMPs

## .. at MAA

- Article 117 of the MDR (requirement for an NBOp) does not apply to ATMPs
- Article 9 REG (EC) No 1394/2007 applies to combined ATMPs
  
- The Guideline on the quality requirements for drug-device combinations will apply in the following cases:
  - Medical devices used as container closure system
  - Medical devices that are co-packaged
  - Separately obtained devices referenced in the SmPC (potential impact on the quality, safety and/or efficacy)
  
- Information on medical devices used during surgical procedures for application, implantation or administration of an ATMP which may impact on efficacy or safety as per Annex I, Part IV, Section 5.2.1 of Annex Dir2001/83/EC is expected in Module 5

# Medicine-medical device combination

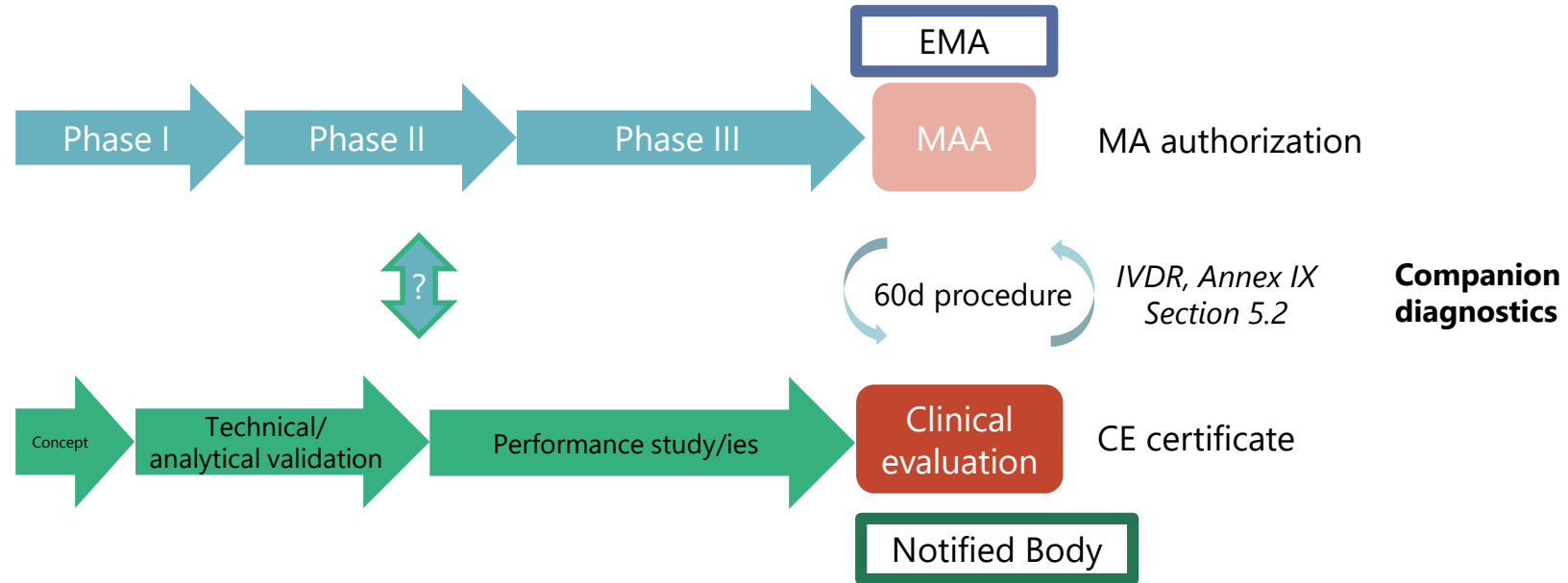
## Characterizing the product



- What type of combination? E.g. component of the product or container closure
- Satisfy requirements of respective components
- Characterize the combination
- When do you introduce the combination and how do you relate it to potential earlier data?

# Where is the overlap?

## Medicinal product and IVD (co)development



# EU Legal Framework

## Regulatory competence

- Are human starting materials involved → **Tissues and cells legislation**
  - Donation, procurement, testing – Dir/2004/23/EC, Dir/2006/17/EC
  - Cells imported from 3<sup>rd</sup> countries – Dir/2015/566/EC
  - Transfer of information from donation site to GMP manufacturer
- Development → **Clinical trials framework**
- **GMO legislation** (*where applicable*)
  - Impacts on manufacturing site, trial sites and approval procedure
- **Medical device legislation (MDR)**
  - Combined ATMP (integral - ATMP Regulation) → technical requirements
  - Delivery device (integral - Device legislation) → technical requirements
  - Specialized medical devices during surgery → CE mark or combined trial; MAA Module 5
- **In-vitro diagnostic regulation (IVDR)** – companion diagnostic

Applicable for First-in-Man

# Guidances

## Regulatory competence

### Guidance for clinical trials

- Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials - *preparation of response to comments*
  - [www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy\\_en.pdf](http://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy_en.pdf)

### Dedicated guidance for GMP – EudraLex Volume 4

- Good Manufacturing Practice Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products
  - [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017\\_11\\_22\\_guidelines\\_gmp\\_for\\_atmps.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf)

**Interface Medical device / In vitro diagnostics Regulation** - Discussions ongoing



# Challenges for a NCA

## In the context of novel concepts

- Novel concepts require a disproportionate amount of effort
- The initial challenge is to know, when and who to ask, and to set up the necessary team/expertise → requirement for joint decisions

To satisfy all product requirements and provide adequate guidance, the assessor needs to consider the totality of requirements →

- National level – increased discussions with GMP, GMO, medical devices/IVDs and T&C colleagues
- EMA/EU level – contribution to multidisciplinary expert groups
- Global level – TCs between regulatory agencies on specific topics

# Concluding

## My personal take..

- Diligently developed ATMPs hold large promise but require rigorous testing
- The legal/regulatory framework is capable of adapting to innovation
- Interfaces between legal frameworks need to be addressed
  - GMOs (ongoing)
  - Medicines/medical devices/IVDs
- Present your innovative concepts to regulators early
- Discuss how manufacturing consistency/safety can be achieved with your product/approach
- Guidance will only be written when sufficient products/experience is available
- Regulators are trying their best – speed is sometimes a challenge

## A new perspective?





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