CMC Considerations for
Accelerated Development of ATMP

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DISCLAIMER: Personal views only, meant to initiate further discussion; may not necessarily reflect views/opinions of MEB, EMA or EDQM.
Outline

- EMA-FDA workshop on Quality support to PRIME & Breakthrough
- ATMP specific challenges
- Sessions included:
  - Comparability
  - GMP-compliance
  - Process validation
  - Control strategy
- Follow-up Actions
Joint EMA-FDA workshop on quality support to PRIME & Breakthrough

Challenges

- **Timelines** (e.g. commercial manufacturing sites/description, validation data, stability, control strategy) *that patient safety, efficacy and product quality are not compromised.*
- **Innovation & complexity** (e.g. product characterisation, potency, comparability)
- **Global development** (e.g. comparability, manufacturing sites, batch release testing)

→ **Module 3 data requirements** in line with scientific guidelines and technical requirements according to the EU legislation *(Annex I of Dir. 2001/83/EC, Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances)*
ATMP typically PRIME products

- ATMP often unmet medical need
- Combined Phase I/II clinical studies.
- If successful: Quickly move to MAA. (PRIME/Breakthrough)
- How to deal with CMC data: from clinical to commercial process
Most critical areas for ATMP manufacturing

- Starting materials (Cells, vector, autologous)
- Raw materials (Feeder cells, Research grade reagents)
- Comparability (Complex, individual variability)
- GMP (Clinical manufacturing site)
- Process validation (e.g. surrogate vs. patient material)
- Analytical control strategy (CQA identification)
- Specifications (potency test) and stability.
Comparability

Session 6. Comparability - Bio

- Prior knowledge / platform
- Risk-based identification of critical QA
- Separate assessment of different changes
- Statistical tools (Reflection paper on statistical methodology)

- Comparability using surrogate material (ATMPs)
- Comparability of few and autologous batches (ATMPs)
- Impact of manufacturing changes on ATMPs

- Risk-based approach for ATMPs

- Conditions to the MA on CMC grounds
- Comparability using non-GMP material
- Concurrent validation based on preliminary specification
- Product launch from clinical manufacturing site/process

*within the existing regulatory framework
Comparability considerations

- Comparability using surrogate non-patient material (e.g. healthy donor material) at scale
- Risk-based identification of critical QA impacted by manufacturing changes and studied in a comparability exercise
- Comparability of few and autologous batches
Impact of manufacturing changes on ATMPs

- Development of more knowledge of the impact of manufacturing changes on ATMPs is needed for an adequate risk assessment
- Available knowledge in registration dossiers
- Great benefit if this information was published
- Create a “safe haven”
- Industry consortia to help generate and disseminate scientific findings relevant to the field through collaborative studies and publication of results
GMP considerations

Session 4. GMP inspections

- Prior Knowledge
  - Process understanding
  - Continuous improvement
  - Risk assessment and management
  - Validation and qualification

- GMP guidance
  - Concurrent validation
  - Continuous process verification
  - Continued/ongoing process verification
  - Scientific advice (with Inspector/assessor interaction)

- Quality risk management and product control strategy
  - GMP comparability plan and gap analysis

- Feasibility to start early commercial supply from a clinical IMP site
  - Alignment of quality review and GMP inspections during accelerated timelines
  - Acceptance of facility scientific input between EMA and FDA

*within the existing regulatory framework
GMP considerations

- Comparability as basis for accepting clinical trial data generated with product manufactured in facility not fully compliant with GMP requirements (e.g. academic laboratory/research hospital).
- Concurrent validation recognized as tool to deal with assurance of manufacturing consistency post-authorisation.
- Explore better link inspectors to concurrent validation activities in the context of an ongoing manufacturing site inspection.
- Management of out-of-specification (OOS) and possible administration of cells/tissues (autologous treatment)
- Acceptability of Master/Working Cell Banks not manufactured under GMP
- Batch release from a laboratory based in a third country
- Increased harmonisation between Regulatory Authorities.
Process validation: Scientific Elements & Regulatory Tools

Session 2. Process validation

- Prior knowledge
- Risk assessment (B/R)
- Validation of process at target scale, additional process understanding studies post-approval
- Register a constrained process & revise post-approval

- Concurrent validation
- Continuous process verification
- Continued/ongoing process verification
- Validation protocols
- PACMPS
- Provision of PV data during review

- Use clinical batches in validation
- Use non-validated API for launch
- Decoupling API and FP process validation activities
- Deferral of process design studies (tight process/restricted control strategy)
- Validation of selective manufacturing process parts
- Integrating prior knowledge into PV
- Use of models
- Launch from clinical manufacturing site
- Tailored validation package
- Tools to ease control strategy post-approval
- Mixed assessment/inspection activities
- Inter-agency cooperation

*within the existing regulatory framework
Control Strategy

Session 3. Control strategy

- Prior knowledge/platform knowledge
- Predictive models
- Real time monitoring & control
- Risk assessment & management
- Prospective raw material control
- Analytical capability

- Performance-based/intelligent control strategy (APC)
- Leverage evolving clinical trial knowledge
- Front-loading of control strategy activities
- New analytical strategies (e.g. Multi-attribute methods)

Industry consortia to look at scientific challenges & make results publicly available

- PACMP
- Post-approval commitments
- Pharmacovigilance measures
- PQS

- International alignment on requirements of PACMPs
- CMC development plan

*within the existing regulatory framework
Control strategy/Process validation

Session 5. Control strategy/process validation - Bio

- Statistical tools for setting specs
- Clinical qualification
- Analytical testing (mass spec) of product extracted from patient serum
- Using statistical process control to set specifications
- Decoupling validation activities
- Rolling data submission (FDA)
- Existing reg/proc tools* to be explored
- Adapting protocols for inclusion in regulatory files
- Linking the PQS to ongoing monitoring of specifications
- Regulatory mechanism to ensure revision of specifications post-approval

*within the existing regulatory framework
Process Validation and Control

- Process validation using surrogate material
- Concurrent validation using patient material
- Risk-based identification of critical QA
- Product launch from clinical manufacturing site/process
- Comparability of non-GMP material (see also session 4 on GMP)
- Validation with few and variable autologous batches
(In Use) Stability

Session 7. Stability

- Prior knowledge
- ICHQ1E
- ICHQ5C
- risk-based impact assessment

- Submission of stability data (post-approval commitments?)
- Legally binding commitments

*predictive stability models (e.g. accelerated stability models)
Reliance on accelerated stress data

Scientific elements available

Scientific elements to be explored

Existing reg/proc tools*

Reg/proc tools* to be explored

*within the existing regulatory framework
Regulatory tools

Session 9. Regulatory tools

- PRIME, BT, RMAT
- SA/PA
- Parallel SA/Consultative advice
- Presub/Clarification meetings
- PACMP
- PAMs/PMCs: Recommendations, Annex II conditions
- Rolling review (US)

- PACMP - detail/flexibility/modification
- Informal flexible meetings with Rapporteurs/Reviewers
- Tools to report comparability data from batches used to treat patients after licensing
Joint EMA-FDA workshop: follow-up

- **Follow up actions**
  - Development of a toolbox (EMA)
  - Collaborative activities FDA-EMA