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

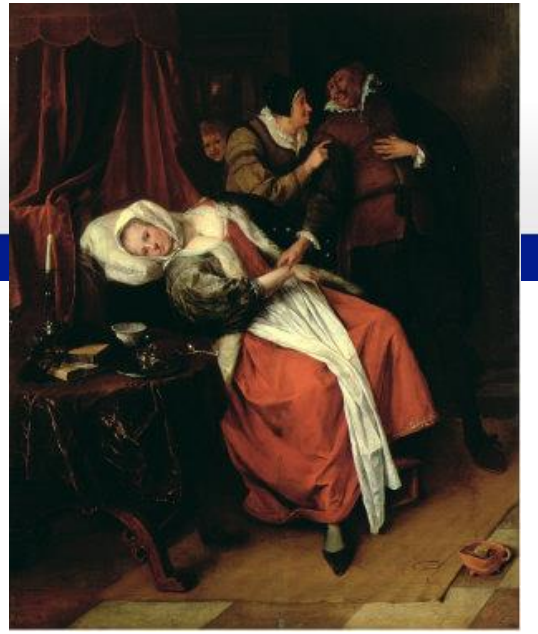
Challenges

- **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*)

Slide courtesy of Veronika Jekerle



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

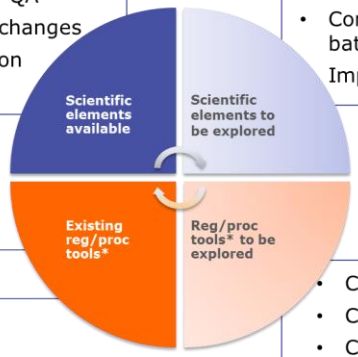
Most critical areas for ATMP manufacturing

- 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

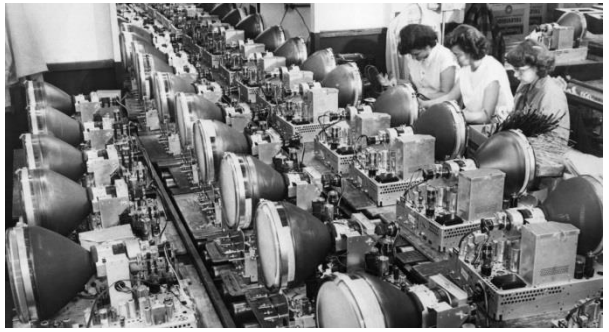
*within the existing regulatory framework

Comparability considerations

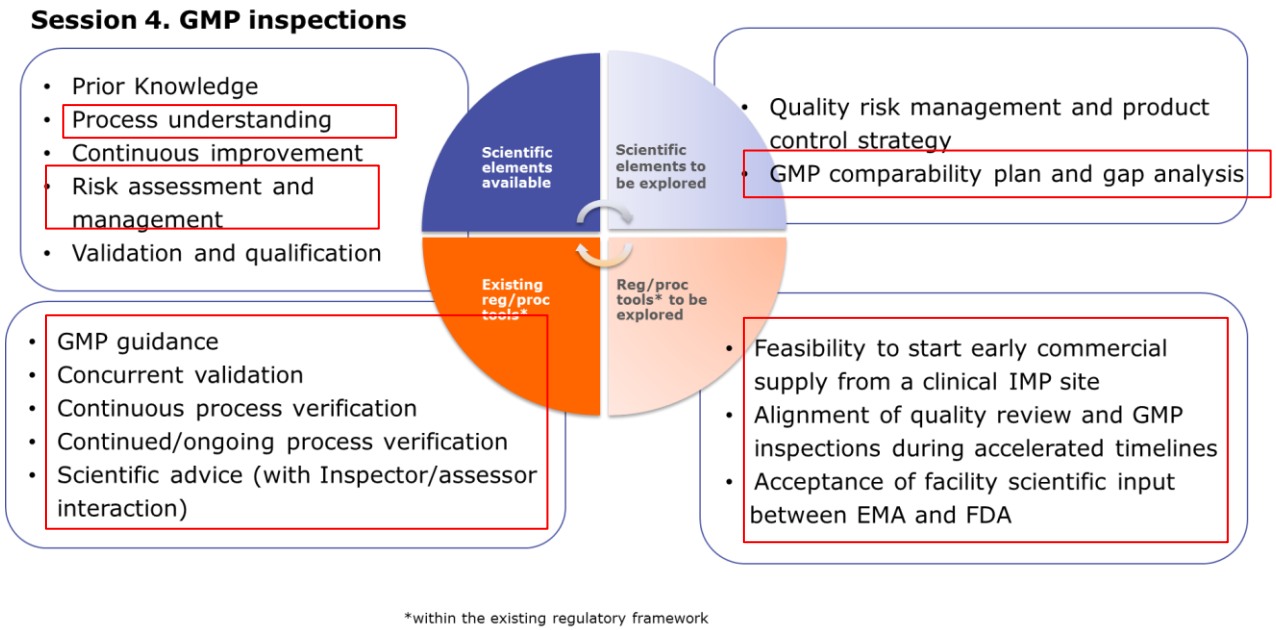
- Comparability using surrogate non-patient material (e.g. healthy donor material) at scale
- Risk-based identification of critical QA impacted by manufacturing changes and studied in a comparability exercise
- Comparability of few and autologous batches

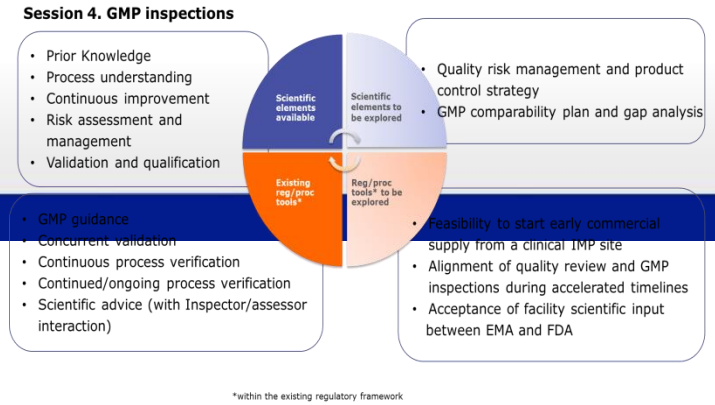
Impact of manufacturing changes on ATMPs

- 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

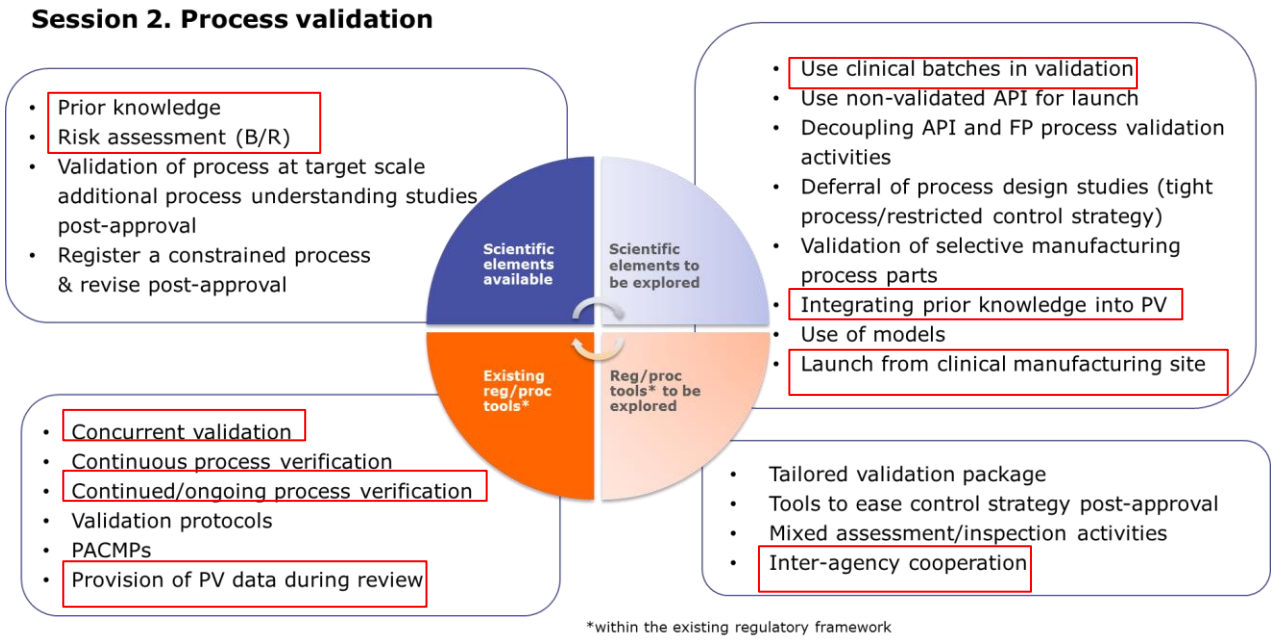




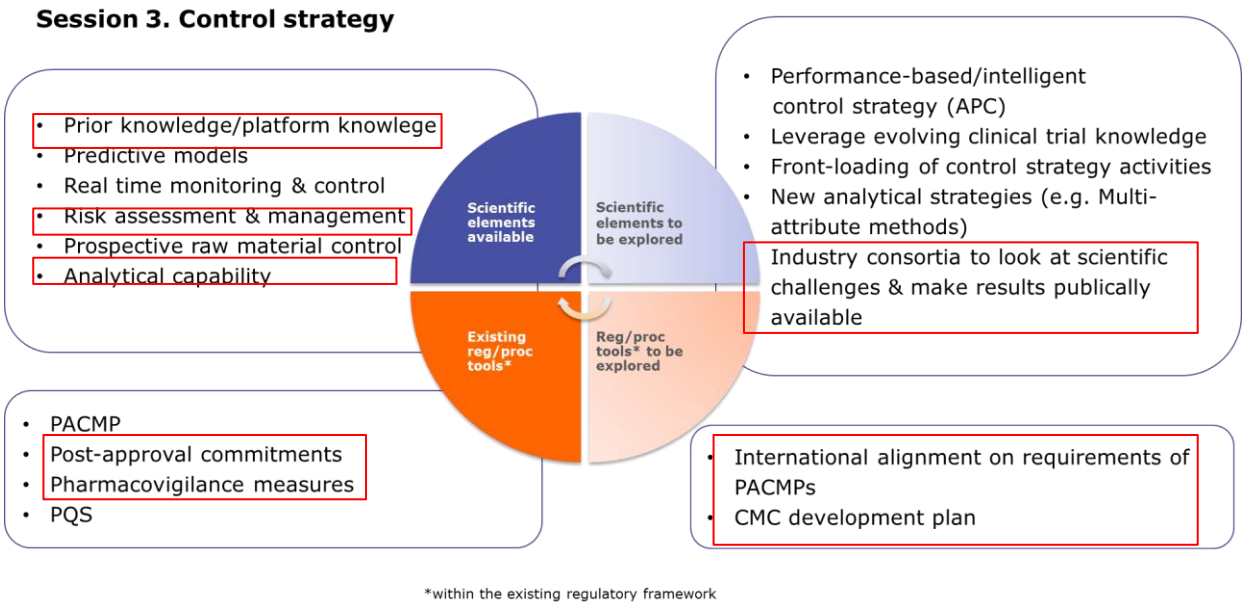
GMP considerations

- 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)
  - Q&A document: EMA/CAT/224381/2019)
- 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

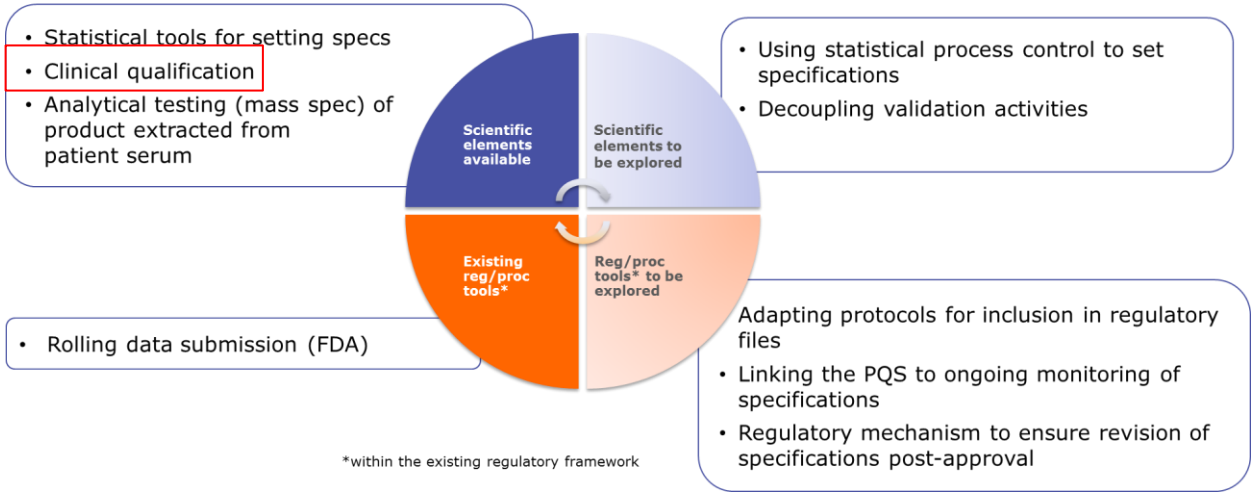


Control Strategy



Control strategy/Process validation

Session 5. Control strategy/process validation - Bio



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

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Human Medicines Research and Development Support Division

Draft Agenda

Workshop on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)

26 November 2018, European Medicines Agency, London

Purpose

The European Medicines Agency (EMA) and the US FDA launched the PRIME and Breakthrough Therapy schemes, respectively, to strengthen their support for the development of medicines that address unmet medical needs with the aim to help patients to benefit from these therapies as early as possible. Experience to date has shown that Applicants face challenges to complete quality and manufacturing development and data requirements during accelerated development. In order to address/overcome these challenges EU and US FDA Regulators wish to support Applicants with guidance and risk-based flexibility regarding their pharmaceutical development programme including, e.g. product characterisation, specification setting, validation and stability testing as well as early identification of quality issues / attributes that are critical to the clinical use of the medicinal product. The aim of this workshop, which constitutes a joint collaboration between EU regulators comprising BWP, QWP, and international partners including US FDA, is to discuss between Regulators and Industry these quality challenges and scientific and regulatory approaches which could be used to facilitate development and preparation of robust quality data packages, to enable timely access to medicines for patients whilst providing assurance that patient safety and product quality are not compromised.

These general discussions will be further elaborated through a number of specific industry case studies (covering chemical molecules, biologicals and ATMPs) and a discussion of experiences to date from early access approaches.

The conclusions from the workshop will be captured in a report, which will be published. The development of further follow-up guidance may be considered.

People interested in participating are invited to register by sending an email to xxx@ema.europa.eu by 31 October 2018. As the number of spaces is limited, EMA will allocate places per stakeholder group to allow attendance of a wide range of stakeholders.

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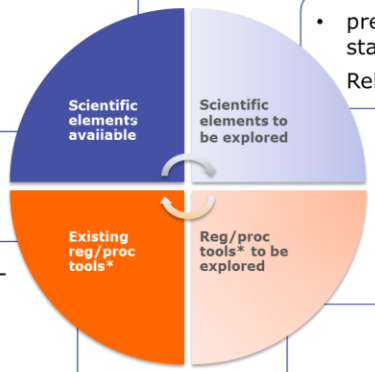
Process Validation and Control

- 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



- predictive stability models (e.g. accelerated stability models)

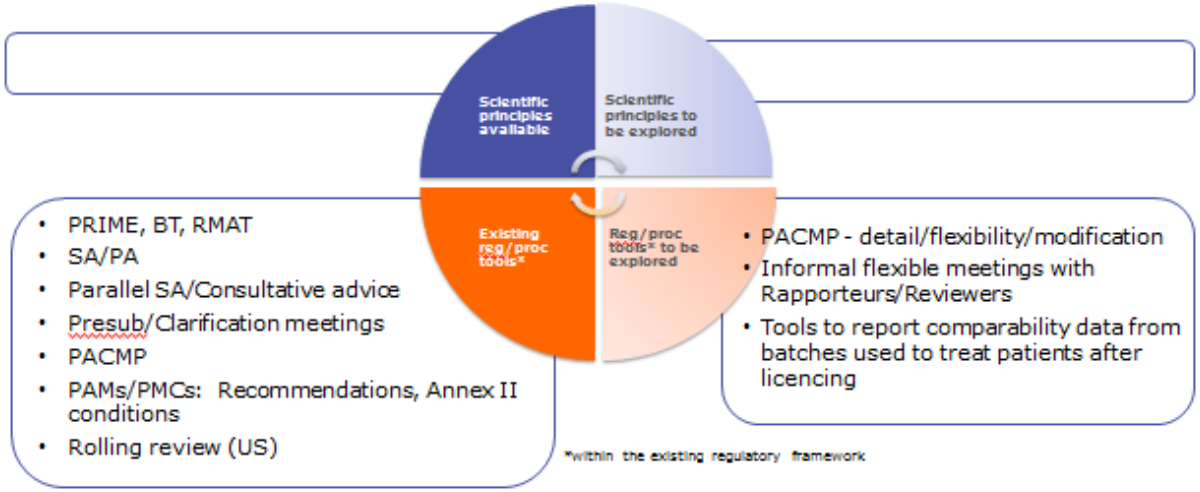
  Reliance on accelerated stress data

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

*within the existing regulatory framework

Regulatory tools

Session 9. Regulatory tools



Joint EMA-FDA workshop: follow-up

- Report July 2019 (https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approa
- Workshop Presentations / Videos https://www.e
  workshop-support-quality-development-early-access-approaches-suc
- Follow up actions
  - Development of a toolbox (EMA)
  - Collaborative activities FDA-EMA