Recent developments in ATMP Regulation in Europe

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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

- Joint EMA-FDA workshop on quality support to PRIME & Breakthrough
- Clinical trials GTP: interplay with GMO framework
- Q&A: Use of Out-of-Specification ATMP
Joint EMA-FDA workshop on quality support to PRIME & Breakthrough

Challenges

• **Timelines** (e.g. commercial manufacturing sites/description, validation data, stability, control strategy)

• **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)*
Regulatory tools outcome

**Existing reg/proc tools***

- **PRIME scheme** (support, frequent interactions, early Rapporteur appointment)
- **Scientific advice** (including parallel scientific advice (FDA/HTA))
- **Managing deferral of data** (recommendations, Annex II conditions, etc.)
- **Change management** (PACMPs, life cycle strategy)
- **Alternative data sources** (e.g. Prior knowledge)

**PACMP ‘with flexibility’**: level of detail, flexibility and possibility for adaptation/modification of the protocol

**Regulatory follow-up on comparability**: Tools to report comparability data from batches used to treat patients after licencing (i.e. variations/recommendations)

Reg/proc tools* to be explored
Regulators conclusions

- **PRIME** is a **support scheme** for development with the aim to achieve product quality that is not compromised.

- **Global alignment** to answer similar challenges (FDA-EMA joined follow-up actions)

- **Flexibility** can be considered in terms of **when** the quality data comes in (partly post-authorisation) (& managed Annex II conditions, recommendations)

- Alternative data sources (e.g. platform/pilot scale data) can help build the case (see EMA Prior knowledge workshop: [Meeting report - Prior knowledge workshop](https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough))

- **Risk-based thinking** to relate the available quality data vs. requirements

- Quality to be considered in the context of the **benefit/risk assessment**

- Meeting report drafted


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5  CASSS – 2019 CMC strategy forum – Seville - PRIME and early access - Jekerle
Example (ATMP)
support to PRIME product during pre-authorisation & MAA (on Quality)

Year 1
- PRIME eligibility
- Kick-off meeting
- Scientific advice (quality)

Year 2
- Scientific advice (quality)
- Scientific advice (quality)

Year 3
- Month: -4
- Application received
- List of Questions
- MAA start
- Comparability over process changes
- GCP inspection(s)
- GMP inspection(s)

Year 4
- CHMP/CAT Rapporteur & EMA team appointment & ad hoc interactions
- CAT/CHMP pos. opinion
- 1 month clock-stop

Comparability over process changes
Starting materials control
Potency/biological activity
Process validation
Clinical trials with gene therapy medicinal products: interplay with GMO framework

Application of GMO framework

Pre-clinical development
Clinical trial
MA
Post-MA

National processes
Centralised process

"Without prejudice to GMO legislation"
GMO aspects covered by MA

Slide: Courtesy of Rocío Salvador Roldán
Member States have national requirements for GMO in clinical trials

- GMO and Clinical trial applications can be Single, Parallel or Sequential procedures
- GMO legislation following either Deliberate release (DR) or Contained use (CU)

Repository of national requirements published in:

Slide: Courtesy of Rocío Salvador Roldán
ATMPs:
interplay pharma-GMO

Initiatives agreed with NCAs in 2018:

- **Good Practice on the assessment of genetically modified cell by means of retro/lentiviral vectors:**
  - Streamlined approach to facilitate conduct of CTs agreed by all MS, except BG, HR, LT, LV, NL, PL, SL, SK and UK.
  - Common application form.

- **Q&A:**
  - Streamlined approach to clinical trials with gene therapy products that have already been granted a MA agreed by all MS, except BG, LT, LV, NL, PL and SK.

https://ec.europa.eu/health/human-use/advanced-therapies_en

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*Slide: Courtesy of Rocío Salvador Roldán*
EMA Questions & answers document
Use of Out-of-Specification ATMP

- What is the pathway for the exceptional administration of out-of-specification (OOS) batches of ATMPs with marketing authorisation?
- Who should be notified and when?
- How should the manufacturer/importer/MAH notify the EMA of the OOS batch(es)?
- Are National Competent Authorities involved?
- Are there any other obligations or expectations?
- What information should be provided to the patient?