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EMA / EuropaBio Information Day

GMP Specific Considerations for ATMPs

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About uniQure

- uniQure
  - A leader in the field of gene therapy
  - The focus and the pipeline are only on gene therapies
  - Glybera®: The first approved gene therapy in the western world
  - Launched in Europe by our commercialization partner, Chiesi Farmaceutici
  - The first fully integrated gene therapy company in Europe

- LPLD (liposomal lipase deficiency)
  - A serious, debilitating disease caused by mutations in the LPL gene
    - Leading to absent or diminished activity of the LPL protein
  - Resulting in: acute and recurrent pancreatitis; frequent admission to hospitals and ICUs; pancreatic insufficiency
  - An ultra rare disease: Prevalence approx. 1-2 per million
    - Approx. 30% eligible as per label → ~150-300 patients in EU

Glybera Production

- The last clinical trials materials were made ~several years ago
- Regulatory dossier: 27 patients; 3 studies; 5.8 years (max) F/U
- Dose: ~20-25 vials (x 1 ml.) of Glybera (IM injections in one sitting)
- uniQure only needs to manufacture several batches per year
  - Glybera process is not full time
- The next batches (Commercial) were made more recently
  - Several years later
  - Need to maintain know-how and ensure reproducibility
- Production is in a validated lab area
  - Wave bags are currently used
  - Finalizing state-of-the-art gene therapy facility in the US
- Process changes, new WSV, some different characteristics
- All changes have been requested to EMA as Variations

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GMP Challenges of ATMPs

Compliance to GMP is essential → ensure Quality (and Safety)

However, ATMP's have specific compliance challenges due to their intrinsic characteristics:

- Manufacturing process challenges
  - Variability of starting materials
    - Cells and tissues
  - Small batch sizes
    - Due to small patient populations
  - Short shelf-life
    - Can be limited due to living cells
- Early research phases (& manufacturing) may take place in a "hospital" setting
  - Operating under a different quality system than "industry"

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ATMP-Specific Considerations for GMP Compliance to Ensure Quality

- Many aspects of GMP Guidelines are valid also for ATMP's
- But ATMP's do not readily lend themselves to all "standard" guidelines
- Some not applicable; some insufficient or inadequate
- ATMP-specific considerations are needed in the following areas:
  - > Risk-based Approach
  - > Personnel; Premises
  - > Equipment; Documentation
  - > Starting & Raw Materials; Seed Lot & Cell Bank System
  - > Production; Qualification & Validation
  - > Qualified Person & Batch Release
  - > Quality Control; Outsourced Activities
  - > Quality Defects & Product Recalls
  - > Environmental Control Measures
  - > Reconstitution of Product after Batch Release
  - > Automated Production

Consultation Document

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Risk-Based Approach (RBA)

- ATMPs are complex products; varying degrees of risk
  - Finished product may entail a high degree of variability
    - Use of biological materials; complex manipulation steps (e.g. cell cultivation)
  - Quality strategies will be dependent on manufacturing process
- Therefore, some flexibility is required to implement GMP
  - Particularly for earlier phases
  - However, Quality can never be compromised
- Ultimately, the manufacturer is responsible
  - Put in place all necessary measures (beyond GMP guidelines if necessary)
  - Consider all potential risks when identifying control measures
- INITIAL COMMENTS: In agreement
  - Some areas with even more conditions suggested
    - “...quality AND CONSISTENCY of the product...
    - “Add additional level of detail regarding the application of RBA in the Guidelines”

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Personnel

- GMP: Adequate number of personnel with the necessary qualifications

ATMPs:

- Specific training given where contamination is a hazard
- Personnel handling GMOs trained to prevent:
  - …cross-contamination risks and potential environmental impacts
  - …transfer of communicable diseases from biological raw and starting materials to operators
- Health monitoring of staff should be proportional to the risks
  - Where necessary, personnel should be vaccinated
- INITIAL COMMENTS: In agreement
  - Some areas with even more conditions suggested:
  - “Provide more details on the specific training requirements for staff...
  - “Protective equipment open to interpretation; additional guidance would be useful”
  - “Specifc qualifications for QP’s releasing ATMP’s to be further specified...”

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Premises

- GMP: Premises should be kept clean and carefully maintained

ATMPs:

- Microbial contamination during production process is key challenge - requirements for clean areas and processing for first in human studies to be evaluated
- Commercial production premises to be fully validated
- Clean areas: In general, A grade with background of B grade is required for pivotal clinical trials and commercial production
  - Consultation document: Allow A grade with C or D background for early clinical trials? (except gene therapies, provided risks controlled)
- INITIAL COMMENTS: Mostly in agreement
  - Because of limited batches and campaigns: "An RBA should be undertaken to assess the possibility to use a multi-product facility..." [c/f Glybera]
  - C or D background: Could be possible, based on risk assessment (Q/S assessment)
  - Also: Patient population and severity of disease to be considered

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Other Comments and Considerations (1)

- The effort (and opportunity to provide input) is appreciated
- Labeling: Multi-language labels difficult for small containers
- Left-over tissues: A written procedure should be in place
- Additional guidance requested on process development and validation of tissue and cell-based products
- Container closure integrity: Additional guidance for frozen products
- RBA: Good to have a separate chapter; more examples requested
- Storage: Include separate sections on storage and shipment qualification and validation
- Starting materials of animal origin: Additional guidance requested

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In Conclusion:

- ATMPs must to conform to GMP Guidelines
- ...but need special consideration in certain areas
  - > Sometimes they cannot follow the same “rules” as non-ATMPs
  - > Sometimes the existing GMP criteria are not specific enough or incomplete
- Key differences exist in Risk-based Approach, Premises, Production, Equipment, Documentation, etc.
- The Consultation Document will address all of these issues
- Consolidated initial feedback from industry is positive and generally aligned (and stricter in some instances)
- Additional comments until Nov. 12 → maximum input needed

Result will be a major step forward in adapting GMP to meet the specific needs of ATMP, while continung to maintain the highest standards of Quality

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