A Risk-Based Approach to the Determination of the Control System for an AAV-based Gene Therapy Product

A fictitious case study

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Presentation objectives

- Present a fictitious case for the application of a Risk Based Approach (RBA) to determine a quality control strategy
- Present the thought through process and spark conversations
- Focus on the Risk Based Approach rather than on scientific challenges

Introduction to RBA in gene therapy - Roche's perspective

- Unique attributes of ATMPs drive the need for a multidisciplinary approach to risk management to identify, evaluate and address risks during the development life cycle
- Establishment of the product risk profile as important part of the RBA for ATMPs
  - incl. benefit-risk assessment and risk management plan
  - developed early in the product development cycle
  - continually updated as data becomes available on risk and risk factors that impact the product safety, efficacy and durability of the effect
- Holistic approach to risk profiling
  - Increased need for ATMPs for robust data analysis and correlative assessment
  - Essential to derive understanding of product performance, interrelationships of product quality attributes and mechanism of action in a multidisciplinary way

Introduction to RBA in gene therapy - Roche's perspective

- Risk Profiling* for individual and inter-related risks specific to an ATMP to integrate all available information concerning risks and risks factors; four steps
- Identify risk:
  - e.g. immunogenicity, disease transmission or exacerbation, inadvertent germline transduction, toxicity due to impurities or components of the drug
- Identify risk factors:
  - attributed to e.g nature and composition of the product, off target effects, unintended systemic effects
- Create data maps/matrices to evaluate contribution of the risk factor to the identified risk
- Conclude on the relationship between risk and the risk factor

**Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC for ATMP; EMA/CAT/CPWP/686637/2011*

Case Study Presentation: A Fictitious Case

- Product:
  - AAV based GT product for rare genetic disorder - unmet medical need, small patient population
  - potentially curative with a single administration; complex and costly therapy alternative
- Clinical program development:
  - Ph I/II studies completed
  - Ph III pivotal studies started and ongoing; safety profile confirmed, signs of efficacy in interim analysis
- CMC change prior to entering Phase III studies
  - switch from adherent to suspension cell culture to cover needs for Ph III/commercial supply
  - significant improvement of the product with this change and addtl. process development
  - Pre- and post-changed material are mostly similar except for Full / Empty particle ratio which is significantly lower

Case Study Presentation: Full / Empty particle ratio

- Empty capsids (capsid shell lacking vector genome) are inherent to a vector manufacturing process (packaging & insufficient removal capability by the purification process based on high similarity with full capsids)
- Analytical detection via analytical ultracentrifugation (AUC), Transmission electron microscopy (TEM), chromatographic separation with detection systems (SEC-MALS)

Clinical Development	Process Version	Full/ Empty Capsid Ratio
Phase I/ II	Adherent Culture	5:1
Phase III / commercial	Suspension Culture	3:1

- Impact:
  - Potential impact on safety/ immunogenicity: increase of antigenic load triggering innate and adaptive immune responses
  - Potential impact on efficacy: clearance of transduced cells through capsid-specific cytotoxic CD8+ T cells; may compete with full capsids for receptor binding on target cells
  - No impact on dosing (based on genomic titer)

Case Study Presentation: Risk Based Approach

- Application of a Risk Based Approach for the determination of the control strategy for control of empty capsids
  - Risk Factor: Increase in product related impurities, i.e. amount of empty capsids
  - Risk: Immunogenicity, Toxicity and Treatment Efficacy

Case Study Presentation: Risk Based Approach

Risk	Immunogenicity	Toxicity	Treatment efficacy
Risk factor **Increased amount of empty capsids**	Empty capsids increase the overall antigenic load and can potentially trigger immunogenic reactions	Empty capsids may contribute to the elicitation of capsid-reactive lymphocytes (CD8+ T cells)	Empty and full capsid competitions for receptor binding on target cells may lead to decreased efficacy. Decreased transduction efficacy due to distruction of transduced cells or full capsids because of increase immune response
Studies to assess risk impact	**Toxicology studies**: preliminary safety data collected before start of Ph III **Clinical studies:** Ph III study assessed unwanted immunogenicity of post-change material; Sentinel dosing	**Toxicology studies**: toxicity assessed before start of Ph III **Clinical studies:** Ph III monitoring the CD8+ T cells status of patients	**Toxicology studies:** assessment of transduction efficacy (also in vitro) **Clinical studies:** efficacy assessment based on dose determined in Ph II as similar potency established in vitro and in non clinical studies
Outcome	No safety effects observed in toxicology study; In clinics, a slight increase in immune response (anti-capsid Abs) was observed but within acceptable tolerable ranges; no clinical manifestation towards adverse events	Tolerable increase of CD8+ T cells in toxicological and clinical study	Comparable efficacy within the expected variability of the endpoint

Case study presentation: Control System Proposal

- Control System proposal:
  - control of full to empty capsid ratio via release specification testing
  - acceptance criteria derived from pre- and post-change material
- Justification: no significant impact on clinical outcome
- Long term follow up proposal for safety and efficacy: periodic assessment and re-evaluation of acceptance criteria based on risk review
- RMP: No inclusion into the RMP based on robust non-clinical and clinical data

Case study presentation: Parameters controlled

- Identity
  - Capsid ID
  - Plasmid sequence (ITR to ITR)
- Potency
  - Genomic titer
  - Transgene expression
- Safety
  - Microbial and viral safety
  - Replication competent viruses

- Purity
  - Capsid protein concentration
  - Protein concentration
  - Capsid protein composition
  - Monodispersion/ Aggregation
  - Full / Empty capsid ratio
  - Residual host cell protein
  - Residual host cell DNA
  - Residual plasmid DNA
  - Residual process impurities (e.g. Nuclease)

Summary & Conclusion

- Advantages of utilization of a RBA:
    - Enables the development and justification of a control strategy for a not well understood CQA where the uncertainty around the clinical impact may lead to strict requirements for control of a high F/E ratio
    - Aligns the control of the CQA with the risk it is posing to safety and efficacy
    - Enables alignment with process capability as it relates to process improvements
    - Enables the collection of additional scientific evidence to understand the impact of the CQA and need for future control

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