AstraZeneca

Anticipating the Exceptional Release Bottleneck

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June 10, 2025

Background

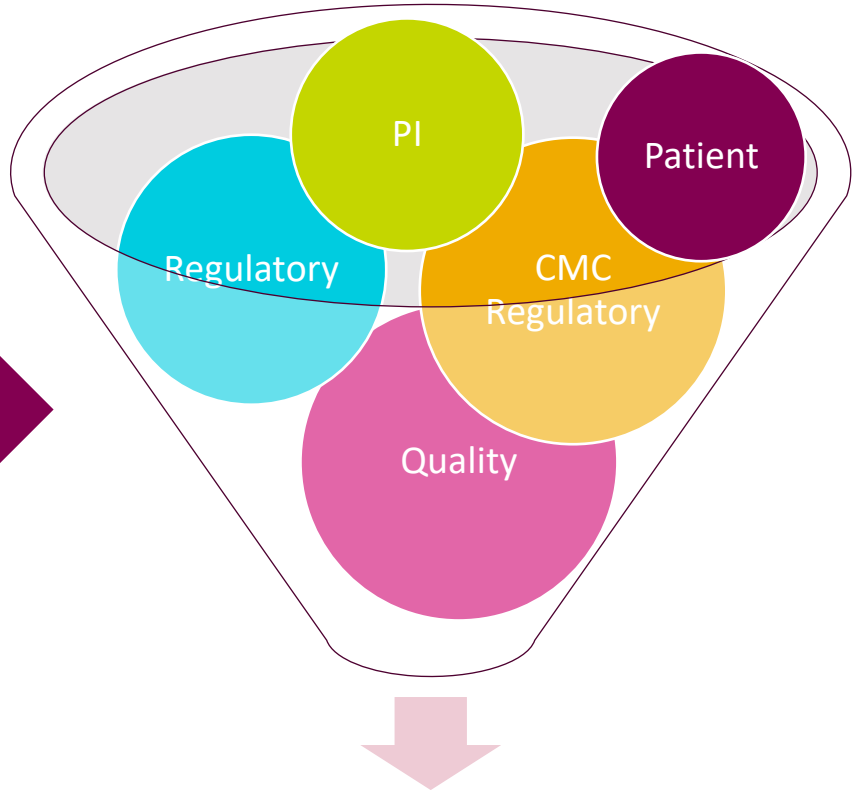
- **In this accelerated world of cell and gene therapy development, out of specification events at release are likely to occur.**
  - **Potential sources of OOS include starting material variability, raw materials used, manufacturing process consistency, microbial contamination, and analytical test method integrity.**
- **It is critical to have a harmonized and rapid process across functions to ensure continuity in providing life-saving treatments to patients in clinical trials.**

Internal Stakeholders	External Stakeholders
☐ Quality	☐ Patient
☐ Manufacturing	☐ Study Physician/Clinical Lead
☐ Process Development	☐ Principal Investigator
☐ Regulatory Affairs	☐ Treating Physician
☐ CMC Regulatory Affairs	☐ Health Authorities

What Causes the Bottleneck?

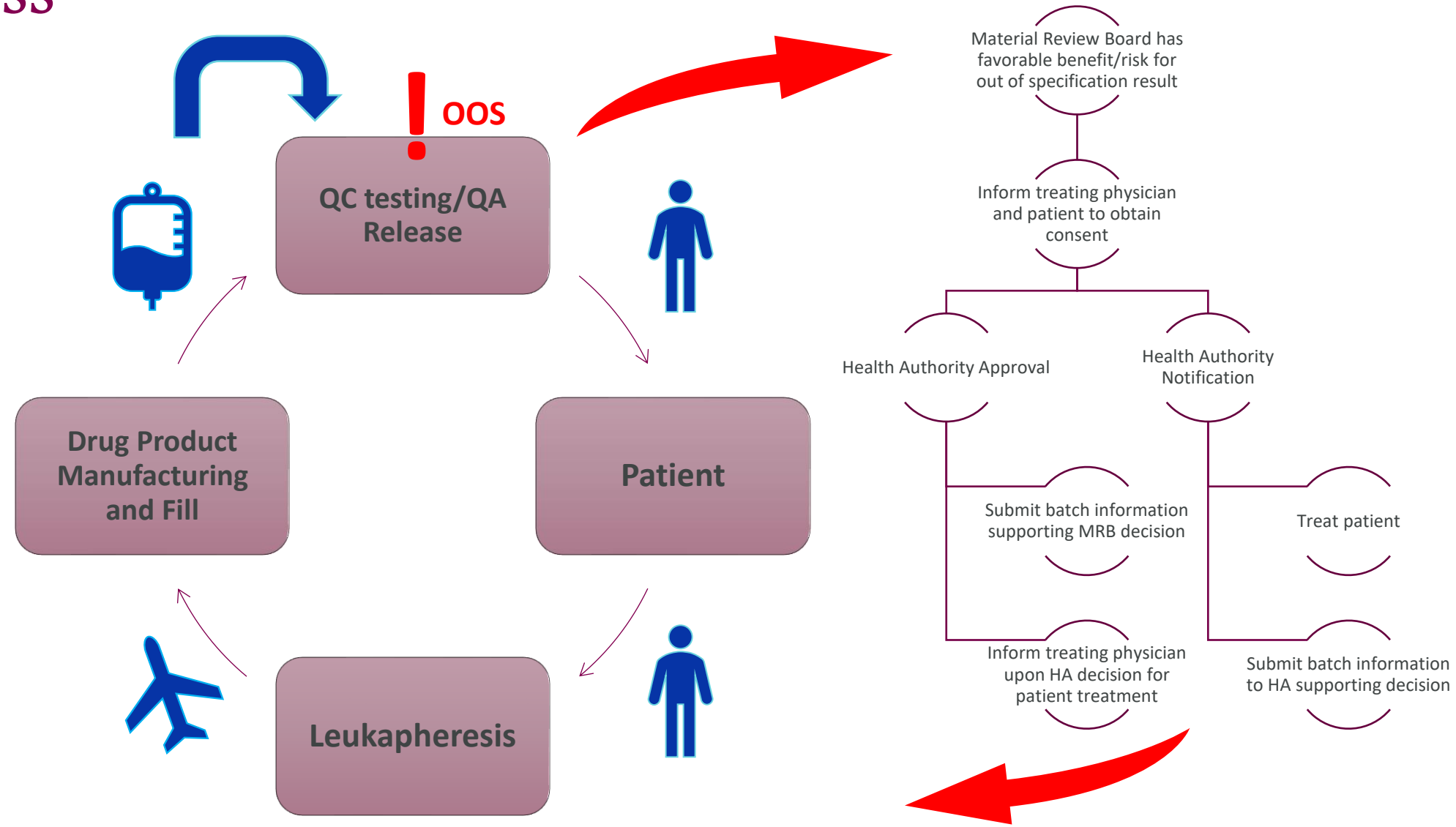
Common Challenges

- **Material Availability: Autologous CAR-T**
- **Time constraints: Need for rapid internal action to release investigational medicinal product**
- **No standardized process to address health authority requirements**
- **No harmonization of cross functional teams to enable streamline process**



Establish a standard procedure to act rapidly on releasing investigational medicinal product without compromising quality and ensuring patient safety

Process


OOS
QC testing/QA Release
Patient
Leukapheresis
Drug Product Manufacturing and Fill
Material Review Board has favorable benefit/risk for out of specification result
Inform treating physician and patient to obtain consent
Health Authority Approval
Health Authority Notification
Submit batch information supporting MRB decision
Treat patient
Inform treating physician upon HA decision for patient treatment
Submit batch information to HA supporting decision

Summary


Timely release of safe and efficacious material to the patient
Rapid standardized process
Involves key stakeholders
Considers health authorities notification vs approval
Centers around patient safety and regulatory compliance

Acknowledgements

- Jennifer Eck
- Alex Beumer Sassi
- Chenghong Wei
- Jenny Heidbrink Thompson
- Rashi Srivastava
- Joshua Montgomery
- Brooke Szymanski
- David Peel

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) - Guidance for Industry (FDA)
- Out of Specification Advanced Therapy Medicinal Products - Guidance for Healthcare Organisations, Pan UK Pharmacy Working Group for ATMPs (NHS)
- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (EMA)

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