Releasing Challenging Products
Advanced Therapy Medicinal Products (ATMPs) - Investigational Medicinal Products (IMPs)

A QP Challenge !

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Topics

The Qualified Person and Clinical Trial Legislation

Advanced Therapy Medicinal Product (ATMP) Regenerative Medicine; The Galway Story

QP challenge - ATMP specific examples

Guidance on actions to mitigate potential issues

Final Comments and Acknowledgments

The Qualified Person Legislation

Clinical Trial Regulation (EU) 536/2014 Key Reference for the QP:-

Chapter IX article 62 'Responsibilities of the Qualified Person' and article 63 'Manufacturing and Import'.

The Code of Practice for Qualified Persons in the Pharmaceutical Industry:-

- Supports the EU Legislation
- Details the particular requirements for formal qualifications and practical experience
- Provides Operational Guidelines for carrying out the functions of the QP
- Code can be referred to for Disciplinary proceedings against the QP
- Each holder of an Investigational Medicinal Product manufacturer's licence/authorisation must, at a minimum name one QP on their authorisation.

Clinical Trial Regulation

Compliance to Clinical Trial (EU) Regulation 546/2014 repealing directive 2001/20/EC which aims to in summary:-

- Protect the Clinical Trial Subject
- Improve Quality and harmonise clinical research
- Apply GMP as a legal requirement:
  - All member states
  - All phases of a clinical programme
  - All products imported into the EEA must be released by a QP.
  - Apply product specific requirements e.g. in case of ATMPs the Guidelines on GMP specific for Advanced Therapy Medicinal Products was implemented in May 2018
  - Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014. GMP guidelines for Investigational Medicinal Products.

ATMPs – Challenging Products

ATMPs are one of the more complex medicinal products; the complexity may vary according to the type of product, nature/characteristics of the starting materials and the nature of the manufacturing process.

- Human cell-based medicinal products are heterogeneous with regard to the origin and type of the cells which add to the complexity of the product.
- Cells may be self-renewing stem cells, progenitor cells or terminally differentiated cells.
- Cells may be of autologous or allogeneic origin. In addition, the cells may also be genetically modified.
- The cells may be used alone, associated with biomolecules or other chemical substances or combined with structural materials that alone might be classified as medical devices (combined advanced therapy medicinal products).
- Specifications to be established for release testing include:- identity, purity, potency, impurities, sterility, cell viability and total cell number (unless otherwise justified).

Potency remains the biggest challenge to overcome for cellular therapies.

The Galway Story

On the “Wild Atlantic Way” in the West of Ireland, a unique and established supply chain has been in operation over several years to procure, manufacture and deliver GMP approved clinical therapy (ATMP) products to patients.

This involves Galway University Hospital (GUH), Galway Blood and Tissue Establishment (GBTE), the Clinical Research Facility (CRF) and the Centre for Cell Manufacturing (CCMI-REMEDI) at the University of Galway, Ireland.

The Regenerative Medicine Institute (REMEDI) at the University of Galway were instrumental in establishing the Centre for Cell Manufacturing Ireland (CCMI) as part of their translational mission to deliver actual stem cell therapies to the clinic. To that end, after successfully securing regulatory authorisation to manufacture human Mesenchymal Stem Cells (hMSCs) for use in clinical trials, CCMI have delivered on CLI Trial EudraCT. No 2013-003447-37, ADIPOA-2 Trial EudraCT. No 2015-002125 and Nephstrom Trial EudraCT. No 2016-000661-23.

Galway Story Cont'd

The ultimate objective of these clinical programs is to offer patients with debilitating, incurable conditions an alternative treatment through advanced therapies. These State-EU funded treatments were clearly "Not for profit" and the challenge to commercialise such treatments is a pressing goal for all stakeholders in the ATMP – Cell and Gene Therapy space.

The intention of this part of the presentation is; using ADIPOA-2 clinical trial as an example, to offer an insight into the challenges and complexities, based on experiences gained from delivering such therapies from a Hospital - University - Hospital setting.

Osteoarthritis

ADIPOA-2

No approved pharmacological intervention, biological therapy or procedure prevents the progressive destruction of the Osteoarthritic joint.

All current approved treatments, without exception, produce symptomatic rather than regenerative results.

Cellular therapy may deliver solutions for Osteoarthritis.

Clinical Trial :

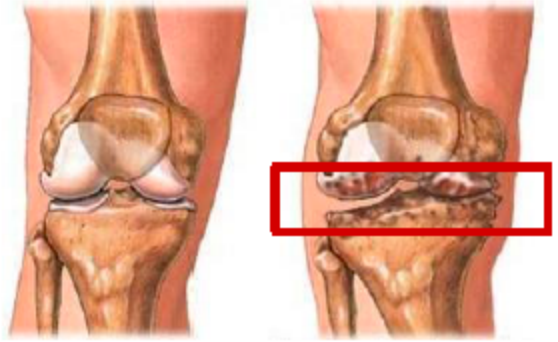
A phase 2b Study Evaluating the Efficacy of a Single Injection of Autologous Adipose Derived Mesenchymal Stromal Cells in Patients with mild to moderate Knee Osteoarthritis.

CCMI
Centre for Cell Manufacturing Ireland

Osteoarthritis

ADIPOA-2

Presentation

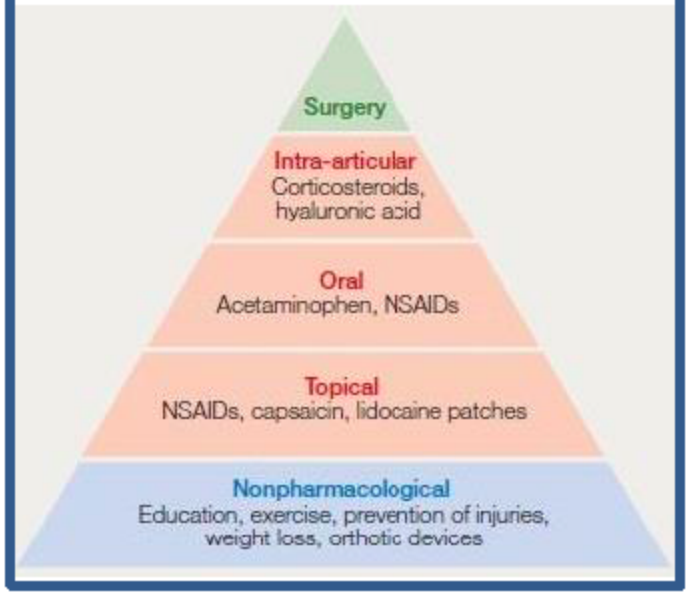


- Cartilage degradation
- Osteophyte formation
- Inflammation
- Pain

Risk Factors

- Age
- Body mass index
- Sex
- Injury
- Genetics

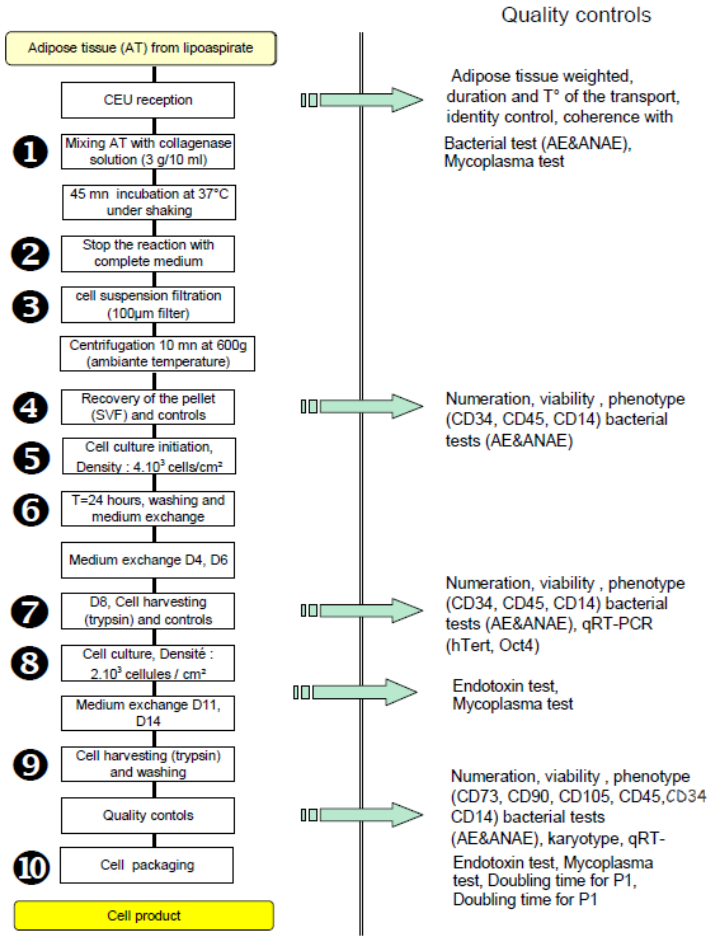
Treatments

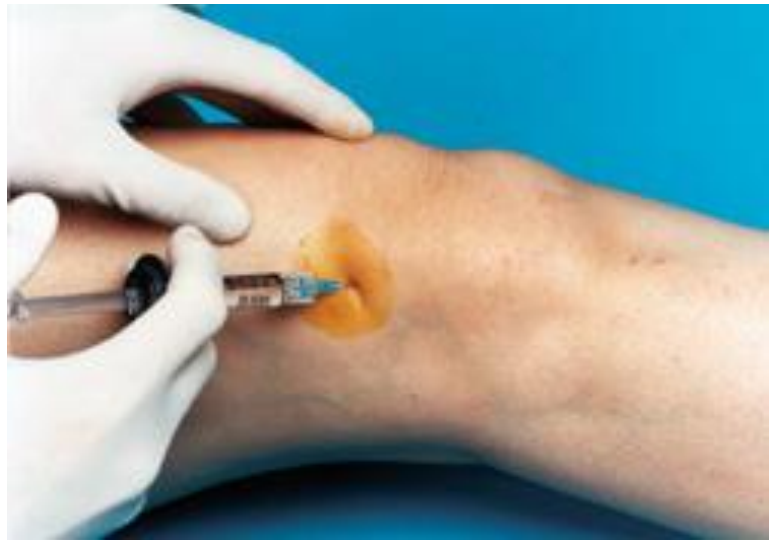


CCMI Centre for Cell Manufacturing Ireland

The ADIPOA Clinical Study

ADIPOA-2





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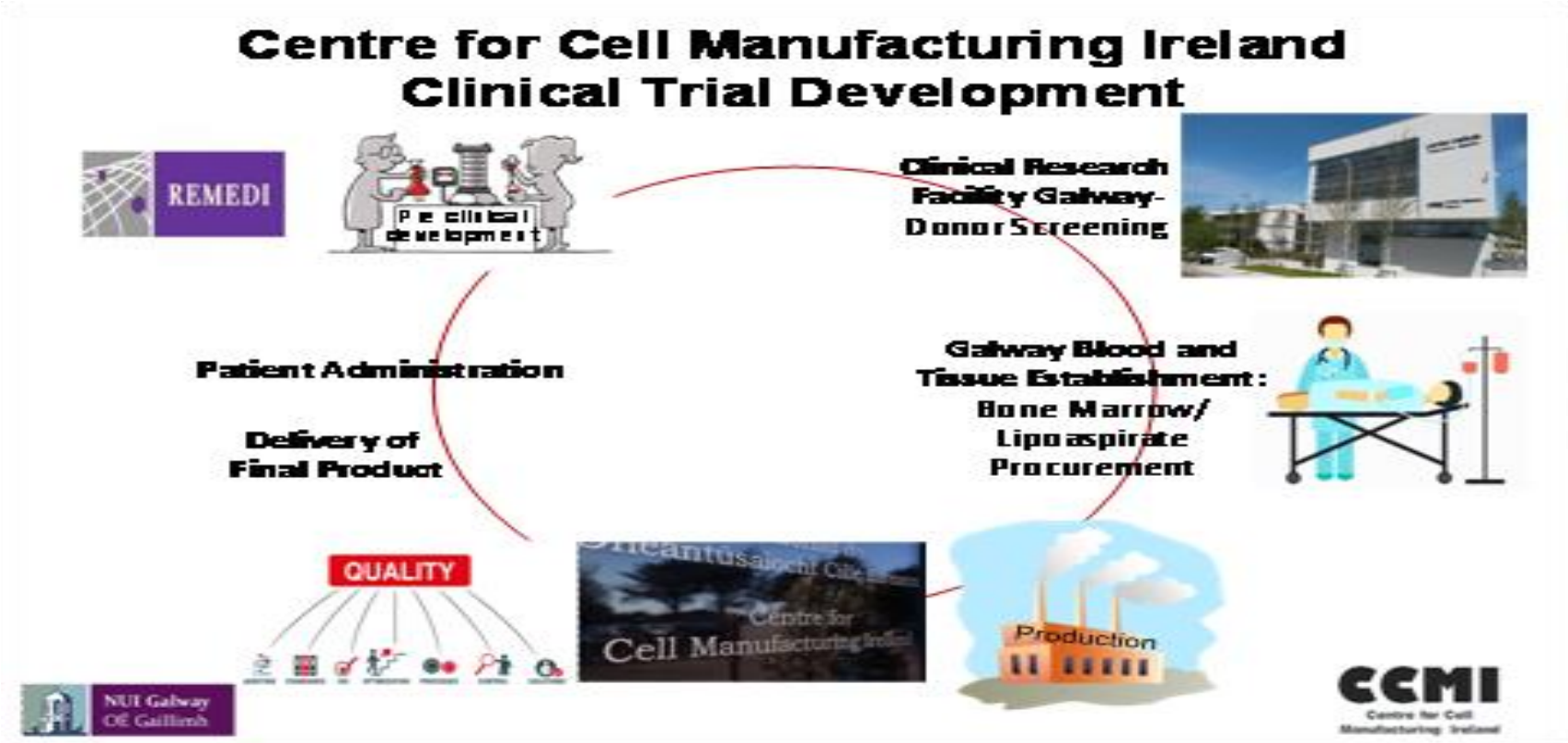
ATMP local Supply Chain



Cell Therapy Manufacture specific challenges

- Developing the GMP mindset from the start in an academic-research setting to achieve and maintain a GMP Licence.
- Donor variability
- Capacity constraints – Incubating batch over 2 to 3 weeks need to schedule accurately
- Harvesting: Continuous Process (not automated), maintain sterility during this process
- No final product filtration possible - aseptic filling – sterility assurance
- Fresh Product vs Cryopreservation (LN2) requirements
- Trial Design challenges; Clinical complexity e.g., Plastic Surgeon, Radiologist, Orthopedic surgeon
- Autologous expanded cell therapy is the most complex option

CCMI
Centre for Cell Manufacturing Ireland

Cell Therapy Manufacture specific challenges cont'd

- Validation Challenges
  - Batch to batch variation,
  - Lack of a clear biological framework relating to therapeutic mechanism,
  - Lack of potency tests
  - Lack of supply of starting material

For example, having to repeat training or validation runs, is not straight forward where one cannot open the fridge or freezer to take out more active starting material. Procuring fresh starting material involves screening a willing donor, securing the services of clinicians, nurses and scientists, to do this.

- Shipping i.e. temperature control requirements for Fresh Product i.e., 24 -hour shelf life @ $2^{o}C$-$8^{0}C$

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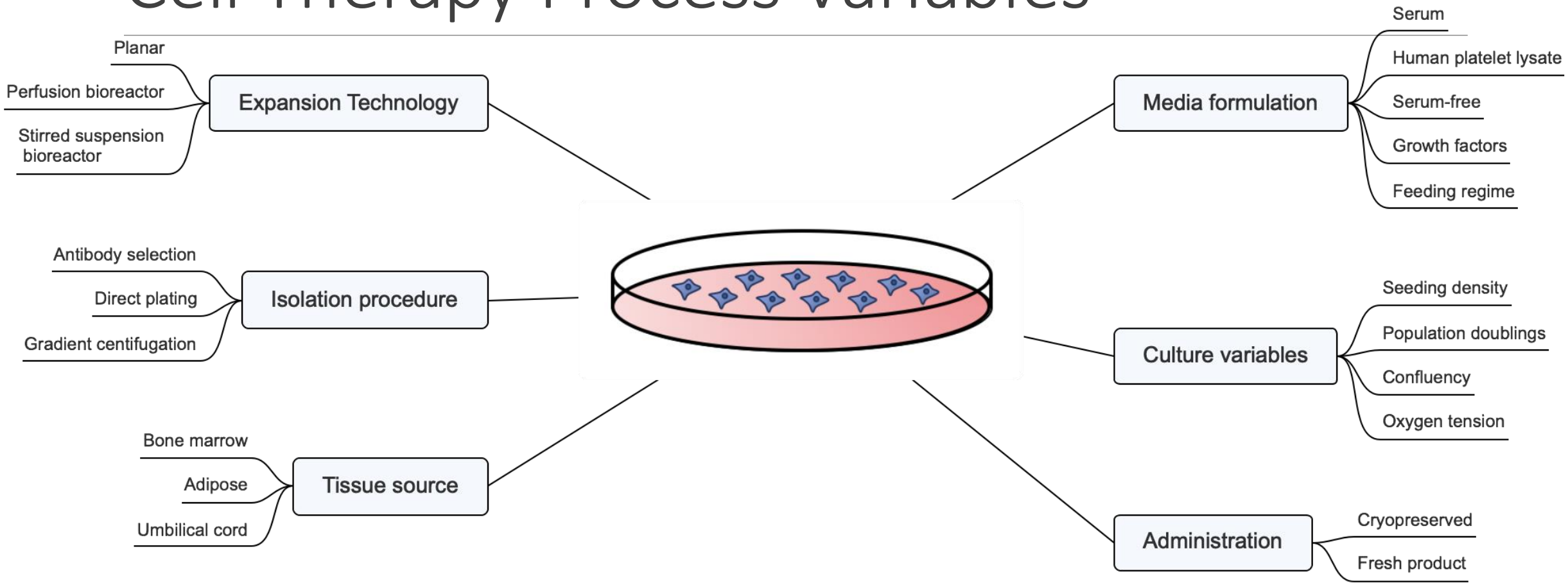
Cell Therapy Process Variables



Challenging Products - QP Disposition of ATMPs

Test Specifications- Sterility Testing

Microbial contaminants found inside or outside the cell.

Cannot be terminally sterilised by filtration.

Testing is limited due to the amount of material for testing and time is limited due to short shelf life.

Risks are controlled via testing of raw materials, validation of aseptic manufacturing process and aseptic qualification of production personnel.

PhEur 2.6.27 Microbiological Examination of Cell-based Preparations chosen – small sample size, detection (Co_2), more sensitive, rapid. Validation of the test using e.g. the ‘ BD Bactec FX 40 system’ within seven days.

In addition Mycoplasma and Bacterial Endotoxin rapid testing carried out – Results should be negative, reference and limit of detection is determined.

Summary of the potential challenges for QP release of ATMP IMPs

- Production and or testing issues resulting in window for QP release being significantly reduced.
- QC testing – Biological testing e.g. Karyotyping, Rapid Mycoplasma or Sterility testing can present challenges.
  - Lack of timely receipt of safety test results for a short shelf life product. *What to do … clinician and patient expecting product ?*
- Typically, ATMPs have short shelf lives and therefore a particular strategy is required to justify release without full test results being available.
  - QP needs to be experienced with the process and product to be comfortable with releasing the product quickly and without all release testing being completed, to meet a short treatment window.
- Initial underestimation of project implementation resources and timelines, complexity of equipment.
- Outsourcing key services can be challenging but is often essential to get the desired result.
- GMP requirements for manufacture of ATMP sterile medicines – Aseptic filling due to nature of product.
- Temperature controls during the shipment of the ATMP- validation of the shipping route

Guidance to mitigate potential issues

Compile and review documentation e.g. batch records in advance or in parallel while testing of IMP in progress. Confirm and review relevant validation/qualification documentation in place.

Review regulatory licences at regular intervals to ensure all activities are covered as required and current.

Ensure good open communication between colleagues at other sites e.g. Clinical Trial site, procurement site, testing sites

Ensure the Quality system is well documented, robust and flexible to meet current clinical trial programme needs e.g. interim release while maintaining GMP.

The QP knowledge of the sites ability to control design-and-build projects that result in high performance and validated facilities, is essential.

Guidance to mitigate potential issues Cont'd

- QP needs to have access to Clinical Trial Protocols, Investigational Medicinal Product Dossier (IMPD), Investigators Brochure (IB), Product Specification File.
- QP needs to know when a Clinical Trial Authorisation (CTA) is "approved" by the Regulatory authorities … and if any restrictions e.g. clinical trial protocol study design changes, provision of QC data to the regulator's at certain additional points to that in the IMPD.
- QP needs to be aware when any amendments to a CTA are proposed/submitted/approved and their possible impact on safety, quality and compliance
- This is where a strong sense of Quality Assurance really comes to the fore and full QP oversight of all aspects of manufacture and testing is paramount.

Final Comments and Acknowledgements

A thorough understanding of biological processes and the variability this brings is required. This understanding coupled with a flexible and pragmatic approach are invaluable.

The EMA have published a Q&A on Exemptions on batch controls carried out on ATMPs to help support QPs in the complex issues which can arise for QP certification of ATMPs.

Acknowledgements and a relevant reference for interest:

Centre for Cell Manufacturing Ireland (CCMI), University of Galway

Marrow changes and reduced proliferative capacity of mesenchymal stromal cells from patients with “no-option” critical limb ischemia; observations on feasibility of the autologous approach from a clinical trial – ScienceDirect

Cytotherapy Journal Volume 24 Issue 12, December 2022.

Comments and Questions welcome ..

Thank you

RELEASING CHALLENGING PRODUCTS & CHALLENGING PRODUCT RELEASES

QP FORUM 13MAY2025

JOHN CAHILL

- The Biologic Product '***QPinumab***' is supplied to multiple international markets ***by QPForum Inc.***

  (Fortunately, QPForum Inc. has an experienced QP Team comprising of this audience!)

- The product is a rare disease medicine and patients are critically dependent on the continuity of this medicine's supply. Patient populations are relatively small (100's/1000s and alternative therapies/medicines don't exist.

- The product is manufactured and tested across an internal and external network of CMOs and CLOs

- The product has a stable history of conformance to specifications and QP Release

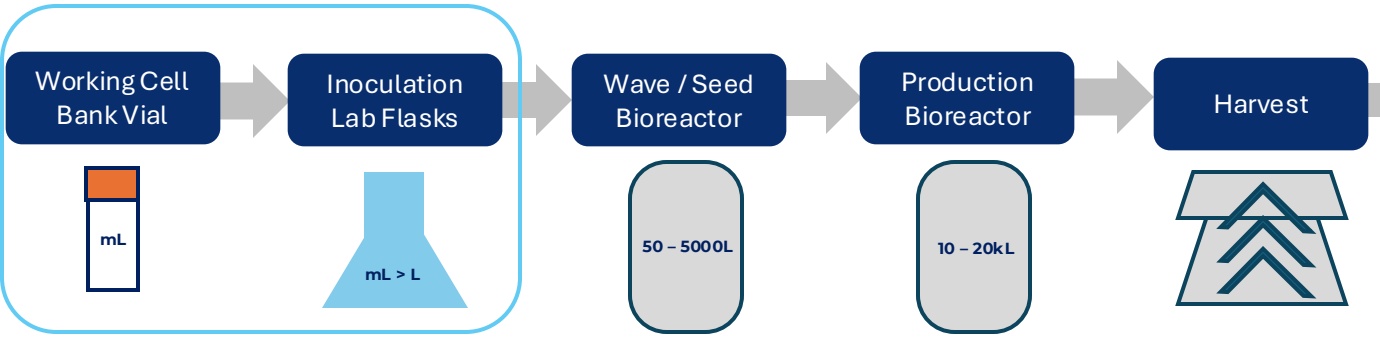
- The end-to-end manufacturing steps follow a standard biologic platform process flow (see next slide)

- DS and DP product is stored at 2-8°C; The shelf-life of the drug product is 24 months

MANUFACTURING OVERVIEW (DS → DP → FP)

DS Upstream Processing

Culturing the cells through a series of expansions up to desired production scale volume



DS Downstream Processing

Focused on purifying and final formulation for filing into product containers (Chrom, UFDF, VI/VF, DS Filling)

- Cell debris / media / viruses **removal** [**S**afety]
- Final buffer / excipient **formulation** [**I**dentity]
- Desired product **concentration** [**S**trength]
- Product **Impurity** reduction [**P**urity]
- Prevent **microbial** ingress [**Q**uality]

Final Fill Bulk Drug Substance

DP (Filling)

FP (Labelling & Packaging)

THERE IS AN EVENT AT OUR CMO WHO MAKE THE DS...

- There is a DS Manufacturing Deviation at our CMO – It isn't considered significant from a criticality perspective to inform QPForum Inc.
- At release of this DS, the DS batch (DS0001) is confirmed OOT for one of the critical quality attributes, tested by HPLC.
- The OOT result is 93.0% where the specification is ≥90.0%.

Q: Should QPForum Inc. be informed of the OOT?

When & Why?

SO, WHAT HAPPENED...?

- The 'most probable' root cause of the OOT result in the DS batch, is attributed to 'atypical manufacturing issues' at the CMO during processing of 2-8°C drug substance (DS) batch DS0001. These 'issues' are captured as part of a quality investigation at the CMO.

What are the key considerations for assessing product impact in this situation?

- Scope/Extent of the issue (other lots affected?)
- Data trending and historical data performance (DS to DP)
- Stability (DS and DP)

THE STABILITY QUESTION?

- A statistical assessment concludes that any Drug Product (DP) batch filled from DS0001 must produce a DP release result of at least 92.0% to ensure conformity with the specification of ≥90.0% through 24-month shelf-life. The assessment concludes that the DP batch DP0002 will remain in specification based on the predicted linear degradation observed typically to date.

Are we going to put this DP batch into our stability programme?

Is QPForum Inc. putting batch DP0002 into our stability programme?

THE PLOT THICKENS...

- At release of the DS in our CMO (and in consultation with the QP at QPinumab), it is decided to place the DP from DS batch DS0001 into the stability programme to monitor this batch to end of shelf-life.
- This DS batch is filled into DP batch DP0002.
- OOT results (unsurprisingly!) are obtained for DP0002 during release testing.
- The HPLC result for DP batch DP0002 is 91.5%.
- Batch DP0002 HPLC release result failed to meet the minimum % value specified in our statistical assessment (92.0%) to ensure conformance to specification to end of registered shelf-life.
- There is currently no other DP available to supply one market.

What options do we have?

What options do we have?

CHOOSING A DIFFICULT OPTION...

- One option considered could be to decrease shelf-life on batch DP0002.

What do we need to consider here?

- The data available to support this change.

- The change control details – impact assessments, getting the right people involved

- The market requirements for the proposed change

- The impact to patient supply of rejecting the batch

BATCH RELEASED...

- To ensure continuity of patient supply in one specific market, a change control is implemented by QPForum Inc. to apply a reduced expiry date of 18 months to batch DP0002.
- As assessed by our statistical analysis, this will provide assurance of compliance to end of shelf-life specification.
- FP0003 (one of two finished product batches FP0003 & FP0004, packed from DP DP0002) can be released by QPForum Inc. to the market identified.

PERFORMANCE OF DP0002 ON STABILITY

- Monitoring of DP0002 is undertaken by QPForum Inc. at each stability timepoint to ensure that the batch was performing in line with the statistical assessment projections over 18 months (as per slide 7).

- At the 6-month stability timepoint all specifications are met, and the HPLC results are performing as expected (HPLC result for DP batch DP0002 @6M is 91.5%).

- However, at 12-months an unexpected OOS result is obtained: 89.5% versus specification of ≥90.0%.

[Our critical quality attribute OOS may cause loss of efficacy and immunogenicity.]

Immediate Actions needed!

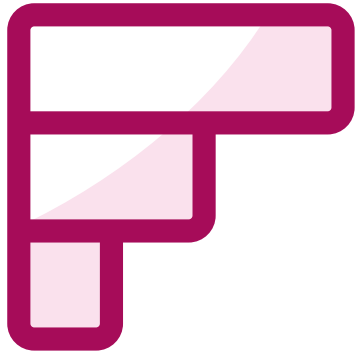
IMMEDIATE ASSESSMENT FOR RELEASED BATCH FP0003

OWNER: JOHN CAHILL

Context: the 12-month stability OOS result is observed when

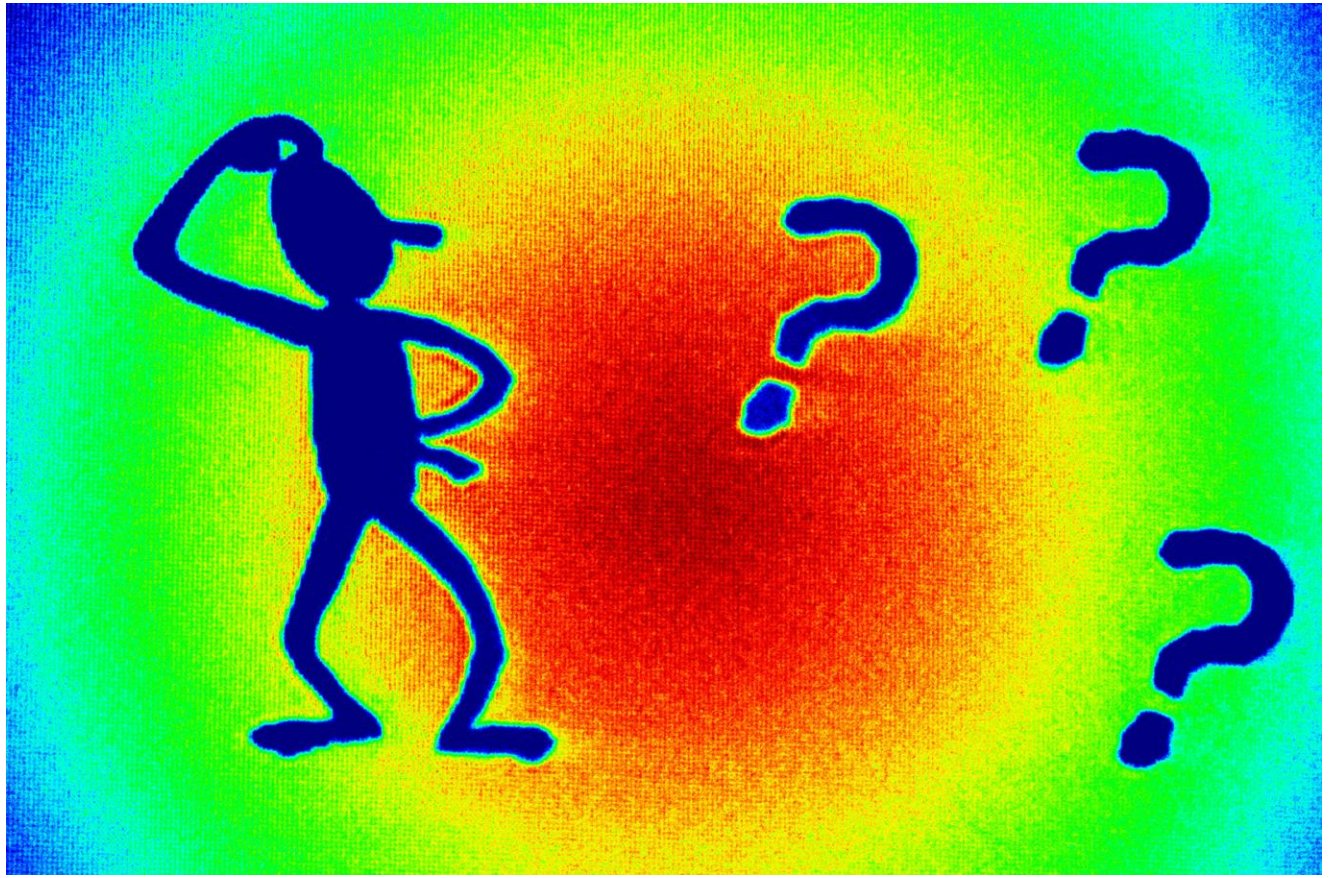
- FP0003 is partially distributed to clinics and hospitals (consumed) and the remaining portion stored at the distributor.
- FP0004 is not yet released by QPForum Inc.

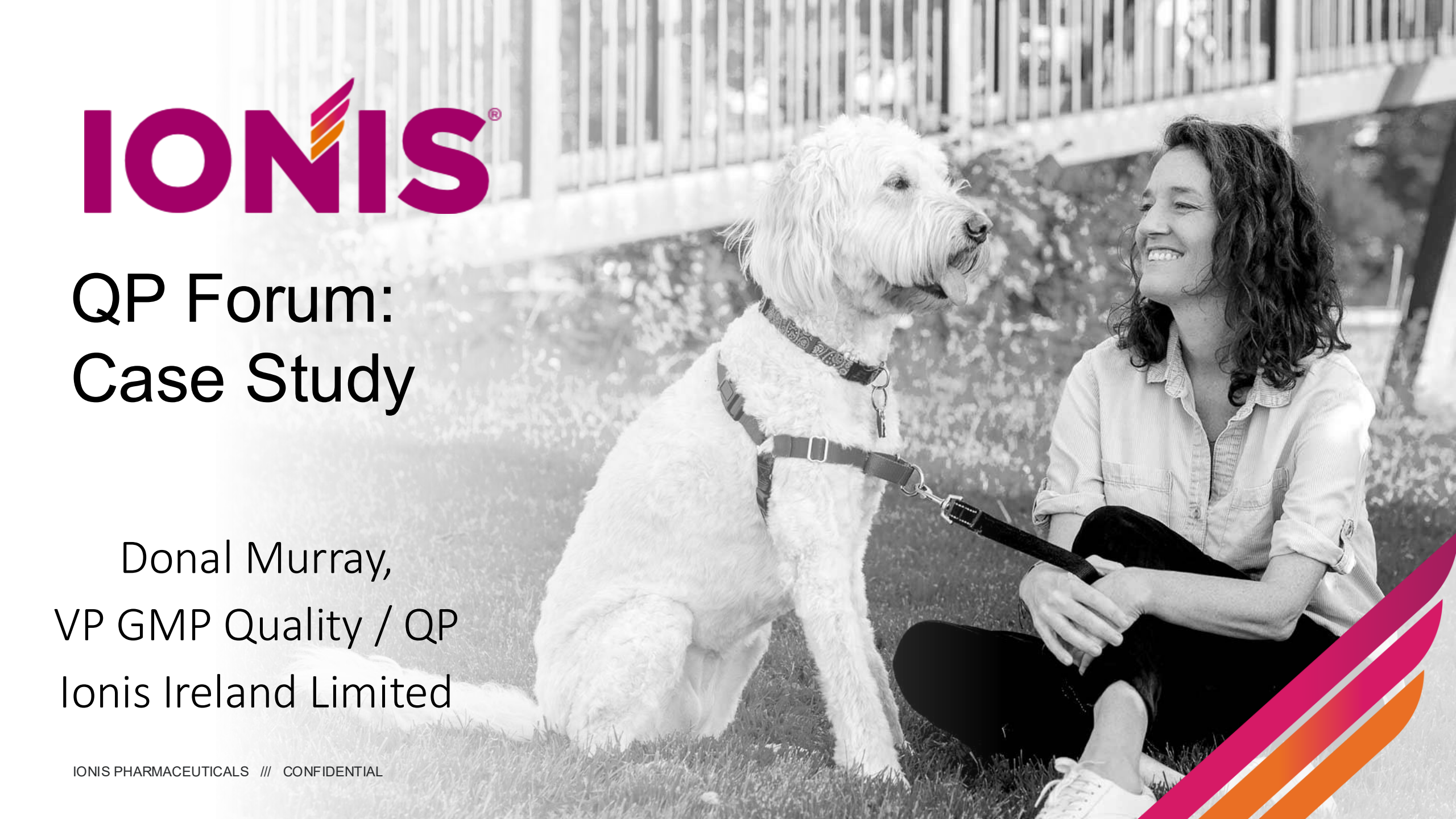
Next Steps...



Rank the following 'next steps' in order of what step will be initiated first, second, third etc.

QUESTIONS





QP Forum: Case Study

Donal Murray,
VP GMP Quality / QP
Ionis Ireland Limited

Purpose

- Alexander's Disease (AxD): rare genetic condition that affects the nervous system caused by a mutation in the GFAP gene.

- The disease primarily affects infants but also impacts adults, with symptoms that range from problems with movement, speech, swallowing and cognitive skills.

Medicine

- ION373 injection, 20 mg/ml, 2.8 ml vial in a buffer solution, with aCNF (artificial CeriboSpinal Fluid) diluent in a separate vial for dose adjustment
- Similar in composition to cerebrospinal fluid (CSF) in the body
- Intrathecal injection (IT) to cross the blood-brain barrier through lumbar puncture (injection)
- ION373 is designed to target the messenger RNA (mRNA) of the GFAP gene. By doing this, it aims to reduce the production of abnormal GFAP protein, which is thought to be the main cause of problems in Alexander Disease.
- The goal is to slow down or stop the progression of the disease, potentially improving or stabilizing symptoms.

IONIS

Clinical Trial

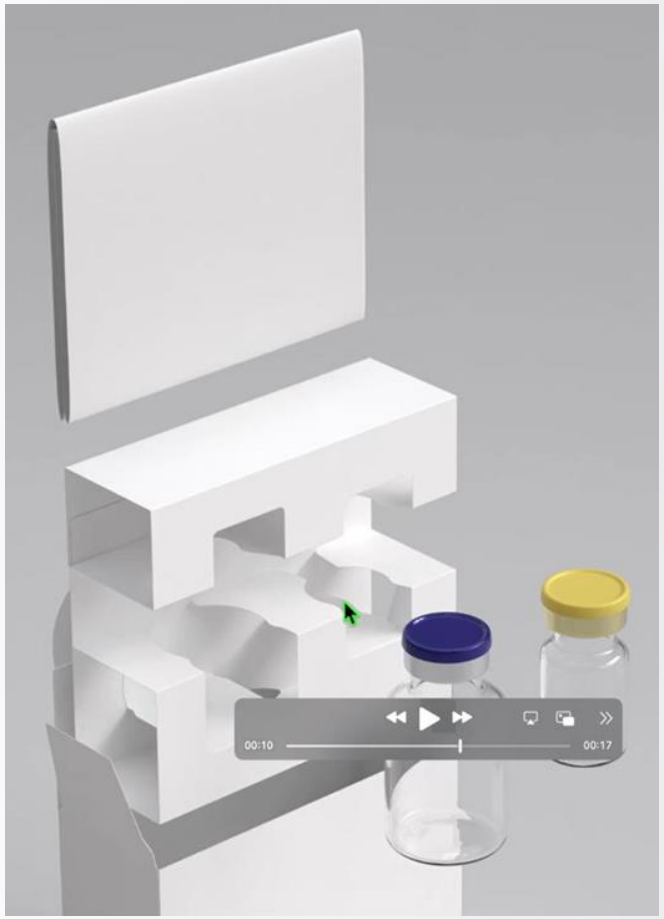
- This study is called “ION373-CS1” and is described as a Phase 1-3, double-blind, randomized, placebo-controlled study.

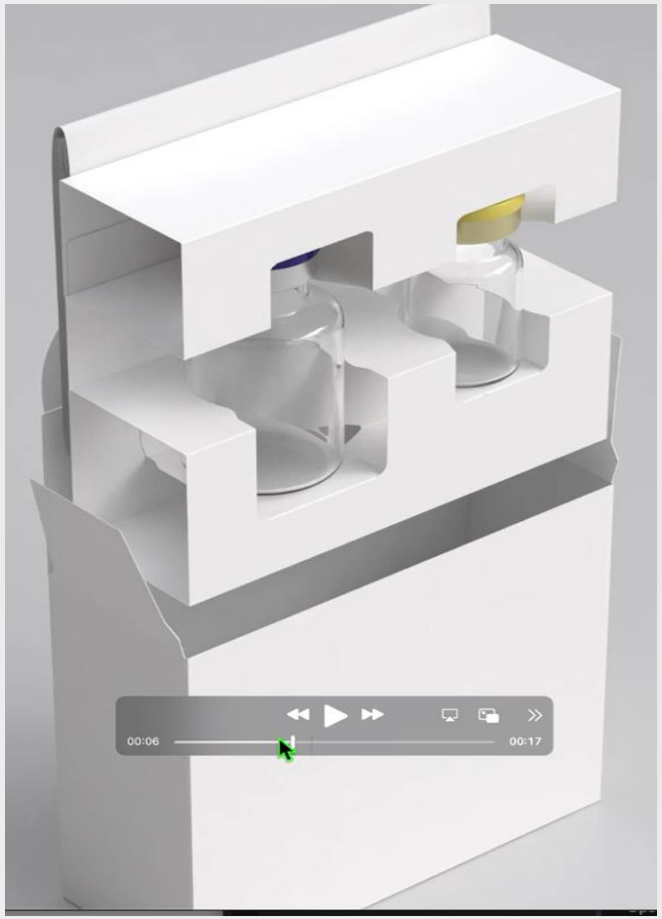
- This means that some participants will receive ION373, while others will receive a placebo (a substance with no active ingredients), and neither the patients nor the doctors will know who is receiving which until the end of the study.

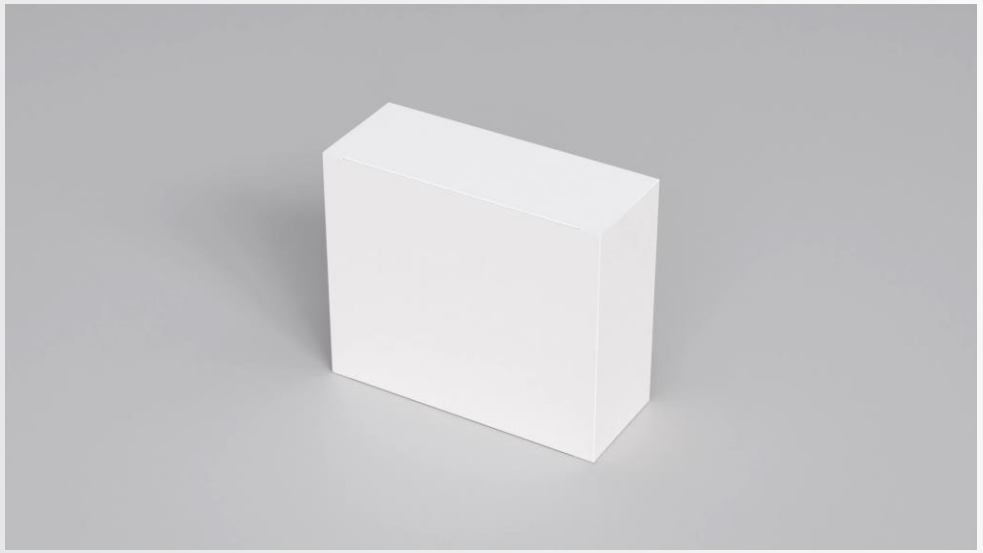
- Objective: Evaluate efficacy in improving or stabilizing gross motor function

IONIS

Potential commercial presentation







- Active in 1 vial, 2.8 ml
- Second vial is aCNF as diluent
- Space for PIL/USPI/IFU (leaflets)

Considerations as a QP

- Nature of injection as intrathecal requires careful review of all documentation, especially change controls, deviations and any laboratory OOS
- Focus should always be on the patient
- Experience as a QP should enable you to make a decision on the quality, safety and efficacy of the medicine

IONIS

Considerations as a QP - Drug Substance

- Drug substance specification is tighter for this material than for other equivalent drug substances

e.g. Bacterial Endotoxins is NMT 0.009 EU/mg, as compared to NMT 1.0 EU/mg

- Total Aerobic Microbial Count (TAMC) and Total Combined Yeast and Mould (TCYM) limits are also tighter

- Trending of manufacturing In-Process Control (IPC) data and ongoing stability is important to determine any trends or unexpected results

IONIS

Considerations as a QP – Drug Product

- Formulation is isotonic, with pH and osmolality control important during aseptic manufacture
- Container closure seal integrity is critical to prevention of microbial contamination
- Bacterial Endotoxins is NMT 0.23 EU/mL as compared to NMT 300 EU/mL for other aseptic injections
- Visual inspection of the finished units is also very important due to the nature of administration
- Trending of manufacturing In-Process Control (IPC) data and ongoing stability is important to determine any trends or unexpected results

IONIS

Considerations as a QP - General

- Specifications, manufacturing methods and critical process parameters must be defined within the IMPD or NDA/MAA based on scientific assessment and justifications

- QP should take into account the patient and the method of administration when assessing:

- Batch manufacturing records
- Analytical results
- Change controls
- Out of Specifications
- Deviations

Thank You