The use of advanced therapy medicinal products – new competencies for hospital pharmacists

Seminar PH4

Anne Black
Assistant Director of Pharmacy - Quality Assurance

Disclosure

Relevant Financial Relationships

None

Off Label Investigational Uses

None

Questions

- Are pharmacists responsible for the use of ATMPs in hospital practice?
- Do pharmacists have the required training to prepare ATMPs?
- Can pharmacists fulfil the requirements of GCP for ATIMPs?

Presentation contents

- Pharmaceutical Governance considerations for ATMP usage in hospitals
- Practical considerations for pharmacy
- Case studies of clinical trials involving ATIMPs

ATMPs are not the same as traditional pharmaceuticals with which we (pharmacists) are familiar

"Fillet of a fenny snake,
In the caldron boil and bake;
Eye of newt, and toe of frog,
Wool of bat, and tongue of dog,
Adder's fork, and blind-worm's sting,
Lizard's leg, and owlet's wing,—
For a charm of powerful trouble,
Like a hell-broth boil and bubble."
Shakespeare's Macbeth

- Traditionally have not entered the hospital via pharmacy
- Largely uncomfortable for a pharmacist at first site!

What is the same about ATMPs?

ATMPs are medicines

- often injectables

Pharmacists need to consider how these medicines are safely

Prescribed

Prepared

Administered

Monitored

We have a duty of care to our patients to ensure that the medicines provided are of suitable quality

Usage of ATMPs in Hospitals

- MA products
  - Centrally regulated
    3 approved with MA in EU
- Clinical Trials as ATIMPs
  - As a manufacturer
  - As a site in a clinical trial
- Unlicensed Medicines
  - Non routine manufacture (Hospital Exemption)
  - Individual patients with special clinical need.

Trials involving ATIMPs

- Manufacture of the ATIMP must occur within a facility holding an MIA(IMP) authorisation.
- Products must be released by a Qualified Person(QP).
- QP must ensure that donation and procurement of cells for use as raw materials in manufacture complies with EU Tissue and Cells Directive.
- CTA must be obtained from competent authority of individual member states

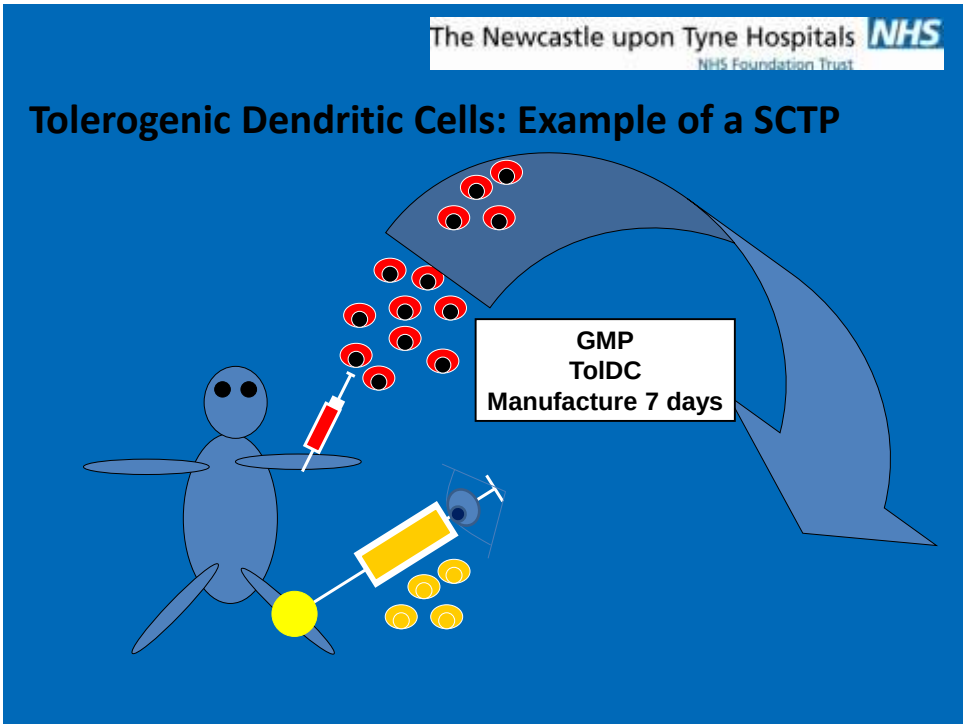
Scenario 1:

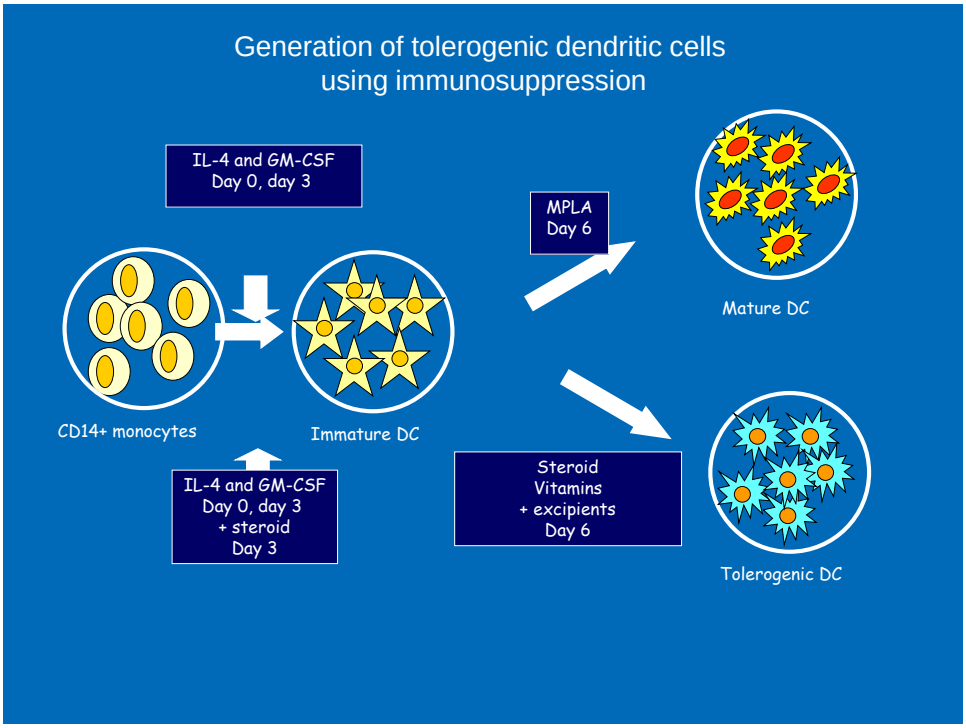
Manufacture in house.

Requires a Manufacturer's authorisation from the competent authority

MIA(IMP) for a clinical trial.
Needs Qualified Person Release

Unlikely unless part of a highly research active organisation who wish to sponsor a clinical trial.

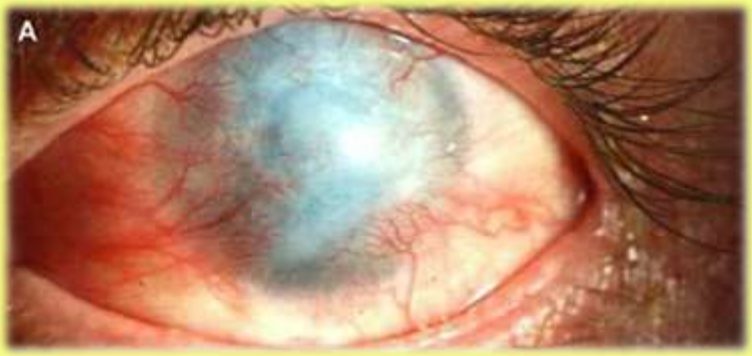


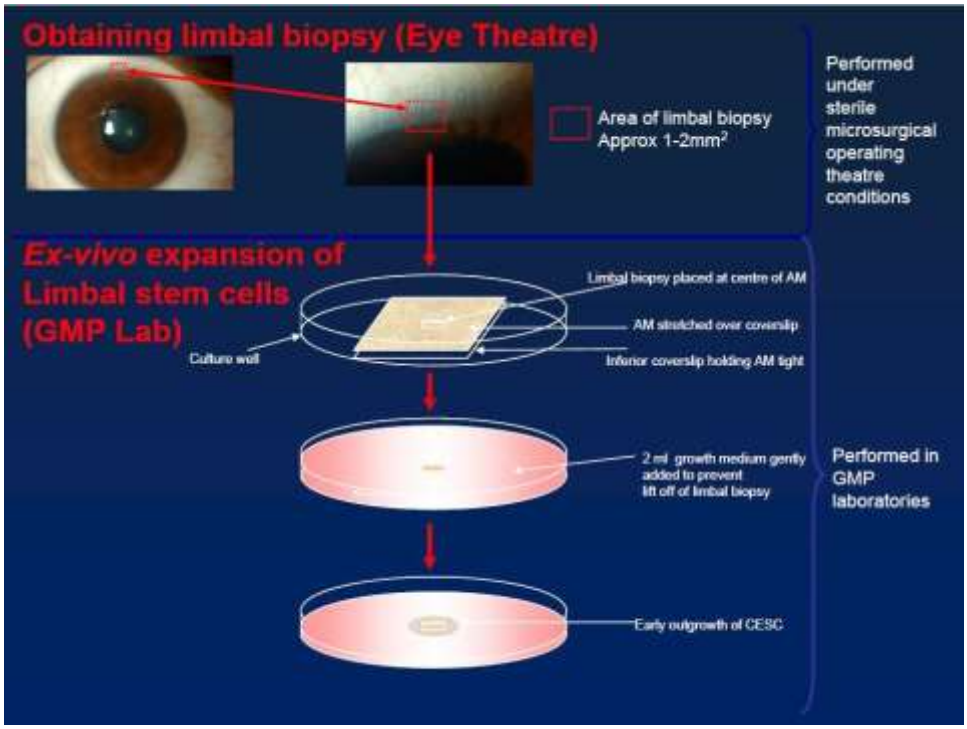


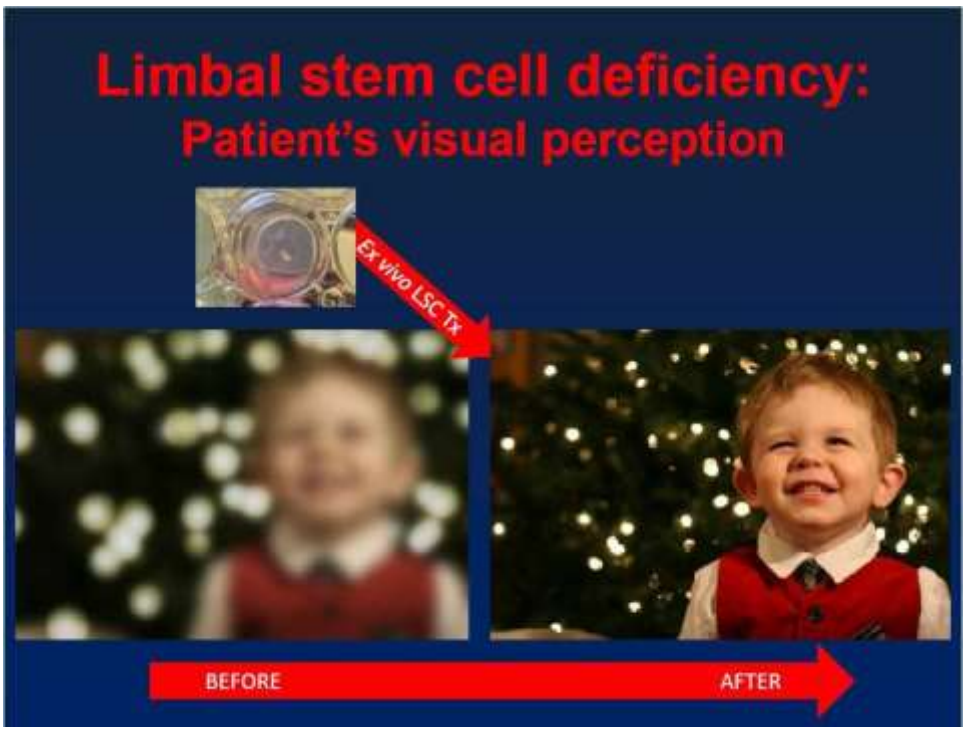
The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Examples of Tissue Engineered Product

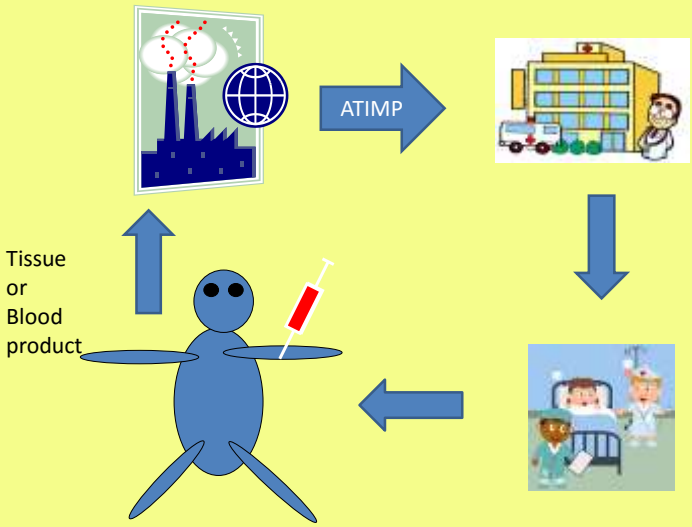
Limbal Stem Cell deficiency




Obtaining limbal biopsy (Eye Theatre)
Area of limbal biopsy
Approx 1-2mm²
Performed under sterile microsurgical operating theatre conditions
Ex-vivo expansion of Limbal stem cells (GMP Lab)
Limbal biopsy placed at centre of AM
AM stretched over coverslip
Culture well
Inferior coverslip holding AM tight
2 ml growth medium gently added to prevent lift off of limbal biopsy
Performed in GMP laboratories
Early outgrowth of CESC

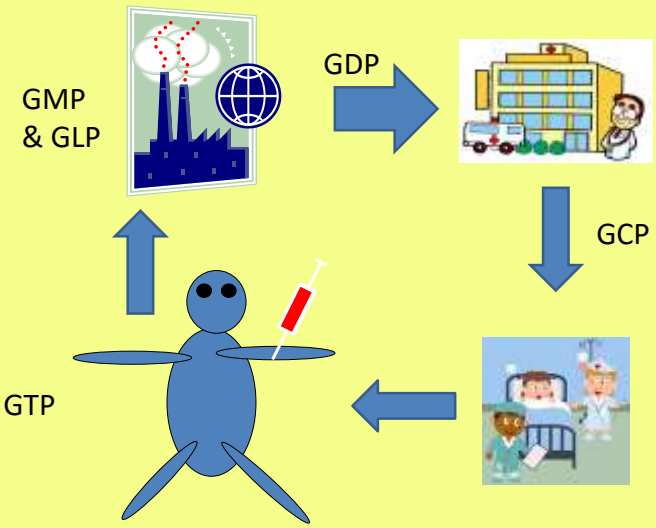

Limbal stem cell deficiency:
Patient's visual perception
Ex vivo LSC Tx
BEFORE
AFTER

Scenario 2: On site Raw material Procurement: Off site IMP Manufacture

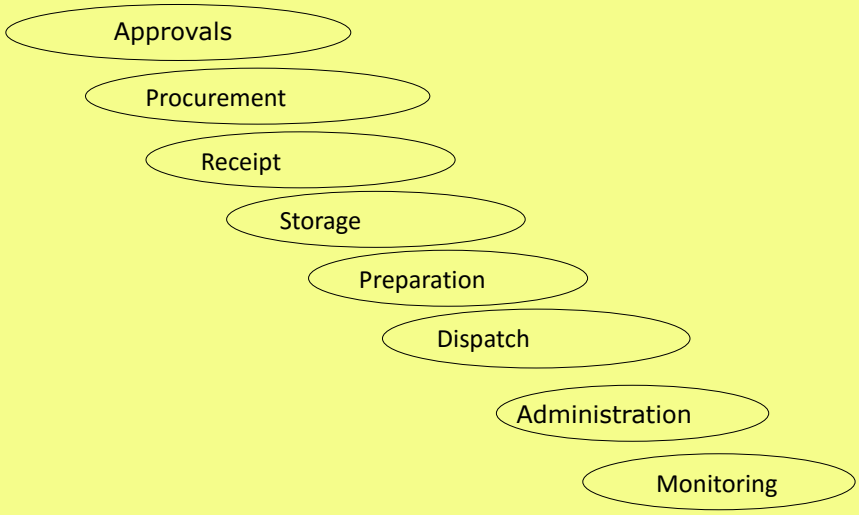


The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Scenario 2: Regulatory GxPs



Pharmacists need to think about the ATMP Journey



Approvals / Governance

- Pharmacists ensure appropriate governance in place for:
  - MA products
  - Clinical Trial products (ATIMPs)
  - Unlicensed Medicines
- Are existing governance mechanisms sufficient?
- Are ATMPs different?

Newcastle Experience

- MA: Access to Drugs Policy / Formulary
- IMPs: Research and Development Process
- ULMs: Medicines Management Committee

Consideration re Expertise deficit.

- Escalated to Clinical Governance and Risk Committee.
- Need all ATMPs to be assessed by expert committee?

  Compare with GMO safety committee requirement.

Procurement / Ordering

- Autologous Product: Standards re procurement of the starting material
- Allogeneic

  Considerations:
  - ATIMPs: CT Pharmacist involvement
  - ULMs: QA involvement

- Logistics need to be understood prior to ordering.
- Up front work always required.

Receipt and Storage

- Fridge item/Ambient
  - Dedicated storage for IMPs. Segregated storage for blood products.
    - Temperature
    - Label
    - Appearance
    - ATMPs often have a short shelf life…logistics
- Cryopreserved - 80°C
    - Dry shipper
    - Handling – pharmacy staff inexperienced
    - -150°C freezer or Liquid Nitrogen tank
    - Not familiar / available to pharmacy. Specialist training required.
  - Routine temperature monitoring and mapping required as for all medicines

Cryopreserved products will require defrosting

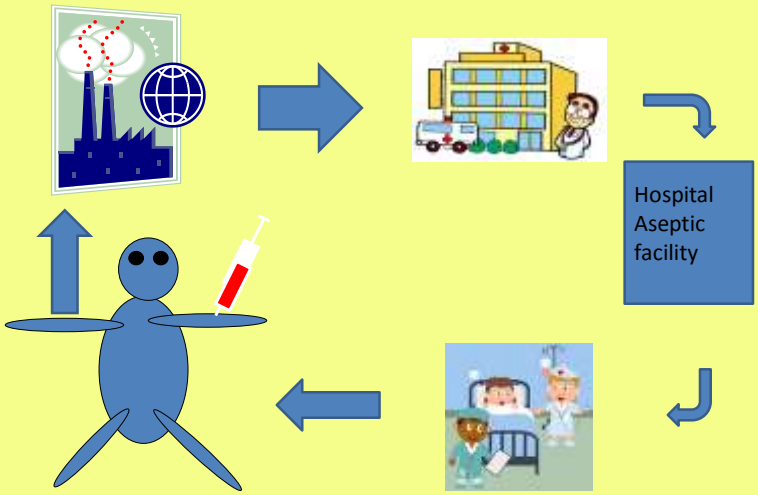
- *Considerations for pharmacy:*
  - *Temperature*
  - *Time to defrost*
  - *Product Integrity*

Space
Staff availability
Staff training

Cryopreserved product will require defrosting

Is this product suitable for administration? Specialist training required.

Scenario 3: On site Raw material Procurement: Off site IMP Manufacture: Specialist Preparation



Processing - location

- Eudralex Volume IV Annex 2: Manufacture of biological active substances
- Manufacture in Grade A environment (isolator or LAF or class 2 safety cabinet)
- Dedicated facilities are not prescriptive. Documented justification required if not used.

MHRA Questions and Answers for Specials manufacturer's Version1

Can a Specials Manufacturer use shared facilities and equipment for Biological Products?

- This will depend on the nature of the products being processed and the processes conducted. It is unlikely that traditional aseptic 'Specials' may be manufactured using the same facilities and equipment as biologicals and a risk assessment should be performed as the basis for any justification.
- Factors to consider include the potential for transfer of viable cellular, viral or genetic contaminants, including adventitious human pathogens, and the control strategies in place to address these risks. There should be awareness of the type of technologies and starting materials used in biological product manufacture (live cells, viral vectors, and human blood and tissues) which each present a different challenge to the prevention of cross contamination.

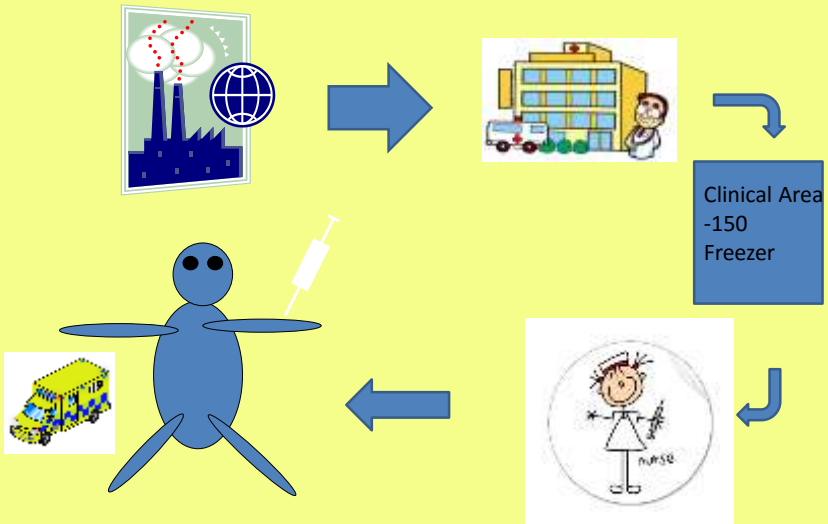
Preparation for Administration – where is best?

- Dedicated Cellular Therapies Facility

- Is a Pharmacy Aseptics suite suitable?
- Does it need to be dedicated to ATMPs?
- Will pharmacy operators need specialist training?
- Need definitive advice for our practitioners.

Risk Assessment is the best answer currently. Assess each request on a case by case basis.
See what other options are available within your organsiation.

Scenario 4: Off site IMP Manufacture – 24/7 recruitment



Can ATMPs be made in clinical areas?

- Clinical Areas
  - Commonly requested for trials
  - A risk assessment is required
  - Staff training

GCP aspects

- Pharmacists have a responsibility re accountability of the ATIMP.
- Issuing
  - Prescription required?
  - ATMPs always issued to inpatients, hence "dispensing" not required
  - In accordance with SOP (trial specific if required)

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

ATMP Journey

- Approvals
- Procurement
- Receipt
- Storage
- Preparation
- Issue / Dispatch
- Administration
- Monitoring

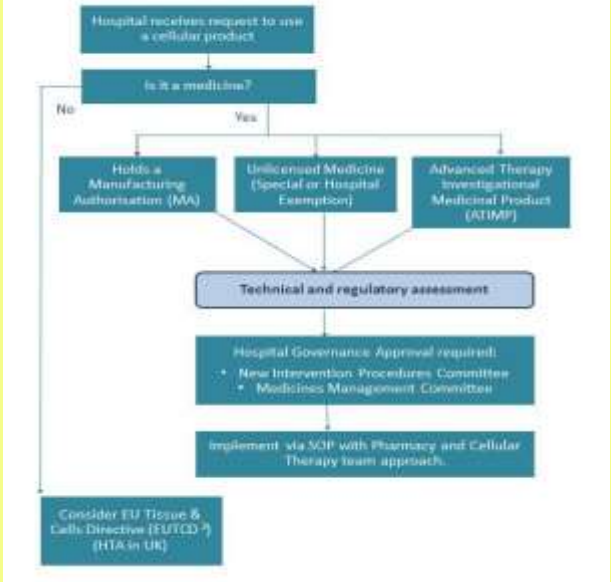
The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Administration

- Nurse Qualification and Training
  - Haematology nurses
  - Research Nurses
- Competency training required
- Organsation discussion required

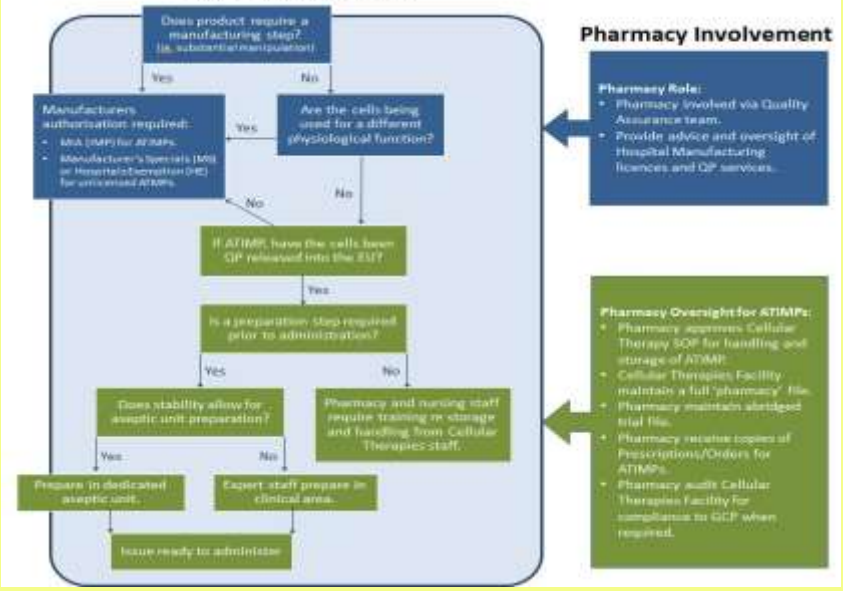
The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Governance Process



The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Technical Assessment



Pharmacy Involvement

Pharmacy Role:
- Pharmacy involved via Quality Assurance team.
- Provide advice and oversight of Hospital Manufacturing licences and QP services.

Pharmacy Oversight for ATIMPs:
- Pharmacy approves Cellular Therapy SOP for handling and storage of ATIMP.
- Cellular Therapies Facility maintain a full 'pharmacy' file.
- Pharmacy maintain abridged trial file.
- Pharmacy receive copies of Prescriptions/Orders for ATIMPs.
- Pharmacy audit Cellular Therapies Facility for compliance to GCP when required.

Conclusions

- ATMPs are medicines and the chief pharmacist is, therefore, accountable for their use.
  - Take action to find out if ATMPs are in use in your hospital.
- Handling of Cellular Products should only be by staff with appropriate training
- GCP and QA advice should be available for ATIMPs
- ATMP Governance processes should be introduced to ensure appropriate procedures in place to ensure patient safety

Questions

- Are pharmacists responsible for the use of ATMPs in hospital practice?
- Do pharmacists have the required training to prepare ATMPs?
- Can pharmacists fulfil the requirements of GCP for ATIMPs?

Thank you for listening.

Does anyone have any questions?