Multiproduct ATMP Manufacturing – a QP and Pharmacist's Perspective

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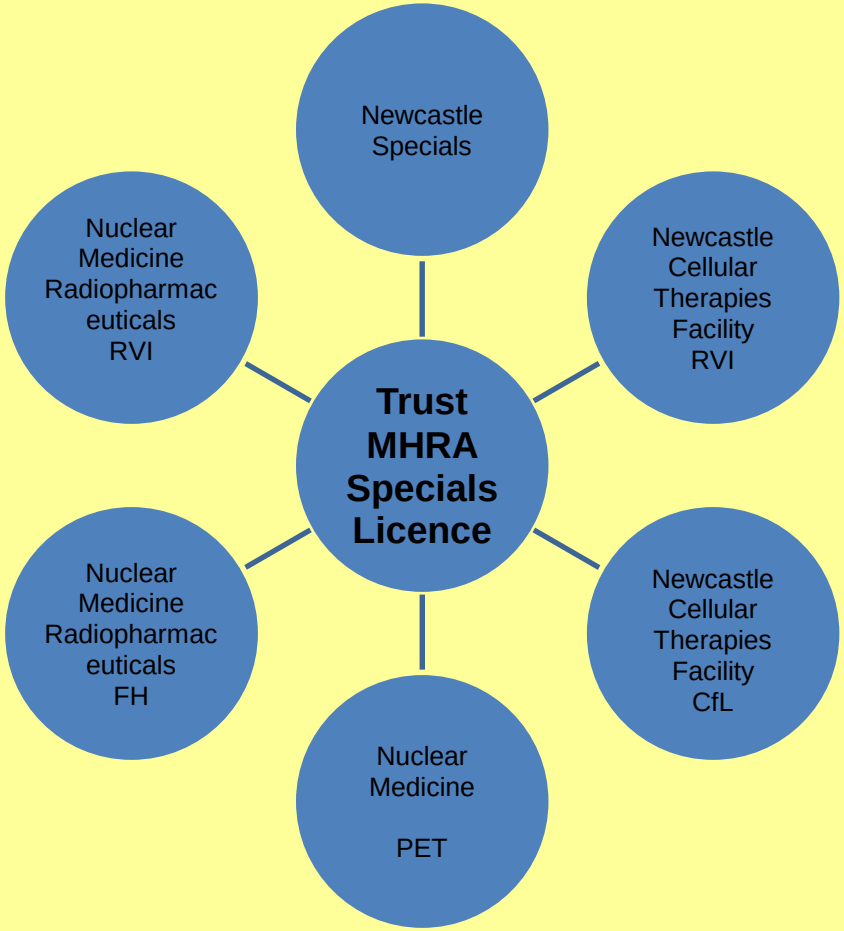
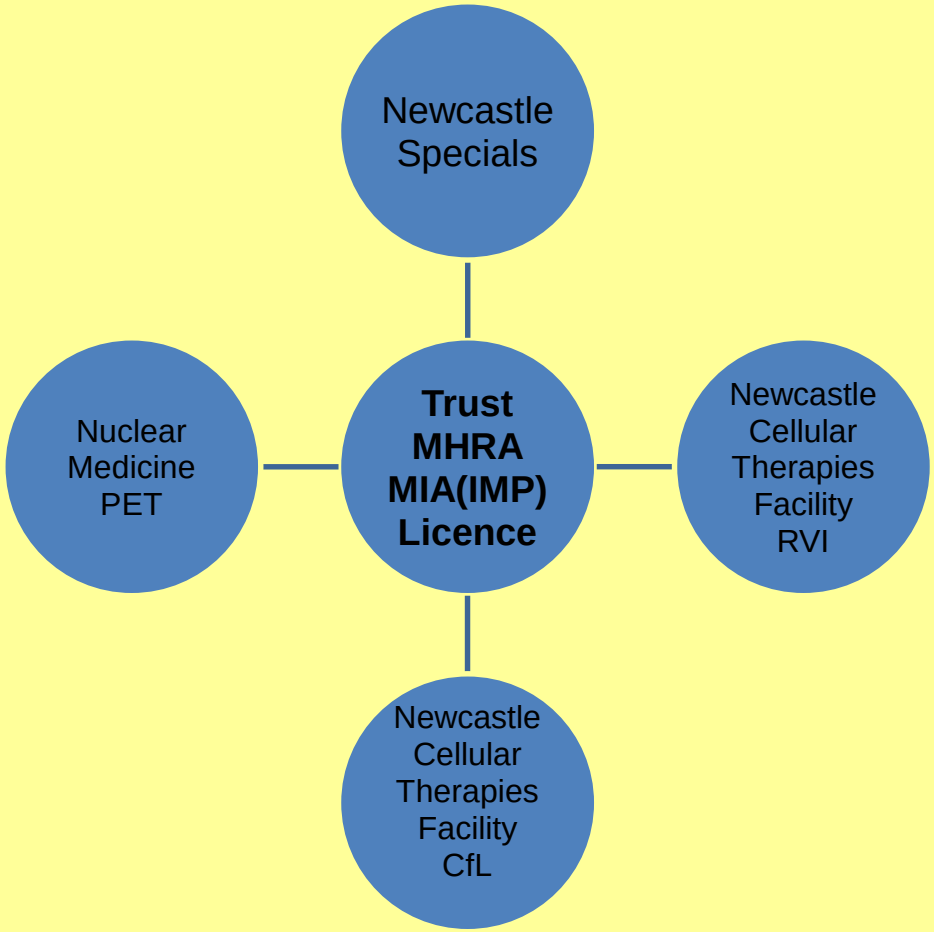
- Newcastle Medicines Manufacture
- Transition from traditional medicines to ATMPs
- ATMP Risks / Mitigation
- Regulatory Hot topics
- Governance requirements for delivery of ATMPs

Overview of Newcastle Therapeutics MHRA Licences



MHRA GMP inspectors audit at intervals defined by organisational risk.

Overview of MHRA Licences



MHRA GMP inspectors audit at intervals defined by organisational risk.

What is a Special: The Legal Bit!

Medicinal products can't be placed on the market in the EU unless they have a Marketing Authorisation (PL (or MA) in the UK)

Article 3 Directive 65/65/EEC

BUT

In the UK there is an exemption if:

- the patient has special needs
- supply is in response to a ‘bona fide’ unsolicited order
- it is formulated in accordance with the specifications of an authorised healthcare professional
- it’s for use by his/her individual patients
- on his/her direct responsibility

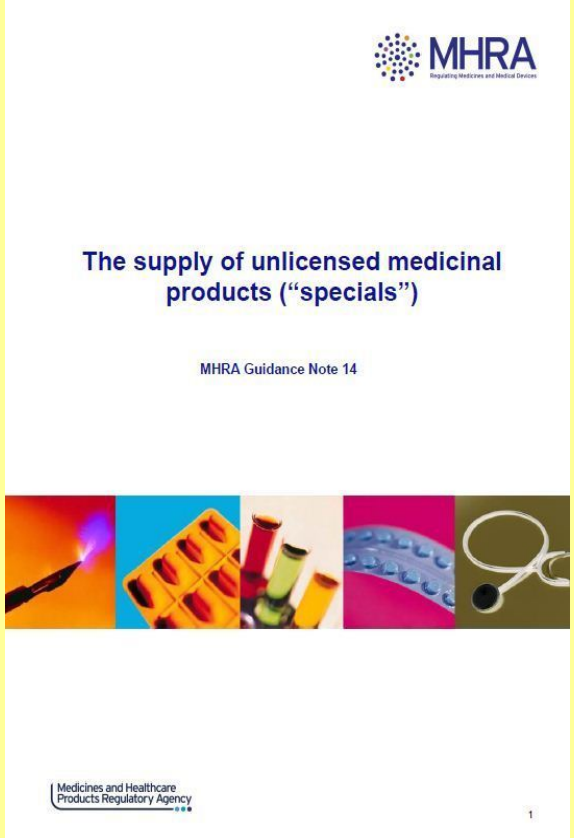
Article 5 Directive 2001/83/EC
Schedule 1 SI 1994/3144

Guidance Note (GN)14

- MHRA interpretation of the law regarding unlicensed medicines
- Updated in 2014 due to legal rulings in European courts
- Justification for use of an unlicensed medicine must be an unmet special clinical need

Examples given by the MHRA include

- a patient who is unable to swallow the licensed oral formulation
- a patient who has an allergic reaction to an excipient in a licensed product



CT Legislation in the EU

- EU Clinical Trial Directive 2001/20/EC
  - Published in April 2001with implementation requirements by 2004
    - UK Law - The medicines for Human Use Act (Clinical Trials) Regulations 2004

Aims to ensure the rights safety and well-being of subjects are protected by:

standardised regulatory procedures in the EU

GCP

GCP

Inspection and enforcement powers

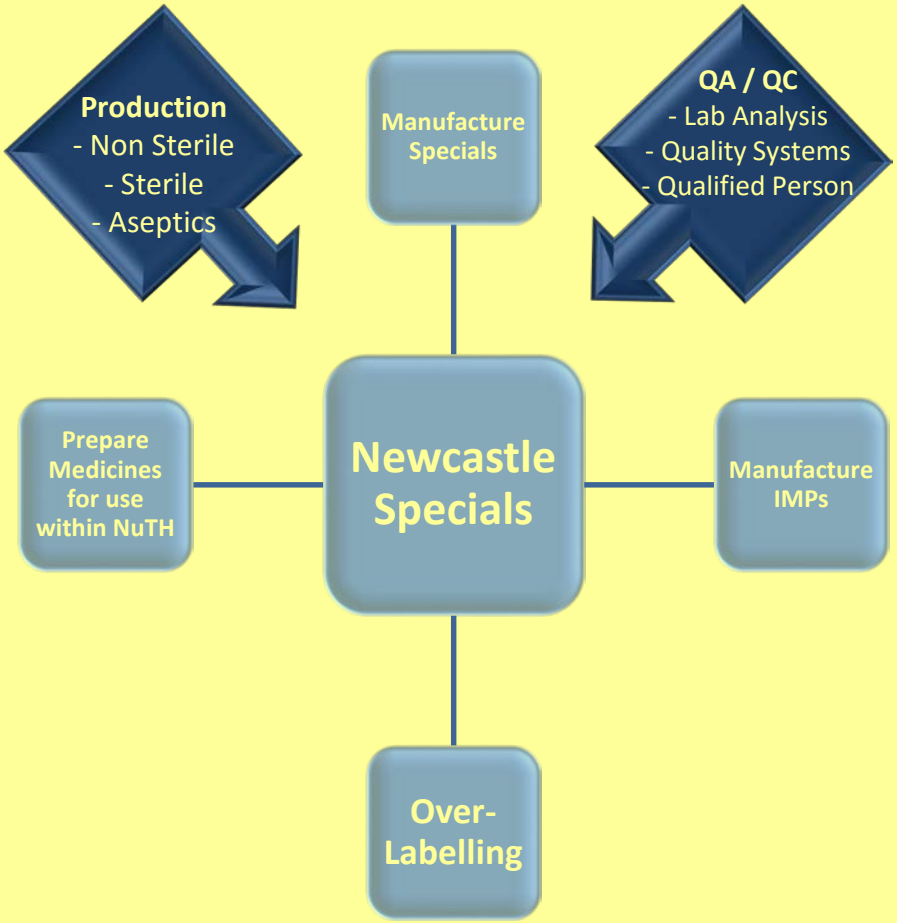
Revision to the CT Directive

- Since 2001/20/EC was implemented, CTs conducted in EU decreased by 25% from 2007 -2011.
- This has led to the CT Regulation 536/2014 which will replace the Directive.
  - "new legislation to cut red tape and bring patient oriented research back…..restore the EU's competitiveness and the development of new and innovative treatments….for the ultimate benefit of patients"
  - The Regulation has not yet been adopted into UK law so the directive still applies.

Main Changes

- Simplified authorisation procedure via a central EU portal
- Introduction of low interventional trials
- Relaxation for trials using diagnostic radiopharmaceuticals
- Removal of Transitional QP status.

Multiple Product manufacture in Pharmacy



Newcastle Specials
NHS Pharmacy Production & Quality Control Unit

Departmental Roles

- **Pharmacy Production**
- 5 specialist production zones including two for aseptic manufacture using isolator technology.

- The following types of manufacture are performed:
- Non Sterile – creams, ointments, suspensions, solutions, lollypops, powder filling, over-encapsulation.
- Aseptic Manufacture – manipulation of sterile starting materials
- Large and Small Volume Terminally Sterilised

Preparation of

- Cytotoxic Chemotherapy
- Parenteral Nutrition
- Centralised Intravenous Additives Service (CIVA)

t - with a personal touch

Newcastle Specials
NHS Pharmacy Production & Quality Control Unit

Departmental Roles

Quality Control

Assure quality of raw materials
Control / testing / acceptance of raw materials against issued specifications
Intermediate product testing
Co-ordinate stability testing
Testing of final product – chemical, physical and bioburdens.
Out-sourced microbiological and TOC testing to contract laboratories.
Test both Newcastle Specials products and contract laboratory work.

Quality Assurance

Quality Management system
- Deviations, Change Control, Action Tracking, Complaints, Out of Specifications

Documentation Control and Approval
Audits

Healthcare at its very bes

What do we mean by multiproduct manufacture?

- Zoned Facilities – each with a separate AHU
- One Facility – One AHU – One Product in manufacture at any one time
- One Facility – One AHU – Two (or more) products in manufacture. Separate Rooms
- One Facility – One AHU – Two (or more) products in manufacture. Same Room

Considerations for Multiproduct Manufacture

- Facilities and Equipment
- Process Flow
- Cross Contamination Potential
- Segregation by time or physical methods
- Process Design
- Line Clearance Documentation
- Cleaning Validation
- Risk Assessment

Risks Associated with Manufacture / Preparation

Low

- Non Sterile Manufacture
- Terminally Heat Sterilised Products

- VHP transfer aseptic manufacture
- Aseptic manufacture terminal filtration

High

- Open system aseptic manufacture
- Preparation for individual Patients

Where do ATMPs feature in this hierarchy?

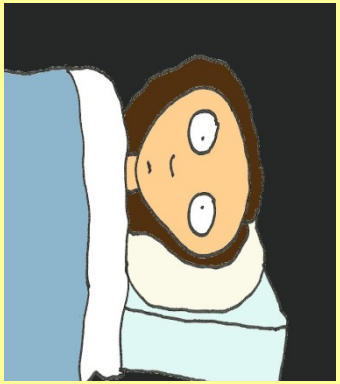
ATMPs are not the same as traditional pharmaceuticals with which traditional manufacturers are familiar.

"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

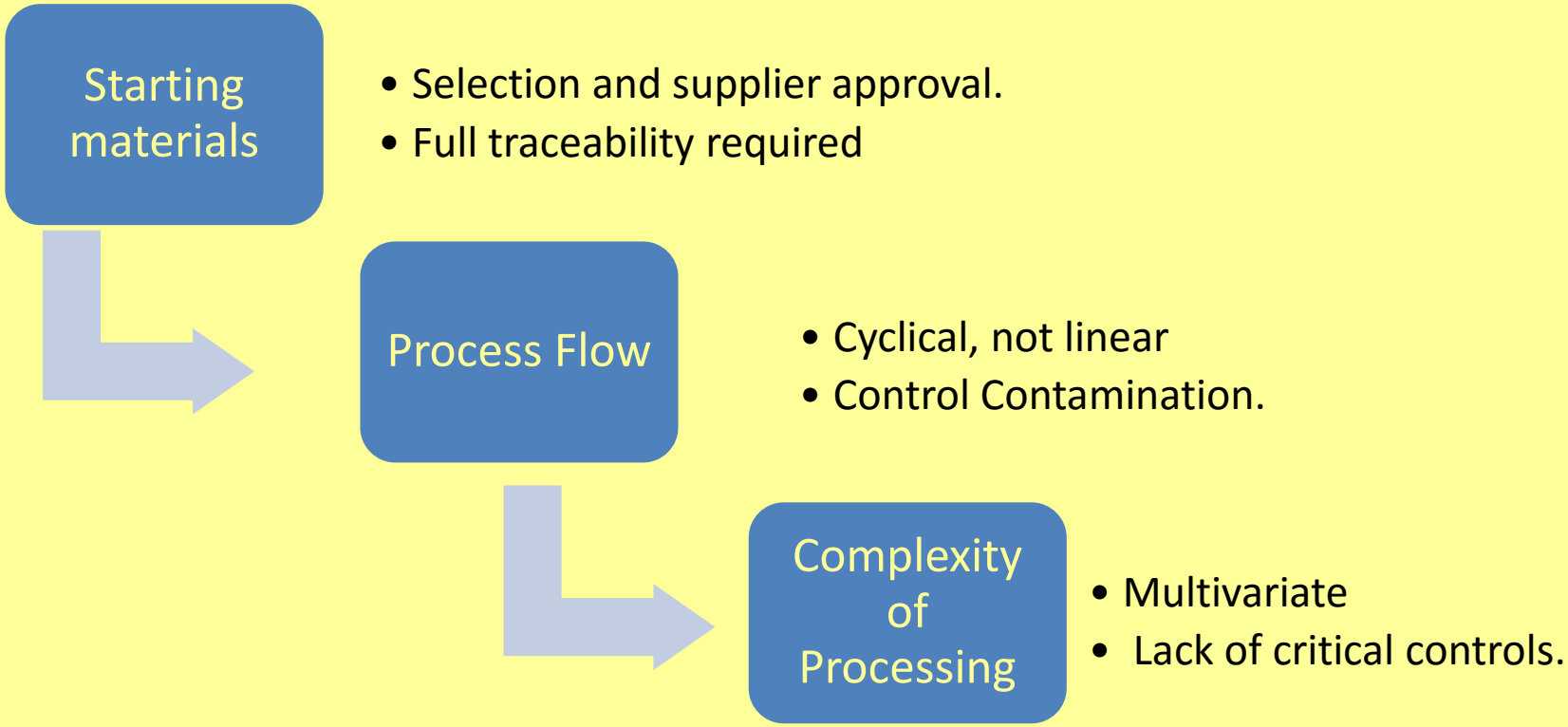
- Traditionally have not entered the hospital via pharmacy
- Largely uncomfortable for a pharmacist at first site!

QP concerns



- Sterility Assurance
- Supplier Approval of starting materials
- Autologous product
- Stability
- Concessionary release concept

QP Considerations for ATMP manufacture

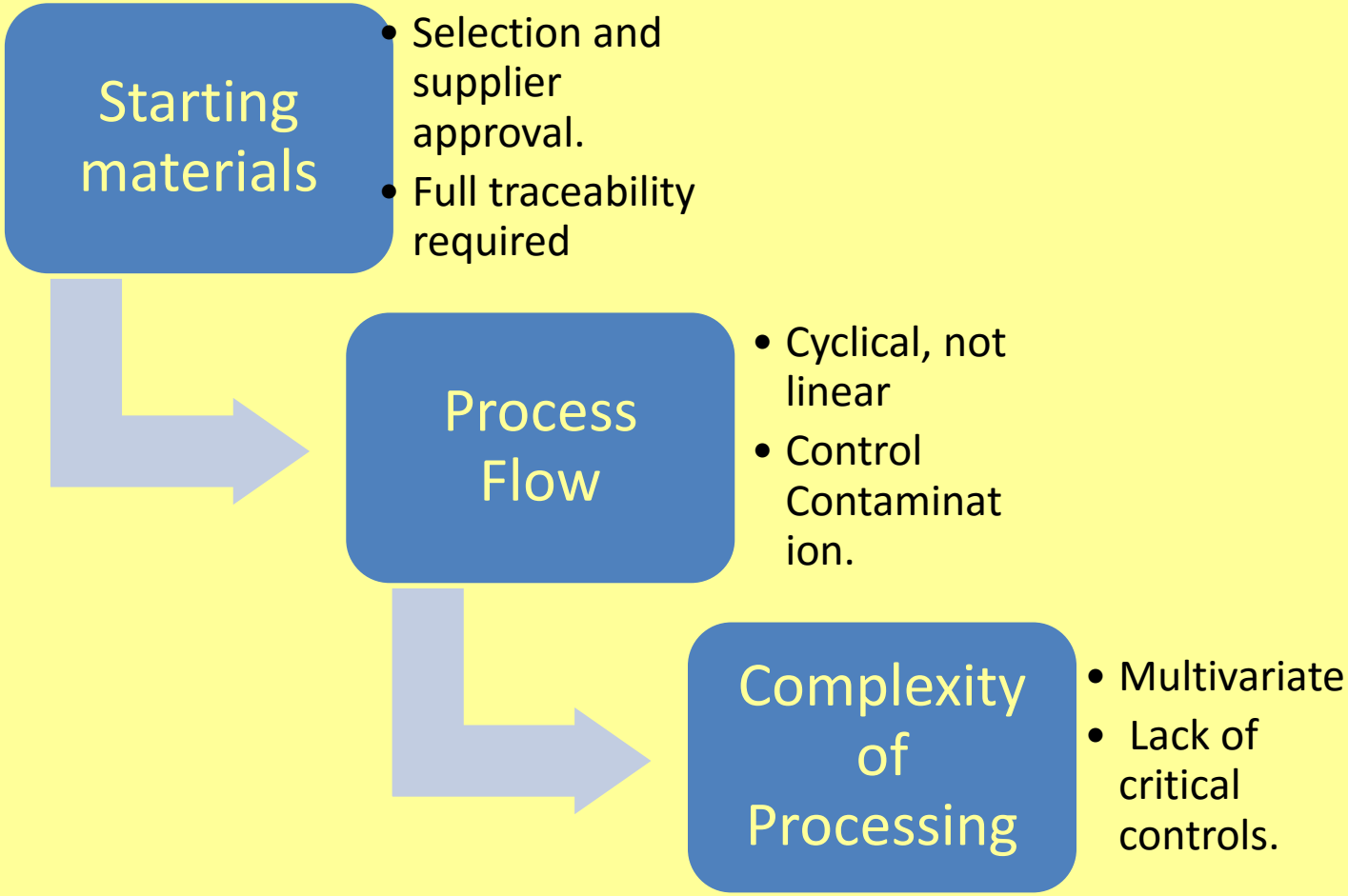


Contamination Control : Product input materials

Material	Risk	Possible Controls
Biological starting material	Contaminated at source / during procurement	Test sample from material (or donor) at procurement. SOPs and training for procurement. Risk to other products.
Non-sterile raw material	Microbial contamination	Licenced (MA) sterile alternatives Test using *Ph Eur 2.6.1* method before use. Sterilise before use (e.g. double 0.22µm filter)
Custom (non CE/MA) raw materials or consumables	Microbial contamination	Certificates of sterilisation from manufacturer Audit manufacturer Reputable companies Technical/ Quality agreement Re-test sterilisation in house or via 3rd party

Supplier evaluation and approval process is critical

QP Considerations for ATMP manufacture



Contamination Control : Process

Stage	Possible Controls
Materials into cleanroom	Selection of packaging (triple wrap) Use of sporicidal agents / VHP Monitor Bioburdens Operator training and testing
Manipulation of the product	Move to closed process, automate where possible Minimise manipulations. Disposable single use sterile consumables Staff training: aseptic processing and microbiology QC testing (CPM, in-process sterility testing) Media Fill

Process engineering and operator training are just as critical as testing

QP Considerations for ATMP manufacture

Starting materials

- Selection and supplier approval.
- Full traceability required

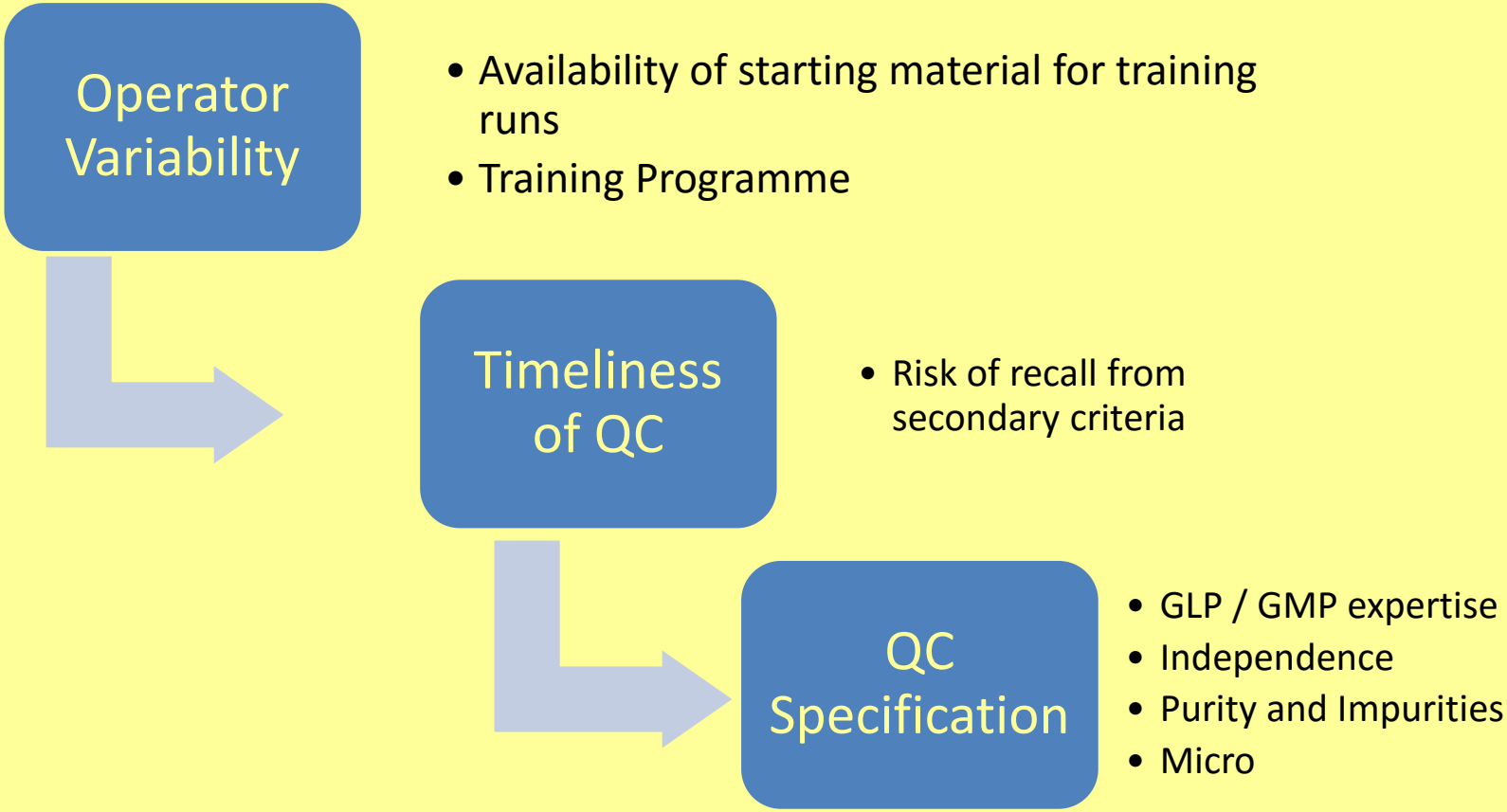
Process Flow

- Cyclical, not linear
- Control Contamination.

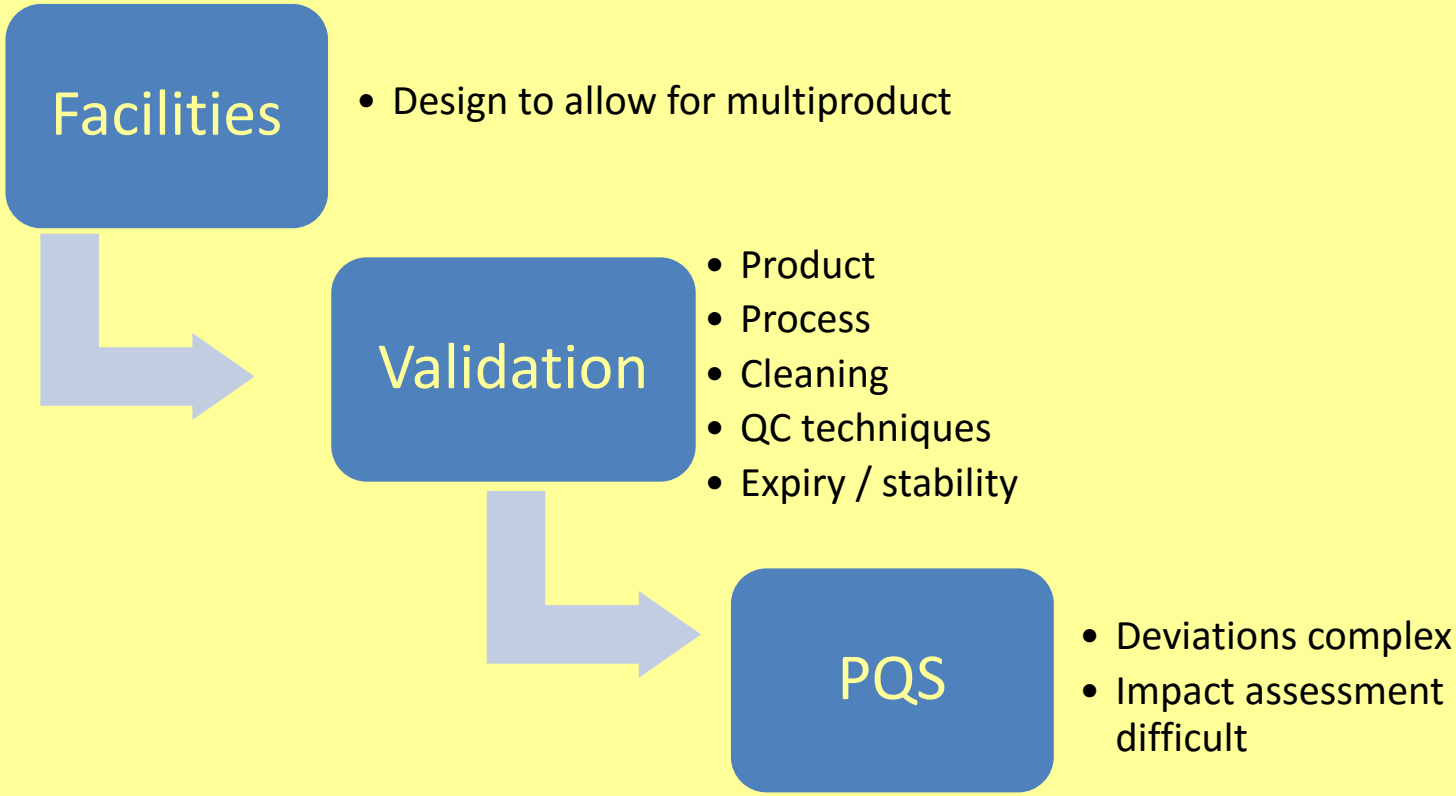
Complexity of Processing

- Multivariate
- Lack of critical controls.

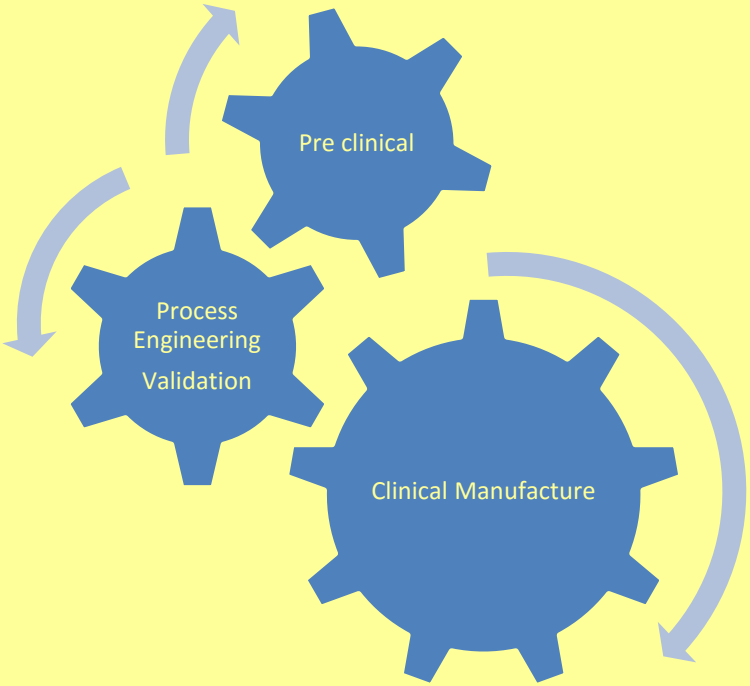
QP Considerations for ATMP manufacture



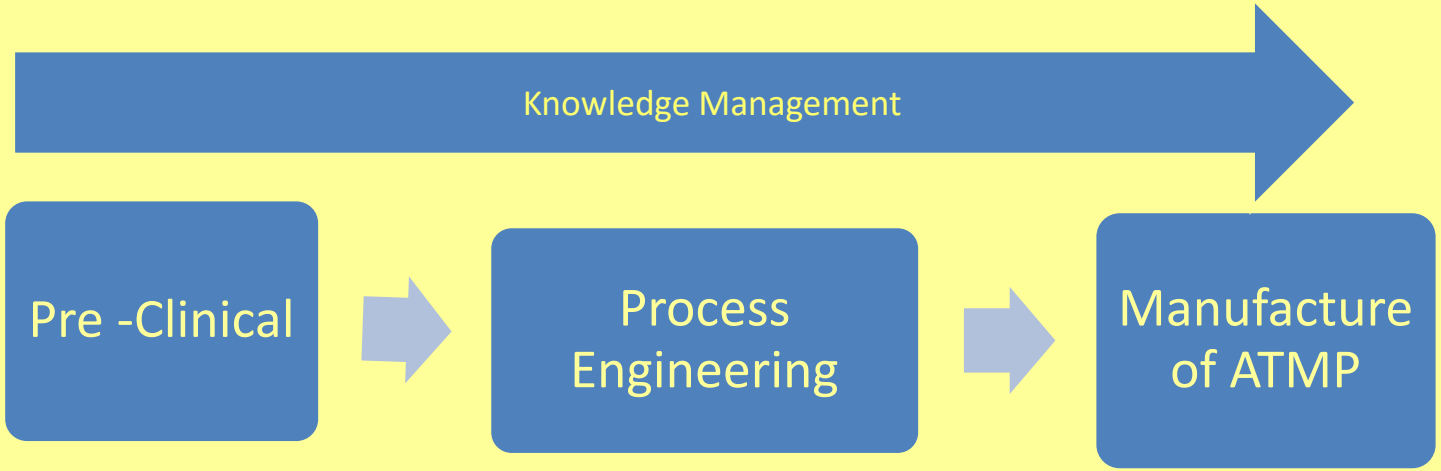
QP Considerations for ATMP manufacture



Product Lifecycle



Process Optimisation



Process engineering requires collaboration between the innovator and the manufacturer.

Defines: materials specifications
process, and in-process controls
Finished Product Specification
Stability programme
Leads into product validation stage

Risks Associated with Manufacture / Preparation

Low

- Non Sterile Manufacture
- Terminally Heat Sterilised Products

- VHP transfer aseptic manufacture
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High

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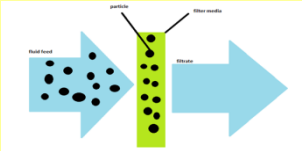
- Preparation for individual Patients

Highest

- Cellular ATMPs

Risks for ATMP Manufacture

ATMPs must be provided sterile as they require injection/infusion or transplantation



BUT….

X Cannot be filtered as cells are too large (blood stem cell >12µm) and tissues must be applied as a whole construct

X Cannot be sterilised by irradiation as the cells would lose function

X Cannot be sterilised by heat as the cells would lose structure and function

X Closed systems not always possible.

Emphasis then goes onto the quality risk management and sterility assurance of the manufacturing and packaging, process and in-process and final product testing .

Failure Mode Effects and Criticality Assessment

REFERENCE NUMBER		Risk Assessment Statement								Proposed action SOD and RPN				Outcome and Actions	
Sub Process, what is the process step or input under investigation	**Potential Failure Mode, in what way can the sub process go wrong**	**Failure Mode Effect, what is the impact**	**S (1-5)**	**Potential Causes**	**O 1-5)**	**Current controls**	**D (1-5)**	**R P N**	**Proposed Action**	**S**	**O**	**D**	**RP N**	**Risk Decision and Acceptance (Y/N) Rationale**	**CAPA ref.**

RPN = S x O x D

FMECA Example

Need to Multiproduct manufacture?

- Use FMECA
- Risk Statement: Risk of Cross Contamination during Manfacture of X and Y
- Break it into sub-processes
- Identify existing controls and outstanding risks.
- Document new controls
- Accept residual risk if tolerable.

Regulatory Issues – hot topics with ATMP significance

- New Annex 1 GMP
- Data Integrity
- Cleaning Validation
- Clinical Trials Regulation
- Annex 16

Regulatory Issues for the QP – Annex 16

- QP required to release IMP in line with approved IMPD.
- QP needs input into the dossier.
- Be careful with wording. E.g. “All mandatory markers will comply with EU TCD, “All markers must be negative”. Appropriate for autologous product?
- QP does not have discretion.
- Concessionary Release concept.
- Governance.

ATMP Working Party – subgroup of the NHS Pharmaceutical QA Committee

NHS

The Role of Pharmacy in the
Successful Delivery of
Advanced Therapy Medicinal Products (ATMPs)

Information for Chief Pharmacists

Edition 1

February 2017

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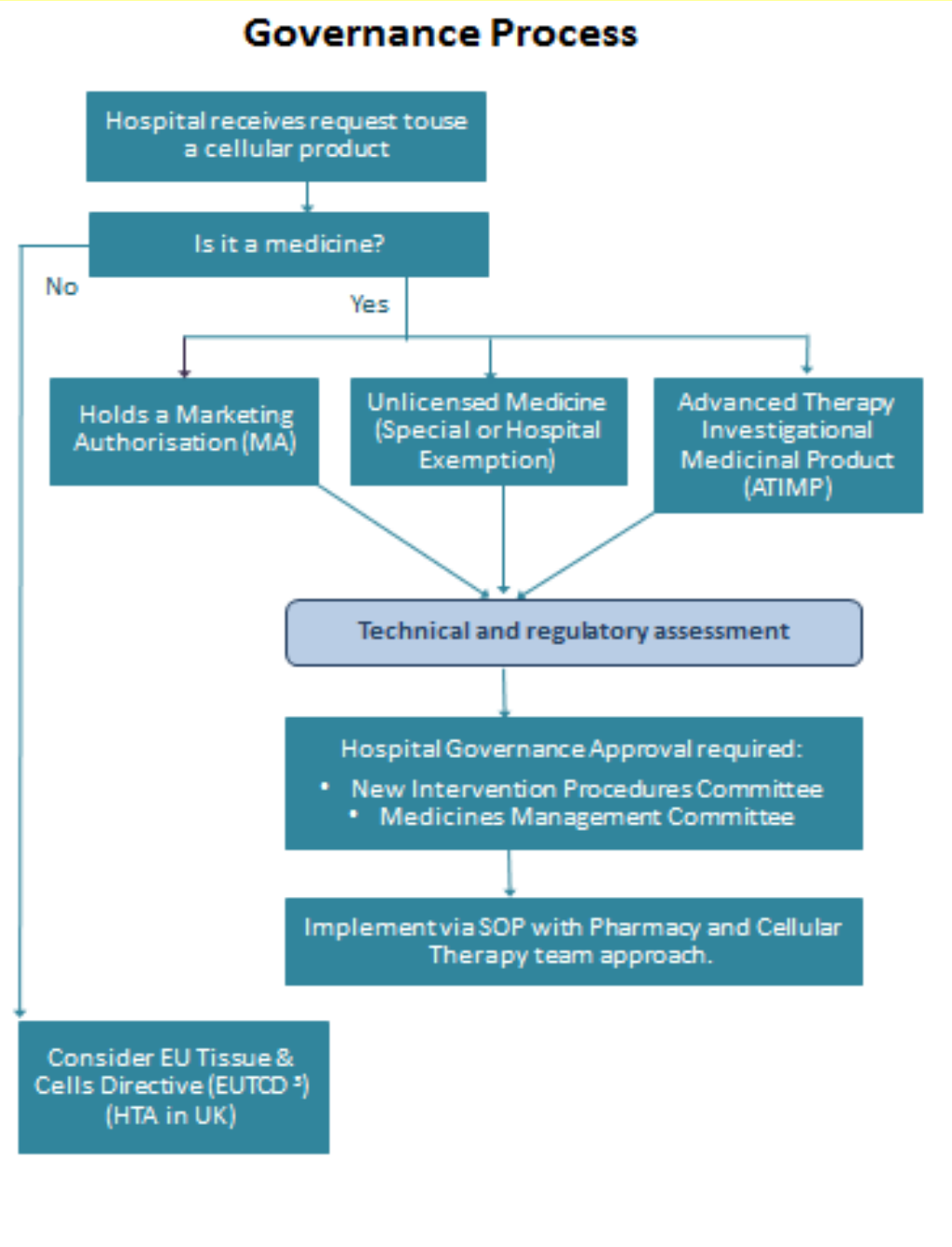
Governance issues

As ATMPs are medicines Chief Pharmacists have overall responsibility for, in hospitals we must develop a processes that ensures that:

- Pharmacy have oversight of all ATIMP clinical trials and remain accountable for good clinical practice.
- Only staff with appropriate training and expertise undertake any handling of cellular products.
- Appropriate technical and pharmaceutical advice is available locally.
- Robust governance for the introduction of advanced therapy medicinal products occurs.



Conclusion: As a QP and a Pharmacist

Exciting Area to be involved with

Regulator's Support

Government's Support

Manufacturing Expertise Exists

QP expertise deficit hence collaboration and teamwork is key.

Delivery / Implementation needs careful facilitation involving all key stakeholders.

Conclusion

ATMPs are medicines and therefore GMP for every element is in the interest of both patient and manufacturer.

ATMP Governance processes should be introduced in healthcare organisations to ensure appropriate procedures in place to ensure patient safety whilst facilitating timely availability of these innovative medicines.

Thank you for listening.

Does anyone have any questions?