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Advanced Therapy Treatment Centres

Pharmacy Institutional Readiness for Ex-vivo (Cell Based) Gene Therapy Medicinal Products

Guidance for Chief Pharmacists

Pan UK Pharmacy Working Group for ATMPs

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The first stop for professional medicines advice

Pharmacy Institutional Readiness for ex-vivo (cell based) Gene Therapy Medicinal Products

Guidance for Chief Pharmacists

1. Background

Advanced Therapy Medicinal Products (ATMPs) are innovative medicines which provide challenges in delivery.

Ex-vivo (cell based) gene therapy medicinal products are classed as ATMPs and as such, Chief Pharmacists are required to ensure that governance arrangements in line with the safe and secure handling of medicines are in place to manage these medicines within their organisations.

Gene therapy medicinal products (GTMPs) are defined as biological medicinal products which have both of the following characteristics:

a) contain an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence.
b) therapeutic, prophylactic, or diagnostic effect relating directly to the recombinant nucleic acid sequence they contain, or to the product of genetic expression of this sequence.

GTMP modes of action are well documented. They are designed to introduce genetic material into cells to:

1. compensate for abnormal genes
2. make a beneficial protein which then multiplies and exerts a positive effect
3. introduce a normal copy of the gene to restore the function of the protein if a mutated gene causes a necessary protein to be faulty or missing.

The manufacture of GTMPs is complex. A carrier, which can be a viral vector or non-viral, e.g. a liposome or a plasmid is required to deliver the gene to the cell. Viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are genetically modified to ensure that they are non-pathogenic and cannot cause disease when used in people. The viruses can be non-replicating or replicating. Retroviruses integrate their genetic material (including the new gene) into a chromosome in the human cell and are known as integrating viral vectors. Adeno-associated introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome – i.e. they are non-integrating viral vectors. If genetic modification occurs inside the body, it is called an in-vivo gene therapy whereas genetic modification which occurs outside of the human body is called an ex-vivo (cell based) gene therapy.

This guidance is for GTMPs that are classified as ‘ex-vivo’ where cells are taken from a donor, usually the patient, and using as the starting material for the medicinal product. A viral vector is used to introduce the gene to the donor cells. The donor cells undergo genetic medication and expansion in cell culture to form the medicinal product. The genetically modified cells, now classed as a medicine, are administered to the patient. Where the starting material originates from the patient’s own cells, this is called an “autologous” therapy. It should also be noted that the starting material may originate from another donor and this is termed “allogeneic” therapy. This guidance should be used in association with the SmPC and/or the Clinical Trial Protocol/Pharmacy Manual.

An example of an autologous ex-vivo (cell based) GTMP treatment is marketed CAR-T (Chimeric Antigen Receptor T cells) products. CAR-T cell therapies have led the way in demonstrating that a consistent approach to implementation encompassing governance and operational issues is required in addition to clinical readiness. To this end Pharmacy Institutional Readiness guidance for CAR-T was prepared and used to good effect in sites commissioned to provide CAR-T cell therapy. In order to manage the pipeline of ATMPs, the Pan UK Pharmacy Working Group for ATMPs has now produced

Pharmacy Institutional Readiness guidance for delivery of ex-vivo (cell based) Gene Therapies. Other newly published guidance includes Pharmacy Institutional Readiness guidance for Somatic Cell Therapies, in-vivo (virus based) Gene Therapies, and Tissue Engineered Products (TEPs).

2. Purpose

The purpose of this document is to outline the key areas where chief pharmacists should focus pharmaceutical expertise prior to an organisation implementing any ex-vivo (cell based) Gene Therapy Medicinal Product (GTMP).

This document presents a flow diagram outlining a stepwise approach to implementing processes to prepare and administer ex-vivo (cell based) GTMP. It is followed by checklists which relate to the various steps presented in the diagram. These are presented as appendices.

In preparation for the implementation of NHS patient treatment, representatives from The Pan UK Pharmacy Working Group for ATMPs and Advanced Therapy Treatment Centres (ATTC) have prepared exemplar documents and templates for some of the key steps in the delivery of ex-vivo (cell based) GTMP (see appendices). This document provides the outputs from this work. The checklists may be used as appendices to local procedures as a way of documenting key steps or as an aid against which to check that local procedures are comprehensive.

As ex-vivo (cell based) gene therapies are routinely individualised for each patient, it is imperative that systems are established to ensure that the therapy is administered to the intended patient and that associated risks , particularly with tracking and traceability, are minimised.

Ex-vivo (cell based) gene therapies may be stored under vapour phase nitrogen and require thawing before administration and in some cases additional aseptic manipulation. Manipulation of cellular medicines requires skilled operators who are trained and understand the risks associated with handling a living product. It is recognised that most Pharmacy Services do not usually have the expertise to manipulate these products and consequently, routinely Pharmacy Services may not come directly into contact with the product if these tasks are performed by other specialists e.g. the Cell Laboratory. However, it is important where Pharmacy Services are not directly performing some of the outlined steps that the roles and responsibilities of those undertaking the aforementioned steps are clearly documented and undertaken with pharmacy oversight. Ideally, an overarching Technical Agreement between the Chief Pharmacist and the Head of the relevant service, with reference made to relevant organisational SOPs should be in place.

The following process flow chart outlines the stages which require Pharmacy consideration when an organisation wishes to use a ex-vivo (cell based) GTMP. Refer to the 'Gene Therapy Medicinal Products - Governance and Preparation Requirements' document for further details.

Process Flow Encompassing Points for Consideration by Chief Pharmacists

Governance

- Chief pharmacists should ensure that governance for GTMPs is documented as follows:

1. Centres will need to meet the requirements of the commissioning process and become a designated centre for administration of the ex-vivo (cell based) GTMP which maybe documented in a National Service Specification.

2. Clinical approval re patient selection:
   - An approved centre will need to understand the national processes for patient selection if applicable.

3. Local Governance:
   - As referenced in Gene Therapy – Governance and Preparation organisational governance prior to providing any ATMP is advised. This may involve an ATMP Committee and/or Medicines Management Committee, and as it is a GTMP it will involve a Genetic Modification Safety Committee (GMSC). Local requirements should be defined prior to implementation of a GTMP service in an organisational policy.
   - Implementation sites may be asked to complete Commercial Agreements with the relevant Pharmaceutical companies. These will require review by Pharmacy.
   - Due to the cost of the GTMP, local financial governance requirements may need to be documented in an SOP as there may be a variation to routine standard financial instructions. Financial approval processes should be defined as part of organisational governance.
   - A centre wishing to provide ex-vivo (cell based) GTMP will define additional local governance requirements e.g. for private patients.

4. Local Medicines Management: a SOP will be required to ensure Pharmacy's involvement with the following process:
   - Process cancellation
   - Credit claims
   - Deviations

An exemplar Medicines Management Checklist is available in Appendix 1

Class and containment level

For clinical trials, the following bullet points are mandated for GTMP with a GMO, however GMSC assessment is recommended for all GTMP regardless of GMO or licensed status.
See Gene Therapy and Preparation for more information.

- Class and containment level of gene therapy medicine (usually class 1 or 2) to be assessed.
- Check hospital site is registered with HSE to handle gene therapy medicines for appropriate class (coordinated by GMSC) if clinical trial.
- Hospital site will have a GMO certificate number issued after notification to HSE of site involvement of containment level 1 and/or 2 viral vectors in clinical trial.
- Risk assessment of risks to human health and environment to be reviewed by Genetic Modification safety committee (GMSC) or biological safety officer.
- Contained use control measures to be put in place in line with risk assessment.

GMSC risk assessment is covered in Gene Therapy and Preparation and involves assessment of the product, the patient and the waste.

An exemplar Pharmacy Class and Containment checklist is available in Appendix 2

Approval of the Order

- Where the patient has been referred from another hospital the clinical pharmacist at the treatment site, should verify the patient's status and ensure all criteria are fulfilled prior to approving the order. Where applicable, the clinical pharmacist at the referral site should provide information to the clinical pharmacist at the treatment site.
- A pharmacist's approval and/or the provision of a pharmacy purchase order is necessary. This will require an SOP to be defined which will need to reference any commercial operating system which an individual ex-vivo (cell based) GTMP company may require to be used. Companies may suggest that the approval required is little more than a data accuracy check, however, recognising that time pressures will exist, the pharmacy SOP should ensure that the process covers all governance aspects detailed above, and any appropriate clinical verification.
- Additionally, links with pharmacy purchasing systems, and prescribing systems will require definition and may form part of this SOP or be documented separately.

An exemplar Pharmacy Patient Referral checklist is available in Appendix 3
&
An exemplar Pharmacy Patient Approval checklist is available in Appendix 4

Apheresis and Manufacture

- For both an “autologous” and an “allogeneic” product the starting material must be collected in the UK under an HTA licence.
- The pathway for the manufacture of the ex-vivo (cell based) GTMP should be clearly described and roles and responsibilities understood.
- If required, regulatory arrangements e.g. HTA licence for export/import, should be identified and implemented.

Product Receipt

- Certain ex-vivo (cell based) GTMP may be supplied in a ready to administer form e.g. Yescarta/Kymriah, following thawing. Other ex-vivo (cell based) GTMP may require further aseptic manipulation.
- Ex-vivo (cell based) GTMP are generally not handled in pharmacy (usually in stem cell laboratories) but receipt, storage, preparation, and issue are pharmacy responsibilities and should be co-ordinated under pharmacy oversight.
- An SOP for receipt of GTMP covering those holding marketing authorisation as well as IMPs is required. Checks on receipt should include integrity of the product, labelling and temperature compliance during transit. Certificate of Analysis/QP certificates detailing the dose, if applicable. This should be reviewed by an appropriately trained clinical pharmacist or Clinical Trials pharmacist.

An exemplar Product Receipt checklist is available in Appendix 5

Storage

- Optimal storage location for ex-vivo GTMP will depend on storage temperature conditions and duration. If ambient, refrigerator or -80ºC freezer or short-term vapour phase nitrogen dewar then pharmacy storage may be an option for ready to administer products. Cell based products should be segregated where possible and always stored in a secure manner which minimises the risk of cross-contamination.
- Ex-vivo (cell based) GTMP will require to be stored under specified temperature storage conditions. This may be at ambient, refrigerated or freezer temperatures. In some cases, this may be as low as -150ºC. It is important that appropriate equipment is sourced, as necessary, to accommodate specific requirements. Stem cell Labs with pharmacy oversight or outsourcing may be an option and the various options should be risk assessed. (See Governance)
- Continuous temperature monitoring is required from receipt through to administration.
- Alarms should be installed and actions in the event of an alarm should be specified.

The exemplar Product Receipt checklist is available in Appendix 5 which covers aspects of storage

Preparation Location Decision

- Some ex-vivo (cell based) GTMPs will require a thaw/preparation/reconstitution step. Optimal location for ex-vivo (cell based) gene therapy preparation will be as per SmPC or clinical trial protocol. Where the location is not specified guidance can be found in Gene Therapy and Preparation. Preparation location should have been defined in the GMSC risk assessment.
- On receipt the product can either be: -
  - Transported to the clinical area and then thawed prior to administration – stability <4 hours
  - Thawed in pharmacy and transported to the clinical area – stability >4 hours
  - Thawed and aseptically manipulated e.g. in stem call laboratories then transported to the clinical area for administration to the patient. Pharmacy oversight is required.
  - Manipulation could be outsourced - Technical agreement is required. (Further Pan UK PWG advice will follow on this)

Aseptic Preparation e.g. stem cell laboratory

Where aseptic preparation/manipulation is to be carried out, Pharmacy oversight needed for the following:

- Governance:
  - Roles and responsibility clear
  - GMSC risk assessment compliance
- Operator protection
- Preparation process
- Cleaning agent suitability
- Waste management
- Transportation
- Worksheet approved in line with SmPC or Protocol
- Confirmation when the patient is ready for ex-vivo (cell based) GTMP treatment.

For further information on each point, see Gene Therapy and Preparation for more information.

Storage and manipulation could be outsourced, in which case a technical agreement will be required. (Further Pan UK PWG advice will follow on this).

An exemplar Pharmacy Aseptic Preparation checklist is available in Appendix 6a

Pharmacy Storage, Issue & Transportation to the clinical area

- Ex-vivo (cell based) GTMPs, where prolonged storage is not required, may be routinely received via Pharmacy. They may be thawed by trained and competent staff and transported to the clinical area – without any further aseptic manipulation.
- Confirmation when the patient is ready for ex-vivo (cell based) GTMP treatment should be obtained.
- Procedure for retrieval from storage, if applicable, or reference to SOP if no different to routine should be available.
- Procedure for pharmacy thaw (if applicable) should be available and competency training in place
- Transportation method to clinical area approved by GMSC.
- Transportation performed by trained and competent staff.
- Spill kit available.

An exemplar Pharmacy Dispensing checklist is available in Appendix 7

Issue & Transportation to the clinical area

The product should then be released by a pharmacist and will be in its ready-to-administer presentation. This should be issued and transported according to a local SOP:

- Procedure for retrieval from storage, if applicable, or reference to SOP if no different to routine should be available.
- Transportation method to clinical area approved by GMSC.
- Transportation performed by trained and competent staff.
- Spill kit available.

An exemplar Pharmacy Dispensing checklist is available in Appendix 7

Clinical Area Preparation

If thaw or any manipulation is required, in the clinical area, (due to insufficient stability for aseptic suite manipulation) then the Chief Pharmacist should ensure that the following are included in the approved Pharmacy SOP.

- Roles and responsibilities should be clearly documented.
- A Pharmacy approved clinical area worksheet in line with the SmPC/Protocol should be issued.
- PPE appropriate to the containment level should be available.
- Any preparation should be undertaken by trained and competent staff and be in line with an SOP detailing whether additional labelling is required.

An exemplar Clinical Area Preparation checklist is available in Appendix 6b

Administration & Monitoring

- The pharmacist with clinical responsibility for the patient needs to be an expert on any required pre-medication, concomitant medication, and post GTMP administration medication. They also need to be aware of toxicity management and contra-indicted medicines.
- Resources available include SmPC and company literature as well as protocol, investigators brochure and Pharmacy Manual for Advanced Therapy Investigational Medicines Products.
- The clinical subgroup of the Pan UK Pharmacy Working Group for ATMPs will endeavour to produce specific clinical guidelines where risk assessment deems it appropriate.

Appendix 1

Ex-vivo GTMP Pharmacy Medicines Management Checklist

Product Name			
Supplier			
Manufacturer (if different to above)			
Regulatory status	Licensed / Unlicensed / Clinical Trial (Record EudraCT number if applicable)		
Checking step	**Yes / No / NA Data**	**Checker Initials**	**Date**
Treatment centre selected by NHS to deliver GTMP	Yes / No		
Treatment centre audited and approved by JACIE (or other as appropriate) to deliver ex-vivo (cell based) gene therapies	Yes / No / NA		
Treatment centre qualified by manufacturer to deliver product	Yes / No / NA		
Governance approvals in place for use of product as applicable: Medicines Management Formulary ATMP Oversight Group (or similar) Clinical trial approval	Yes / No / NA		
Biological safety risk assessment completed / Genetically Modified Organism Safety Committee approval gained	Yes / No		
HSE notification if required for clinical trial	Yes / No / NA		
SmPC and PIL available	Yes / No		
Prescription added to electronic SACT prescribing system	Yes / No		
Product added to Pharmacy Ordering system	Yes / No		

Appendix 1 (cont.)

Checking step	Yes / No / NA Data	Checker Initials	Date
If product requires aseptic manipulation by stem cell laboratory or is outsourced out-with the organisation, then a technical agreement is in place.	Yes / No / NA		
If prepared by nurses: worksheet, SOPs, staff training in place	Yes / No / NA		
Intravenous risk assessment completed	Yes / No / NA		
Trust funding process approved	Yes / No		
Ensure product being tracked by Medicines Finance team and Contracts for Trust reimbursement	Yes / No		

Pharmacy product specific folder in place	Yes / No		
Pharmacy SOP in place for cancellation of order	Yes / No		
Pharmacy SOP in place for credit claims	Yes / No		
Pharmacy SOP in place for deviations	Yes / No		
Pharmacist Final Check	***Print Name***	***Signature***	***Date***
Comments			

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Appendix 2

Ex-vivo GTMP Pharmacy Class and Containment Checklist

Class and containment level **circle as appropriate*	Class 1* / 2* / 3* / 4*		
Check hospital / organisation is registered with HSE to handle gene therapy medicines for appropriate class (coordinated by GMSC)	Yes	No	
Risk assessment			
GMSC			
NPSA			
Waste disposal			
Spillage			
Staff Training and competence			
Genetic Modification Committee (GMC) and/or Advanced Therapy Medicinal Products (ATMP) Committee Approval and/or New Interventional Procedures Committee approval			
Medicine Management Committee approval			
Preparation Facilities: • External to pharmacy • Freezer storage • Transport • Aseptic facilities risk assessment • Personal Protective Clothing			
	Print Name	***Signature***	***Date***

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Appendix 3

Ex-vivo GTMP Pharmacy Patient Referral Checklist

Product Name		
Supplier		
Patient name		
Patient Date of Birth (dd/Mmm/yyyy)		
Patient NHS Number		
Information needed		**Date**
Height (cm), if applicable		
Weight (kg), if applicable		
Medication allergy status		
Current medication history – including chemotherapy and radiotherapy treatment history		
Any abnormal laboratory results		
Any other comments		
Referral Centre Pharmacist completing form	***Print Name***	***Signature*** / ***Date***
Referral Centre Pharmacist Contact details		

Treatment Centre Pharmacist			
Clinical verification for referred patient acceptable and meets eligibility criteria	Yes / No		
Clinically suitable pre-treatment/washout undertaken or planned, if applicable	Yes / No / NA		
Treatment Centre Pharmacist completing form	***Print Name***	***Signature***	***Date***

Appendix 4

Ex-vivo GTMP Pharmacy Patient Approval Checklist

Product Name			
Supplier			
Manufacturer (if different to above)			
Patient name			
Patient Date of Birth (dd/Mmm/yyyy)			
Patient Hospital Number			
Checking step	**Yes / No / NA Data**	**Checker Initials**	**Date**
Governance approval in place	Yes / No		
Patient selection approval number	Yes / No		
Blueteq ID	Yes / No / NA		
Trust funding approved	Yes / No		
Patient consent documented	Yes / No		
Pharmacist accuracy check completed	Yes / No		
Pharmacy order number issued	Yes / No		
Manufacturer's details	Yes / No		
Pharmacist approval documented	Yes / No		
Pharmacist Final Check	***Print Name***	***Signature***	***Date***
Comments			

Appendix 5

Ex-vivo GTMP Receipt Checklist

Product Name			
Supplier			
Manufacturer (if different to above)			
Courier Job Number (& other ref no)			
Date & time received			
Received by			
Checking step\data	**Yes / No / NA Data**	**Checker Initials**	**Date & time**
Tamper-evident ties intact? Outer Inner	 Yes / No Yes / No		
Dry ice competency (as appropriate)	Yes / No / NA		
Transit data logger temperature checked on receipt as per requirement	Yes / No		
Data logger within specification (no alarms)	Yes / No		
All required documentation received: Shipping log Returns documents Certificate of Analysis /QP release	 Yes / No / NA Yes / No / NA Yes / No / NA		
Dose as prescribed and within range	Yes / No		
Quantity received – no of bags			
Donation ID number correct (as required)	Yes / No		
Patient name			
Patient date of birth			
Overwrap			

Appendix 5 (cont.)

Product integrity visual check	Pass / Fail		
Lot/batch number			
Expiry Date	Yes / No		
Storage requirements			
Product placed into storage	Yes / No		
Storage location			
Receipt documented	Yes / No		
1st Check (Print name, sign, date)	***Print Name***	***Signature***	***Date***
2nd Check (Print name, sign, date)	***Print Name***	***Signature***	***Date***
Completed receipt checklist sent to Pharmacy			
Comments			

Appendix 6a

Ex-vivo Stem Cell Lab / Outsourced Aseptic Preparation Checklist

Process Set Up/Governance	Yes / No / NA	Checker Initials	Date & time
Roles and responsibilities documented	Yes / No		
Dedicated Isolator or BSC (II) available or campaign use agreed	Yes / No / NA		
Preparation Location Complies with the requirements in Chart 8.2 in Gene Therapy and Preparation	Yes / No / NA		
Worksheet written in line with SmPC, or Protocol / Pharmacy Manual (for Clinical Trials)	Yes / No / NA		
Appropriate label designed and approved	Yes / No		
Worksheet approved	Yes / No		
Waste pathway clear	Yes / No		
Required PPE is available	Yes / No		
Cleaning agent appropriate	Yes / No		
Process	**Yes / No**	**Checker Initials**	**Date & time**
SOP requires confirmation of patient readiness prior to beginning preparation	Yes / No / NA		
Operators are trained in the process	Yes / No		
Retrieval from storage (SOP available)	Yes / No / NA		
Thaw SOP in place	Yes / No / NA		
Aseptic preparation / manipulation method developed and approved	Yes/ No		
The process is covered by a suitable validation (as required)	Yes / No		
Check and release processes in place	Yes / No		
Transportation arranged	Yes / No		
	Print Name	***Signature***	***Date***

Appendix 6b

Ex-vivo Clinical Area Preparation Checklist

Process Set Up/Governance	Yes / No	Checker Initials	Date & time
Roles and responsibilities documented			
Is the medicine a Class I Gene Therapy*	Yes / No		
Is the shelf life <4hrs post reconstitution*	Yes / No		
Does the SmPC or Pharmacy Manual allow preparation on a clinical area	Yes / No		
Is a Pharmacy approved Worksheet available	Yes / No		
Has the GMSC approved clinical area preparation	Yes / No		
Are operators trained and competent	Yes / No		
Is a process in place for communicating patient readiness to Pharmacy (to avoid prolonged GTMP storage in the clinical area)	Yes / No		
Required PPE is available	Yes / No		
	Print Name	***Signature***	***Date***

*If the answer is no to either of these questions, then check that clinical area preparation is optimal.

Appendix 7

Ex-vivo GTMP Pharmacy Patient Dispensing Checklist

Product Name			
Supplier			
Manufacturer (if different to above)			
Patient name			
Patient Date of Birth (dd/Mmm/yyyy)			
Patient Hospital Number			
Treatment location			
Checking step	**Yes / No / NA Data**	**Checker Initials**	**Date**
Screened prescription available for treatment date	Yes / No		
Certificate of analysis received with product	Yes / No / NA		
Temperature deviations during storage on site	Yes / No		
Record batch number/product identifier on prescription	Yes / No		
Receive and book out GTMP on Pharmacy Dispensing system	Yes / No		

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