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Advanced Therapy Treatment Centres

Pharmacy Institutional Readiness for In-vivo (virus based) Gene Therapy Medicinal Products

Guidance for Chief Pharmacists

Pan UK Pharmacy Working Group for ATMPs

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Version 1

The first stop for professional medicines advice

Pharmacy Institutional Readiness for in-vivo (virus based) Gene Therapy Medicinal Products

Guidance for Chief Pharmacists

1. Background

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

Virus based Gene therapy medicinal products (GTMPs) 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.

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 it contains, 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 ‘in-vivo’ where the GTMP is injected directly into a specific tissue in the body and it is then taken up by individual cells, or where the GTMP is administered, usually but not exclusively, intravenously (IV). Examples of licensed ‘in-vivo’

GTMP are talimogene laherparepvec (*Imlygic*®) and voretigene neparvovec (*Luxturna*®). This guidance should be used in association with the SmPC and/or the Clinical Trial Protocol/Pharmacy Manual.

CAR-T cell therapies (ex-vivo gene 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 have now produced Pharmacy Institutional Readiness Guidance for delivery of in-vivo (virus based) Gene Therapies. Other newly published documents include Pharmacy Institutional Readiness guidance for Somatic Cell Therapies, ex-vivo (cell 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 in-vivo (virus based) Gene Therapy Medicinal Product (GTMP) e.g. IMP for Clinical Trials or Marketed ATMPs.

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

As in-vivo (virus based) gene therapies are not cell or tissue based, it is appropriate for preparation to occur in a pharmacy aseptic unit as directed on Page 18 of the 'Pan UK Pharmacy Working Group for ATMPs - Gene Therapy Medicinal Products - Governance and Preparation Requirements' available on the SPS website.
https://www.sps.nhs.uk/wp-content/uploads/2019/09/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-issue-2.pdf

In preparation for the implementation of NHS patient treatment an operational group consisting of representatives from The Pan UK Pharmacy Working Group for ATMPs was convened in order to provide exemplar documents and templates for some of the key steps in the delivery of in-vivo 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.

The following process flow diagram outlines the stages which require Pharmacy consideration when an organisation wishes to use an in-vivo 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 in-vivo GTMP which may be 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 and approval by the Chief Pharmacist.
   - Due to the value of the medicine, 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 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 is registered with HSE to handle gene therapy medicines for appropriate class (coordinated by GMSC) if clinical trial. (As per Regulation 9 of Contained Use Regulations 2014)
- Hospital 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 in-vivo 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

Product Receipt

- In-vivo (virus based) GTMPs are suitable for handling in Pharmacy. See Gene Therapy and Preparation for more information. On occasion they may require handling of dry ice and Pharmacy receiving areas require competency to undertake this activity.
- An SOP for receipt of GTMPs covering those holding marketing authorisation as well as investigational medicinal products (IMPs) is required. Checks on receipt should include integrity of the product, labelling, temperature compliance during transit, and Certificate of Analysis / QP certificates detailing the dose, if applicable. These should be reviewed by an appropriately trained clinical pharmacist or Clinical Trials pharmacist. Handling precautions should also be considered, including spillage kit when required.

An exemplar Product Receipt checklist is available in Appendix 5

Storage

- Storage requirement is likely to be in -20°C to -90°C for GTMPs. Room temperature stability is often short.
- Continuous temperature monitoring and alarms are required from receipt through to administration. Actions in the event of an alarm should be specified (and in line with anything detailed in the supply agreement with the company/sponsor).
- Deviation processes should be clarified e.g. if short period temperature out-of-specification occurs, the SOP should state that risk assessment and actions to be taken are documented. Pharmacy should be made aware of any on-site storage deviations.

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

Preparation Location Decision

- Some in-vivo GTMPs will require a thaw/preparation/reconstitution step. Optimal location for in-vivo gene therapy 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. Where stability data allows aseptic preparation should occur within a pharmacy aseptic unit.

Pharmacy Aseptic Preparation

Where Pharmacy Aseptic Unit is the optimal location for preparation, consider the following:

- Governance
  - Roles and responsibility clear
  - GMSC risk assessment compliance
- Operator Training
- Operator protection
  - Spill kit available
- Preparation process
  - Cross contamination
- Cleaning agent appropriateness
- Waste management
- Transportation
- Worksheet approved in line with SmPC or Protocol
- Confirmation when the patient is ready for in-vivo GTMP treatment.

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

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

Issue & Transportation of Pharmacy prepared products to the clinical area

The pharmacist-released preparation in its ready-to-administer presentation, should be issued and transported in accordance with a local SOP:

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

An exemplar Pharmacy Dispensing checklist is available in Appendix 7

Issue & Transportation from Pharmacy to the clinical area

- In-vivo GTMPs will be routinely received via Pharmacy. If preparation is to occur in a clinical area, then the Chief Pharmacist should ensure that the following are included in the approved Pharmacy SOP.
- Confirmation when the patient is ready for in-vivo GTMP treatment.
- Dispensing process.
- Procedure for retrieval from storage, if applicable, or reference to SOP if no different to routine.
- Transportation method to clinical area approved by GMSC.
- Transportation performed by trained and competent staff.
- Spill kit available.

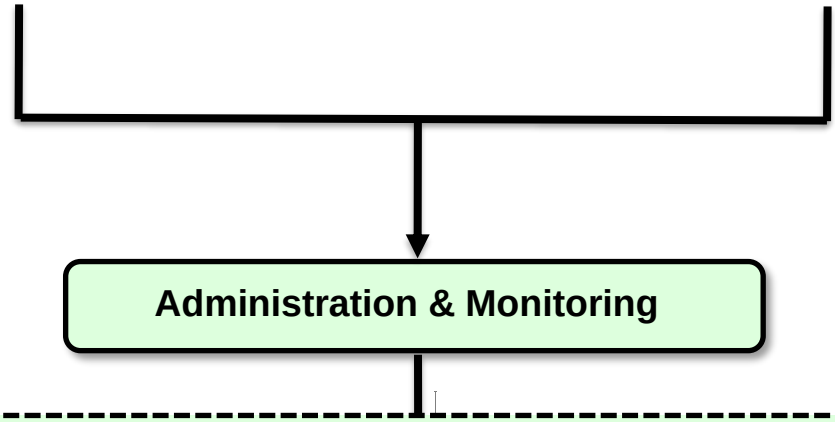
An exemplar Pharmacy Dispensing checklist is available in Appendix 7

Clinical Area Preparation

If thaw or any manipulation is required, in the clinical area, 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/guideline 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



- 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 and should ensure that they are prescribed for the patient. They also need to be aware of toxicity management and contra-indicated medicines. Any data collection and/or adverse event reporting agreed with the pharmaceutical company in addition to Yellow cards should be complied with.
- Any special instructions required for discharge should be understood and managed e.g. waste management instructions for shedding viral vectors.
- 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.
- Management of communication pathways is an important role for clinical pharmacists which may require contact with referral centres, specialised commissioning (BlueTeq requirements) and primary care colleagues.

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Appendix 1

In-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 NHSE to deliver GTMP	Yes / No		
Treatment centre qualified by manufacturer to deliver product	Yes / No / NA		
Commercial agreement in place if required	Yes / No		
Governance approvals in place for use of product as applicable: Medicines Management/Formulary ATMP Oversight Group (or similar) Clinical trial approvals	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 available	Yes / No		
Prescription added to electronic SACT prescribing system	Yes / No		
Product added to Pharmacy Ordering system	Yes / No		
If product requires preparation by pharmacy: worksheet, QA approval, staff training to prepare	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		

Appendix 1 (cont.)

Checking step	Yes / No	Checker Initials	Date
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			

Appendix 2

In-vivo GTMP Pharmacy Class and Containment Checklist

Class and containment level **circle as appropriate*	Class 1* / 2* / 3* / 4*		
Check Hospital is registered with HSE to handle gene therapy medicines for appropriate class (coordinated by GMSC)	Yes	No	
Risk assessment	Yes	No	
GMSC Approval completed	Yes	No	
NPSA Preparation assessment/optimal preparation location defined	Yes	No	
Waste disposal arrangements clear	Yes	No	
Spillage procedures available with kit	Yes	No	NA
Staff Training and competence agreed	Yes	No	
Preparation Facilities: • Pharmacy • External to pharmacy • Freezer storage • Transport • Aseptic facilities risk assessment • Personal Protective Clothing	 Yes Yes Yes Yes Yes Yes	 No No No No No No	
Product Administration: • Approved prescription • Administration Guideline including adverse reaction guide, patient monitoring, supportive drugs/concomitant medication, if required	 Yes Yes	 No No	
Shedding management/ containment: • Patient information • PPE • Interactions with other patients/staff/visitors • Advise to family/carers	 Yes Yes Yes Yes	 No No No No	
Discharge Procedure: • Patient information • Discharge letter	 Yes Yes	 No No	
GMSC approval and class communicated to governance groups as appropriate	Yes	No	No
	Print Name	***Signature***	***Date***

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Appendix 3

In-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		
Any abnormal laboratory results		
Referring Clinical		
Referral notification to supplier/sponsor		
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***	

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Appendix 4

In-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		
Blueteq ID	Yes / No / NA		
Trust funding approved	Yes / No		
Patient consent documented	Yes / No		
GTMP prescribed	Yes / No		
Pharmacist clinical accuracy check completed	Yes / No		
Pharmacy order number issued	Yes / No		
Pharmacist approval documented	Yes / No		
Pharmacist Final Check	***Print Name***	***Signature***	***Date***
Comments			

Appendix 5

In-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	**Yes / No / NA Data**	**Checker Initials**	**Date & time**
Tamper-evident ties intact? Outer Inner	 Yes / No Yes / No		
Dry ice competency	Yes / No / NA		
Transit 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		
Quantity received			
Product integrity visual check	Pass / Fail		
Lot/batch number			
Expiry Date	Yes / No		
Storage requirements			

Appendix 5 (cont.)

Checking step	Yes / No / NA Data	Checker Initials	Date & time
Product placed into storage	Yes / No		
Storage location			
Receipt documented	Yes / No		
1st Check (Print name, sign, date)	***Print Name***	***Signature***	***Date***
Completed receipt checklist sent to Pharmacy			
Comments			

Appendix 6a

In-vivo GTMP Pharmacy 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	Yes / No		
Worksheet approved	Yes / No		
Waste pathway clear	Yes / No		
Required PPE is available	Yes / No		
Cleaning agent appropriate	Yes / No		
Transport to clinical area SOP in place	Yes / No		
Spill kit available at all times	Yes / No		
Process	**Yes / No**	**Checker Initials**	**Date & time**
The process is covered by a suitable validation	Yes / No		
Operators are trained in the process	Yes / No		
SOP requires confirmation of patient readiness prior to beginning preparation	Yes / No / NA		
Retrieval from storage (SOP available)	Yes / No / NA		
Thaw SOP in place	Yes / No / NA		
Check and release processes in place	Yes / No		
Transportation arranged	Yes / No		
	Print Name	***Signature***	***Date***

Appendix 6b

In-vivo GTMP Clinical Area Preparation Checklist

Process Set Up/Governance	Yes / No / NA Data	Checker Initials	Date & time
Roles and responsibilities documented	Yes / No		
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 in a Clinical area	Yes / No		
Is a Pharmacy approved Worksheet available	Yes / No / NA		
Has the GMSC approved clinical area preparation	Yes / No		
Are operators trained and competent including spill kit and waste management	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

In-vivo GTMP Pharmacy Dispensing / Issue 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/clinically checked prescription available for treatment date	Yes / No		
Certificate of analysis/ QP batch certificate received with product	Yes / No / NA		
Temperature deviations during storage on site	Yes / No		
Aseptic preparation worksheet completed or worksheet/guideline available in clinical area	Yes / No		
Record batch number/product identifier on prescription	Yes / No		
Receive and book out GTMP on Pharmacy Dispensing system	Yes / No		
Transport to clinical area according to pharmacy approved sop ensuring availability of spill kit.	Yes / No		
	Print Name	***Signature***	***Date***

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