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Pharmacy Institutional Readiness for In-vivo Non-Genetically Modified Organism (Non-GMO) Gene Therapy Medicinal Products

Pan UK Pharmacy Working Group for ATMPs

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The first stop for professional medicines advice

Pharmacy Institutional Readiness for In-vivo Non-Genetically Modified Organism (Non-GMO) Gene Therapy Medicinal Products

Guidance for Chief Pharmacists

1. Background

Advanced Therapy Medicinal Products (ATMPs) are innovative medicines which provide challenges in delivery. As Gene Therapy Medicinal Products (GTMPs) are classed as ATMPs, Chief Pharmacists are required to ensure that governance arrangements are in place to ensure safe and secure handling of 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.

GTMPs are categorised as **genetically modified organisms (GMO's)** or **non-GMO's.** GMO and non-GMO GTMPs can be further subdivided as in vivo or ex vivo. 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 **in vivo non-GMO GTMPs.** Examples of in vivo non- GMO gene therapies are mRNA-based immunotherapies. Guidance for ex vivo (cell based) non-GMO GTMPs is available. Further guidance for in vivo and ex vivo GMO GTMPs is also available on the SPS website.

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.

Conversely to GMO GTMPs, non-GMO GTMPs do not utilise viral transduction to enable delivery of genetic material to target cells. Instead, non-GMO GTMPs utilise non-viral methods for gene transfer. These new methods can be grouped into two main categories: carrier mediated delivery and non-carrier mediated delivery. Examples of the first group include liposomes or lipid nanoparticles (LNPs), cell penetrating peptides (CPP), inorganic vectors and polymeric delivery systems, which encapsulate the genetic material to be transferred and then taken up by cells. Gene transfer without carriers is achieved using physical or chemical methods to increase cell membrane permeability and is used only during the manufacturing process. For example, electroporation uses electrical stimulation to open pores in the cell membrane allowing the delivery of genetic material into the cells.

mRNA immunotherapies use this innovative technology to deliver mRNA to cells to produce transient expression of a desired protein. In vivo non-GMO GTMPs involves direct delivery of genetic material, either DNA or mRNA, into target cells through an injection to treat a specific mutated gene or insertion of a missing gene. These nucleic acids are developed in a laboratory; they can be classified as 'off the shelf' or personalised to the patient. For the latter group, the nucleic acids are developed using the host's own synthesis mechanisms to upregulate antigen production that recognises a pathogenic cell (i.e. increases the likelihood of recognition).

The application of mRNA technology has now been studied to treat cancerous solid tumours including colorectal, melanoma and head and neck cancers.

This document should be used in association with the SmPC and/or the Clinical Trial Protocol/Pharmacy Manual. In order to manage the pipeline of ATMPs, the Pan UK Pharmacy Working Group for ATMPs has also published Pharmacy Institutional Readiness guidance for Somatic Cell Therapies, ex-vivo GMO (virus based) Gene Therapies, in-vivo GMO (virus based) Gene Therapies, in-vivo non-GMO Gene Therapies and Tissue Engineered Products.

2. Purpose

The purpose of this guidance is to outline the key areas where chief pharmacists should focus pharmaceutical expertise prior to and during the implementation of any in-vivo non-GMO GTMPs.

This document presents a flow diagram outlining a stepwise approach to implementing in-vivo non-GMO GTMPs. It is followed by checklists which relate to the various steps outlined in the diagram. These are presented as appendices.

As previously stated, in-vivo non-GMO GTMPs can either be personalised for the patient or 'off the shelf'. For individualised products, 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.

In-vivo non-GMO GTMPs often require storage in a minus 20^0C or less than minus 60^0C freezer and require thawing before administration. In some cases, additional aseptic manipulation may be required. Manipulation of non-GMO GTMPs requires skilled operators who are trained and understand the risks associated with handling of the product. For further information on training and competencies requirements for ultralow storage, see Handling Dry Ice and Vapour Phase Nitrogen Shippers- advice for hospital pharmacies.

The following process flow chart outlines the stages which require Pharmacy consideration when an organisation wishes to use an In-vivo non-GMO GTMP. Refer to the Requirements for Governance and Preparation of Gene Therapy: Pan UK Pharmacy Working Group for ATMPs document for further details.

Process Flow Encompassing Points for Consideration by Chief Pharmacists

Governance

- Chief pharmacists should ensure that governance for In-Vivo non-GMO GTMPs is documented as follows:

1. Site Qualification:
   - For an investigational ATMP (ATIMP), centres will need to be designated by a Sponsor in a clinical trial.

2. Patient selection:
   - Clinical approval of patient selection (MA)/Trial eligibility (ATMP)

3. Local Governance:
   - As referenced in Requirements for Governance and Preparation of Gene Therapy: Pan UK Pharmacy Working Group for ATMPs document, organisational governance prior to providing any ATMP is advised. This may involve an ATMP Committee and/or Medicines Management Committee. Even though there is **no** statutory requirement for an in vivo non-GMO GTMP to be approved by a Genetic Modification Safety Committee (GMSC), the Pan UK Pharmacy Working Group recommends the use of a risk assessment process for all GTMPs, regardless of GMO or license status, as part of a robust medicine governance process. Local requirements for non-GMO GTMPs should be defined prior to implementation of the product in an organisational policy.
   - A centre wishing to provide In-vivo non-GMO GTMPs will define additional local governance requirements e.g. for private patients.
   - For an unlicensed medicine, local organisational unlicensed medicines policy will apply.

4. Costs and contracting:
5. Implementation sites could be asked to complete Commercial Agreements/mCTA which can include supply and technical quality agreements with the relevant pharmaceutical companies/Sponsor. These will require review by Pharmacy.
6. Due to the cost of GTMPs, 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.

An example of a Pharmacy Governance Checklist and Clinical Pharmacist Checklist has been provided in Appendix 1 and 2.

Risk Assessment

A risk assessment is recommended for all GTMPs regardless of GMO or license status. Therefore, a risk assessment should be completed for In-vivo non-GMO GTMPs by the requesting clinician/principal investigator in collaboration with other healthcare professionals involved in the handling and management of the product.

GMSC approval of the risk assessment is mandated for GMO IMP and ULM. Where organisations choose not to use their GMSC for a non-GMO GTMP, a risk assessment should be considered as part of the governance process to establish optimal operational implementation of the non-GMO GTMP as per Gene Therapy Governance and Preparation Requirements which involves assessment of the product, the patient and the waste.

Ordering and Prescribing

- 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 a SOP to be defined which will need to reference any commercial operating system which an individual in-vivo non GMO 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 example Clinical Pharmacist Checklist covering product ordering is available in Appendix 2

Product Receipt

- In-vivo non GMO GTMPs are suitable for handling in Pharmacy. See Gene Therapy Medicinal Products Governance and Preparation Requirements 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 non GMO 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.

Storage

- Storage requirement is likely to be in -20ºC to -90ºC for GMO GTMPs and 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.

Preparation Location Decision

- Some in-vivo GMO 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 Medicinal Products Governance and Preparation Requirements. Preparation location should have been defined in the GMSC risk assessment. Where stability data allows aseptic preparation should occur within a pharmacy aseptic unit.
- On receipt the product can either be:
  - Transported to the clinical area and then thawed and prepared (if required) prior to administration – stability <4 hours
  - Thawed in pharmacy and transported to the clinical area – stability >4 hours
  - Thawed and aseptically manipulated then transported to the clinical area for administration to the patient.

Pharmacy Aseptic Preparation

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

- Governance
  - Roles and responsibility clear
  - 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 non GMO GTMP treatment.

For further information on each point, see Gene Therapy Medicinal Products Governance and Preparation Requirements for more information.

Pharmacy Storage, Issue & Transportation to the clinical area

- In-vivo non GMO 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 non GMO GTMP treatment.
- Dispensing process.
- Procedure for retrieval from storage, if applicable, or reference to SOP if no different to routine.
- Transportation performed by trained and competent staff.
- Spill kit available.

Issue & Transportation 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.

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 product is handled by trained staff.
- Roles and responsibilities should be clearly documented in a local SOP.
- A Pharmacy approved clinical area worksheet in line with the SmPC/Protocol should be designed.
- PPE appropriate to the hazard classification.
- Any preparation should be undertaken by trained and competent staff and be in line with an SOP detailing whether additional labelling is required (annex 13 compliant).

Administration & Monitoring

- Information regarding product administration should be captured on the risk assessment.
- Administration should be undertaken by trained and competent staff according to local organisational policy.
- 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-indicated medicines.
- Resources available include SmPC and company literature as well as protocol, investigators brochure and Pharmacy Manual for ATIMPs.
- 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

NEW In-vivo non-GMO GTMP PHARMACY GOVERNANCE CHECKLIST

Product Name			
Supplier			
Manufacturer (If different to above)			
Regulatory status	☐ Licensed ☐ Unlicensed ☐ Investigational (Record EudraCT number if applicable)		
Governance Arrangements			
Checking step	Status	Checker initial	Date
NHSE commissioned treatment site status (licensed only)	☐ Site Selected as a site ☐ Site Not Selected as a site ☐ Not Applicable		
Site selection status by sponsor (clinical trials only)	☐ Site Selected as a site ☐ Site Not Selected as a site ☐ Not Applicable		
Local Governance approvals (medicine management/ATMP committee)	☐ Approval issued ☐ Approval in progress ☐ Application not submitted ☐ Approval by other committees Specify:		
Checking step	Status	Checker initial	Date
Trust funding process	☐ Approved ☐ Not Approved		
Supply agreement/mCTA	☐ Signed ☐ In progress		
Pharmacy arrangements			
Checking step	Status	Checker initial	Date
NPSA ATMP risk assessment (Proforma 1)	☐ Completed and submitted to the committee ☐ Not Completed ☐ Not applicable		
Product preparation	☐ No preparation required ☐ Preparation by provider/nurses- worksheet designed: ☐ Yes ☐ No		
	☐ Product built		

Prescription build status on the electronic system	☐ Request form completed and submitted by the lead clinical pharmacist, awaiting build ☐ Request form not completed		
Product added to Pharmacy Ordering system	☐ Yes ☐ No		
Product added to formulary (licensed only)	☐ Yes ☐ No		
Pharmacy specific documents (Covering product ordering, receipt, storage, clinical check, deviations, etc.)	☐ SOP covering pharmacy process finalised ☐ SOP covering pharmacy process drafted		
Financial arrangements			
Blueteq required* (licensed only) CDF, EAMS	☐ Yes- Blueteq, CDF, EAMS available ☐ Yes- Blueteq, CDF, EAMS not available ☐ No		
Arrangements in place to track the product and seek reimbursement by medicine finance team	☐ Yes ☐ No		
Pharmacist final check sign off: Pharmacist name and signature:		Date:	

*Blueteq will only be enabled once regional contracts have been signed off between regional commissioner and commissioned provider.

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Appendix 2

In-vivo non-GMO GTMP CLINICAL PHARMACIST CHECKLIST

Part 2: Approval/Ordering

Product Name				
Supplier				
Patient name				
Manufacturer (if different to above)				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
Patient Trial ID				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**To be Checked/ completed by***
BlueTeq, CDF, EAMS Form completed ID number:	☐ ----------			PH/CT
Patient consent documented	☐			PH/CT
Purchase order raised PO number for commercial products only :	☐ ----------			PT
Pharmacist final check all details complete (Print name, sign, date)	Print Name	Signature and Date		PH
Comments				

*** Pharmacist (PH), Procurement Team (PT), Clinical Team (CT)**

Appendix 2 (cont.)

In-vivo non-GMO GTMP CLINICAL PHARMACIST CHECKLIST

Part 5: Receipt/Release/Issue

Product Name				
Supplier				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
Patient Trial ID				
Chain Of Identity (COI) ID for personalised GTMP				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**Teams involved***
Receive GTMP on pharmacy dispensing system	☐			PH and PT
Patient is fit to receive GTMP infusion	☐			CT to confirm PH to check confirmation
Clinically check GTMP prescription	☐			PH to check
Issue GTMP on Pharmacy Dispensing system	☐			PH and PT
BlueTeq, CDF, EAMS Form (product administration) completed ID number:	☐ ----------			CT
Pharmacist final check all details complete (Print name, sign, date)	Print Name		Signature and Date	
•				
Comments				

*** Pharmacist (PH), Procurement Team (PT), Clinical Team (CT), Outsourced Storage Provider (OSP)**

Appendix 3

In-vivo non-GMO GTMP Receipt Checklist

Product Name			
Patient Name			
Patient Date of Birth (dd/mm/yyyy)			
Patient Trial ID			
COI Number			
Relevant patient virology details			
Supplier			
Manufacturer (if different to above)			
Date & time received			
Received by			
Checking step\data	**Yes / No / NA Data**	**Checker Initials**	**Date & time**
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		
COI ID number matches	Yes / No		
Patient name matches	Yes / No		
Patient date of birth matches	Yes / No		
Patient Trial ID matches (personalised references in the GTMP batch/CoA/QP documents	Yes / No		

Appendix 3 (cont.)

Checking step\data	Yes / No / NA Data	Checker Initials	Date & time
Overwrap			
Dose as prescribed	Yes / No		
Quantity received – no of vials			
Product integrity visual check	Yes / No		
Products labelled correctly	Yes / No		
Lot/batch number			
Within Expiration Date	Yes / No		
Storage requirements			
Time and Date product placed into storage			
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 if not received products is not processed by pharmacy			
Comments			

Appendix 4

In-vivo non-GMO 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 risk assessment	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 5

In-vivo non-GMO GTMP Clinical Area Preparation Checklist

Process Set Up/Governance		Yes / No	Checker Initials	Date & time
Roles and responsibilities documented		Yes / No		
Is the shelf life <4hrs post thaw/reconstitution*		Yes / No		
Does the SmPC or Pharmacy Manual allow preparation in a clinical area*		Yes / No		
Is a Pharmacy approved Worksheet and SOP available		Yes / No		
Has the governance process approved clinical area preparation		Yes / No		
Is the clinical area appropriate for preparation e.g., enough space for equipment and staff members		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		
Approval	***Print Name***	***Signature***		***Date***

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

The Pan UK Pharmacy Working Group for ATMPs would like to thank the following people for their contribution towards this document:

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