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

Pan UK Pharmacy Working Group for ATMPs

November 2025

Version 1.1

The first stop for professional medicines advice

Pharmacy Institutional Readiness for ex-vivo (cell based) 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 the 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 **ex vivo (cell based) non-GMO GTMPs.** Guidance for in 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.

The cell genome can be modified ex-vivo using different technologies such as:

- **Gene Editing**

  Gene editing refers to a group of technologies used during the manufacturing process to modify the DNA of cells. These technologies allow genetic material to be added, removed, or altered at particular locations in the genome following a cut in the DNA at that specific point. Several approaches to gene editing have been developed. A well-known one is the use of molecular scissors, called nucleases, such as Transcription Activator-Like Effector Nucleases (TALEN), CRISPR-Cas system and Zinc Finger Nuclease (ZFN). Another approach involves the use of transposon/transposase systems such as “Sleeping Beauty” or “PiggyBac” in which the gene editing tools allow the DNA of a cell to translocate from a specific location in the genome to another through a “cut-and-paste mechanism”.

- **mRNA-based CAR-T immunotherapy**

  mRNA- based CAR-T immunotherapy is an innovative technology that delivers mRNA to cells producing a transient expression of a desired protein (i.e. Chimeric Antigen Receptors (CARs)). Non-viral CAR-T cells can be generated using both in vivo (LNP) (not within the scope of this guide) and in vitro (electroporation and nanoparticle systems) transfection techniques. The latter will fall under the category of ex vivo non-GMP GTMP.

Ex vivo non-GMO GTMPs are where cells are taken from a donor, usually the patient, and used as the starting material for the medicinal product. The donor cells undergo genetic modification 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. An example of an autologous ex-vivo non-GMO GTMP treatment is marketed Casgevy®, which is the world’s first CRISPR–Cas9 gene editing therapy that aims to cure sickle cell disease and transfusion-dependent β-thalassemia. Further guidance on Pharmacy Institutional Readiness for the Introduction of Casgevy® is available.

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 ex-vivo non-GMO GTMPs.

This document presents a flow diagram outlining a stepwise approach to implementing ex-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 ex-vivo non-GMO 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 non-GMO gene therapies may be stored under cryopreservation and require thawing before administration and in some cases additional aseptic manipulation. It is recognised that Pharmacy Services do not currently have the expertise to manipulate cellular products and that, routinely, Pharmacy Services may not come directly into contact with the product. However, it is important that, where Pharmacy Services are not directly performing some of the outlined steps, the roles and responsibilities of those undertaking the aforementioned steps are clearly documented in an overarching technical agreement with reference made to organisational pharmacy approved SOPs. 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 chart outlines the stages which require Pharmacy consideration when an organisation wishes to use an ex-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 Ex-Vivo non-GMO GTMPs is documented as follows:

1. Site Qualification:
   - For a marketed product, centres will need to meet the requirements of the commissioning process and become a designated centre for administration of the ex-vivo (cell based) non-GMO GTMP which may be documented in a National Service Specification.
   - For an investigational ATMP (ATIMP), centres will need to be designated by a Sponsor in a clinical trial.

2. Patient selection:
   - An approved centre will need to understand the national processes for patient selection (MA only)
   - Clinical approval of patient selection (MA)/Trial eligibility (ATIMP)

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 a 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 ex-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.
   - An SOP will be required to ensure Pharmacy's involvement with the following process:
     - Process cancellation
     - Credit claims (if applicable)
     - Deviations (including OOS)

4. Costs and contracting:
5. Implementation sites will 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 ex-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

- Provisions for prescribing of the drug should be in place (i.e. design of prescription form, build on electronic prescribing system).
- Pharmacy procurement setup should be completed for each ex-vivo non-GMO GTMP.
- For marketed products:
  - 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.
  - Commercial operating systems require a pharmacist's approval and/or the provision of a pharmacy purchase order. Access to the portal needs to be arranged for trained pharmacy staff to review the order and enter a PO on the portal. This will require an SOP to be defined, which will need to reference the commercial operating system that an individual pharmaceutical company may require to be used. 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.

Mobilisation, Apheresis and Manufacture

- Check for relevant medication restrictions (medicines that must be omitted for a defined time period) when planning the apheresis schedule.
- Stem cell mobilisation with G-CSF and/or Plerixafor may be required prior to apheresis for some ex-vivo non-GMO GTMPs (such as Casgevy®).
- For both an "autologous" and an "allogeneic" product the starting material must be collected in the UK under a Human Tissue Authority licence (human application). For products manufactured outside the UK, an HTA licence for export/import will also be required.
- In local site documentation the pathway for the manufacture of the ex-vivo non-GMO GTMP should be clearly described and roles and responsibilities understood. Local site documentation should also be clear that, during manufacture, GMP compliance is required and that the Qualified Person employed by the manufacturer has overall responsibility for certification of the product.

An exemplar mobilisation checklist is available in appendix 2.

Product Receipt

- Pharmacy is responsible for overseeing and approving all procedures relating to the handling and storage of GTMPs. Ex-vivo non-GMO GTMPs are not routinely 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 GTMPs is required and should cover licensed, unlicensed and investigational products. Checks on receipt should include integrity of the product, labelling and temperature compliance during transit. Certificate of Release/Certificate of analysis/QP certificates detailing the dose, if applicable, should be reviewed by an appropriately trained clinical pharmacist or clinical trial pharmacist as part of product release process.

An example product receipt checklist is available in Appendix 3

Storage

- Ex-vivo non-GMO GTMPs require to be stored under specified temperature storage conditions. In most cases, required temperature storage conditions may be as low as -150^{o}C. It is important that appropriate equipment is sourced, as necessary, to accommodate specific requirements.
- Optimal storage location for ex-vivo GTMPs will depend on storage temperature conditions and duration. If refrigerator, -80^{o}C freezer or short-term vapour phase nitrogen dewar, then pharmacy storage may be an option. Cell based products should be segregated where possible and always stored in a secure manner to minimise the risk of cross-contamination.
- Stem cell labs with pharmacy oversight or outsourcing may be an option for products requiring prolonged storage in in vapour phase nitrogen dewars or dry shippers. In this instance, an overarching technical agreement between Pharmacy and the Stem Cell labs or the outsourced storage provider will be required to outline the roles and responsibilities of each party (see A Template TA for ATMPs or TA for ATIMPs for further details).
- All the different storage options should be risk assessed, and the optimal storage location should be defined in the product specific risk assessment.
- Continuous temperature monitoring and alarms are required. Actions in the event of an alarm should be specified by local organisational governance.
- Deviation processes should be clarified e.g. if short period temperature out-of-specification occurs, the SOP should state actions to be taken. Pharmacy should be made aware of any on-site storage deviations.
- Details of the receipt, storage and handing must be covered in a local product specific SOP.

Conditioning Chemotherapy

- Only when the non-GMO GTMP has been received onsite should conditioning chemotherapy start.
- Check for relevant medication restrictions prior to starting conditioning chemotherapy and the GTMP infusion.
- Examples of conditioning chemotherapies include myeloablation with Busulfan and lymphodepletion with Cyclophosphamide and Fludarabine.
- Where Pharmacokinetic (PK) monitoring is required, PK sampling times will depend on the test method and should be confirmed by the laboratory undertaking the testing.
- Conditioning chemotherapy will be prepared in the aseptic unit.
- Clinical pharmacist should check conditioning chemotherapy regimens and confirm completion of chemotherapy prior to GTMP administration.
- Supportive care should be prescribed with conditioning chemotherapy e.g., anti-seizure agents, VOD prophylaxis, anti-emetics.
- Following completion of the conditioning chemotherapy, the GTMP should be infused within the time frame specified by the manufacturer/sponsor.

A condition chemotherapy checklist has been provided in Appendix 2.

Preparation Location Decision

- Some ex-vivo non GMO GTMPs will require a thaw/preparation/reconstitution step. Optimal location for ex-vivo non-GMO gene therapy preparation will be as per SmPC or clinical trial protocol. Where the location is not specified refer to clinical trials/pharmacy aseptic team/stem cell lab and risk assess the different location options and establish preparation location. A preparation risk assessment tool (see proforma 1) for cell and tissue-based Advanced Therapy Medicinal Products (ATMPs) can be found on SPS website. Optimal preparation location should be defined in the risk assessment.

- 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/ stem cell lab (SCL) and transported to the clinical area – stability >4 hours
  - Thawed and aseptically manipulated e.g. in stem cell laboratories then transported to the clinical area for administration to the patient. Pharmacy oversight is required.

Aseptic Preparation e.g. stem cell laboratory

- Where aseptic preparation/manipulation is delegated to a stem cell laboratory or an outsourced provider, a technical agreement is required to outline the roles and responsibilities of each party (see A Template TA for ATMPs or TA for ATIMPs for further details).
- Pharmacy oversight is needed to ensure that:
  - The preparation process is in line with SmPC or protocol and an approved worksheet is in place.
  - PPE, in line with any other cellular product, is available
  - Waste is handled and disposed of as any other cellular product in accordance with local guidelines on handling human-derived material

  Confirmation of when the patient will be ready to receive GTMP infusion is obtained. The confirmation process should be detailed in a local SOP

An exemplar aseptic preparation checklist is provided in Appendix 4.

Issue & Transportation to the clinical area

Products prepared by stem cell labs or outsourced providers should be released by pharmacy or with pharmacy oversight according to local governance arrangements and be in their ready-to-administer presentation. The Chief pharmacist should ensure that the following are in an approved SOP:

- Confirmation that conditioning chemotherapy is completed.
- Procedure for retrieval from liquid nitrogen tank/freezer, if applicable, or reference to an approved SOP if no different to routine.
- Transportation method to clinical area (i.e. dry ice/vapour phase dewar).
- The product is transported by trained staff (e. stem cell lab staff).
- Communication with pharmacy for booking out, and billing purposes, if required.

Pharmacy checks will be documented as part of the clinical pharmacist checklist **(see Appendix 4 for an exemplar checklist).**

Pharmacy Storage, Issue & Transportation to the clinical area

- Ex-vivo non-GMO 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.
- The following should be included in an approved SOP:
  - Confirmation that the patient is ready to receive GTMP infusion.
  - Procedure for retrieval from liquid nitrogen tank/freezer, if applicable, or reference to an approved SOP if no different to routine.
  - Procedure for pharmacy thaw (if applicable) should be available and competency training in place. All training should be documented.
  - Transportation method to clinical area (i.e. dry ice/vapour phase dewar).

Transportation should be performed by trained and competent staff according to local organisational policy.

An exemplar Pharmacy release and issue

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.

A clinical area preparation checklist has been included in Appendix 5.

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 ex-vivo non-GMO GTMP PHARMACY GOVERNANCE CHECKLIST

Product Name			
Supplier			
Manufacturer (If different to above)			
Regulatory status	☐ Licensed ☐ Unlicensed ☐ Investigational (Record trial identifier)		
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		
JACIE accreditations (For admin of immune effector cells, allo and auto transplantation, apheresis, cell processing)	☐ Accredited ☐ Not Accredited		
HTA licensing status	☐ Covered under current HTA licence		
	☐ New licence required- licensed issued		
	☐ New licence required application in progress		
Technical Agreement	☐ Established ☐ Not Established		
Site qualification status by manufacturer/sponsor	☐ Qualified (audit and inspection conducted) ☐ Not Accredited		
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 SCL/outsourced provider/nurses- worksheet designed: ☐ Yes ☐ No		
Prescription build status on the electronic system	☐ Product built		
	☐ 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)	☐ Yes- Blueteq available ☐ Yes- Blueteq 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.

Appendix 2

Ex-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				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**To be Checked/ completed by***
National patient selection approval confirmation (Patient MDT ID code)	☐			PH
BlueTeq Form completed ID number:	☐ ----------			CT
Patient consent documented	☐			CT
Purchase order raised PO number:	☐ ----------			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)**

Ex-vivo non-GMO GTMP CLINICAL PHARMACIST CHECKLIST

Part 3: Mobilisation-if applicable
(To be completed with each mobilisation attempt)

Product Name				
Supplier				
Manufacturer (if different to above)				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**To be Checked/ completed by***
Mobilisation attempt number:	1st / 2nd / 3rd			CT
BlueTeq Form completed ID number:	☐ ----------			CT
Medication restrictions checked	☐			CT and PH
Patient weight (kg)				CT
Blood tests checked	☐			CT and PH
Mobilisation prescribed	☐			CT
G-CSF counselling (if self-administering) inc. dose & timing	☐			PH
Mobilisation prescription clinically verified	☐			PH
Plerixafor doses ordered (if relevant) Total number of plerixafor doses used	☐ ----------			PH
Pharmacist final check all details complete (Print name, sign, date)	Print Name	Signature and Date		PH
Comments				

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

Appendix 2 (cont.)

Ex-vivo non-GMO GTMP CLINICAL PHARMACIST CHECKLIST

Part 4: Conditioning chemotherapy

Product Name				
Supplier				
Manufacturer (if different to above)				
Patient name				
Patient Date of Birth (dd/mm/yyyy)				
Patient Hospital Number				
Patient NHS Number				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**Teams involved***
Receive GTMP on pharmacy dispensing system when receipt confirmed by stem cell lab/outsourced storage provider	☐			SCL, OSP, PH and PT
Medication restrictions checked	☐			CT and PH
Patient weight (kg)				CT
Patient height (cm)				CT
Medication allergy status				CT and PH
Blood tests checked (e.g. full blood count, renal & liver function, virology)	☐			CT and PH
Conditioning Chemotherapy prescribed & clinically verified	☐			CT and PH
Supportive medicines prescribed	☐			CT and PH
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), Stem Cell Lab (SCL), Outsourced Storage Provider (OSP)**

Appendix 2 (cont.)

Ex-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				
COI ID				
Checking step	**Confirm/Enter details (✓)**	**Checker Initials**	**Date**	**Teams involved***
Receive GTMP on pharmacy dispensing system when receipt confirmed by stem cell lab/outsourced storage provider *(if not already done)*	☐			SCL/OSP, PH and PT
Conditioning chemotherapy completed	☐			PH to check
Patient is fit to receive GTMP infusion	☐			CT to confirm PH to check confirmation
Clinically check GTMP prescription	☐			PH to check
Cells authorised by pharmacy and cell release communicated to the SCL/ OSP *(By checking certification of analysis, checking the dose and matching patient identification)*	☐			PH and SCL, OSP
Issue GTMP on Pharmacy Dispensing system	☐			PH and PT
BlueTeq Form (product administration) completed ID number:	☐ ----------			CT
Pharmacist final check all details complete (Print name, sign, date)	Print Name		Signature and Date	
Once cells are administered to patient, file the following in the product specific folder which is kept in Pharmacy: • Copy of certificate of analysis/release (if available) • Copy of the completed cell receipt checklist (provided by SCL/OSP) • Copy of the completed preparation (if applicable) and administration worksheet • Completed copy of this checklist				
Comments				

*** Pharmacist (PH), Procurement Team (PT), Clinical Team (CT), Stem Cell Lab (SCL), Outsourced Storage Provider (OSP)**

Appendix 3

Ex-vivo non-GMO GTMP Receipt Checklist

Product Name			
Patient Name			
Patient Date of Birth (dd/mm/yyyy)			
COI Number			
Donor Identification Number			
Relevant patient virology details			
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		
COI ID number matches	Yes / No		
Patient name matches	Yes / No		
Patient date of birth matches	Yes / No		
Donor Identification Number matches	Yes / No		

Appendix 3 (cont.)

Checking step\data	Yes / No / NA Data	Checker Initials	Date & time
Overwrap			
Dose as prescribed and within range	Yes / No		
Quantity received – no of vials / bags			
Product integrity visual check	Pass / Fail		
Products labelled correctly	Pass / Fail		
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			
Comments			

Appendix 4

Ex-vivo non-GMO GTMP Stem Cell Lab / Outsourced Aseptic Preparation Checklist

Process Set Up/Governance	Yes / No / NA	Checker Initials	Date & time
Roles and responsibilities documented	Yes / No		
Preparation Location Complies with the requirements detailed in the risk assessment	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		
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		
Communication with pharmacy for booking out, and billing purposes	Yes / No / NA		

Approval	***Print Name***	***Signature***	***Date***

Appendix 5

Ex-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/SCL/OSP (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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