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Advanced Therapy Treatment Centres

Pharmacy Institutional Readiness for Somatic Cell 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 Somatic Cell Therapy Medicinal Products

Guidance for Chief Pharmacists

1. Background

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

Somatic cell therapy medicinal products (sCTMPs) 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.

Where a product is autologous (uses a patient's cells or tissues as starting materials) there are potentially disastrous consequences if the medicine is administered to patient for whom it is not intended. There is a role for the Chief Pharmacist in ensuring that the risks, particularly around tracking and traceability, are minimised.

A Somatic Cell Therapy Medicinal Product is a biological medicinal product which has the following characteristics:

> *(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor and*
>
> *(b) is presented as having properties for, or, is used in or administered to human beings with a view to treating, preventing, or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.*

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.

It should be pointed out, that this list of non-substantial manipulations is non-exhaustive.

It should be noted, that in order to be considered a sCTMP both the characteristics (a) and (b) have to be fulfilled.

Examples of *substantial manipulation* include cell expansion/culture, enzymatic digestion of tissue and differentiation or activation with growth factors. A somatic cell is any cell of a living organism other than the reproductive (sperm and egg) cells

sCTMPs are defined Directive 2001/83/EC, Annex I, Part IV as amended, more information can be found in:

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf#:~:text=According%20to%20Article%202%281%29%28a%29%20of%20Regulation%20%28EC%29%20No.1394%2F2007%2C,IV%20of%20Annex%20I%20to%20Directive%202001%2F83%2FEC%2C%20as

The manufacture of sCTMP may be complex. A sample of cells either from the patient or a donor is used as the starting material., Particular cells are isolated and then substantially manipulated before being administered to the patient (now classed as a medicine) in order to treat, prevent or diagnose disease. Where the starting material originates from the patient's own cells, this is called an "autologous" therapy. Where the starting material originates from a donor, this is termed "allogeneic" therapy.

An example of an licenced sCTMP is Darvadstrocel (Alofisel) consisting of expanded human allogeneic mesenchymal adult stem cells, extracted from adipose tissue and indicated for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Another example, currently being evaluated by clinical trials, is autologous tumour infiltrating lymphocytes (TILs). TILs are isolated from the patient tumour, expanded ex vivo, and infused back into the patient followed by interleukin-2 (IL-2) administration.

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 Somatic Cell Therapy Medicinal Product (sCTMP).

This document presents a flow diagram outlining a stepwise approach to implementing processes to prepare and administer sCTMPs. 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 prepared exemplar documents and templates for some of the key steps in the delivery of sCTMP and other ATMPs (see appendices). 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.

sCTMP may be stored in 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 have the expertise to manipulate the products and consequently, Pharmacy Services may not come directly into contact with the product routinely. 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, 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 sCTMP. Other documents which may be useful written by the Pan-UK Pharmacy Working Group for ATMPs are available from: https://www.sps.nhs.uk/networks/pan-uk-pharmacy-working-group-for-atmps/

Process Flow Encompassing Points for Consideration by Chief Pharmacists

Governance

- Chief Pharmacists should ensure that governance for sCTMPs 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 sCTMP 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:
   - Organisational governance prior to providing any ATMP is advised. This may involve an ATMP Committee and/or Medicines Management Committee; Local requirements should be defined prior to implementation of a sCTMP 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 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 sCTMPs will define additional local governance requirements e.g. for private patients.
   - Where the product requires tissue collection a Human Tissue Authority (HTA) licence for human application needs to cover:
     - A specific relevant procurement tissue e.g. tumour infiltrating lymphocytes
     - Export if the product is manufactured outside the UK/EU

4. Local Medicines Management: a SOP will be required to ensure Pharmacy's involvement with the following process:
   - Process cancellation, credit claims, deviations, handling out of specification products

5. Specific training for individual sCTMP handling requirements may be necessary and should be identified and undertaken prior to the implementation.

An exemplar Medicines Management Checklist is available in Appendix 1

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 sCTMP 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 2
&
An exemplar Pharmacy Patient Approval checklist is available in Appendix 3

Collection of starting material & Manufacture

- For both an autologous and an allogeneic product, the starting material must be collected under an HTA licence.
- The pathway for the manufacture of the sCTMP should be clearly described and roles and responsibilities understood.
- If required, regulatory arrangements e.g. export, should be identified and implemented.

Pharmacy may wish to understand these arrangements but is not responsible for them

Product Receipt

- Certain sCTMP may be supplied in a ready-to-administer form e.g. alofisel. Other sCTMP may require thawing or further manipulation.
- Receipt, storage, preparation, and issue are pharmacy responsibilities although some sCTMP may not pass through pharmacy (e.g. they may be stored in stem cell laboratories). The Chief Pharmacist should seek assurance regarding the governance of this pathway and should seek sufficient pharmacy oversight if it is necessary to deliver directly to the clinical area or to an area where staff are competent to handle and store cells and tissues.
- An SOP for receipt of sCTMP 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 4

Storage

- Optimal storage location for sCTMP 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.
- Some sCTMPs may require prolonged storage at -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 optimal.
- 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.
- 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 sCTMPs will be provided ready to use, storage must follow SmPC or clinical trial protocol and if not frozen short expiry is likely and must be borne in mind, pharmacy staff must be proactive in ensuring it is used by the expiry.
- Others will require a thaw/preparation step. Optimal location for preparation will be as per SmPC or clinical trial protocol.
- On receipt the product can either be:
  - Transported to the clinical area in the shipping container and drawn up immediately prior to use
  - Transported to the clinical area 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
- 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 sCTMP treatment.

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 Aseptic Preparation checklist is available in Appendix 5a

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:

- Confirmation that pre-conditioning (if required) is complete and/or the patient is ready
- Procedure for retrieval from storage, if applicable, or reference to SOP if no different to routine should be available.
- Transportation performed by trained and competent staff and approved by pharmacy

Pharmacy Storage, Issue & Transportation to the clinical area

- sCTMPs may be routinely received via Pharmacy, supplied ready to use or thawed and transported to the clinical area – without any further aseptic manipulation.
- Confirmation when the patient is ready for sCTMP 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 performed by trained and competent staff.

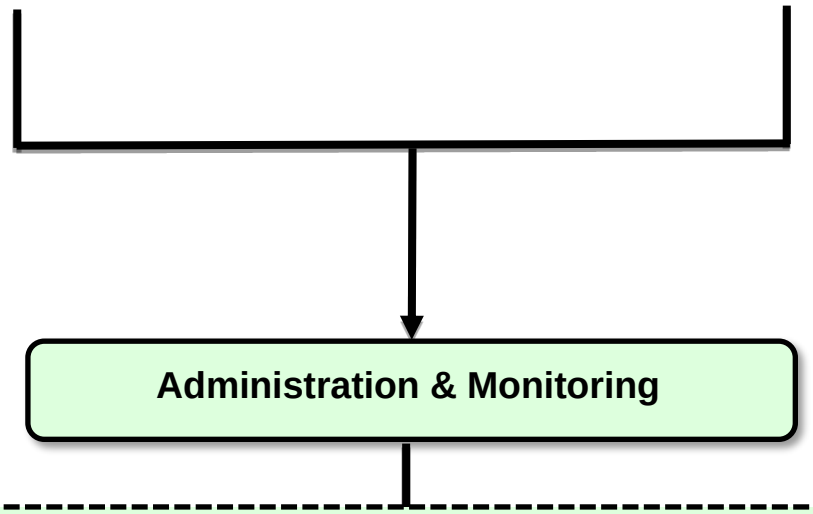
An exemplar Clinical area preparation checklist is available in Appendix 5b

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 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 Pharmacy Dispensing checklist is available in Appendix 6



- The pharmacist with clinical responsibility for the patient needs to be an expert on any required pre-medication, concomitant medication, and post sCTMP 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 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

sCTMP 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 sCTMP	Yes / No		
Treatment centre audited and approved by JACIE (or other as appropriate) to deliver sCTMP	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 HTA licence appropriate for starting material and export, if applicable	Yes / No / NA		
SmPC/PIL /Protocol available	Yes / No		
Prescription added to electronic prescribing system	Yes / No		
Product added to Pharmacy Ordering system	Yes / No		
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		
Product specific training undertaken	Yes / No		

Appendix 1 (cont.)

Checking step	Yes / No / NA Data	Checker Initials	Date
Procedure for transportation, PPE, Waste disposal, cleaning, spills, destruction etc available	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

NB this checklist is intended to help transfer of information between pharmacies, and is not intended to replace the official referral from the clinicians

sCTMP 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			
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 3

sCTMP 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**	**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 4

sCTMP 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**
Any visible damage to shipper?	Yes / No		
Tamper-evident ties intact? Outer Inner	 Yes / No Yes / No		
Dry ice /shipper 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/vials			
Donation ID number correct (as required)	Yes / No / NA		
Patient name (if applicable)			
Patient date of birth (if applicable)			
Overwrap (if applicable)			

Appendix 4 (cont.)

Checking step / data	Yes / No / NA Data	Checker Initials	Date & time
Product integrity visual check	Pass\Fail		
Lot/batch number			
To be administered before 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 (if applicable)			
Comments			

Appendix 5a

sCTMP Stem Cell Lab / Outsourced Aseptic Preparation Checklist

Process Set Up/Governance	Yes / No / NA Data	Checker Initials	Date & time
Roles and responsibilities documented	Yes / No		
Suitable location/isolator for 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 / NA Data**	**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 preparation process is covered by a suitable media validation.	Yes / No		
Check and release processes in place	Yes / No		
Transportation arranged	Yes / No		
	Print Name	***Signature***	***Date***

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Appendix 5b

sCTMP Clinical Area Preparation Checklist

Process Set Up/Governance	Yes / No / NA Data	Checker Initials	Date & time
Roles and responsibilities documented			
Is the shelf life <4hrs post reconstitution*	Yes / No / NA		
Does the SmPC or Pharmacy Manual allow preparation in a clinical area	Yes / No		
Is a Pharmacy approved Worksheet available (if not ready to use formulation)	Yes / No		
Are operators trained and competent	Yes / No		
Is a process in place for communicating patient readiness to Pharmacy (to avoid prolonged sCTMP storage in the clinical area)	Yes / No		
Required PPE is available	Yes / No		
	Print Name	***Signature***	***Date***

*If the answer is no to this question, then check that clinical area preparation is optimal.

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Appendix 6

sCTMP 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**	**Checker Initials**	**Date**
Screened prescription available for treatment date	Yes / No		
Confirmed that patient treatment is going ahead	Yes / No		
Certificate of analysis received with product	Yes / No / NA		
Receipt checklist completed and signed	Yes / No		
Temperature deviations during storage on site	Yes / No		
Record batch number/product identifier on prescription	Yes / No		
Name of medication on prescription matches product label(s)	Yes / No		
Patient name on prescription matches product label (s)	Yes / No		
Patient ID on prescription matches product label(s)	Yes / No		
Dose on prescription matches product label(s)	Yes / No		
Expiry of product within range	Yes / No		
Receive and book out sCTMP on Pharmacy Dispensing system	Yes / No		

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