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ATTC Advanced Therapy Treatment Centres

Pharmacy Institutional Readiness for Tissue Engineered 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 Tissue Engineered Products

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1. Background

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

Tissue Engineered Products (TEPs) 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.

A TEP consists of or contains engineered cells or tissues and is used in or administered to human beings with a view to regenerating, repairing, or replacing a human tissue.

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 a patient for whom it was not intended. The starting material harvest and the administration are often part of a surgical procedure. There is a role for the chief pharmacist in ensuring that the risks, particularly around tracking and traceability, are minimised. Examples of the TEPs include limbal stem cells and chondrocytes.

CAR-T cell therapies have led the way in demonstrating that a consistent approach to implementation encompassing governance and operational issues is required in addition to clinical readiness. To this end, guidance on Pharmacy Institutional Readiness 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 guidance on Pharmacy Institutional Readiness for delivery of TEPs for Somatic Cell Therapies, in-vivo (virus based) Gene Therapies and ex-vivo (cell based) Gene Therapies.

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 Tissue Engineered Product.

This document presents a flow diagram outlining a stepwise approach to implementing Tissue Engineered Products. It is followed by checklists. These are presented as appendices.

It is recognised that most Pharmacy Services do not usually have the expertise to manipulate these products and consequently, routinely Pharmacy Services may not come directly into contact with the product if these tasks are performed by other specialists e.g. the Cell Laboratory. However, it is important where Pharmacy Services are not directly performing some of the outlined steps that the roles and responsibilities of those undertaking the aforementioned steps are clearly documented and undertaken with pharmacy oversight. Ideally, an overarching Technical Agreement between the Chief Pharmacist and the Head of the relevant service, with reference made to relevant organisational SOPs should be in place.

In order to assist horizon scanning and implementation of new TEPs for NHS patient treatment, an operational group consisting of representatives from centres experienced through trials and/or the use of licensed TEPs was convened in order to provide exemplar/templates for some of the key steps in the delivery of TEPs (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.

Points for consideration by Chief Pharmacists

Governance

- Chief pharmacists should ensure that governance for TEPs 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 TEP which maybe documented in a National Service Specification.
2. Clinical approval regarding patient selection:
   - An approved centre will need to understand the national processes for patient selection if applicable.
3. Local Governance:
   - As referenced in the "The Role of Pharmacy in the successful delivery of ATMPs - information for Chief Pharmacists, (Edition 1, Feb 2017)", organisational governance prior to providing any ATMP is advised. This may involve Drug & Therapeutics Committees, GMP Safety Committees and local requirements should be defined prior to implementation of a TEP service and should be defined 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 should be gained prior to placing an order.
   - A centre wishing to provide TEP will define additional local governance requirements e.g. for private patients.
   - Where the product is autologous a Human Tissue Authority (HTA). Licence for Human application needs to cover
     - A specific relevant procurement tissue e.g. limbal tissue for Holoclar®▼, chondrocytes for Spherox®▼.
     - Export (see further information here)
4. Local Medicines Management: an SOP will be required to ensure Pharmacy's involvement with the following process:
   - Process cancellation
   - Credit claims
   - Deviations
   - Handling of out-of-specification products
5. Specific training for individual TEP 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.

An exemplar pharmacy patient referral checklist is available in appendix 2

- 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 TEP 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 approval checklist is available in appendix 3

Tissue Collection & Manufacture

- For an autologous product, the starting material must be collected (procured) under an HTA licence (see governance). Infectious disease markers will also be tested. Procurement of the starting material may involve a surgical procedure. The pathway of the starting material should be clear.
- Local site documentation should be clear that during manufacture, GMP compliance is required and that the Qualified Person employed by the manufacturer has overall responsibility for release of the product, and what to do if a deviation is apparent.

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

Product Receipt

- TEPs are routinely supplied in a ready to administrator presentation. Receipt, storage, preparation & issue are pharmacy responsibilities, although TEPs may not pass through a Pharmacy in every case. The Chief Pharmacist should seek assurance regarding the governance of this pathway and ensure 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 the final (licensed medicinal) product is required to include integrity of the product, labelling and temperature compliance during transit. Certificate of Analysis / QP certificates detailing the dose in the bag check, if applicable. This should be reviewed by an appropriately trained clinical pharmacist.

Storage

- Storage requirement is likely to be limited for TEPs as the expiry 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.
- 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 available in appendix 4 covers aspects of storage

Issue & Transportation to the clinical area

TEP often may be received via Pharmacy or via a Pharmacy approved location and issued on the same day. The Chief Pharmacist should ensure that the following are included in the approved SOP.

- Confirmation that any pre-conditioning is complete and/or the patient is ready for surgery.
- Procedure for retrieval from storage, if applicable, or reference to SOP if no different to routine.
- Transportation method to clinical area approved by Pharmacy.
- Transportation performed by trained and competent staff.
- Communication with pharmacy for booking out, and billing purposes, if required.
- Some sites have opted to provide oversight by implementing a pharmacist check.

An exemplar pharmacy dispensing, and shipping checklist is available in appendix 5

Preparation

- It is not anticipated that TEPs will require a preparation/ reconstitution/thaw step. However, if a TEP is marketed which requires such a step a Pharmacy approved worksheet in line with the SmPC/Protocol should be issued. Any preparation should be undertaken by trained and competent staff and be in line with an SOP detailing whether additional labelling is required.

Administration & Monitoring

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

Appendix 1

Tissue Engineered Product (TEP) 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	Yes / No		
Treatment centre qualified by manufacturer to deliver product, if applicable	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 Yes / No Yes / No / NA Yes / No / NA		
SmPC/Protocol available	Yes / No		
Electronic prescribing system (EPS) designed and available. Prescription added to EPS if available or other process approved.	Yes / No Yes / No		
Product added to Pharmacy Ordering system	Yes / No		
Administration risk assessment completed	Yes / No		
Trust funding process approved	Yes / No		
Specific TEP Product training required and undertaken	Yes / No / NA		
Ensure product being tracked by Medicines Finance team and Contracts for Trust reimbursement	Yes / No / NA		

Appendix 1 (cont.)

Checking step continued	Yes / No / NA Data	Checker Initials	Date
Pharmacy SOP in place for spillage and destruction?	Yes / No		
Pharmacy product specific folder in place (if required)	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

TEP 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***

**circle as appropriate*

Appendix 3

TEP 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**
National patient selection approval, if applicable	Yes / No / NA		
Clinical Pharmacist verification complete	Yes / No		
Blueteq ID, if applicable	Yes / No / NA		
Trust funding approved	Yes / No		
Pharmacy order number issued	Yes / No		
Pharmacist approval documented on manufacturer's ordering portal, if applicable	Yes / No / NA		
Pharmacist Final Check	***Print Name***	***Signature***	***Date***
Comments			

Appendix 4

TEP Receipt Checklist

Product Name			
Supplier			
Manufacturer (if different to above)			
Courier Job Number (& other ref no)			
Date & time received			
Received by			
Checking step\data	**Yes / No / NA Data**	**Checker Initials**	**Date & time**
Tamper-evident ties intact: Outer Inner	 Yes / No / NA Yes / No / NA		
Transit Logger temperature checked on receipt as per requirement *Any deviation, inform Pharmacy*	Yes / No		
Data Logger Within specification (no alarms) *Any deviation, inform Pharmacy*	Yes / No		
All required documentation received: Shipping log Returns documents Certificate of Analysis /QP release Product Specific Documentation	 Yes / No / NA Yes / No / NA Yes / No / NA Yes / No / NA		
Dose as prescribed and within range	Yes / No		
Quantity received			
Packaging integrity visual check	Pass / Fail		
Lot/batch number			
Donation Identification Number or unique donation identifier correct	Yes / No / NA		
Expiry Date	Yes / No		
Patient Name Correct	Yes / No		
Patient Date of Birth Correct (dd/Mmm/yyyy)	Yes / No		

Appendix 4 (cont.)

Checking step / data	Yes / No / NA Data	Checker Initials	Date & time
Product placed into storage, if applicable	Yes / No / NA		
Storage location monitored and alarmed	Yes / No / NA		
Receipt documented	Yes / No		
Pharmacy informed of receipt, if applicable	Yes / No / NA		
1st Check	***Print Name***	***Signature***	***Date***
2nd Check	***Print Name***	***Signature***	***Date***
Completed receipt checklist sent to Pharmacy	Yes / No		
Comments			

Appendix 5

TEP Pharmacy Patient Dispensing and Shipping Checklist

The following checklist should be used or should be incorporated into local procedures where TEPs are delivered to a Pharmacy/Pharmacy approved location and require onward transportation to the clinical area for use.

Product Name			
Supplier			
Manufacturer (if different to above)			
Patient name			
Patient Date of Birth (dd/Mmm/yyyy)			
Patient Hospital Number			
Patient DIN Number, if applicable			
Treatment location			
Storage Location			
Quantity stored			
	Yes / No / NA Data	**Checker Initials**	**Date**
Temperature deviations during storage on site	Yes / No		
Pre-conditioning regimen or necessary pre-meds administered to patient, if applicable	Yes / No / NA		
Screened prescription available for treatment date	Yes / No		
Certificate of analysis received with product, if applicable	Yes / No / NA		
Name on prescription matches product and certificate of analysis, if applicable	Yes / No / NA		
Patient identifier on prescription matches product	Yes / No		
Dose on prescription matches product and certificate of analysis, if applicable	Yes / No / NA		
TEP receipt checklist is complete and signed for release by Pharmacy or Pharmacy approved staff	Yes / No		
Clinic confirmed patient ready to receive	Yes / No		

Appendix 5 (cont)

Removal from Storage			
	Yes / No / NA Data	**Checker Initials**	**Date**
Transport container checked prior to loading TEP for temperature and logger	Yes / No / NA		
Courier Booked	Yes / No / NA		
TEP Removed from Storage	Time:		
TEP/Dose/Patient Details Check	x 2 persons		
Placed in Transport container	Time:		
	Yes / No	**Checker Initials**	**Date**
Record batch number/product identifier on prescription	Yes / No		
Receive and book out TEP on Pharmacy Dispensing system	Yes / No		
Pharmacist Final Check	***Print Name***	***Signature***	***Date***

It is not anticipated that TEPs will require a preparation/reconstitution/thaw step. However, if a TEP is marketed which requires such a step a Pharmacy approved worksheet in line with the SmPC/Protocol should be issued.

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