



Quality Technical Agreement for Outsourcing the Receipt, Storage, and Onward Supply of Cryopreserved ATIMPs

Pan UK Pharmacy Working
Group for ATMPs
V1.0

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QUALITY TECHNICAL AGREEMENT

**FOR THE RECEIPT, STORAGE, AND ONWARD SUPPLY OF CRYOPRESERVED ADVANCED
THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS (ATMPs)**

SITE DOCUMENT REFERENCE NUMBER

Between

SITE PHARMACY

And

VENDOR PROVIDING SERVICE

QUALITY TECHNICAL AGREEMENT

FOR THE RECEIPT, STORAGE, AND ONWARD SUPPLY OF CRYOPRESERVED ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) ON BEHALF OF **SITE PHARMACY**

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QUALITY TECHNICAL AGREEMENT (Site Document Ref. xxxxxx)

FOR THE RECEIPT, STORAGE, AND ONWARD SUPPLY OF CRYOPRESERVED ADVANCED THERAPY
INVESTIGATIONAL MEDICINAL PRODUCTS (ATIMPs) ON BEHALF OF **SITE PHARMACY**

This Technical Agreement is made between:

SITE PHARMACY

Site Address

Site Address

Site Address

Site Address

Site Address

hereinafter referred to as Contract Giver 'CG'

and

SERVICE PROVIDER

Provider Address

Provider Address

Provider Address

Provider Address

Provider Address

hereinafter referred to as Contract Acceptor 'CA'

List any additional sites if more than one here

List any relevant regulatory authorisations if the activity is carried out under those authorisations

1. Definitions

ATMP	Advanced Therapy Medicinal Product
ATIMP	Advanced Therapy Investigational Medicinal Product
CA	Contract Acceptor; the provider of services within this agreement
CAPA	Corrective Action Preventative Action
CG	Contract Giver; The Site Pharmacy responsible for oversight of the outsourced activity under the terms of this agreement
CTA	Clinical Trial Application
GCP	Good Clinical Practice;
GMP	Good Manufacturing Practice; Guidance on the manufacture and testing of medicinal products, as defined in EudraLex Volume 4 Annex 13 and supplemented by Eudralex Volume 4 Guidelines on Good Manufacturing specific to Advanced Therapy Medicinal Products
GDP	Good Distribution Practice; Guidance on the storage and distribution of medicinal products. This is not mandatory for IMPs, but application of the principles of GDP is expected to ensure safety and security of the supply chain, and maintenance of appropriate storage conditions to maintain product quality. Guidance can be found in EC 2013/C 343/01
IMPD	Advanced Therapy Investigational Medicinal Product Dossier
MHRA	Medicines and Healthcare Products Regulatory Authority; the Competent Authority responsible for medicines manufacture and supply.
PPM	Planned Preventative Maintenance; the scheduled, planned maintenance work performed on critical equipment to ensure it remains within calibration and operational parameters
PQS	Pharmaceutical Quality System; the system setting out responsibilities, processes and risk management principles in relation to the sites activities
RP	Responsible Person; the individual named on the site WDA(H) as responsible for the management and maintenance of the PQS in order to remain compliant with the requirements of GDP
QTA or TA	Quality Technical Agreement; this Agreement describing the allocation between the parties of roles and responsibilities relating to quality and operational responsibilities with regard to the provision of the activities described
VMP	Validation Master Plan; a document summarising the key elements of the sites qualification and validation programme
WDA(H)	Wholesale Dealers Authorisation for Human Medicinal Products; the Licence issued by the MHRA

2. Scope of agreement

This Technical Agreement defines the roles and responsibilities between the CG and CA in ensuring compliance with GMP, GDP and the Human Medicines Regulations 2012 (SI 2012:1916 as amended) with regards to the provision of pharmaceutical services as specified in 'Appendix 1: Services', of this agreement.

All parties will strictly observe the detailed pharmaceutical responsibilities which are specified in 'Appendix 2: Responsibilities of each Party', of this agreement.

All parties must appoint Contact Persons as named in 'Appendix 3: Key Contact Persons' of this agreement.

In circumstances where CA subcontracts certain activity, this is permitted where agreed in advance and accepted by CG. Any providers to whom activity is sub-contracted by CA will be listed in 'Appendix 4: List of Subcontractors', of this agreement. The responsibilities defined in this agreement apply to the sub-contractor as they do to CA. Additionally, CA must ensure appropriate agreements are in place with sub-contractors which compliment those contained in this TA.

This agreement covers activity relating to the receipt, storage and onward supply of cryopreserved ATIMPs on behalf of CG. Any additional 'preparation activities' subcontracted remain the responsibility of CG and may either be added to this agreement where required, or managed via a separate TA. Any such arrangements must take into account the requirements of the IMPD and GMP as it relates to the activities involved. Where these services are provided, the provider must operate within the regulatory framework which applies (for example, compliance with GMP and operating under the terms of the Pharmacy Manual or other relevant document supplied by the Sponsor or CG). Finally, where additional services beyond receipt, storage and distribution are included, a thorough review of the content of this TA is recommended to ensure it covers the necessary activity.

3. Regulatory information

The parties acknowledge that CG shall procure the ATIMP via the sponsor of the clinical trial, and arrange for its delivery directly to CA. Thus, CG will perform all the obligations and responsibilities of a participating trial site. Sponsor will own the product throughout the activity.

This TA is supplementary to any site agreement between the Sponsor and CG as it relates to the quality of the ATIMP. This TA can be shared with Trial Sponsors in support of their assessment of appropriate arrangements when conducting site qualification assessments of prospective clinical trial sites. The CG responsibilities contained in this TA cannot be delegated to the Sponsor.

CA has the full capability and appropriate authorisations to carry out the activity described in this TA as described in Appendix 1 of this agreement. Any services will be at all times processed and controlled in compliance with the appropriate regulations, where applicable, controls equivalent to Good Distribution Practices for medicinal products for human use will be applied to the storage and transportation of ATIMPs..

4. The Technical Agreement (including termination)

This Agreement becomes effective on the date of the final signature and shall remain valid up to 5 years ("Term"). This agreement will be reviewed and updated every **five (5) years** unless the parties agree to amend the agreement prior to this with mutual consent, in writing.

Any variances from this Agreement must be in writing and approved by all Parties to this Agreement. Appendices may be modified and updated independently from the main Agreement, it is the responsibility of both parties to ensure that all sections of the Agreement on file is current.

Each party may terminate this Agreement at 3 (three) months' notice in written form to the other party.

Termination of this Agreement, however caused, shall not prejudice or affect any rights, action or remedy which shall have accrued before termination or shall accrue thereafter to any party.

This Agreement and its Appendices shall be made available to the relevant authorities in the concerned countries upon their request.

Compliance with this Technical Agreement may be jointly reviewed annually by both parties. Resolution to any noncompliance, where it is identified, must be jointly agreed by both parties within defined timelines.

This agreement may be executed digitally using appropriate electronic signatures, or physically with wet signatures. Where the former is used, the fully executed digital version will be considered the original and must be provided to both parties. Where wet signatures are used, the Agreement must be executed in duplicate originals with each Party retaining one original for its records. Each party agrees to deliver to the other all such documents and information as may be required for the other party to perform its obligations under this Agreement.

5. Documentation Practices

Completed documentation will be archived in accordance with current regulatory guidance and retained for a period of at least 5 (five) years after the expiry of the product to which it relates. This documentation includes, but is not limited to the following:

- Delivery notes
- Temperature monitoring data
- Deviation reports
- Validation data

6. Quality Assurance

CA must maintain a suitable Pharmaceutical Quality System, which meets the requirements of GDP and GMP as relevant. Any regulatory inspection results for sites involved in activity covered by this TA must be communicated to CG, and major or critical observations identified during regulatory inspections must be assessed for their impact on the ATIMPs which have been handled under the terms of this agreement. Appropriate CAPA must be agreed by both parties with appropriate timescales for implementation.

CG is responsible for sourcing ATIMPs from bona fide suppliers and establishing they are of suitable quality through suitably robust measures agreed between CG and Sponsor. These checks may be facilitated by CA, but final checks on the integrity of the product must be completed by CG at the point of receipt from CA.

7. Complaints

Any complaint from CG regarding quality of the supplied service must be acknowledged by CA within 2 working days.

A report containing details of the investigation with corrective and preventative actions must be forwarded to CG within 30 working days. CA must make every effort to complete investigations and provide feedback, including actions assigned, to CG in a timely manner. CG will liaise with Sponsor to ensure they are informed.

8. Recall and Returns

CG must notify CA of any recall or near miss (Sponsor or MHRA-led) relating to any drug product(s) handled under this Agreement. Coordination of the return of such products will be performed between Sponsor and CG, CA will facilitate any collections and ensure stock subject to recall is appropriately quarantined and stored until it is returned.

CG and CA maintains the right to notify the relevant regulatory authority of potential recall situations where they believe this is the correct course of action but is not agreed by the Sponsor or the manufacturer.

9. Audit

CG or their representative is entitled to conduct a routine audit of CA facilities relevant for the services detailed in this agreement on a 2 yearly basis. Dates for routine audits should be mutually agreed at least 4 weeks in advance.

CG or their representative will be permitted to perform a 'for-cause' audit in response to a critical deviation affecting the services or products covered by this TA with a minimum of 7 days' notice.

Any activity sub-contracted by CA must be in line with CA vendor qualification procedures, any audit reports should be made available to CG on request.

CA may be audited by competent authorities in line with their risk-based approach to inspections where relevant to the tasks undertaken by CA. These may be GMP or GCP audits as relevant.

10. Confidentiality

The information contained in this agreement is confidential and must not be divulged to any other party without the permission of all signatories with the exception of regulatory authorities.

11. Final Provision

Amendments to this Quality Technical Agreement and its Annexes may only be carried out by mutual consent and shall be made in writing. Any amendments to the appendices **1 to 7** may be made in isolation to the rest of the document provided they do not contradict any content. Upon signing by both CA and CG the amended appendices will be binding on both parties and replace the previous appendix.

Appendix 1: Services

FOR THE RECEIPT, STORAGE, AND ONWARD SUPPLY OF CRYOPRESERVED ADVANCED THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS (ATMPs) ON BEHALF OF **SITE PHARMACY**

Use this section to describe in broad terms the activity which will be outsourced, examples of a suitable scope is stated below, but this must be reviewed to ensure it covers all applicable activity. Where additional activity needs are identified later, this can be added to a new version of this TA, or can be described in a stand alone TA. All activities described in this TA must have been considered and accepted during the assessment of the CAs capability to perform the activity by CG or their representative. Where specific activity was not covered within the scope of CA assessment, additional ‘top-up’ vendor assurance should be considered by CG.

Services Provided:

Description	Start date	Product Specific or General	Contact Person
Activity below are examples, amend according to local requirements.			
Receipt of ATIMP			
Storage of ATIMP			
Onward transportation of ATIMP to CG site			
ADDITIONAL ‘EXTRA’ ACTIVITY (Consider regulatory requirements where these are included)			
Thawing of ATIMP			
Reconstitution of ATIMP and preparation for administration			
Labelling of ATIMP with Annex 13 label			
Labelling of ATIMP with shipping label			

Receipt

Upon receipt check that the tamper evidence is intact and ensure material has been transported in accordance with requirements contained in the IMPD or ATIMP pharmacy manual:

- If evidence of tampering is identified contact CG immediately
- Supplies must be appropriately labelled and segregated to prevent mix-up (especially when handling autologous ATIMPs)
- Deliveries may include additional monitoring equipment such as temperature logging devices, shock sensors or GPS tracking devices. CA must comply with the requirements of both the Sponsor and CG in terms of handling these devices, downloading and transmitting data, and quarantine status of the product until the data has been analysed and product authorised for use where this applies

Storage

- Products must be stored according to the Sponsor's instructions as stated in the IMPD or ATIMP pharmacy manual
- Storage areas must be validated and subject to routine PPM in line with the equipment manufacturer's recommendations and CAs VMP
- Storage areas must be continuously monitored using appropriately calibrated monitoring systems. Arrangements for responding to alarms in the event of system failure or temperature deviations must be in place including out-of-hours arrangements
- Products must be appropriately segregated and identifiable throughout
- Temperature deviations must be formally assessed and communicated to CG. The impact of any deviations affecting products under this agreement must be assessed by the Sponsor
- Appropriate arrangements must be in place to allow for redundancy in the event of equipment failure (e.g. emergency backup generators or UPS systems)

Onward Transportation to CG Site

- Products must be packaged and transported according to the Sponsor's instructions as stated in the IMPD or ATIMP pharmacy manual
- Where this activity is subcontracted, the supplier of the service must have been qualified by CA, and be named in Appendix 4: List of Subcontractors
- Any deviations during transportation must be treated as they would should they have occurred when the product was in the possession of CA (e.g. notification, impact assessment etc)
- Collection and delivery must be performed as agreed with CG, no transportation of the product is permitted without prior written consent (email is acceptable)

Further processing at CA site

Any further processing should be performed in accordance with GMP or other local regulations which apply.

- Activities carried out as 'reconstitution' do not require regulatory authorisations where they are carried out by or under the supervision of a pharmacist, but should be performed applying the principles of GMP, ensuring product quality is not compromised during these activities
- Additional processing activity may be required in several forms, specialist advice is advised when adding such activity to a Technical Agreement, this section has been included as a 'placeholder' only
- Any products prepared in such a manner must be labelled with a shipping label only, and further Annex 13 compliant labelling must be performed under the supervision of a pharmacist at the trial site

Temperature Excursion Management

Sponsor is required to perform the review, assessment and final disposition decision for temperature excursions that occur during transportation, storage at depots onward transportation to clinical sites. Sponsor may supply (dependant on available stability data) a temperature excursion memorandum that will detail allowable excursion ranges. Any excursions should be communicated to CG, who should then escalate them to the manufacturer.

Notifications and Recalls

If during the course of the study, CA becomes aware of any issue affecting the quality of the material, CA will notify CG, in a timely manner, who must then notify the Sponsor. The responsibility for the recall of any investigational medicinal products lies with the Sponsor or MHRA, following consultation with CA, CG and/or any other company in the case of services supplied by them.

CG must notify CA of any changes to the IMPD/CTA that may affect the storage of the ATIMP concerned. CG must inform CA of these changes to ensure compliance with live documents.

Destruction

Destruction of stock remaining at CA site is to be performed by CG, in accordance with Good Manufacturing Practice, Good Distribution Practice, Good Clinical Practice and in accordance with any National Regulatory requirement. Authorisation of destruction of stock at storage sites is the responsibility of CG.

Appendix 2: Responsibilities of each Party

The following are examples of responsibilities which may be included in a Technical Agreement and should be reviewed for applicability to the planned activity

Regulatory	CG	CA
Approve the technical agreement	X	X
Supply regulatory and product specific documents required for outsourced activity	X	
Provide updated documents to CA as soon as practicable when these are received from the manufacturer	X	
Maintain all authorisations required for planned activity		X
Maintain and archive all records required to perform contracted activity		X
Drug Products		
Order supplies of ATIMP to CA site from Sponsor	X	
Coordinate delivery of ATIMP to CA site	X	
Receipt of ATIMP according to requirements of IMPD or Sponsor supplied SOPs/ATIMP pharmacy manual		X
Confirmation that Sponsor has appropriate arrangements in place for supply of ATIMP via an authorised route (e.g. UK QP certified or imported from EU with UK QP oversight)	X	
Maintain a live stock management system to identify storage location of all products on site		X
Store ATIMP according to the product requirements according to the IMPD or Sponsor's instructions		X
Any processing steps (reconstitution, thawing, dilution) must be carried out following the principles of GMP (as defined by EudraLex Volume 4)		X
Packaging and Processing Materials		
Procurement of packaging materials		X
Supplier approval (packaging and process materials)		X
Generate label drafts		X
Approve label drafts	X	
Creation of a batch file for all processing and packaging operations		X
Maintain appropriate facilities, staff and resources to comply with the requirements of contracted services in accordance with relevant regulations and this TA.		X
Printing of shipping labels		X
Manage any required unblinding activity if applicable	X	
Secure storage of all packaging, randomisation data and labels	X	X
Coding and assigning of batch numbers for finished product if applicable		X
Secondary packaging and control		X

Assignment of expiry date(s) based on information received from manufacturer for processed material		X
Printing and application of Annex 13 compliant label	X	
Documentation		
Archiving original processing documents for at least 5 (five) years after expiry of the product		X
Retention of relevant documentation according to Eudralex Volume 4 GMP Annex 13		X
Notification of intention to discontinue to treat patients with products that require this service	X	
Destruction		
Destroy materials or records (those not controlled under records retention policies) following notification by CG		X
Communicate authorisation to destroy materials or records (those not controlled under records retention policies) according to local practices following agreement with Sponsor	X	
Destruction of remaining products (which may have expired) that remain at CA when authorised by Sponsor via CG		X
Destruction of remaining products (which may have expired) that remain at CG	X	
Storage and Logistics		
Place orders with CA when ATIMP is required at the trial site	X	
Provide information concerning special requirements for packaging and monitoring supplies during shipment	X	
Storage and management of stock at CA		X
Storage and management of stock at trial Site	X	
Selection of carrier for shipping and shipping conditions of drug products from CA to CG		X
Supply of temperature monitoring data for shipping of finished products (if applicable) to trial sites		X
Fulfil orders following local procedures, and the requirements of the IMPD or CTA.		X
Use in-house or contracted logistics providers and qualified transportation methods appropriate to the storage conditions of the ATIMP		X
Continuously monitor storage areas and equipment for maintenance of required storage condition using qualified monitoring system		X
Report any deviations from storage requirements to CG within 1 working day during product storage or transportation		X
Communicate with Sponsor to determine batch disposition in response to a temperature deviation	X	
Take immediate action as necessary to mitigate against any storage condition deviation including out-of-hours		X
Determination of CAPA following deviations during storage or transport to clinical sites.	X	X
Complaints and Product recall		
When notified of a recall by Sponsor, inform CA within timescales required by the recall classification (Class 1 = Immediately including out of hours, Class 2 = within 48 hours, Class 3 = within 5 days)	X	

Make available relevant information to assist in investigations relating to product recalls.a	X	X
Comply with all instructions provided by a regulator or Sponsor in order to execute a product recall	X	X
Receive, collect and administer any SUSARs, SAEs and Adverse Reactions (ARs) suffered by patients, which are or may possibly be due to the product. These must be reported to the Sponsor	X	
Investigate complaints related to activity under this agreement, these may or may not relate to ARs reported to sponsor		X
Maintain a complaints system		X
Handling of any product returns		
Storage in an appropriately controlled, dedicated area		X
Communicate with CG regarding any product returns and obtain their decision on product disposition	X	
Data		
Patient identifiable data will not be shared between organisations unless absolutely necessary and subject to approval from sponsor	X	X
Where patient data is required to be shared, CG authorises the method by which this data is shared and confirms compliance of the agreed process with NHS Data Security requirements and approval from sponsor	X	
CA must comply with all Data Security requirements of CG		X
Change Control		
Notification to CG of all major changes to process covered by this agreement in advance of implementation (e.g. changes in storage locations, logistics providers, key personnel, etc.)		X
Approval of all major changes to contracted process	X	
Update of relevant documents affected by changes	X	X
Deviations		
Notification to CG of all deviations relating to activity covered by this agreement (e.g. non-compliance with internal procedures, equipment failure) within 1 working day of identification of the deviation		X
Agree appropriate mitigating action with CA within appropriate timescales	X	
Comply with actions and timelines agreed with CG in the event of deviations		X
Submit a written report including investigation of deviations to CG within 1 week of identification. Extensions to this deadline may be agreed in advance with CG		X
Approve closure of all deviations relating to contracted services within 1 week of receipt of the final report	X	
Update of relevant documents affected by changes	X	X
Quality Audits and Auditing		
Permit CG or its representatives to audit the site (specific to the services covered in this agreement) providing at least four (4) weeks' notice is given for routine audits.		X

Where CG or sponsor determines a 'for-cause' audit is required, permit CG or its representatives or sponsor to audit the site (specific to the services covered in this agreement) providing at least ONE (1) weeks' notice		X
Permit regulatory authorities to audit the site.		X
Inform CG of regulatory audits and observations relevant to the services covered in this agreement.		X
Selection and audit of vendors (sub-contracted parties) for outsourced activity via a formally documented vendor-approval process		X
Supply of appropriate documentation requested by CA to enable approval of selected vendors for outsourced activity		X
Approval of selected subcontractors for outsourced activities	X	X

Appendix 3: Key Contact Persons

CG

Name	Designation	Contact number	E-mail

CA

Name	Designation	Contact number	E-mail

Appendix 4: List of Subcontractors

e.g. Couriers, Monitoring System Providers and Contractors

CA Subcontractors	
Logistics Provider	Add description of activity subcontracted here
Temperature Monitoring Services	Add description of activity subcontracted here
Contract QP Services	Add description of activity subcontracted here

Appendix 6: Technical Agreement Approval

Agreed on behalf of the CG

Name:

Name:

Title:

Title:

Signature: _____

Signature: _____

Date: _____

Date: _____

Agreed on behalf of CA

Name:

Name:

Title:

Title:

(Responsible Person)

Signature: _____

Signature: _____

Date: _____

Date: _____

Appendix 7: Version History

Version Number	Date of Amendment	Amendment(s) Made
1		First Issue



Specialist
Pharmacy
Service



NHS Specialist Pharmacy Service
www.sps.nhs.uk