Specialist Pharmacy Service

Outsourcing of Storage or Preparation of ATIMPs Across Legal Boundaries

Pan UK Pharmacy Working Group for ATMPs

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Foreword

This document has been developed by the Pan UK Pharmacy Working Group for ATMPs and National Pharmacy Clinical Trials Advisory Group with input provided by the MHRA, Clinical Trial Unit, GMP and GCP Inspectorates. This document is intended to be used by pharmacy clinical trials teams to complement existing legislation and guidance and reflects current thinking re the practicalities to facilitate the implementation advanced therapy investigational medicinal product clinical trials.

The contents of this document do not replace existing requirements. Users of this document should be aware that this document has no legal status and may be affected by future changes in legislation and guidance.

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Outsourcing of **ATIMPs across legal boundaries**

Introduction

As the use of advanced therapy medicinal products becomes more widespread, many Trusts are wishing to establish access for their patients to these innovative medicines. Clinical Trials involving Advanced Therapy Investigational Medicinal Products (ATIMPs) often have very specific additional requirements which require specialist knowledge and expertise to address. As a result, some organisations may need to outsource specific aspects of their handling in order to maintain the quality of the product. The information below sets out the regulatory position and identifies practical issues which need to be addressed when considering outsourcing a range of activities supporting the delivery of ATIMPs such as storage, preparation, thawing and reconstitution.

Regulatory Position

The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) define **manufacture** and **assembly** in relation to investigational medicinal products (IMPs) as follows:

1) *Manufacture*

*"**manufacture**", includes any process carried out in the course of making the product, but does not include dissolving or dispersing the product in, or diluting it or mixing it with, some other substance used as a vehicle for the purposes of administering it;*

Hence aseptic reconstitution of an injectable medicine is not considered as a manufacturing activity and does not, therefore, require a Manufacturer's Authorisation for Investigational Medicinal Products (MIA(IMP)).

In relation to ATIMPs, further detail on what activities are considered reconstitution steps (and therefore do not require a manufacturing authorisation, is contained in EudraLex Volume 4, Part 4:

- *Thawing, washing, buffer exchange, centrifugation steps necessary to remove preservation solution (e.g. DMSO), removal of process related impurities (residual amount of preservation solution, dead cells) including filtering.*
- *(Re)suspension, dissolution or dilution with solvent/buffer, dispersion.*
- *Mixing the product with patient's own cells, with an adjuvant and/or with other substances added for the purposes of administration (including matrixes). However, the mixing of a gene therapy vector with autologous cells is a manufacturing activity that should be conducted under GMP.*
- *Splitting the product and use in separate doses, adaptation of dose (e.g. cell count).*
- *Loading into delivery systems/surgical devices, transfer to an infusion bag/syringe*

2) *Assembly*

*To "**Assemble**", means— (a) enclosing the product (with or without other medicinal products of the same description) in a container which is labelled before the product is sold or supplied, or used in a clinical trial, or (b) where the product (with or without other medicinal products of the same description) is already contained in the container in which it is to be sold or supplied, or used in a clinical trial, labelling the container before the product is sold or supplied, or used in a clinical trial, in that container, and "assembly" has a corresponding meaning;*

It is therefore clear that whilst aseptic reconstitution of a medicinal product is not considered as an assembly activity, the act of labelling an ATIMP with an annex 13 compliant label is considered to be assembly and therefore requires an MIA(IMP) unless subject to an exemption.

Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) provides an exemption for hospitals and health centres to allow assembly activity to be undertaken according to the following conditions:

(a)the assembly is carried out in— (i) in a hospital or health centre, and (ii) by a doctor, a pharmacist or a person acting under the supervision of a pharmacist; and

(b)the investigational medicinal products are assembled exclusively for use in— (i) that hospital or health centre, or (ii) any other hospital or health centre which is a trial site for the clinical trial in which the product is to be used.

However, Directive 2005/28/EC defines good clinical practice and Article 9(2) states that:

Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC [an MIA(IMP)], shall not be required for reconstitution prior to use or packaging, ***where those processes are carried out in hospitals, health centres or clinics,*** *by pharmacists or other persons legally authorised in the Member States to carry out such processes and* ***if the investigational medicinal products are intended to be used exclusively in those institutions****.*

In summary, reconstitution activity requires neither the use of the Regulation 37 exemption nor a manufacturer's authorisation.

Annex 13 compliant labelling is considered a manufacturing activity, however the exemption permits assembly to occur in hospital or health centre sites which are participating in the clinical trial without the need for a MIA(IMP) when performed by or under the supervision of a pharmacist.

Labelling

Good Clinical Practice Guide (The Grey Guide, 6.7.2) states that where preparation e.g. a reconstitution step is performed, the label applied to the final ready to administer presentation should be undertaken in line with standard hospital practice. Annex 13 compliance is not a legal requirement but, where reconstitution is undertaken in a pharmacy aseptic unit under the Regulation 37 exemption, it is standard hospital practice to add a dispensing label which is also annex 13 compliant.

Due to the complexity of handling of ATIMPs, and the atypical supply chains involved, great care needs to be exercised when considering any labelling function. It is recommended that standard hospital practice which requires Annex 13 compliant labelling to be applied to the ATIMP is followed. This must be performed under a Regulation 37 exemption (i.e. by a doctor or pharmacist, or under the supervision of a pharmacist, and at a hospital or health centre participating in the trial). Where this is not possible and the product needs to be transported from one legal entity to another, a shipping label will be required in order to maintain traceability of the product and an annex 13 compliant dispensing label should be added at the receiving trial site.

Implication of UK Exit from the EU

A Separate guidance document has been published describing the impact of legislative changes as a result of the UKs exit from the EU, and the responsibilities of Trial Sites[1]:

Practice Scenarios

The above excerpts from the legislation and guidelines should be interpreted as follows in relation to seven common scenarios encountered by NHS clinical trials pharmacy staff. To facilitate research in the UK, for the reconstitution activities described above only, a pragmatic approach has been agreed with the regulators in relation to the use of NHS and commercial non-NHS aseptic units which do not hold an MIA(IMP) authorisation but where compliance with EU GMP can be demonstrated for the planned activities (e.g. MS holders, HTA licence holders).

Appropriate oversight of the third party provider is the requirement of the site pharmacy and should include a Technical Agreement (see notes below).

Scenario 1: Ultra-low temperature storage of ATIMP outsourced by Site A (NHS Hospital) to third party provider (e.g. a blood transfusion service; NOT a hospital or health centre), supplied to site cryopreserved in a Vapour Phase Nitrogen dry shipper.

The storage of an ATIMP may be performed without any regulatory authorisations. Site A must satisfy themselves the third party provider is capable of performing the required tasks to appropriate standards and a Technical Agreement should be in place. Assurance of third party capability should be established following the **Third Party Capability Assessment** guidelines below.

Pharmacies may receive frozen products. As thawing is a reconstitution step (not manufacture), it is permitted to be carried out by the recipient pharmacy or under the oversight of pharmacy by e.g. local stem cell lab[2]. Site A must ensure staff have had appropriate training and this is documented in their training files. An assessment of the method of thawing the product at Site A should be performed to confirm this is within the capability of the pharmacy before agreeing to handle ATIMPs in this way.

[1] See SPS document on Operational Implications of UK Exit from the EU for NHS Clinical Trial Sites available at https://www.sps.nhs.uk/articles/operational-implications-of-uk-exit-from-the-eu-for-nhs-clinical-trial-sites

[2] See SPS document on Pharmacy Oversight and Supervision Requirements for Preparation of Licensed ATMPs for advice on supervision of third party provider sites available at https://www.sps.nhs.uk/articles/pharmacy-oversight-and-supervision-requirements-for-preparation-of-licensed-atmps/

Scenario 2: Ultra-low temperature storage of ATIMP outsourced by Site A (NHS hospital) to third party provider (e.g. a blood transfusion service; NOT a hospital or health centre), product thawed and supplied to Site A at 2-8°C.

Thawing ATIMP is considered to be a reconstitution step (therefore not manufacture), and may be performed by a third party provider without any regulatory authorisation. In this scenario, an Annex 13 compliant label is present, therefore when thawed the product can be supplied to the Site A pharmacy for receipt and issue.

As an additional Annex 13 compliant label is already present pharmacist supervision under Regulation 37 is unnecessary. A dispensing label may be applied by Site A pharmacy prior to issue in line with local practice.

Scenario 3: Ultra-low temperature storage of ATIMP outsourced by Site A to Site B (both NHS Hospitals). Both sites participate in trial. Site B performs thaw, cell wash, dilution and labelling before providing ready-to-administer ATIMP to site A.

Thaw, cell wash and dilution are classified as reconstitution steps, therefore may be performed by Site B with no regulatory authorisation. As Site B is also participating in the trial, the ATIMP may be labelled with an Annex 13 compliant label under Regulation 37 exemption by a doctor or pharmacist, or under the supervision of a pharmacist at Site B.

Site A must satisfy themselves that Site B have appropriate arrangements in place to safely carry out this activity, which would be controlled by an appropriate Technical Agreement. Assurance may be supported by the mechanisms described in the **Third Party Capability Assessment** section below.

Scenario 4: Ultra-low temperature storage of ATIMP outsourced by Site A to Site B (both NHS hospitals, both are non-MIA(IMP) holders). Only Site A participates in trial. Site B performs thaw, cell wash, dilution and labelling before providing ready-to-administer ATIMP to site A.

Thaw, cell wash and dilution are classified as reconstitution steps, therefore may be performed by Site B with no regulatory authorisation. Where Annex 13 is required this may only be performed at Site A as Site B is not participating in the trial. Site B must label the product with a shipping label and supply to Site A. Site A would then apply an Annex 13 label under the regulation 37 exemption within the pharmacy and subsequently supply the product to the clinical area. It is assumed that this process will be followed where the expiry of the product permits otherwise refer to scenario 5.

Scenario 5: Ultra-low temperature storage of ATIMP outsourced by Site A to Site B (both NHS hospitals, both are non-MIA(IMP) holders). Only Site A participates in trial. Site B performs thaw, cell wash, dilution and labelling before providing ready-to-administer ATIMP to site A. The shelf-life of the product following preparation is too short to allow labelling at recipient site pharmacy.

As in scenario 4, the product would be prepared and labelled with a shipping label at Site B. Supply direct to the clinic may be most suitable in this scenario. In line with Regulation 37 exemption a doctor or pharmacist (or someone acting under the supervision of a pharmacist) may apply a pre-printed Annex 13 label to the product prior to administration in the clinical setting.

Scenario 6: Preparation of an in-vivo (virus based) gene therapy by a third party provider

In-vivo gene therapies are routinely handled by pharmacies and the guidance contained in Supply of aseptically - prepared doses of IMPs across legal boundaries[3] should be followed.

The scenarios may be applied to outsourcing activities involving in-vivo gene therapies. Responsibilities associated with these products remain with the Chief Pharmacist. Additional guidance can also be found in Pharmacy Institutional Readiness for In-vivo (virus based) Gene Therapy Medicinal Products[4].

Other Factors for Consideration when outsourcing the preparation of IMPs

Quality Assurance:

In any outsourcing scenario, the clinical trial site outsourcing the reconstitution activity (traditional reconstitution, thawing, dose-adaptation), should be aware of their responsibility to assure themselves of the quality of the products they receive, and to monitor the performance of the contractor. In any outsourcing arrangement, a technical (quality) agreement must put into place.

- Quality checks of each delivery against the pre-defined specification will be required to be performed and documented. Where organisations do not already have systems set up for this, pharmacy clinical trials teams will need to implement a system for performing and documenting such checks.
- Trials sites will need to agree suitability of QA arrangements with the Trial Sponsor. Where outsourcing of activity is required, consideration of tripartite Technical Agreements is recommended to ensure all parties are aware of every party's responsibility.

Third Party Capability Assessment

- Assessment the capability of a third party to carry out the intended activity must be carried out by the trial site outsourcing the activity.
- The responsibility for determining if a provider is suitable lies with the Chief Pharmacist of the trial site outsourcing the activity.
- Depending on the planned activity, several methods of gathering sufficient information in order to make this assessment may be employed such as:
    - Audit of the third party provider carried out by an appropriately trained and experienced auditor on behalf of the site, specific to the individual trial
    - Questionnaire assessing capability, authorisations and experience for providing the planned services
    - Access to an audit carried out by NHS QA staff independent of the provider organisation covering the activity planned
    - Results from regulatory inspections of the facility covering the activity planned

[3] Supply of aseptically - prepared doses of IMPs across legal boundaries available at https://www.sps.nhs.uk/wp-content/uploads/2019/11/Supply-of-Aseptically-Prepared-Doses-of-IMPs-Across-Legal-Boundaries-Version-2-Oct-19.pdf

[4] Pharmacy Institutional Readiness for In-vivo (virus based) Gene Therapy Medicinal Products available at https://www.sps.nhs.uk/wp-content/uploads/2020/07/Pharmacy-Institutional-Readiness-for-in-vivo-virus-based-Gene-Therapy-Medicinal-Products-V1-July-2020.pdf

- The detail of the assurance process used to qualify the third party provider may be requested by the trial sponsor

Logistical Considerations:

- The assigned shelf life of the reconstituted product should be assessed by the site to ensure that it is in line with the Trial protocol and suitable to allow sufficient time for:
    - Transportation, receipt QA checks
    - Additional labelling under Regulation 37 under the supervision of a pharmacist, if required
    - Dispensing / Checking of the IMP
    - Transportation to the clinical area for administration
    - Timely arrival in the clinical area in-line with protocol (consider pharmacokinetic sampling requirements, time allowed from thaw to administration, where each stage of the process will happen)
- Additional temperature monitoring requirements to demonstrate acceptable conditions are maintained during transit from outsourced supplier:
    - Continuous temperature monitoring requirements for ambient or cold chain products.
    - Resource for downloading and reporting temperature data.
    - Investigation of out of specification results, if required.
    - Requirement to communicate temperature data with manufacturer prior to 'release' to clinicians
    - Handling requirements and experience for VPN / cryogenic / Dry ice shippers

Trials sites will need to agree suitability of logistical arrangements with the Trial Sponsor.

Financial Considerations:

- Costing tools and templates are likely to require revision to accommodate both outsourced activities, and the assurance and oversight processes associated with management of these activities.
- Indemnity arrangements will require clarity for sites outsourcing reconstitution activities. The Sponsor will need to accept arrangements and related costs from each site.

Summary and Conclusion

From a regulatory standpoint, reconstitution of an ATIMP does not require an MIA(IMP). Standard Hospital best practice requires Annex 13 labelling of the reconstituted IMP, this can be performed at a hospital or health centre trial site operating under the Regulation 37 exemption.

Outsourcing of logistics, storage and aseptic preparation of ATIMPs is possible, but should only be undertaken with careful consideration and impact assessment. Guaranteed continuity of supply will be required and any implications for patients should be considered within the impact assessment. It is the responsibility of pharmacy staff at the receiving trial site to assure themselves of the quality of the services they receive and confirm Sponsor acceptability. Where stability data only allows a short shelf life after thaw / reconstitution / preparation, the effect on recruitment rates to the clinical trial should also be considered.

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