Supply of aseptically - prepared doses of IMPs across legal boundaries

Version 2

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National Pharmacy Clinical Trials Advisory Group

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Version 1	Issued December 2017
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Introduction

In the NHS, there is an increasing desire to utilise off-site aseptic preparation of ready–to-administer injectable products in clinical trials which may result in the need for supply across legal boundaries. The information below sets out the regulatory position and identifies practical issues which need to be addressed when considering the use of aseptically prepared outsourced products.

Regulatory Position

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

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

"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 reconstitution of an aseptic product is not considered as an assembly activity, the act of labelling an IMP is considered to be assembly.

Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulations 2004 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**.*

Reconstitution is not included in the definition of manufacture within the Human Medicines Regulations 2012 or the Medicines for Human Use (Clinical Trials) Regulations 2004 and therefore the use of the Regulation 37 exemption or a license is not required for this activity. Annex 13 compliant labelling is considered a manufacturing activity however the exemption permits assembly to occur in sites which are participating in the clinical trial without the need for a MIA(IMP).

If the labelling activity requires the application of a blinded label(s) according to a randomisation list, supplied by a sponsor, this is acceptable for an individual patient. However, where multiple units are selected and require blinding labels to be applied before storage, then this becomes a 'batch' labelling operation and it is recommended that enhanced quality measures (such as line clearance, label and product reconciliation, batch documentation) be implemented. It is recommended that this is carried out by an organisation with a MIA(IMP) authorisation and QP certified where possible.

The above excerpts from the legislation should, therefore be interpreted as follows in relation to eight common scenarios encountered by NHS clinical trials pharmacy staff. To facilitate research in the UK, ***for reconstitution activities 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 (e.g. MS holders).

Scenario 1: Aseptic reconstitution performed by NHS aseptic unit at Site A and shipped to site B for administration. Both site A and site B are participating in the trial. (Neither site hold an MIA(IMP))
Reconstitution can occur at site A as it is not a manufacturing activity and therefore does not require an MIA(IMP).

Where Annex 13 compliant labelling is required, this can occur at either NHS site under the Regulation 37 exemption as both sites are participating in the trial.

Scenario 2: Aseptic reconstitution performed by NHS Aseptic unit at Site A and shipped to NHS site B for administration. Site A is NOT participating in the trial but site B is participating in the trial. (Neither site hold an MIA(IMP)).

Reconstitution can occur at site A as it is not a manufacturing activity and therefore does not require an MIA(IMP).

Where Annex 13 compliant labelling is required, this can only occur at NHS site B under a Regulation 37 exemption. NHS site A can only apply a shipping label*.

* a shipping label will maintain the traceability between the reconstitution facility and the trial site but cannot be the Annex 13 compliant label.

Scenario 3: A manufacturing unit holding an MIA(IMP) (NHS or commercial non-NHS) undertakes aseptic reconstitution and clinical trial Annex 13 compliant labelling before shipping to NHS site A for administration in a clinical trial. Site A does not hold an MIA(IMP)).

The unit with the MIA(IMP) authorisation can reconstitute the product and label with the appropriate clinical trial label under their authorisation. The finished labelled IMP requires QP certification under the provisions of the MIA(IMP) holder prior to release for administration. Alternatively, the manufacturing unit could reconstitute and transfer the product labelled with a shipping label* to NHS Site A for Annex 13 compliant labelling under the exemption.

Scenario 4: The NHS Site A participating in the trial routinely buys in commercially available aseptically compounded stock where the starting material holds a marketing authorisation (e.g. dose-banded prefilled syringes of chemotherapy). Some of this medicine is taken from the available stock and administered in a clinical trial as an IMP with the site adding Annex 13 compliant labelling at the point of dispensing.

Removal from stock and relabelling for use in the clinical trial is permitted if the labelling is conducted under the Regulation 37 exemption.

Where there are differences from the SmPC e.g. extended stability is applied to the product, sites should inform the sponsor who will determine the impact and will notify the MHRA as part of their submission.

Scenario 5: The NHS Site A participating in the trial buys in aseptically compounded stock where the starting material holds a marketing authorisation but is not usually held or routinely used by the Trust. This medicine is then taken from the stock and administered in a clinical trial with the site adding annex 13 compliant labelling at the point of dispensing.

Removal from stock and relabelling for use in the clinical trial is permitted if the labelling is conducted under the Regulation 37 exemption.

Where there are differences from the SmPC e.g. extended stability is applied to the product, sites should inform the sponsor who will determine the impact and will notify the MHRA as part of their submission.

Scenario 6: NHS Site A receives novel IMP from the sponsor (QP released IMP but does not hold a marketing authorisation) which is then transferred to a commercial (non-NHS) unit for reconstitution and then shipped back to the NHS Site A for Annex 13 labelling under the Regulation 37 exemption. (Neither site holds an MIA (IMP)).

Reconstitution can occur at the commercial unit as it is not a manufacturing activity and therefore does not require an MIA(IMP).

Where Annex 13 compliant labelling is required, this can only occur at NHS site A under a Regulation 37 exemption. The commercial unit can only apply a shipping label*.

Scenario 7: NHS Site A receives IMP from the sponsor which is then transferred to a NHS unit for reconstitution at Site B (which is participating in the trial) and then shipped back to the NHS Site A for Annex 13 labelling under the Regulation 37 exemption. (Neither site holds an MIA (IMP)).

Reconstitution can occur at site B as it is not a manufacturing activity and therefore does not require an MIA(IMP).

Where Annex 13 compliant labelling is required, this can occur at either NHS site under the Regulation 37 exemption as both sites are participating in the trial.

Scenario 8: NHS Site A receives IMP and / or placebo kit from sponsor for randomized blinded trial. Site A selects the appropriate randomisation number and sends the kit to commercial or NHS unit for reconstitution. Reconstituted IMP or placebo shipped back to site for application of blinded Annex 13 compliant labelling under the Regulation 37 exemption. (Neither site holds an MIA (IMP))

Reconstitution can theoretically occur at the commercial NHS or non-NHS aseptic unit as it is not a manufacturing activity. As the contents of the kit are unknown the shipping label must state the

kit/randomisation number from which the dose was derived. Example text such as 'Blinded/masked product for clinical trial use – kit number XXX' should be used be on the shipping label.

Other Factors for Consideration when outsourcing the preparation of IMPs

Quality Assurance resource:
In any outsourcing scenario, the clinical trial site outsourcing the aseptic reconstitution 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 should be 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.

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 line with protocol (consider pharmacokinetic sampling requirements etc.).

- 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.

  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 outsourced preparation.
- Increased reliance on commercial (non-NHS) aseptic capacity may lead to increased preparation charges as commercial capacity is saturated (which, coupled with the potential loss of pharmacy expertise and facilities may be difficult to counter.)
- The risk of NHS dependency on commercial companies who may take commercial decisions to withdraw if recruitment is slow, or increasing charges where protocol amendments and extensions are required.
- 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 IMP does not require an MIA(IMP). Where Annex 13 labelling is required, this can be performed at a clinical trial site operating under the Regulation 37 exemption.

Therefore, outsourcing of aseptic preparation of IMPs 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 products they receive and confirm Sponsor acceptability. Where stability data only allows a short shelf life after reconstitution / preparation, the effect on recruitment rates to the clinical trial should also be considered.