National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP GUIDANCE DOCUMENT

Guidance on the management of sourcing and supply of SACT items from third party suppliers

This document was developed by the NCCP in conjunction with the SACT Resilience Group with input also from HSE Procurement and the HPRA.

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1. Background

Compounded systemic anticancer therapy (SACT)[1] products are specific medicines produced to meet an individual patient requirements for the treatment of cancer. The compounded product is supplied as an Exempt Medicinal product (i.e. unauthorised) on foot of orders/prescription from individual hospitals (HSE and non-HSE). Aseptic compounding services supplying SACT to patients in Irish public hospitals are a component of hospital pharmacy services. Some hospitals have capacity and aseptic compounding facilities to produce these items in-house while other hospitals do not have these facilities and outsource[2] the supply of some or all of these SACT products from third party suppliers.

Outsourced SACT is available as:

- Fixed dose/dose banded stock items e.g. syringes and infusion bags/filled infusors
- Individual patient specific dose items

Many hospitals utilise dose banding[3] and outsource their supply of ready-to-administer SACT products as dose banded stock or patient specific items. Dose banding is an enabler of outsourcing, however it is possible to outsource SACT without dose banding and it is possible to dose band without outsourcing.

A hospital may decide to outsource SACT from a third party supplier for a number of reasons:

- Operational reasons - periods of high demand/ inability to meet demand at specific times e.g. Christmas
- Lack of aseptic compounding facilities or upgrading/maintenance of existing facilities
- Staffing – short-staffing, optimise the use of staff in other areas

[1] SACT involves systemic treatment for cancer; involving parenteral and oral anti-cancer therapies, including but not limited to chemotherapy, targeted therapies and immunotherapies

[2] Outsourcing for the purposes of this document is the compounding/preparation and supply of a SACT product by a third party to a hospital.

[3] Dose banding is a system whereby doses of Systemic Anti-Cancer Therapy (SACT) are calculated on an individualised basis and then rounded up or down to predetermined standard doses. Further information is available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/dosebanding/

- Quality Assurance – extended shelf life due to additional environmental monitoring and aseptic facilities
- Costs – more efficient waste management and cost savings due to extended shelf life and dose banding of items
- Capacity management – planned and predictable outsourcing maximises in-house capacity for unscheduled treatment and other activities
- Risk management – outsourced product is consistently produced to cGMP approved standards
- Stock management – consistent outsourcing improves stock management and financing of stock holding

2. Scope

This document provides guidance on the factors and processes involved in outsourcing and the necessary control measures that should be in place to minimise risks. This guidance document is intended for hospitals who are considering or already sourcing systemic anticancer therapy (SACT) from third party suppliers.

3. Contractual Considerations

3.1 Licensing Authority

Compounded medicinal products are considered exempt medicinal products (EMPs) and are not required to hold a product authorisation. However, the process of compounding is subject to authorisation to ensure that the manufacturer is compliant with EU good manufacturing practice (GMP).

The Health Products Regulatory Authority (HPRA) is the regulatory authority for the manufacturing sites in Ireland. Irish manufacturers of compounded products are required to hold a Manufacturing and Importation Authorisation (MIA) for the manufacture of aseptically prepared compounded medicines. The Medicines Healthcare products Regulatory Authority (MHRA) is the regulatory authority for manufacturing sites in the UK. A UK manufacturer must hold a manufacturer's licence or a manufacturer's 'specials' licence (MS) covering the manufacture of aseptically prepared medicinal products.

It is a legal requirement that the importation of EMPs from countries outside of the EEA, including the UK, must be performed by an authorised entity located within the EEA. From 1st January 2021, all EMPs sourced from the UK will need to be sourced through an authorised operator, i.e. a holder of a manufacturing and importation authorisation or a wholesaler authorisation located in the EU/EEA.

However, in certain cases, for example the supply of short dated EMPs from the UK, it is possible for hospitals to physically receive the products directly from the third country. In this scenario, the authorised wholesaler/manufacturer financially procures the EMP and financially supplies it onwards in Ireland, without taking physical receipt of the product. The hospital receives the product directly. In these circumstances, the wholesaler/manufacturer is required to verify the details of the physical product and transportation to ensure the product integrity and legitimacy of the supply chain. It is also the responsibility of the authorised manufacturer/wholesaler to ensure that the imported EMP is notified to the HPRA. The HPRA maintains a database of EMPs and this information is required in the event of a product recall.

It is also possible that a hospital directly procures a medicine from an entity in a third country which is physically imported into Ireland to an authorised manufacturer or wholesaler. The purchasing hospital should establish that the source and supplier is authentic and appropriately authorised in that territory to ensure the quality and safety of the product purchased. The importing manufacturer / wholesaler is responsible for verifying the legitimacy of the supply chain, checking the integrity of transportation and notification of the products to the HPRA.

Additional customs checks and regulations are in place for imported products which may disrupt/ delay the supply chain.

3.2 Responsibilities

It is the responsibility of the hospital/purchaser to verify that the aspects relevant to maintaining quality of the outsourced products are acceptable i.e. labelled conditions of storage are accepted by the purchasing hospital, unless further

manipulated upon receipt. Hospital pharmacists (acting as the purchaser) should be particularly aware of their responsibility for specifying a suitable product and not be reliant on the manufacturer (contract acceptor).

The decision to outsource the supply of SACT products should be agreed by pharmacy with the hospital governance and management structures with responsibility for chemotherapy and/or medicines, e.g. Drug and Therapeutics Committee and Finance.

The Chief Pharmacist has overall responsibility for medicines management within the organisation. They are ultimately responsible for ensuring that effective governance arrangements are in place across the organisation for all injectable medicines, whether prepared in pharmacy or outsourced. If a decision is made to outsource SACT products, the Chief Pharmacist therefore has the final responsibility to ensure that the appropriate approvals and Quality Assurance checks are in place, in the same way as they would be required to for doses prepared in-house.

The responsibilities of both the contract giver (purchaser) and contract acceptor (manufacturer) should be clearly defined and formally agreed by each party in line with EU GMP[4] good practice recommendations.

Service level agreement (SLA) and technical (quality) agreements (TA), detailing the key aspects of the service, responsibilities and Key Performance Indicators (KPIs), should be agreed - these must consider specific local circumstances and needs. Realistic expectations of service provision must be agreed between both parties and responsibilities for quality should be defined in the agreement. The hospital (the contract giver) needs to ensure adequate staff resource, both in terms of time and seniority, is available to monitor agreements.

The manufacturer (contract acceptor) will be responsible for any breaches of Good Manufacturing Practice (GMP), but cannot take responsibility for the clinical suitability of the products purchased, unless providing a clinical pharmacy service is part of the contract (which is outside the scope of this guidance).

[4] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/vol4-chap7_2012-06_en.pdf

3.3 Managing Capacity for SACT Supply

The outsourcing of SACT can be beneficial in facilitating the workload of pharmacy aseptic compounding units, but balance is required, with the hospital maintaining aseptic unit capacity to prepare SACT whilst taking advantage of commercially-prepared dose-banded products that can facilitate capacity in aseptic units, and should reduce waste.

It should be noted that the workload associated with the ordering, checking and dispensing of outsourced products, and monitoring the technical agreement (TA) and Service Level Agreement (SLA) (see below), is often underestimated and should also be taken into account in capacity calculations.

It is important to ensure that contingency measures are in place to minimise the risk of disruption to the supply chain, for example, where a quality assurance issue may arise within a compounding facility leading to delays in the delivery of SACT products. This highlights the need for resilience in the service, especially in the current climate of Covid-19 and Brexit.

Hospitals must assure themselves that any outsourced supplier realistically has the capacity to provide the volume of products that they will be using. However, they must also ensure that they will provide accurate and realistic data to the supplier about the volume and length of supply likely to be needed.

3.4 Contract Agreements

A contract agreement contains the legal responsibilities, obligations and liabilities of the commercial transaction between the manufacturer and hospital. It does not detail the technical (quality) or service aspects of the outsourcing arrangement - these are separate documents. However, the contract agreement, technical agreement (TA) and service level agreement (SLA) can be drafted as one comprehensive document with the TA and SLA included as schedules in the document[5].

[5] See NCCP website for the most up to date version of template agreement. https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/nccp%20qa%20resources%20for%20hospital%20pharmacy%20cancer%20services.html

3.5 Technical (Quality) Agreement

A technical agreement (TA) describes, in practical terms, the arrangements and responsibilities of both parties with regards to the safety and quality aspects of the products provided and therefore should be agreed by those with responsibilities for those aspects of the service rather than for sales/contracting.

Hospitals must be assured that the chosen supplier will not further subcontract work without an agreed written authorisation being received from them. This should be formalised in the TA. Any subcontractor agreed upon should be appropriately authorised.

Purchasers must be assured that the service provider's operations are in line with best practice and have been appropriately authorised

3.6 Service Level Agreement (SLA)

A Service Level Agreement (SLA) defines the arrangements for the provision of a timely, cost effective and efficient service. This should be signed by both parties by a senior person in a procurement role, in line with the purchaser's procurement policies.

The following details should be considered for the inclusion in a contract agreement which may encompass the TA and SLA:

- Purpose of the agreement
- Parties participating in the agreement
- Period of the Service
- Communication pathway including contact details
- Financial terms of the agreement – fees, claims, VAT status
- Ordering procedures with proof of a robust ordering system in place
- Ordering information and delivery schedules
- Agreed turnaround times
- Forecasting (predicting trends and demands)
- Complaints procedures
- Recall and returns procedures to include drugs, diluents, consumables
- Good manufacturing practice (GMP) compliance

- Transport details including transit times
- Packaging - cold chain transfer details, product segregation details
- Clear labelling to identify hazardous products
- Quality and Performance Management – key performance indicators, incident management, termination
- Services that are not included in the agreement

3.7 Contracting and Ordering

Hospitals considering outsourcing are advised to undertake a budget impact assessment of outsourced products, and where applicable, compare this to local compounding costs. Consideration should be given to the tendering process and complying with procurement regulations[6]. Quality and sustainability of supply are as important considerations as unit price. The supplier with the cheapest commercial price may not necessarily be the preferred supplier.

Hospitals should document the costs of supplying outsourced SACT (including the costs of dispensing an individual dose and the costs of managing the supply chain) to be met, especially where a switch in supply route will result in a change of costs for the hospital. Order lead times should be considered to ensure that the manufacturer has adequate time to process, manufacture and release the products in a timely and safe manner, while also ensuring that the hospital will not be required to hold excessive stock levels resulting in waste. This should be covered in the SLA/TA.

Consideration should be given to the running unit costs and requirements of an in-house aseptic compounding service:

- Asset costs – estates and equipment require maintenance and renewal. Yearly depreciation of these items should be considered
- Overheads – utilities, waste management, staffing, consumables
- Pharmacy staff training and skill mix
- Quality Management System to ensure quality and safety
- Stock holding

[6] https://ogp.gov.ie/public-procurement-guidelines-for-goods-and-services/

When deciding to outsource SACT items the cost of compounding a SACT item should be compared to the outsourcing cost of a similar items to determine best value usage. A nominal cost could be devised and applied to these items.

This nominal cost would incorporate:

- the complexity banding of compounding the specific drug (lower complexity could be easily outsourced)
- drug and consumable cost
- shelf life /reduced wastage
- staffing resource costs

Lower nominal cost items could be outsourced. Other considerations could include freeing up internal capacity for expensive, more complex items, patient specific items and clinical trials.

3.8 Contingency Plans

Hospitals must have in place, contingency plans, for continued supply of essential SACT products for patients should outsourced suppliers be unable to meet demand.

Suppliers should have contingency plans in place to ensure continuation of agreed supplies. Contingency plans need to consider how the service will cope with increasing demand, and reduced capacity due various reasons such as staff illness, planned down-time, natural disaster, fire, quality assurance issues etc. These considerations should account for the supplier's staff and facilities and infrastructure connecting the supplier to the purchasing authority.

The contract acceptor must notify the purchaser before any contingency arrangement is implemented. The product supplied under any such arrangement must be identical to that supplied by the main contractor unless otherwise agreed. This should specifically be in the TA/SLA.

Hospitals must assure themselves that their chosen supplier's plan is realistic and actionable. It is appropriate to ask the supplier for evidence of the effectiveness of the plan to minimise risk to patients.

3.9 Complaints and Key Performance Indicators (KPIs)

Formal systems with agreed, named contacts are required for communication between the hospital and the manufacturer regarding complaints associated with products and/or services.

The process for dealing with complaints and suitable timelines should be agreed and responsibilities defined in the TA. Hospitals need to be assured that robust systems are in place to provide timely feedback on subsequent investigations and corrective and/ or preventative actions.

Responsibilities and timescales for responses to recalls should be agreed in the TA/SLA. Suppliers should be able to provide assurance that they have sufficient infrastructure in place to communicate with all their customers in a timely manner, including confirmation to the purchaser of receipt of the recall.

A meaningful set of KPIs should be agreed by both the purchaser and supplier.

Purchasers should continuously monitor trends in KPIs and a formal mechanism should be agreed for raising any significant concerns and discussed at a review meeting as agreed in the SLA. These include service-related items e.g. turnaround times, contract and/or forecasted volumes, out-of-specification results, complaints, etc.

4. Logistical Considerations

4.1 Delivery from Suppliers

Hospitals should be aware of the logistical arrangements for the delivery of outsourced SACT to their site and agree with the manufacturers that these arrangements are appropriate and will give a high degree of assurance that the products have not been adversely affected during transport. Deliveries need to be made according to GDP (Good Distribution Practice[7]) (1). The responsibility for transport should be included in the SLA/TA.

Issues to be considered include:

- Ordering systems are fit for purpose.
- Transit times
- Presentation of packaging, storage and handling requirements
- Delivery arrangements – this should include importing and customs
- Adverse weather conditions

Cold/Ambient Chain considerations:

- Refrigerated transport or time-limited cold chain transfer
- Management of temperature excursions
- Exposure of variable temperatures during transit
- Clear identification/labelling of storage requirements

Consideration should be given to arrangements in place for the receipt of deliveries out-of-hours, if applicable.

Hospitals must also ensure they understand the impact of Bank Holidays and planned service down-time on ordering lead times. Hospitals need to plan for lead times being affected not only by production schedules being changed but also by increased demand for service from other customers.

[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2013.343.01.0001.01.ENG&toc=OJ:C:2013:343:TOC

4.2 Logistics within Hospitals

Consideration should be given to the risk of duplication of transcriptions within the hospital prior to transmission to the supplier/manufacturer and transcriptions received by the supplier which may result in the delivery of incorrect orders.

Orders containing patient-identifiable data must be in line with local information governance policies.

Failed/delayed deliveries may result in unexpected pressures for the hospital which can have an impact on capacity and adversely affect patient experience. Hospitals, during the contracting process, should seek to identify how suppliers will communicate any delays to them. This should be documented in the TA.

5. Quality Considerations

5.1 Stability and Shelf Life

Hospitals should accept shelf lives being offered by the supplier, but they should obtain an insight into the source and quality of the data being used as an established basis for the shelf life decision, and they should assure themselves that the shelf-lives specifically applies to their products when undertaking an outsourcing agreement with the supplier. The responsibility for assigning shelf lives and expiry dates to outsourced products lies with the manufacturer, this responsibility is in line with GMP. However, as these are unauthorised products, it should be noted that these shelf lives, in most cases, will not have been reviewed or approved by a competent authority and the basis for the shelf life may not be as robust as that of authorised medicinal products.

Consideration needs to be given to the presence of potentially harmful degradation products as well as active chemical components and microbiological stability. In addition, stability testing, particularly for biological products, needs to consider the impact of transportation.

5.2 Risk of Composition Errors and Microbiological Contamination

Aseptically prepared SACT products are subject to risk of microbiological contamination and composition errors. The agreement should require the

manufacturer to communicate to its competent authority any issues which may impact upon the sterility assurance level of the compounded products (e.g. confirmed sterility failures, failed process simulation / media fill test results) and the competent authority would then review / investigate the issue. If a product recall or other market action is required, the competent authority will instruct the manufacturer / wholesaler in that regard, and communications to the hospitals will be made, usually by the manufacturer / wholesaler, but in some cases, by the HPRA. Suitable arrangements should be in place within the purchasing organisation to knowledgeably assess the significance of such communications. Final responsibility to use a product will rest with the pharmacy if the manufacturer deems there is no cause to recall it.

6. References

1. Eudralex Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Volume 4 Chapter 7 Outsourced Activities. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/vol4-chap7_2012-06_en.pdf accessed 27.10.2020
2. Guidance on managing the sourcing and supply of ready-to-administer chemotherapy doses for the NHS (2016)
3. Quality Assurance of Aseptic Preparation Services: Standards Parts A & B| Fifth edition. 2016 Beaney A.M. on behalf of the NHS Pharmaceutical Quality Assurance Committee and the Royal Pharmaceutical Society
4. American Society of Health-System Pharmacists. ASHP guidelines on outsourcing sterile compounding services. Am J Health-Syst Pharm.2015; In press.

Appendix A: Checklist for Hospitals Undertaking Outsourcing

The following should be reviewed and agreed with the manufacturer (some steps may be undertaken as part of contracting process):

1. Drugs and dose ranges to be included in the agreement
2. A specification for each product. (The manufacturer may have an existing specification - this should be carefully assessed for suitability e.g. labelling, presentation, and protection from light).
    a. The syringe or final bag volume for each dose should be outlined as part of the specification, ensuring that the volume in a syringe does not exceed the maximum recommended percentage.
    b. The information required for any patient specific individualised doses, ensuring it meets the needs of clinical areas, and complies with hospital medicines and information governance policies.
3. Ensure there is an established basis for the shelf life applied to each product.
4. Ensure validation of the cold chain supply has been undertaken, including special considerations for seasonal variation and distance to travel, especially if using an overnight or overseas delivery.
5. The information to be included with the documentation received routinely with the product, in line with the product specification.
6. The capacity limits of the manufacturer should be detailed in the SLA. Include in the SLA the proviso of notification when maximum capacity is being approached by the manufacturer.
7. A contingency supply plan to account for the manufacturer being unable to meet the demand to ensure continuity of SACT provision should be outlined. This plan could include SLAs with alternative suppliers of chemotherapy, but should note that that other hospitals may also be seeking contingency support at the same time.
8. Order deadlines, minimum orders, etc.
    a. These should be shared with relevant staff in pharmacy as appropriate.
9. The process for placing orders with suppliers and receiving feedback on order handling and expected delivery dates and times. To be undertaken internally within pharmacy for outsourced dose-banded products.

10. Review the standardised order form for banded doses (listing doses and quantities in units) and create procedures for stock management, ordering and for the transcription of orders, where required, particularly for individual patient specific prescriptions, ensure that there are robust procedures for the creation and checking of orders.
11. Create SOP(s) for receipt, QA assessment, storage and release of outsourced products into pharmacy stock and ensure there is sufficient capacity within pharmacy to carry out quality checks of outsourced products prior to, or as part of, the dispensing process.
12. Train staff on the requirements for the receipt, QA assessment and storage of products.
13. Identify a robust process for the dispensing, labelling and packaging of products being labelled from stock, and for segregation of stock, dispensed items pending checks and outbound goods.
14. Prepare SOP(s) for dispensing of outsourced patient specific doses and include these as competencies to be met in individual staff training documentation. Consider including guidance on label placement as well as adequate light and microbiological protection to be provided to the dispensed product.
15. Stocks of externally sourced dose-banded products should come pre-labelled with the agreed label (see points 2 and 4 above). Pharmacy departments dispensing dose-banded products will need to label the product with a minimum of patient name, patient identifier, e.g. hospital number and date issued as per local policy.
16. Prepare an SOP for labelling and dispensing of dose-banded products from stock.
17. Update any existing pharmacy procedures describing the processes to be followed in the event of a Drug Alert/Product Recall/Devices Alert to ensure that the impact on products supplied through third parties is adequately considered. Test the SOPs to ensure that the accountability process is sufficiently robust to be able to identify any doses at any stage of the supply chain through to patient level. To be undertaken internally across the chemotherapy service.
18. Establish prescription receipt deadlines for patient specific individualised doses.
19. Set timelines for routine delivery of product(s), incorporating dispensing time and distribution from the pharmacy to the clinical areas.
20. Establish details for out-of-hours contact.