# NCCP Guidance on Inter Hospital Supply of Compounded Parenteral Systemic Anti-Cancer Therapy (SACT) as a Business Continuity Measure

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All comments and feedback are welcome at oncologydrugs@cancercontrol.ie

The detail contained in this document is subject to revision pursuant to any changes in legislation or guidance following the approval date of this document.

## Acknowledgements

This document has been developed by the NCCP with input from the Pharmaceutical Society of Ireland (PSI) and the Health Products Regulatory Authority (HPRA). In addition the NCCP Parenteral SACT Resilience Group provided input into this document through a consultation process.

The HPRA's role has been to clarify the conditions that are required to satisfy the exemptions in national legislation for manufacturing and wholesaling authorisations and exemptions for product marketing authorisations.

# 1 Summary Conclusions and Recommendations

1. Patient centred care should be at the centre of all decision making when considering the supply of compounded parenteral SACT between hospitals.
2. There are no barriers in legislation relating to the supply of compounded parenteral SACT between hospitals if the conditions and exemptions described in legislation are adhered to.
3. Ideally an agreement should be in place between the hospitals.

# 2 Background

Systemic Anti-Cancer Therapy (SACT)[1] is one of the main cancer treatment options together with surgery and radiation. Parenteral SACT is primarily delivered in 26 acute hospitals nationally, including nine Cancer Centres, either as a day patient or for more complex treatments, as an in-patient.

Parenteral medicines with a marketing authorisation are packaged and presented in a form that usually requires a preparation step before the medicine can be administered to a patient. This preparation step is known as aseptic preparation or aseptic compounding or extemporaneous compounding. The term 'compounding' is frequently used in English speaking literature while continental Europe mainly use the term 'pharmacy preparation'. A position paper published by the EAHP regarded both terms 'pharmacy preparation' and 'compounding' as interchangeable(2). Another term related to preparation is 'reconstitution' which is used in the Resolution CM/Res(2016)1 and 2 of the Council of Europe(3, 4).

The Council of Europe Resolution CM/Res(2016)1, on good reconstitution practices in healthcare establishments for medicinal products for parenteral use, recognised that aseptic preparation of licensed medicinal products for administration does not fall under the same EU GMP regulation as the manufacturing of a medicinal product, but advise that GMP can be used as a reference for quality assurance measures.[2].

In the period 2015 to present there have been disruptions to patient treatment with parenteral SACT due to capacity challenges experienced by within hospitals and also by third party providers of SACT. As a result the continuity of supply of parenteral SACT for the treatment of patients has been a key consideration for the HSE, the Department of Health, the HIQA and patient advocacy groups over the last number of years. This has been of particular concern during Brexit.

[1] Systemic Anti-Cancer Therapy is defined as all drugs with direct anti-tumour activity that are administered for the treatment of cancer. It encompasses biological therapy and cytotoxic chemotherapy but excludes hormonal therapy used to treat cancer

[2] The development of a national framework and quality assurance standards pertaining to extemporaneous compounding is in progress with the NCCP

The NCCP established the NCCP Parenteral SACT Resilience group in 2019 with the aim of developing a strategy to optimise resilience in the supply of SACT in Ireland. This group developed a document to support SACT services in the management of local and national aseptic compounding capacity (5).

Hospitals have business continuity plans in place, in line with HSE Business Continuity Policy, which should include plans for the continuity of treatment for patients where there is a breakdown in their normal supply of compounded parenteral SACT (6).

## 3 Purpose

Historically hospitals have supplied compounded parenteral SACT to other hospitals in response to a business continuity need. In the NCCP Best Use of SACT Aseptic Compounding Capacity guidance document, one action was to determine and clarify the legislation on the inter hospital supply of compounded parenteral SACT medicines.

This document is intended to provide guidance on the inter hospital supply of compounded parenteral SACT as a business continuity measure. It summarises the relevant legislation and professional responsibilities of pharmacists and may inform hospitals business continuity plans for compounded parenteral SACT.

The commercial / wholesale supply of compounded parenteral SACT between hospitals is outside the scope of this document.

## 4 Definitions

For the purposes of this document the following definitions are outlined below:

**Aseptic compounding**

Aseptic compounding is the manipulation of a medicinal product to enable the use or administration of a medicinal product using aseptic technique. Aseptic compounding involves the reconstitution or 'mixing' of drugs into ready-to-use intravenous (IV) preparation and can range from simple dilution to complex manipulation. Pharmacy preparation may sometimes be used as an alternate term for compounding.

**Aseptic Compounding Unit**
A dedicated area with a controlled environment where aseptic compounding takes place. Controlled areas are supplied with HEPA filtered air to maintain environmental cleanliness to specified limits for viable and non-viable particles.

**Dispensing pharmacy[3]**
Defined by the EU Council Resolution CM/Res(2016) as the pharmacy which receives the prescription for a patient and which provides the prepared medicinal product to the patient – this definition is used for the purposes of this document.

**Extemporaneous preparation or manufacture**
The process by which a pharmacist, using traditional compounding techniques, produces a medicinal product to meet the special needs of a patient, or group of patients, when no suitable authorised medicinal product is available – this includes compounded parenteral SACT.

**Preparing pharmacy**
This is the pharmacy that compounds the parenteral SACT product and supplies it to the dispensing pharmacy.

**Reconstitution/ Preparation/ Compounding**
The addition of a diluent to a powdered medication to prepare a solution or suspension. The manipulation of a medicinal product to enable the use or administration of a medicinal product. For products with a marketing authorisation issued by any competent medicines regulatory authority the reconstitution is carried out in accordance with the instructions given in the summary of product characteristics (SmPC) or the patient information leaflet.

# 5 Supply of compounded parenteral SACT products

There are 26 hospitals in Ireland providing SACT cancer services. The centralisation of SACT preparation in pharmacy departments followed from the publication of the Department of Health's "Guidelines for the safe administration of cytotoxic medical preparations in the treatment of patients with cancer" and the National Cancer Strategies of 1996 and 2006. There are a number of different models used in the preparation and provision of compounded parenteral SACT:

- Compounded in-house for use in the hospital using:
    - An aseptic compounding unit to facilitate advance preparation of SACT
    - A stand-alone isolator for immediate use

[3] Medicinal Products (Control of Manufacture) Regulations 2007 - 'dispensing pharmacy' means a shop being lawfully kept open for the dispensing or compounding of medical prescriptions under the Pharmacy Acts 1875 to 1977 and includes the pharmaceutical department of a hospital

    - Other processes e.g. bench top preparation (7)
- Outsourced to a third party provider of compounded parenteral SACT medicines (8)
- Hybrid where a hospital may compound in-house and outsource some to a third party provider

# 6 Business continuity – continuity of compounded parenteral SACT supply for patient treatment

In line with the HSE Business Management Continuity Policy hospitals are responsible for ensuring that business continuity plans are in place locally to ensure patient safety and continuity of care in the event of a breakdown in their normal supply of compounded parenteral SACT - either internal or external. This is to ensure the continuity of treatment for patients in a safe and timely manner. These business continuity plans should detail the processes to be followed when acute issues arise that lead to supply problems with compounded parenteral SACT (e.g. equipment breakdown, shutdown of compounding unit, disruption to outsourced supply, temporary relocation of ward to another site).

The hospital's business continuity plan may involve options such as the:

- hospital outsourcing supply to a third party provider
- hospital having an arrangement with another hospital for intra hospital supply of compounded parenteral SACT[4]

To ensure clarity the responsibilities of the preparing hospital pharmacy and the dispensing hospital pharmacy should be detailed in an agreement defining the processes to be followed and the responsibilities of each hospital including but not limited to:

- Pharmacy preparations (also referred to as compounded product) should be distributed to the ward by the dispensing pharmacy noting that this pharmacy receives the prescription for the patient.
- The preparing pharmacy should be responsible for ensuring that an appropriate quality assurance system is in place.
- Prescription verification
    - In line with normal local processes and consider the relevant NCCP national guidance documents.
- Compounding of products
    - In line with normal local processes and clearly defined standard operating procedures (SOPs) in the preparing pharmacy which should be satisfactory to the dispensing pharmacy receiving the compounded product

[4] On foot of a SACT prescription for a named patient

- Labelling and releasing of product in line with NCCP recommendations for patient specific products(1)
- Transporting and cold chain requirements should be detailed and agreed between sites
- Financial arrangements

# 7 Summary of Legislation

The following is a summary of the relevant legislation relating to the intra hospital supply of compounded parenteral SACT. Full details of the relevant legislation are included in Appendix.

1. A pharmacist working in a Hospital Pharmacy Department registered as a Retail Pharmacy Business[5], can supply an extemporaneously prepared item on foot of a prescription by a doctor for use in his/her patients. This includes compounded parenteral SACT. This is an act of dispensing and therefore the correct records must be maintained and the prescription must conform to legislative requirements(9).
2. A manufacturer's licence or a wholesaling licence is not required for this supply[6] but there are conditions required to be met.
3. The exemptions in the legislation requires that all activities must be carried out under the personal supervision of a pharmacist. Supervising Pharmacists in hospital departments (e.g. chief pharmacists) which provide extemporaneous compounding services should ensure that in the provision of this service that appropriate systems of governance and quality assurance are in place, and that practice-specific requirements, policies and procedures are in place to govern all processes in this regard(10).
4. The EU Council Resolution CM/Res(2016)1 recognise that aseptic preparation of licensed medicinal products for administration does not fall under the same EU GMP regulation as the manufacturing of a medicinal product, but advise that GMP can be used as a reference for quality assurance measures.

# 8 Professional Responsibility

Under the PSI Code of Conduct and Regulation 9 and 10 of the Regulation of Retail Pharmacy Businesses Regulations 2008 pharmacists

a. Have a professional and legal responsibility to ensure that prescription-only medicines and non-prescription medicines are supplied safely(11, 12).

[5] At the time of writing this document, the 26 SACT hospitals are registered as retail pharmacy businesses with the PSI

[6] This excludes stock items prepared in advance of receipt of the individual order. If a hospital pharmacy department produces stock without receiving the individual orders (specifications), the act of dispensing must be done by the pharmacy which manufactures the medicinal product under the exemptions. If this condition cannot be met a manufacturer's authorisation would be required.

b. Are expected to use their professional judgement and clinical expertise in order to make ethical decisions which will involve balancing different responsibilities including the following relevant principles in the code[7]:
    - Put the Patient First
    - Work with Others
    - Show Leadership
    - Maintain Competence

## 9 Clinical Indemnity

The Clinical Indemnity Scheme (CIS) confirmed that "the pharmacists, and the hospitals within which the pharmacies are located and the pharmacists are working, will be covered by the CIS in respect of intra hospital supply of compounded SACT as a Business Continuity Measure."

## References

1. Heckmann P, McCarthy T, Walsh O, Hanan T. NCCP Oncology Medication Safety Review Report. HSE; 2014.
2. Pharmacists EAoH. EAHP Position Paper on Pharmacy Preparations1 and Compounding. 2020.
3. Europe Co. Resolution CM/Res(2016)1on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. 2016.
4. Europe. Co. Resolution CM/Res(2016)2 on good practice in the reconstitution of medicinal products for parenteral use in health care establishments 2016.
5. NCCP. NCCP Guidance: Making Best Use of SACT Aseptic Compounding Capacity. 2019.
6. HSE. Business Continuity Management Policy v8. 2016.
7. NCCP. NCCP Guidance: Pharmacy Benchtop Preparation of monoclonal antibodies (mAbs) used in the treatment of cancer. 2020.
8. NCCP. Guidance on the management of sourcing and supply of SACT items from third party suppliers. v1 ed2021.
9. Regulation of Retail Pharmacy Businesses Regulations 2008 (SI 488 of 2008), (2008).
10. DoH. Pharmacy Act 2007. 2007.
11. Pharmaceutical Society of Ireland. Code of Conduct: Professional Principles, Standards and Ethics for Pharmacists. 2019.
12. S.I. 488 Regulation of Retail Pharmacy Business. 2008.

[7] PSI Code of Conduct for Pharmacists
https://www.thepsi.ie/Libraries/Pharmacy_Practice/PSI_s_Code_of_Conduct_2019.sflb.ashx

# Relevant legislation and guidance

## Medicinal Products Directive 2001/83/EC

The Medicinal Products Directive 2001/83/EC[8], as amended does not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient; (Art 3(1))
2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia. (Art 3(2)).

In addition, Art 5(1) of the Medicinal Products Directive 2001/83/EC, as amended, provides that a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of the directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

The Medicinal Products Directive 2001/83/EC, as amended, has been transposed into Irish law. In terms of manufacturing, the Manufacturing Regulations[9] (SI 539/2007, as amended) provide that the requirement to hold a manufacturer's authorisation does not apply to the extemporaneous manufacture of a medicinal product in response to a bona fide unsolicited order to fulfil a special need and which is carried out –

i. in a dispensing pharmacy (which is defined in the Manufacturing Regulations as 'a shop being lawfully kept open for the dispensing or compounding of medical prescriptions under the Pharmacy Acts 1875 to 1977 and includes the pharmaceutical department of a hospital') by or under the personal supervision of a pharmacist
   - in accordance with the specifications of a registered medical practitioner or registered dentist for use by his or her individual patients on his or her direct personal responsibility

   or

   - for the purpose of maintaining a stock of a medicinal product for dispensing exclusively in such pharmacy to meet the orders of the aforementioned registered medical practitioner or registered dentist, or
   - in accordance with the prescriptions of a pharmacopoeia for supply to patients attending that pharmacy,

   or

[8] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf
[9] http://www.irishstatutebook.ie/eli/2007/si/539/made/en/print

ii. by or under the personal supervision of a registered medical practitioner or a registered dentist for the treatment of one of his or her patients on his or her direct personal responsibility,

and provided in each case that the medicinal product concerned is not the subject of any advertisement or representation and that no other medicinal product of appropriate composition, that is the subject of a marketing authorisation, is available for use in the circumstances. (Regulation 5 of the Manufacturing Regulations)

### Marketing Authorisation – S.I No. 540/2007 – Medicinal Products (Control of Placing on the Market) Regulations 2007

The Control of Placing on the Market ('CPM') Regulations (SI 540/2007[10], as amended) provide that the requirement to hold a marketing authorisation for a medicinal product does not apply in a variety of circumstances, and this includes:

the sale or supply of a medicinal product in accordance with any exception or exemption set out in the Medicinal Products Directive 2001/83/EC, as amended (Schedule 1, paragraph 1 of CPM Regulations). (As noted above Art 3(1) and Art 3(2) provide exemptions.)

### Wholesale Regulation

The Wholesale Regulations[11](SI 538/2007, as amended) provide that the requirement to hold a wholesaler's authorisation does not apply to the sale by or under the personal supervision of a pharmacist in a dispensing pharmacy (which is defined in the Wholesale Regulations as 'a shop being lawfully kept open for the dispensing or compounding of medical prescriptions under the Pharmacy Acts 1875 to 1977 and includes the pharmaceutical department of a hospital'), to a registered medical practitioner, a registered dentist, a registered dispensing optician, a registered optometrist, a registered veterinary surgeon, a person who is acting as a pre-hospital emergency care provider and a person lawfully entitled to obtain medicinal products for administration to patients in the course of a business as a hospital, for administration to patients in the course of a professional practice or service.
(Regulation 6 of the Wholesale Regulations).

[10] http://www.irishstatutebook.ie/eli/2007/si/540/made/en/print
[11] http://www.irishstatutebook.ie/eli/2007/si/538/made/en/print

## Extemporaneous Dispensing

The legal basis for the preparation of a medicinal product in a pharmacy, otherwise than in accordance with a manufacturer's authorisation from the Health Products Regulatory Authority (HPRA), is contained in Regulation 5(1) (a) of the Medicinal Products (Control of Manufacture) Regulations 2007. The manufacture and supply of such products is often known as extemporaneous compounding or extemporaneous dispensing. Please note the following legislative provisions would apply to all extemporaneously manufactured products, irrespective of the complexity of the medicine or the specific provisions related to its compounding.

Regulation 5 of the Medicinal Products (Control of Manufacture) Regulations 2007, provides an exemption to the requirement to hold a manufacturer's authorisation for the extemporaneous manufacture of a medicinal product in response to a bona fide unsolicited order to fulfil a special need and which is carried out:

i. In a dispensing pharmacy by or under the personal supervision of a pharmacist
   - In accordance with the specifications of a registered medical practitioner or registered dentist for use by his or her individual patients on his or her direct personal responsibility or
   - for the purpose of maintaining a stock of a medicinal product for dispensing exclusively in such pharmacy to meet the orders of the aforementioned registered medical practitioner or registered dentist, or
   - in accordance with the prescriptions of a pharmacopoeia for supply to patients attending that pharmacy,

   or

ii. by or under the personal supervision of a registered medical practitioner or a registered dentist for the treatment of one of his or her patients on his or her direct personal responsibility, and provided in each case that the medicinal product concerned is not the subject of any advertisement or representation and that no other medicinal product of appropriate composition, that is the subject of a marketing authorisation, is available for use in the circumstances.

The legal basis for the supply of a medicinal product, otherwise than in accordance with a marketing authorisation, is set out in Regulation 6(4) and Schedule 1 to the Medicinal Products (Control of Placing on the Market) Regulations 2007, and Article 3.2 of Directive 2001/83/EC. The Control of Placing on the Market Regulations 2007, provides an exemption to the requirement to hold a marketing authorisation for a medicinal product in a variety of circumstances, and this includes the sale or supply of a medicinal product in accordance with any exception or exemption set out in the Medicinal Products Directive 2001/83/EC, as amended (Schedule 1, paragraph 1). These exemptions are provided in Art 3(1) and Art 3(2)

of the Directive and include circumstances where a medicinal product is prepared in a pharmacy in accordance with a medical prescription for an individual patient.

The Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended provide that the requirement to hold a wholesaler's authorisation does not apply to the sale by or under the personal supervision of a pharmacist in a dispensing pharmacy, to a registered medical practitioner, a registered dentist, a registered dispensing optician, a registered optometrist, a registered veterinary surgeon, a person who is acting as a pre-hospital emergency care provider and a person lawfully entitled to obtain medicinal products for administration to patients in the course of a business as a hospital, for administration to patients in the course of a professional practice or service (Regulation 6).

Further to the above, pharmacists in governance positions in a pharmacy practice providing extemporaneous compounding services should ensure that in the provision of this service that systems of governance and quality assurance are in place, and that practice- specific requirements, policies and procedures are in place to govern all processes in this regard.

All pharmacists have professional responsibilities under the Code of Conduct for pharmacists (2019). Under the Code of Conduct Pharmacists are expected to use their professional judgement and clinical expertise in order to make ethical decisions which will involve balancing different responsibilities including the following principles in the code:

- Always put the patient first and make their health, wellbeing and safety your primary focus. Make sure patients' needs are recognised, assessed and responded to.
- Work in partnership with patients and members of all healthcare disciplines to ensure that the patient receives safe and effective care. Build effective working relationships with patients, colleagues and other healthcare professionals in order to deliver person-centred care.
- Collaborate with your colleagues and other healthcare professionals to build confidence, respect and understanding. Act as a leader in the safe and effective use of medicines and healthcare resources.
- Promote and strengthen a culture of quality and safety, acting as a role model for the safe supply of medicines
- Apply your knowledge and skill in decision making to ensure safe and effective care for the patient.

**Pharmacy Act 2007**

Section 26(1) and Section 27(d), 28(c) or 29(d) of the Pharmacy Act 2007 (as appropriate to the ownership structure of the pharmacy) requires that the sale and supply of medicinal

products in the premises in which the business is carried on is conducted in those premises, by or under the personal supervision of a registered pharmacist.

**Regulation of Retail Pharmacy Business Regulations 2008**

- Regulation 4(1)(a) of the Regulation of Retail Pharmacy Businesses Regulations 2008 (as amended) requires the pharmacy owner to "provide and maintain such staff, premises, equipment and procedures for the storage, preparation, dispensing, compounding, sale and supply of medicinal products.... and that he or she shall not use for any such purposes premises other than those that constitute his or her retail pharmacy business and which have been specified in his or her application for registration under section 17 of the Act". This means that the regulations do not permit elements of the dispensing process being carried out in one pharmacy premises and the remainder of same to be carried out in another pharmacy premises.
- Regulation 4(2) of the Regulation of Retail Pharmacy Businesses Regulations 2008 (S.I. No. 488 of 2008)(as amended) requires the pharmacy owner to ensure that the arrangements and layout of the premises are such as to enable personal supervision to be exercised by a registered pharmacist of any preparation, dispensing or compounding and of the sale or supply of medicinal products, including veterinary medicinal products, at one and the same time.
- Regulation 5(1)(d) of the Regulation of Retail Pharmacy Businesses Regulations 2008 (as amended) requires that the sale or supply of medicinal products, including veterinary medicinal products, and the preparation, dispensing and compounding of prescriptions, including veterinary prescriptions, at the premises, are carried out by or under the personal supervision of a registered pharmacist.
- The sourcing of medicines by a registered retail pharmacy business is regulated by Regulation 6 of the Regulation of Retail Pharmacy Businesses Regulations 2008(as amended), which requires that a person carrying on a retail pharmacy business shall obtain his or her supplies of medicinal products from persons
    - (a) who are themselves the holders of a manufacturer's authorisation or a wholesaler's authorisation in respect of such products, or
    - (b) who are the holders of an authorisation granted by the competent authority of another EEA State authorising the manufacture of such products or their wholesale distribution.

- Regulation 9 of the Regulation of Retail Pharmacy Businesses Regulations 2008 (as amended) provides a legislative basis for the review of medicine therapy and counselling of patients in the supply of medicinal products on foot of a prescription. Regulation 10 of the same regulations provides a legislative basis for counselling in the supply of medicinal products other than on foot of a prescription.

## Council of Europe Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients

The purpose of the resolution is to promote the harmonisation of requirements for medicinal preparations, support health professionals with appropriate guidance to prevent risk of health damage caused by drug preparation errors and, ultimately, ensure that patient needs are fully met. This resolution applies to pharmacy preparations also known as unlicensed pharmaceutical preparations, i.e. medicinal products which are prepared for the special needs of patients by community and hospital pharmacies and to comparable processes and preparations of medicinal products as referred to in paragraph 10.2. It applies also to the reconstitution of medicinal products in health care establishments.
The provisions cover all pharmacy preparations, both extemporaneous and for stock, and their applicability depends on the outcome of the risk-assessment of the pharmacy preparation.

If the preparing pharmacy and the dispensing pharmacy are not identical their different responsibilities, including the sharing of those elements of the product dossier essential for the safe use of the product, should be defined either in the regulations or a contractual agreement. Pharmacy preparations should always be distributed by a dispensing pharmacy because this pharmacy receives the prescription for the patient. The preparing pharmacy should be responsible for ensuring that an appropriate quality assurance system is in place.

All pharmacy-prepared medicinal products should be prepared using an appropriate quality assurance system. Before preparation, a risk assessment should always be carried out in order to define the level of quality assurance system which should be applied to the preparation of the medicinal product.
A possible model procedure for risk assessment, provides an aid to distinguishing between two risk levels ("high-risk preparation" and "low risk preparations") and between two levels of quality system based on a risk-graded application of quality assurance principles.
**I**t is recommended that the GMP Guide be used as a reference for an appropriate quality system for "high-risk preparations", and that the PIC/S GPP Guide be used for "low-risk preparations". The application of other guidelines with an equivalent quality level is possible, depending on the national legislation or guidance.

For extemporaneous preparations, it will not usually be possible to compile a complete product dossier containing all possible information mentioned in section 5.1. as it could lead to a delay in the supply of necessary medicines. For extemporaneous preparations, however, the pharmacist and the prescriber should always consider the risks for the patient, which include the risks posed by a medicinal product without documentation specifying the added value of the pharmacy preparation and the quality assurance system applied to its production, versus the risks related to the unavailability of this medicinal product.

<u>Reconstitution of medicinal products in health care establishments</u>
In general, reconstitution of medicinal products should preferably take place in a pharmacy, assuming that the requirements concerning the safe preparation of sterile products can be fulfilled. Reconstitution considered to be low risk can be done on the wards. If the residual risk has been assessed systematically (see Note "Checklist for the identification, assessment

and reduction of risk posed by the reconstitution of medicinal products in clinical areas", Resolution CM/Res(2016)2 on good reconstitution practices in healthcare establishments for medicinal products for parenteral use), the health care establishment could decide on and document whether or not a medicinal product is suitable for reconstitution in a particular clinical area.

9.1. Responsibilities of the health care establishment
The health care establishment should decide and document decisions on reconstitution in line with Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use.

9.2. Role of the authorities
As reconstitution is not generally considered a process in the context of pharmacy preparations, national responsible authorities should develop, in co-operation with the relevant professional bodies, specific legislation and guidance taking into consideration the provisions set out in Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use

**Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use**

This resolution applies to the reconstitution of medicinal products for parenteral administration which are administered to patients of the given health care establishment.

**Clinical Trial Regulation (CTR), (EU) No. 536/2014**
The Clinical Trial Regulation (CTR), (EU) No. 536/2014, came into effect on 31st January 2022 and CTR Article 61(5) provides new exemptions from the requirement for a manufacturer's authorisation for investigational medicinal products (IMPs) which apply to the following manufacturing processes carried out in hospitals, health centres or clinics;

a) re-labelling or re-packaging
b) preparation of radiopharmaceuticals used as diagnostic IMPs
c) preparation of investigational medicinal products in a pharmacy in accordance with a medical prescription or in accordance with a pharmacopoeia.

The processes must be carried out by or under the personal supervision of a registered pharmacist, a registered medical practitioner, or a register dentist. The IMPs are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the State.

Reconstitution or dilution are not considered manufacturing processes under the CTR. Processes that are considered exempt are not required to meet the good manufacturing practice requirements that all other IMPs must meet. However, the processes under Article 61(5) should be carried out in accordance with proportional and appropriate requirements.