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Quality assurance standards and their use in the preparation of parenteral systemic anticancer therapy products in healthcare establishments: a scoping review

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ABSTRACT

Objectives The use of parenteral systemic anticancer therapy (SACT) has led to improved cancer survival. A quality assurance (QA) system of the aseptic compounding process is necessary to ensure safe and consistent production of parenteral SACT. This scoping review identifies international evidence and practice relating to QA standards in the preparation of parenteral SACT in healthcare establishments.

Methods Standards relating to aseptic compounding in hospital pharmacies and literature exploring the aseptic compounding of parenteral SACT were included. Literature relating to the non-aseptic compounding of medicines and records specific to sterile manufacturing in industrial settings were excluded. A search of several electronic databases, trial registries, the grey literature and websites of key European hospital pharmacy groups and accreditation bodies was conducted on 16 March 2022. A narrative discussion was performed by country, and content analysis of articles was conducted.

Results Thirty-seven records were included. Standards reviewed covered the work environment, the preparation process and the safety of the workers who are potentially exposed to hazardous chemicals. It was a common practice to include frequent audits to ensure adherence to standards. Some standards also recommended external inspections to allow for further learnings. Periodic reviews are encouraged to ensure standards maintain relevance. National standards of the countries reviewed were based on international standards, with minor adaptations for local conditions.

Conclusions The main limitation of this review is that it is limited to countries with a high human development index. The review shows that the use of an internationally recognised standard as a basis for national standards is best practice, and will allow for relevance into the future.

BACKGROUND

Cancer is the leading cause of death globally.¹ In 2020, there were approximately 19.3 million cases of cancer internationally. This is predicted to increase by 47% by 2040. This presents a challenge for cancer care services, which are complex and multidisciplinary.¹

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The importance of ensuring high standards in aseptic compounding of parenteral systemic anticancer therapy (SACT) has been recognised internationally to protect both patients and operators. There is variation in recommended practice between various national and international standards and guidelines.

WHAT THIS STUDY ADDS

⇒ Our review identifies national and international evidence and practice relating to quality assurance (QA) standards and their use in the preparation of parenteral SACT in healthcare establishments. This review provides recommendations for the basis and approach to national QA standards and guidelines, to meet the needs of pharmacy aseptic compounding units and to provide a safe, quality-driven service.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review describes national and international standards and guidelines that promote the safe, accurate and consistent aseptic compounding of parenteral SACT.

Systemic anticancer therapy (SACT) is one of the three main cancer treatments available for patients. SACT includes chemotherapy, targeted therapies, immunotherapy and other drugs and agents. The 2019 National Cancer Registry Ireland report estimated that the number of patients receiving SACT will increase by approximately 70% between 2015 and 2045.² European cancer drug expenditure has approximately doubled, from €17 billion in 2010 to €32 billion in 2018.³ Increased SACT use also carries with it an increased risk of harm due to adverse drug reactions or medication errors.^{4,5}

Ensuring high standards in aseptic processing has been recognised internationally by organisations such as the Institute for Safe Medication Practices (ISMP) in the United States and the NHS in the UK.^{6–10} Implementing standards such as Good Manufacturing Practice (GMP) for aseptic

compounding reduces the staff exposure risk to teratogens and carcinogens.^{11,12}

The aim of this scoping review was to identify international evidence and practice relating to quality assurance (QA) standards in parenteral SACT product preparation in healthcare establishments, and to develop recommendations for standards and guidelines.

METHODS

This review was guided by the Joanna Briggs Institute methodology for scoping reviews,¹³ and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scoping reviews checklist extension¹⁴ (protocol: Open Science Framework registry <https://osf.io/7wa8u>).

Eligibility criteria

Eligibility criteria were predetermined using the population, exposure and outcome (PEO) framework.¹⁵

- ▶ Population: hospital pharmacists
- ▶ Exposure: standards relating to hospital pharmacy aseptic compounding and literature exploring the aseptic compounding of parenteral SACT
- ▶ Outcomes: national/international standards, the way standards compare to one another in content and scope, legislative requirements to uphold the standards, regulator overseeing/enforcing the adherence to these standards and the audit process

National/international standards, guidelines, regulations, audits, process improvement exercises and monitoring reports were included from the UK, Australia, New Zealand, the US, Canada, the Netherlands, Denmark, Sweden, Norway and Germany. These countries were chosen as they have similar healthcare systems, infrastructure and human development indices.¹⁶ Primary studies, reviews and trials were also eligible for inclusion. Literature relating to the non-aseptic compounding of medicines and literature specific to sterile manufacturing in industrial settings was excluded.

Search strategy

Academic Search Complete, CINAHL, MEDLINE, PubMed, Scopus, Web of Science, the Cochrane review database and ClinicalTrials.gov were searched on 16 March 2022. The following keywords were searched based on title or abstract: ((Asep* OR non-touch OR "non touch" OR Steril* OR Germ-free OR "Germ free") N3 (Compound* OR Prepar* OR Manufactur* OR Process* OR Method*)) AND Pharmac*. Records published from January 2011 to March 2022 were sought.

OpenGrey, TRIP Pro, OAIster, National Institute for Health and Care Excellence clinical guidance and Google were also searched. Websites of hospital pharmacy groups and accreditation bodies were also searched. Results were organised based on relevance, and the first 100 hits or 10 pages were reviewed for each website.¹⁶ Reference lists were also screened to locate additional records.

Study selection and data charting

All records were uploaded into Covidence online software and duplicates automatically removed.¹⁷ Titles and abstracts were screened. The full text of potentially relevant papers was then retrieved and assessed against the inclusion criteria. Data were extracted using two purposefully developed data extraction tools under the following headings: reference; country; standard implemented; responsible authority; and audit process.

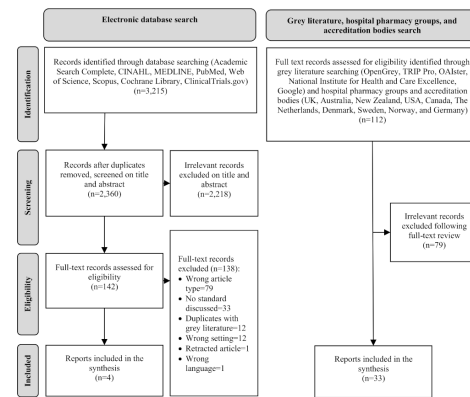


Figure 1 PRISMA flow diagram.

Empirical data identified were extracted as follows: QA standard referenced; intervention; comparator; and outcome. Data were extracted by one reviewer and cross-checked by the review team.

Data analysis

A narrative discussion was performed by country (online supplemental file 1). Content analysis of articles was also conducted. This is presented in tabular form, where all documents were visually compared and contrasted (online supplemental file 2). This facilitated the development of recommendations for best practice standards.

RESULTS

Record selection

A total of 3215 records were identified. Following deletion of duplicates and title and abstract screening, 142 full-text records were screened and 138 were excluded. Grey literature searching yielded 112 records and 79 were excluded. Therefore, 37 records were included for review (figure 1).

Synthesis of results

Three pairs of documents were merged into single documents, as each pair related to a standard and one of its annexes.^{18–21} Findings from the 37 records are presented in online supplemental appendix 1.

In the EU, the pharmaceutical industry demonstrates a high level of quality management in the development, manufacture and inspection of medicinal products.¹⁸ The EU GMP is a legislative reference that is enforceable during competent authority inspections.¹⁸ Volume 4 of 'The rules governing medicinal products in the EU' contains GMP guidelines for medicinal products.¹⁸ As they are pharmaceutical manufacturing guidelines, their applicability to hospital aseptic compounding unit (ACU) operations is variable. In the UK for example, for an ACU holding a Medicines and Healthcare Products Regulatory Agency (MHRA) Manufacturers (Specials) licence, implementation of EU GMP is mandatory, or will result in licence withdrawal.²² Unlicensed UK units are incorporated into other specific ACU standards, implemented via the national external audit process.²² In contrast, Ireland has no nationally agreed standards.

In 2016, the Council of Europe adopted two resolutions to harmonise requirements for medicinal preparations and minimise the health damage risk caused by drug preparation errors.²³ European Council Resolution CM/Res (2016) 1 applies to pharmacy preparations and medicinal product reconstitution in healthcare establishments.²⁴ A risk categorisation system is proposed based on factors such as final product type and

preparation size. For high-risk preparations, EU GMP is recommended, while low-risk preparations are guided by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Good Preparation Practices (GPP).²⁴ The second resolution, Resolution CM/Res (2016) 2, provides guidance on good reconstitution practices in healthcare establishments for parenteral medicinal products.²⁵ The resolution recommends developing national manuals on handling preparations.^{25,26} It is suggested that regular risk assessments and auditing are performed at least once per year.²⁶ A designated person with direct access to management should be responsible for approving Standard Operating Procedures (SOPs), and ensuring appropriately trained personnel.²⁶ Regarding external inspections, risk-based inspections should be guided by a notification system.²⁵

Directive 2004/37/EC aims to cover the protection of workers from exposure risk to work hazards, including carcinogens.²⁷ The 2017 and 2022 updates included reduced carcinogen limit values.²⁷ While no audit process is outlined, it stipulates regular assessment of worker exposure risk.²⁷

Regulation (EU) No 536/2014 establishes harmonised rules that apply to EU clinical trials.^{28,29} As such, it will not impact most ACU operations; however, awareness is important for ACU preparations used in clinical trials.

In parallel with EU guidelines, PIC/S GMP and GPP Guides have been developed.³⁰ PIC/S is an international cooperation which aims to harmonise inspection procedures worldwide.³⁰ The PIC/S GMP applies to industrial manufacture of distributed medicinal products,³⁰ while the PIC/S GPP applies to the preparation of medicinal products in healthcare establishments for direct patient supply.²¹ For this review, the GPP guidelines have greater relevance to preparation. Although guidelines, routine inspections may be conducted by competent authorities.^{21,30} In relation to GMP and GPP, recommendations include regular QA systems examination.³⁰ Both recommend annual self-inspections.^{21,30} PIC/S guides are preferred for many participating PIC members. Non-participating countries tend to use the WHO good manufacturing principles for pharmaceutical products.³¹

The International Society of Pharmacy Practitioners (ISOPP) released the Standards for the Safe Handling of Cytotoxic Drugs in 2022.³² Guidance is provided for specific categories of SACT such as monoclonal antibodies. It does not provide audit recommendations but provides an audit toolkit.³³

The European Society of Oncology Pharmacists published the Quality Standard for the Oncology Pharmacy Service (QuapoS) 6 in 2018.³⁴ QuapoS provides recommendations on all aspects of ACU SACT production. No recommendations are given for specific audits, nor are there regular inspections, other than compliance.

Besides international organisations, national standards and guidelines from Australia, Canada, Germany, Ireland, the Netherlands, Sweden, the US and the UK are reported on below.

Australia has national standards which are used in the practice of preparation of medicinal products in healthcare.^{35,36} The Pharmaceutical Society of Australia (PSA) have professional practice standards that provide guidance relevant to this review on personnel, equipment and premises. It provides a risk matrix to determine the risk level of a compounding operation. The Therapeutic Goods Administration, responsible for manufacturing standards for medicinal products, has adopted PIC/S GMP as the industrial standard.³⁵ The Australian pharmacy regulator, Pharmacy Board of Australia, provides guidance on sterile injectable preparations, and stipulates that there must be

adherence to PIC/S GMP, PIC/S GPP or United States Pharmacopoeia (USP) 797.⁷ Internal audit guidance follows those of PIC/S GPP. The Society of Hospital Pharmacists of Australia have two sets of guidelines: Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments (2010), and Standards of Practice for the Safe Handling of Cytotoxic Drugs in Pharmacy Departments (2005).^{37,38} The former is guidance for hospital pharmacy preparations and endorses PIC/S GPP.^{21,37} The latter is more specific to SACT preparations.³⁸ It does not give self-audit guidance, but gives recommendations on specific monitoring, such as annual revalidation of personnel technique.

Canada uses two national standards from the National Association of Pharmacy Regulatory Authorities: Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations, and Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations.^{39,40} As both are similar in content, we will focus on the latter. It recommends that personnel should complete a competency assessment, including a theoretical and practical component.^{39,40} Frequency varies by category and risk level.^{39,40} All records required by the model standards must be completed by a sterile compounding supervisor, and be available for audit and inspection.^{39,40}

The German national standard recommends regular self-inspections.⁴¹ Moreover, staff working as auditors must have regular training.⁴¹ The Federal Association of German Hospital Pharmacists guideline on aseptic production and testing of ready-to-use parenterals refers to current German pharmacy law, pharmacopoeias and standards/guidelines, including EU GMP, PIC/S GPP and USP 797 standards.⁴² Requirements include that all compounding personnel must undertake internal and external training at least once per year.⁴² The quality of the aseptic production must also be ensured using validated processes.⁴²

In Ireland, there are currently no nationally agreed standards. Aseptic compounding in Irish hospital pharmacies does not require manufacturer's authorisation once certain criteria are met.⁴³ In response, the Hospital Pharmacy Association of Ireland (HPAI) began to develop guidelines in 2010.⁴⁴ HPAI consulted with other national stakeholders, and as a result, the PIC/S GPP was chosen as guidance for aseptic compounding.⁴⁴ The primary guidance for clinical trials is the Guide to Clinical Trials Conducted under the Clinical Trials Regulation.⁴⁵ This document refers to Regulation 536/2014, described earlier.²⁸ Additional guidance is provided by the Health Service Executive in their Guideline on the Safe Handling of Cytotoxic Drugs.⁴⁶ This guidance aims to reduce healthcare worker risk by minimising the exposure risk to cytotoxic drugs.⁴⁶ Local senior managers are responsible for implementation and regular audits. The National Cancer Control Programme Oncology Medication Safety Review focuses on the national policy development of safe and high-quality SACT services.⁴⁷ The review provides recommendations on aspects of ACU operations at a national level, but no recommendations on auditing or inspection.

In the Netherlands, the Dutch Association of Hospital Pharmacists (NVZA) has published the GMP-Z, the standards for preparation in hospital pharmacy.¹⁹ GMP-Z uses EU GMP as the basis of their standards and provides additional guidance on preparation of medicines; for example, preparation of radiopharmaceuticals. Of specific interest is Annex 1, which is concerned with the manufacture of sterile medicines.²⁰

The Swedish Medical Products Agency provides regulations on the manufacture of extemporaneous drugs.⁴⁸ Pharmacies manufacturing extemporaneous medicinal products should ensure that the process is done in accordance with GMP.⁴⁸ As part of QA, a pharmacy must conduct regular self-inspections, at

least annually.⁴⁸ Staff must undertake introductory training and regular retraining that includes both theory and in practice.⁴⁸ While the guidance does not outline an external inspection process, the Swedish Medical Products Agency is responsible for overseeing this process.⁴⁸

In the US, national standards are used for the preparation of SACT medicines in healthcare establishments.^{49–50} USP 797 outlines standards for the compounding of sterile preparations.⁴⁹ Similarly, USP 800 provides standards for the safe handling of hazardous drugs.⁵⁰ While USP 797 focuses on the protection of the sterility of the drug, USP 800 is concerned with the safety of workers.^{49–50} Regulatory bodies are responsible for ensuring compliance and SOPs are required to be reviewed annually.^{49–50} Under USP 797, compliance is required in key areas, including staff training and policy and procedure implementation.⁴⁹ Regular staff training in sterile compounding principles and practices are required annually.⁴⁹ Personnel are required to perform an aseptic manipulation competency test semi-annually, and to enrol in a medical surveillance programme.⁴⁹ The current American Society of Health-System Pharmacists (ASHP) Guidelines on Compounding Sterile Preparations aims to harmonise with the USP 797 standards.⁵¹ The guidelines aim to help personnel to compound sterile preparations of high standard, and reduce the risk of harm.⁵¹ Environmental monitoring is required at the certification of new facilities and semi-annually during recertification.⁵¹ Any controlled-temperature area used for sterile preparation compounding must be monitored at least daily.⁵¹ Where a preparation is for an individual patient and within a healthcare establishment, compounding is not overseen by the Food and Drug Administration.

The American Society of Clinical Oncology (ASCO) standards for Safe Handling of Hazardous Drugs were developed based on a systematic literature review by an expert panel. While the document largely endorses existing USP standards, they do differ in some ways.⁵² The ASCO standards have identified several key areas where more research is needed to measure the level of risk linked with handling hazardous drugs.⁵² No audit process is outlined under the ASCO standards.⁵² The ISMP released its Guidelines for Safe Preparation of Compounded Sterile Preparations in 2016.⁵³ These guidelines specifically endorse USP 797 as guidelines for ensuring sterility; however, they focus on error prevention.^{49–53} The guidelines make recommendations on specific aspects of the compounding process, such as regular monitoring of storage conditions and competency assessment of staff. The National Institute for Occupational Safety and Health, the organisation responsible for reducing the risk of work-related harms in the US, released its updated Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings report in 2016, to provide guidance to healthcare establishments in reducing exposure risk to anticancer drugs.⁵⁴

The UK uses the QA of Aseptic Preparation Services standards, which are a joint initiative between the Royal Pharmaceutical Society and the NHS Pharmaceutical QA Committee.⁵⁵ Adherence to these standards is the responsibility of regional QA teams in the NHS to assure the quality of unlicensed pharmacy aseptic units.⁵⁵ An audit programme should be determined in advance, with an action plan including timelines and responsible persons.⁵⁵ An SOP should also be in place, with details of the management and review of the action plan.⁵⁵ Internal audits must be conducted on a regular basis by designated staff. A quality review of the Pharmaceutical Quality System is also required.⁵⁵ Audit reports must be submitted for review to senior management.⁵⁵ External audits should be conducted by

a regional QA specialist or an accredited auditor at least every 12 to 18 months.⁵⁵ Moreover, the MHRA Guidance for Specials Manufacturers provides guidance on interpretation of GMP standards for the manufacture of aseptically prepared products under a Manufacturers (Specials) licence.²²

DISCUSSION

In recent years, standards described in this review have started to converge. PIC/S aims to lead the international development, implementation and maintenance of harmonised standards and quality systems for medicines' manufacturing.⁵⁶ The main instruments for harmonisation have been the PIC/S GMP and GPP. Due to increasing public health concerns and the multiple actors involved in both industry and among regulatory authorities, the recommendation is to further increase harmonisation efforts among standards.⁵⁷ This includes PIC/S, which should become more global and representative, and expand to other continents including America, Asia and Africa.⁵⁷ It is recommended that PIC/S should continue to harmonise and modernise its GMP standards, while ensuring that the PIC/S GMP Guide remains a high-standard international guide. Recommendations based on this review can be summarised as follows:

- ▶ Standards should be developed and agreed by key stakeholders, and reviewed on a regular basis cognisant of future trends.
- ▶ National standards should comply with legislation that presently applies to the practice of aseptic SACT compounding in a hospital pharmacy environment.

There are two international standards stated as examples by the Council of Europe: PIC/S and the WHO.^{30–31} It should be noted, however, that these WHO standards are from 2011, and there have been significant changes in QA standards in the past 12 years.³¹ It is imperative that to remain relevant, these standards are urgently reviewed and updated in line with current expectations for GMP.

These standards may be reviewed and assessed for appropriateness to the relevant healthcare environment. Notwithstanding this, national standards should be broadly applicable and relevant for any healthcare establishment without a manufacturing licence involved in the aseptic preparation of SACT.

Strengths and limitations

All records were double screened, and data extraction was cross-checked by the full review team. This review presents hospital pharmacists with evidence on which future standards relating to the preparation of parenteral SACT can be based. The global generalisability of our findings, however, is limited, as the records published are primarily in countries with high human development index within a 10-year timeframe. In addition, EU GMP Annex 1 was updated in 2022 after data analysis had commenced; however, it was deemed not to change the conclusions of the analysis.¹⁸

CONCLUSION

Increasing use of SACT as a cancer treatment modality has resulted in an increased demand on SACT service delivery. To safeguard the public and healthcare providers, it is vital that this increased demand does not result in any compromise in the consistency and/or delivery of standards. This review identifies international evidence and practice relating to QA standards, including safe handling standards and practice, and their use in the preparation of parenteral

SACT products in healthcare establishments. It is imperative that up-to-date, consistent, international quality standards for aseptic compounding of parenteral SACT be developed, agreed and then endorsed by the relevant professional bodies and/or regulatory authorities in each country.

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