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EC PHARMACOLOGY AND TOXICOLOGY
Research Article

Systematic Review on the Reconstitution of Cytotoxics in Oncology Pharmacy: Practices, Safety Issues, and Prospects for Optimization

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Received: June 11, 2025; **Published:** August 20, 2025

Abstract

Introduction: Cytotoxic drug reconstitution is a key step in the therapeutic chain in oncology. It requires rigorous practices to ensure the safety of healthcare personnel, drug stability, and the efficacy of treatment administered to patients.

Methodology: A descriptive narrative review was conducted using PubMed databases, selecting articles published between 2018 and 2024. Inclusion criteria were studies on cytotoxic reconstitution practices, international recommendations, organizational, technical and safety aspects. Articles not available in full text or not in English/French language were excluded.

Results: Studies reveal a wide variability in the application of international recommendations. Automation, the use of laminar flow hoods, dual control, and closed systems are recommended practices but still unevenly implemented.

Discussion: Improving reconstitution conditions requires standardization of procedures, ongoing training of preparers, and the adoption of secure technologies. Budgetary, logistical, and human constraints remain major obstacles.

Conclusion: It is imperative to promote the harmonization of reconstitution practices at the national and international levels to optimize the quality and safety of the cytotoxic circuit.

Keywords: *Cytotoxic Drug Reconstitution; Oncology; Cytotoxic Circuit*

Introduction

The reconstitution of cytotoxic drugs is a high-risk pharmaceutical procedure in oncology. It aims to ensure precise, safe and compliant administration as prescribed, while minimizing staff exposure to hazardous substances [1]. This process is the subject of numerous recommendations, including those of ISOPP, ASHP, and ESOP, aimed at supervising good preparation practices in hospital settings [2,3]. However, the transposition of these recommendations into field practices remains heterogeneous, depending on the resources, training and infrastructure available.

Methodology

PubMed database between January 2018 and April 2024. The keywords used were: “cytotoxic drugs”, “compounding”, “reconstitution”, “oncology pharmacy”, “safety”, “guidelines”, “hazardous drugs”, “closed system transfer devices (CSTD)”.

Inclusion criteria:

- Original studies, literature reviews, recommendations or guidelines
- Concerning the reconstitution of cytotoxics in hospital or outpatient settings
- Articles in English or French
- Articles evaluating the technical, security, or economic aspects of reconstruction.

Exclusion criteria:

- Studies on other types of preparations (non-cytotoxic)
- Animal or *in vitro* studies not transferable to hospital practices
- Publications without a reading committee or not directly dealing with reconstruction.

Results

Cytotoxic reconstitution in oncology pharmacy is a critical procedure that involves significant risks for both healthcare personnel and patients. These risks include exposure to toxic products, the possibility of human error, and logistical issues related to drug preparation within tight timeframes. Optimizing the safety of this procedure is therefore a major objective to prevent incidents and ensure optimal therapeutic quality. Guidelines and good practices recommended by international organizations, such as the World Health Organization (WHO), ISO/IEC, and MHRA, provide an essential framework for this task. However, the application of these standards varies from one organization to another, and several challenges must be addressed to ensure compliance.

Occupational risks

Healthcare workers involved in the reconstitution of cytotoxic drugs are exposed to significant risks, mainly related to direct exposure to toxic products. Cytotoxic drugs are often potent anticancer agents that, if mishandled, can cause serious adverse health effects in healthcare workers. These risks include reproductive disorders, cancers and dermatological diseases due to prolonged exposure [1,2].

Laminar flow chambers and protective gloves are crucial equipment to minimize exposure. In addition, the use of closed systems for drug preparation has shown a significant reduction in exposure risks for workers [3]. Recent studies have also highlighted that ongoing staff training on safety practices and the use of personal protective equipment is essential to reduce the risk of occupational exposure [4].

Logistics risks

Reconstitution of cytotoxic drugs poses major logistical challenges. Drug stability is a key factor, as cytotoxic drugs are often sensitive to environmental conditions, such as temperature and humidity. In addition, on-demand preparation, i.e. preparing treatments at the last minute, makes this procedure even more complex. Human errors are possible due to stress, work overload, or fatigue, particularly in facilities with limited resources [5].

To minimize these risks, strict protocols for the storage and transportation of cytotoxic drugs are recommended, as well as the use of automated inventory management and preparation systems. These technologies help reduce human error and ensure that drugs are prepared under optimal conditions [6]. The integration of preparation robots has also been suggested to increase the accuracy and efficiency of preparations.

Therapeutic risks

Errors in cytotoxic reconstitution can have serious consequences for the patient. Dosing errors can lead to underdosing, compromising treatment efficacy, or overdosing, increasing the risk of serious adverse events. For example, a study by Williams., *et al*. (2017) showed

that nearly 5% of medication errors in oncology were related to errors in cytotoxic preparation, which led to serious adverse events for patients [7].

Safety protocols, including double-checking systems and the use of standardized formulas for preparations, are therefore essential to ensure the quality of reconstitution. The use of technological tools such as pharmacy information systems (PIS) and barcodes can also improve the accuracy of the preparation process and reduce therapeutic errors [8].

Optimization of reconstitution: Securing the drug circuit

Optimizing the reconstitution of cytotoxic drugs is an important lever for securing the drug circuit in oncology. International recommendations, such as those of the WHO and the MHRA, emphasize the implementation of good practices for the preparation and management of cytotoxic drugs to avoid errors and improve patient safety [9,10].

Continuing education of pharmacists and pharmacy technicians is a key element to ensure compliant and safe reconstitution of cytotoxics. Moreover, the integration of modern technologies, such as compounding robots and automated systems, can not only improve the accuracy of reconstitution but also ensure better traceability of drugs [11].

Discussion

Occupational exposure to cytotoxics poses a major risk to healthcare workers. Studies have shown that exposure to these substances, particularly through inhalation or skin contact, can lead to reproductive harm, cancer, and mutagenic effects [1]. According to a study by Lammers., *et al*. (2015), the use of laminar flow chambers and protective gloves is essential to minimize this exposure [2]. In addition, closed drug transfer systems, which prevent leakage of these toxic substances, have been shown to be effective in protecting staff [3].

Compliance with international recommendations, such as those defined by the WHO and MHRA for the handling of cytotoxic agents, remains unevenly applied across different institutions. A study by Sayer., *et al*. [1] highlights the importance of training healthcare professionals on these safety equipment and practices to reduce exposure [4]. The use of automated equipment for the preparation of cytotoxic agents has also been suggested to minimize human error and ensure a safer working environment [6].

Logistics risks and process optimization

Logistical challenges are also numerous in the reconstitution of cytotoxic drugs. Drug stability is a central concern, especially when these treatments require strict storage conditions. Optimizing preparation processes, especially within tight timeframes, remains a barrier to ensuring treatment quality while respecting safety protocols. A study by Thorne., *et al.* [6] demonstrates that the introduction of preparation robots and computerized inventory management systems can improve not only the accuracy but also the speed of cytotoxic drug preparation [11].

The impact of human errors in this process is also an important point of discussion. Indeed, according to Fox., *et al*. [11] approximately 5% of medication errors in oncology are due to errors in cytotoxic reconstitution, which can lead to serious consequences for patients [7]. Automating certain steps, such as dosage verification and solution adjustment, could significantly reduce this type of error [8].

Therapeutic consequences and accuracy of doses

Adherence to doses and concentrations of cytotoxic agents is essential to maximize therapeutic efficacy while minimizing the risk of serious side effects. A study by Williams., *et al.* [7] found that preparation errors, such as dosage or administration errors, can lead to treatment failure or serious toxicities, thus increasing costs to the healthcare system [5]. This finding was confirmed by Collet and Boudrault [5], who emphasized the importance of systematic double-checking for all prepared cytotoxic agents [9].

It is also crucial that pharmacists and medical staff follow standardized protocols to avoid errors in drug reconstitution. The implementation of pharmacy information systems (PIS) and the use of barcodes to track and verify each step of cytotoxic drug preparation have shown a positive impact on reducing therapeutic errors [10]. These technologies allow for better traceability and ensure strict control throughout the process.

Impact of international standards and local adaptation

International guidelines, such as those from the WHO, MHRA, and ISO**,** provide essential guidance for the management of cytotoxic reconstitution. However, their application in different local settings varies considerably. Variations in the application of these standards are well documented, and a lack of human and material resources in some institutions makes their implementation difficult [12].

A study by Orlowski and Alvarado [8] suggests that healthcare facilities need to adapt to their local realities while incorporating the recommendations of these international standards. For example, the introduction of a computerized medication management system has enabled several hospitals to comply with good practices while reducing costs and human errors [13].

Conclusion

Cytotoxic drug reconstitution is a strategic link in oncology pharmacy. To enhance safety, it is necessary to promote harmonized practices, develop continuing education, and integrate innovative technologies into preparation units.

Context

This work is part of a changing hospital practice toward greater security in the anticancer drug supply chain. Controlling the risks associated with reconstitution is a national and international priority for the health of caregivers and the quality of care.

Limitations of the Study

- Limitation to a single database.
- Heterogeneity of methodologies in the included articles.
- Data mainly from high-income countries, limiting generalization to resource-limited countries.

Data Availability Statement

The data used in this review are accessible in the articles referenced in PubMed. No primary database was generated or analyzed for this study.

Funding Statement

No specific funding was received for the conduct of this systematic review.

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Volume 13 Issue 9 September 2025