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Occupational exposure to antineoplastic drugs and the development of tailor-made risk control strategies in South African oncology pharmacies

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Johannesburg, South Africa, 2025

Declaration

This thesis is submitted in the integrating narrative format of published work, approved by the Faculty of Health Sciences.

I, Ruan Botha, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the School of Public Health, University of the Witwatersrand, Johannesburg, South Africa. This work has not been submitted previously for any degree or examination at this, or any other university.

I have read the sections on referencing and plagiarism in the Wits Plagiarism Policy, and I have followed the required conventions in referencing the thoughts and ideas of others. I understand that the University of the Witwatersrand may take disciplinary action against me, including suspension or permanent expulsion if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:



Date: 7 June 2025

Johannesburg

Dedication and acknowledgements

This PhD thesis is dedicated to my family of teachers. Theuns, my dad and my mother, Tonetti, both teachers par excellence! My brother, Innes, and my sister, Ané (also a teacher), my brother-in-law, Hendrik Klue (another teacher!), and their two girls, Lieke and Livvie. They reside in Auckland, New Zealand. None of this would have been possible without the continuous support of my life partner, André (the smartest person I know) who, through difficult times, stood by me despite the little time that I was able to spend with him while I was busy with research for my PhD. A special word of thanks to Carien van der Merwe and the members of the South African Society of Oncology Pharmacists (SASOPh) who provided meaningful industry-related inputs to steer the study, Carlo Natali from ICU Medical for his indispensable support. A special word of thanks to Prof. Derk Brouwer and Prof. Gill Nelson for their excellent scientific guidance and rigour, which they applied throughout the study. I am forever grateful to them.

Hierdie PhD-tesis word opgedra aan my gesin van onderwysers. Theuns, my pa, my ma, Tonetti - beide onderwysers par excellence! My broer Innes my suster Ané (ook 'n onderwyser), my swaer Hendrik Klue (nog 'n onderwyser!) en hulle twee dogtertjies, Lieke and Livvie. Hulle woon in Auckland, New Zealand. Geen van hierdie werk sou moontlik gewees het sonder die aaneenlopende ondersteuning van my lewensmaat, André (die slimste persoon wat ek ken), wat deur moeilike tye steeds by my gestaan het nieteenstaande tye wat ek nie saam met hom kon spandeer nie. 'n Spesiale woord van dank aan Carien van der Merwe en die lede van die Suid-Afrikaanse Vereniging van Onkologie Aptekers (SASOPh) vir hul betekenisvolle industrie verwante insette asook vir Carlo Natali van ICU Medical. 'n Besondere woord van dank aan prof Derk Brouwer en prof Gill Nelson vir hulle uitstekende akademiese ondersteuning en leiding. Ek is hierdie indivudië vir ewig dankbaar.

“It seems probable that once the machine thinking method had started, it would not take long to outstrip our feeble powers… They would be able to converse with each other to sharpen their wits. At one stage therefore, we should have to expect the machines to take control.”

— Alan Turing

Cancer's a funny thing

I wish I had the voice of Homer
To sing of rectal carcinoma,
Which kills a lot more chaps, in fact,
Than were bumped off when Troy was sacked.
Yet, thanks to modern surgeon's skills,
It can be killed before it kills
Upon a scientific basis
In nineteen out of twenty cases.
I noticed I was passing blood
(Only a few drops, not a flood).
So pausing on my homeward way
From Tallahassee to Bombay
I asked a doctor, now my friend,
To peer into my hinder end,
To prove or to disprove the rumour
That I had a malignant tumour.
They pumped in $BaSO_4$.
Till I could really stand no more,
And, when sufficient had been pressed in,
They photographed my large intestine,
In order to decide the issue
They next scraped out some bits of tissue.
(Before they did so, some good pal
Had knocked me out with pentothal,
Whose action is extremely quick,
And does not leave me feeling sick.)
The microscope returned the answer
That I had certainly got cancer,
So I was wheeled into the theatre
Where holes were made to make me better.
One set is in my perineum
Where I can feel, but can't yet see 'em.
Another made me like a kipper
Or female prey of Jack the Ripper,
Through this incision, I don't doubt,
The neoplasm was taken out,
Along with colon, and lymph nodes
Where cancer cells might find abodes.
A third much smaller hole is meant
To function as a ventral vent:
So now I am like two-faced Janus
The only [†] god who sees his anus.
I'll swear, without the risk of perjury,
It was a snappy bit of surgery.
My rectum is a serious loss to me,
But I've a very neat colostomy,
And hope, as soon as I am able,
To make it keep a fixed time-table.
So do not wait for aches and pains
To have a surgeon mend your drains;
If he says "cancer" you're a dunce
Unless you have it out at once,
For if you wait it's sure to swell,
And may have progeny as well.
My final word, before I'm done,
Is "Cancer can be rather fun".
Thanks to the nurses and Nye Bevan
The NHS is quite like heaven
Provided one confronts the tumour
With a sufficient sense of humour.
I know that cancer often kills,
But so do cars and sleeping pills;
And it can hurt one till one sweats,
So can bad teeth and unpaid debts.
A spot of laughter, I am sure,
Often accelerates one's cure;
So let us patients do our bit
To help the surgeons make us fit.

New Statesman, 21 February 1964: 298.

[†] In India there are several extra faces, up to four, but both in Brahma and in Shival, own myself an unbeliever.

John Burdon Sanderson (J.B.S.) Haldane, FRS (5 November 1892 – 1 December 1964), was an English evolutionary biologist and larger-than-life character. With the use of statistics in biology, he was a co-founder of neo-Darwinism. Despite his lack of an academic degree, he taught at Cambridge University, the Royal Institution, University of California Berkley and University College London. Renouncing his British citizenship, he became an Indian citizen in 1961 and worked at the Indian Statistical Institute until his death in 1964.

Preface

The literature overwhelmingly confirms that occupational exposure to antineoplastic drugs (ADs) poses significant health risks. The genotoxic effects that may arise once ADs are absorbed into the body are of paramount concern. Repeated low-concentration exposure can have severe health consequences over time, while high doses are used therapeutically. The United States Centres for Disease Control and Prevention (CDC), through the National Institute for Occupational Safety and Health (NIOSH), maintains a list of hazardous drugs; in its 2024 iteration, this list includes 125 identified hazardous agents, most of which are antineoplastic compounds. These are generally organic molecules, although some include platinum as a heavy metal, and their genotoxic effects are indisputable. Several factors, such as the physicochemical and pharmacokinetic characteristics of each AD and the specific selection and quantity of ADs handled in an oncology pharmacy, can modulate the extent of these adverse effects. Ultimately, the occupational health risk remains undeniable, but contemporary contamination levels and potential health impacts may still be underappreciated. Likely, the full understanding of the long-term health effects of exposure to ADs on oncology pharmacists will only become apparent in the future.

As a developing nation, South Africa suffers from critical shortages of healthcare professionals in the public sector. In contrast, the private healthcare sector—where most oncology pharmacies operate—has, over the past two decades, implemented a complex supply chain that moves ADs from wholesalers to oncology pharmacists. This pathway did not emerge without risks, and it circumvented the Pharmacy Act (53 of 1974) by effectively treating the compounding of ADs as something other than a dispensing phase. Consequently, the so-called "oncology pharmacy" does not legally qualify as a registered pharmacy, even though pharmacists in these facilities routinely handle needles, syringes, and parenteral ADs.

In many developed nations, oncology pharmacy has evolved over the past few decades into a dedicated sub-discipline, supported by peer-reviewed journals publishing state-of-the-art clinical and practice-based research. Regions such as North and South America, continental Europe, much of Asia, and Australasia now benefit from specialised experts and academics who develop and enforce oncology pharmacy guidelines and standards. In South Africa,

however, the situation—particularly in the private sector—is more convoluted, and the enforcement of local guidelines remains fragmented. Major role-players in the country's private medical oncology sector include managed care organisations (MCOs), oncologists, service providers (SPs), and the South African Pharmacy Council (SAPC). These entities collectively shape the practice of oncology pharmacy in South Africa, yet their interrelationships are complex.

The South African Society of Oncology Pharmacists (SASOPh) estimates that there are approximately 160 "oncology pharmacies" in the country, with the majority operating in the private sector. Notably, the SAPC does recognise certain specialised pharmacist types, such as radiation pharmacists; however, despite the larger number of oncology pharmacists, they remain unregulated. Under the Pharmacy Act No. 53 of 1974. The SAPC is mandated to oversee the pharmacy profession and issue the Good Pharmacy Practice (GPP) guidelines, which set forth minimum standards and requirements for registered pharmacies. Although the GPP addresses oncology pharmacy, most oncology pharmacies currently fall outside its domain due to the abovementioned circumvention, and are consequently not legally considered to be pharmacies. Nonetheless, compounding ADs resides within the purview of pharmacists, raising questions as to why no concrete action has been taken to regulate the speciality, despite extensive evidence of health risks from exposure. Matters are further complicated by the fact that some oncology pharmacies do hold SAPC registration—but only as community or institutional pharmacies since there is no dedicated oncology pharmacy designation.

It is worth acknowledging that MCOs have, to an extent, stepped in by establishing guidelines and accreditation processes for unregistered private oncology pharmacies. During this study, however, it became obvious that certain pharmacies have either declined to adopt these guidelines or refused to implement them for reasons that remain unclear. It would appear that MCOs are unaware of this, ignorant about it, or tolerant of this defiance.

On a personal note, this research holds great significance to me as there are hundreds of pharmacists across South Africa who routinely handle ADs, the extent of which exposure remains uncertain and, arguably, underestimated. Individuals engaged in AD compounding may thus be at risk of serious health issues. To address these concerns, SPs must collaborate constructively and explore innovative strategies to reduce exposure to ADs, especially those entities capable of instigating legal or regulatory reforms.

Presentations arising from this research

1. Botha R, Nelson G, Brouwer D. Occupational exposure to antineoplastic drugs and the development of tailor-made risk control strategies for South African oncology pharmacies. South African Society of Medical Oncology (SASMO) conference, Durban International Convention Centre, Durban, South Africa; 6-18 November 2018 (oral presentation).

2. Botha R, Nelson G, Brouwer D. South African oncology pharmacy facilities and procedures: how do we compare to best practice? South African Society of Medical Oncology (SASMO) conference, Cape Town International Convention Centre, Cape Town, South Africa; 5-7 April 2024 (oral presentation).

Publications and other writings arising from this research

Peer-reviewed manuscripts

1. Botha R, Nelson G, Brouwer D. A pilot study of South African oncology pharmacy facilities: comparison with best practice guidelines. *Europ J of Oncol Pharm,* 2024; 7(3): 1-5. doi: 10.1097/OP9.0000000000000056.

2. Botha R, Brouwer D, Nelson G. A critical appraisal of South African oncology pharmacy guidelines and legislation compared to international benchmark guidelines. *J Oncol Pharm Prac, 2024; 0(0). doi: 10.1177/10781552241289922.*

3. Botha R, Nelson G, Sessink P, Brouwer D. Assessing antineoplastic drug contamination in South African oncology pharmacies: workplace and biological monitoring. *J Oncol Pharm Prac, 2025; 0(0). doi: 10.1177/10781552251321150.*

4. Botha R, Nelson G, Brouwer D. Recommending tailor-made risk control strategies to mitigate dermal exposure to antineoplastic drugs in South African oncology pharmacies. *Submitted to Occupational Health Southern Africa, March 2025.*

Other writings

1. Botha R. Comment on good medicine manufacturing practice (GMCP). SAHPGL-INSP-07 Guideline for Good Medicine Compounding Practice (GMCP), Doc Number: OF-QA-09A. Published 6 June 2023. Authored on behalf of the South African Society of Oncology Pharmacists (SASOPh).

2. Botha R. Response to BN 480 of 2023 'Rules relating to good pharmacy practice' *Government Gazette, 29 September 2023,* Authored on behalf of the South African Society of Oncology Pharmacists (SASOPh).

Abstract

Background

Occupational exposure to antineoplastic drugs (ADs) poses significant health risks, with oncology pharmacy personnel in South Africa potentially experiencing higher and more exposure than their international counterparts due to insufficient regulatory frameworks and poor compliance with guidelines. Given the anticipated rise in cancer incidence in sub-Saharan Africa by 2030, addressing these occupational risks has become increasingly critical. Current South African guidelines exhibit notable inadequacies and contradictions with key legislative documents, and empirical evidence on workplace and biological contamination within local oncology pharmacies remains absent.

The aim of this research was to assess occupational exposure risks to ADs among oncology pharmacy personnel in South Africa and, subsequently, develop tailored risk control strategies (TMRCS).

The study objectives were:

1. To evaluate the adherence of South African oncology pharmacy personnel to national and international guidelines via observational surveys.
2. To identify shortfalls through a comparative analysis of local guidelines, the Good Pharmacy Practice (GPP) and Independent Clinical Oncology Network (ICON) guidelines, against international benchmarks.
3. To investigate demographic and occupational factors influencing workplace and biological contamination, using surface wipe sampling, biological monitoring (urine analysis), and the semi-quantitative DeRmal Exposure Assessment Method (DREAM).
4. To develop TMRCS based on identified compliance shortcomings and AD contamination as measured in the participating oncology pharmacies.

Methods

Oncology pharmacies were recruited for participation in the study, through the South African Society of Oncology Pharmacists (SASOPh) from March to September 2023. The pharmacies originated from two service providers (SPs): SP1 and SP2. Study methods included:

- Observational cross-sectional surveys using a 43-item compliance checklist derived from international guidelines.
- Comparative document analysis evaluating GPP and ICON standards against the International Society of Oncology Pharmacy Practitioners (ISOPP) 'Safe handling of cytotoxics guideline and the European Society of Oncology Pharmacy (ESOP) 'QuaPos' (Quality Standard for the Oncology Pharmacy Service) across 10 safety domains.
- Surface wipe sampling for nine ADs pre- and post-decontamination, and urine sampling to determine occupational exposure to the same ADs.
- Synthesis of findings into practical, evidence-based interventions, using a structured performance table.

In these studies, oncology pharmacy practices were systematically evaluated by converting checklist scores to compliance percentages and comparing them against international standards, while HPLC-MS/MS quantified antineoplastic drug contamination from surface wipes and urine. Descriptive and inferential statistics—including regression imputation, t-tests, Wilcoxon tests, and Spearman correlations—assessed decontamination efficacy and exposure risk associations.

Results

Recruitment proved challenging, resulting in the enrolment of only six pharmacies (three each in Gauteng and Western Cape provinces). Six pharmacy personnel participated (mean age: 51.1 ± 6.7 years; mean employment duration: 11.7 ± 5.7 years; mean daily AD exposure: 6.0 ± 1.8 hours). Observational surveys indicated checklist compliance variability of 33.1%–79.3% within the 10 domains used in a previous study, with notable deficiencies in engineering controls and medical monitoring. Pharmacies within service provider 2 (SP 2) exhibited better

adherence, particularly concerning personal protective equipment (PPE) and administrative practices.

The document analysis revealed that there are substantial inadequacies within the GPP guidelines compared to the more comprehensive ICON, ISOPP, and QuaPos standards. Workplace sampling confirmed widespread AD contamination, with higher contamination in SP1 facilities. Antineoplastic concentrations post-decontamination showed only a modest 17.4% reduction. Biological monitoring detected cyclophosphamide and ifosphamide in urine samples from SP1 personnel, confirming occupational exposure.

Based on the findings from the first three objectives, interventions to reduce exposure to ADs were identified. These prioritised improved decontamination protocols, mandatory PPE usage, and comprehensive staff training. Closed-system transfer devices (CSTDs) were identified as beneficial adjuncts rather than standalone measures.

Conclusion

The findings from this research underline the critical need for improved regulatory standards and compliance enforcement within South African oncology pharmacies. Enhanced guidelines, compulsory PPE protocols, regular training, and effective decontamination methods are essential to mitigate occupational exposure. Facilities demonstrating higher compliance with best practices provide practical models for national improvement, informing policy advocacy for robust occupational health safeguards and patient safety assurances.

Keywords: antineoplastic drugs, oncology pharmacy, occupational exposure, contamination, best practice guidelines, biological monitoring, safety standards, South Africa

List of abbreviations and acronyms

AD	Antineoplastic drug
ASHP	American Society of Health-system Pharmacists
BSC	Biological safety cabinet
CDC	Centres for Disease Control and Prevention
CPD	Continuous professional development
C-PEC	Containment primary engineering control
CSTD	Closed-system transfer device
DREAM	Dermal exposure assessment method
ECS	Exposure Control Sweden
ESOP	European Society of Oncology Pharmacists
HD	Hazardous drug
GPP	Good pharmacy practice
ISOPP	International Society of Oncology Pharmacy Practitioners
ICON	Independent Clinical Oncology Network
LFT	Liver function test
LMIC	Lower- middle-income country
LOD	Limit of detection
MCO	Managed care organisation
NIOSH	National Institute for Occupational Safety and Health
OEL	Occupational exposure limit
OHSA	Occupational Health and Safety Act
PPE	Personal protective equipment
QuaPos	Quality Standard for Oncology Pharmacy Service
SAOC	South African Oncology Consortium
SAPC	South African Pharmacy Council
SASCRO	South African Society of Clinical and Radiation Oncology
SASMO	South African Society of Medical Oncology
SDS	Safety and data sheet
SOP	Standard operating procedure
SP	Service provider
TMRCS	Tailor-make risk control strategy
USP	United States Pharmacopoeia
WTS	Walk-through survey

Glossary

Antineoplastic drug: A schedule 4 (chemotherapeutic) substance that slows or terminates the proliferation of neoplastic cells (cancer cells). Also known as cytostatics, chemotherapy, chemo, antiblastic or antineoplastic medications.

Containment-primary engineering control: A vertical airflow, HEPA filtration biological safety cabinet that ensures the microbiological inertness of a parenteral preparation and protection of the operator from anti-neoplastic drugs.

'**De-facto' pharmacy**: An establishment that is not registered in terms of the Pharmacy Act (53 of 1974) where the reconstitution/compounding/add-mixture of anti-neoplastic drugs occur, usually situated in a doctors' practice. Also known as an oncology pharmacy.

Dispensing phase: The minimum requirements as set out by the South African Pharmacy Council (SAPC) for the dispensing of medicine of scheduled substances on the prescription of an authorised prescriber in a registered pharmacy.

Managed care organisation: A provider network of doctors, other related healthcare professionals and facilities to which oncology services are rendered by using standard treatment protocols with an emphasis on effective care.

Oncology pharmacy: A broad term used to describe a pharmacy (that may, or may not be registered as a pharmacy in terms of the Pharmacy Act) that is, to a large extent, concerned with the compounding, preparation and mixing of parenteral antineoplastic medications.

Parenteral administration: The administration of medications by a non-oral route (usually by injection) into a vein, muscle, sub-cutaneous or a cavity like the cerebral-spinal or peritoneal cavity.

Pharmacist: A person registered with the South African Pharmacy Council to perform certain duties under terms of the Pharmacy Act (53 of 1974).

Pharmacy-related personnel: A group of persons who are directly in contact with antineoplastic drugs but are not necessarily legal persons in terms of the Pharmacy Act (53 of 1974). Persons include Receiving staff, clerks and cleaners.

Preparation or compounding of anti-neoplastic drugs: The reconstitution and/or dilution of antineoplastic drugs in a suitable container for patient administration, in normal saline or glucose 5% bags, or in a syringe.

Registered pharmacy: A pharmacy premises that is registered in terms of the Pharmacy Act (53 of 1974). Registration is compulsory for the lawful practice of pharmacy and the dispensing of medicines, with relevant regulations regarding the storage, handling, and dispensing of medicines.

Service provider: A business entity owning oncology pharmacies in a group that is responsible for the employment of subordinate pharmacy-related staff and the provision of un-reconstituted anti-neoplastic drugs to the medical oncology facility.

Tailor-made risk control strategy (TMRCS): A strategy to customise risk management practices to fit the specific needs, context, and characteristics of an organisation or project.

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CHAPTER 1: INTRODUCTION

Antineoplastic drugs (ADs) have played a pivotal role in the treatment of cancer since their initial development in the mid-20th century. Early research on mustard gas analogues (used in the Second World War) led to the first cytotoxic chemotherapy agents, which targeted rapidly dividing cells. Over subsequent decades, advancements in molecular biology facilitated the emergence of novel ADs, including targeted therapies and immunotherapies, significantly improving clinical outcomes. These developments spurred the growth of oncology pharmacy as a specialised field, encompassing not only the compounding and dispensing of hazardous agents but also the establishment of rigorous safety protocols to protect both patients and pharmacy personnel.

Despite the existence of international guidelines—such as those from the International Society of Oncology Pharmacy Practitioners (ISOPP) and the European Society of Oncology Pharmacy (ESOP)—the implementation of best practices varies globally. In South Africa, oncology pharmacy has evolved in a complex private sector environment that often operates under outdated or incomplete local regulations. The sections that follow outline the South African oncology pharmacy environment, discuss the primary pharmacy SPs and societies, describe the roles of managed care organisations, and review the Occupational Health and Safety Act, all of which shape the practice of oncology pharmacy in the country.

1.1. Oncology pharmacy in South Africa

The private oncology pharmacy sector in South Africa is characterised by a diverse array of facilities—ranging from small clinics to large hospital-based units—that provide chemotherapy services to insured patients. Unlike many high-income countries, where oncology pharmacy is well-defined and rigorously regulated, South Africa's private sector faces notable gaps in regulatory oversight. Currently, the South African Pharmacy Council (SAPC) does not offer specialist registration for oncology pharmacists, and Good Pharmacy Practice (GPP) guidelines devote only limited attention to antineoplastic drug handling.



Figure 1. A Containment-primary engineering control (C-PEC), otherwise known as a vertical airflow HEPA filtration laminar flow unit or biological safety cabinet (BSC) where antineoplastic drugs are typically compounded

The local supply chain for ADs is multifaceted. Some oncology pharmacies are fully registered with the SAPC, whereas many operate as “de facto” oncology pharmacies in oncologists’ practices or infusion lounges not formally recognised as pharmacy premises. In these unregistered settings, antineoplastic drugs are often prepared by nursing staff, a practice at odds with international best practice guidelines. The resulting variability in training and infrastructure can increase the risk of occupational exposure to ADs for personnel, especially when engineering controls (Figure 1) or continuous medical surveillance are lacking.

1.2. Pharmacy service providers and societies

Several service providers (SPs) and societies shape oncology pharmacies in South Africa. Pharmacy SPs facilitate the procurement and distribution of antineoplastic agents, often navigating complex contractual arrangements with private healthcare providers. The SPs typically supply un-compounded ADs to oncology facilities, where final preparation (reconstitution and compounding) occurs (Figure 2).

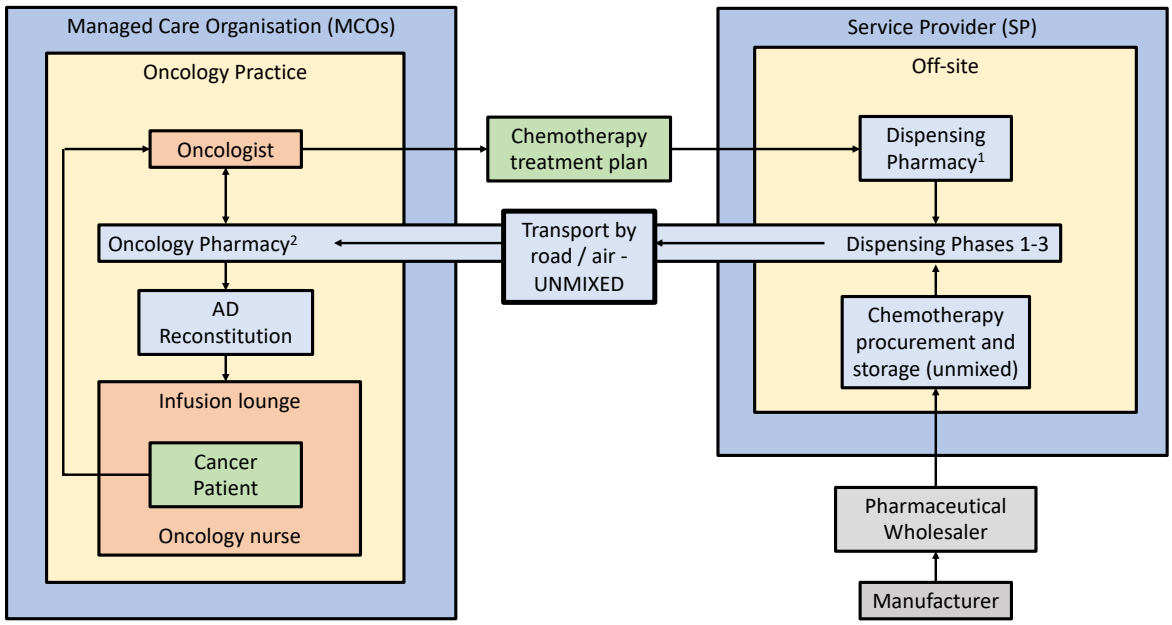


Figure 2.. Anti-neoplastic drug supply chain

[1] The dispensing pharmacy (off-site) is a registered pharmacy with SAPC where unmixed ADs are dispensed.

[2] The 'on-site' oncology pharmacy (not required to register with the SAPC, where the ADs are mixed for patients)

Professional societies also influence standards and practices. The South African Society of Oncology Pharmacists (SASOPh) is a voluntary organisation that provides a platform for education, networking, and advocacy, though membership remains limited. SASOPh encourages adherence to international guidelines—such as ISOPP's 'Safe Handling of Cytotoxics' and ESOP's 'Quality Standard for the Oncology Pharmacy Service' (QuaPos)—in the absence of robust local regulations. Other pharmacy associations, including those representing hospital or community pharmacists, may address oncology-related topics but generally do not offer specialised training in antineoplastic handling.

1.3. Managed care organisations

Managed care organisations (MCOs) play a pivotal role in standardising oncology care within the private sector. Two major entities—the Independent Clinical Oncology Network (ICON) and the South African Oncology Consortium (SAOC)—oversee clinical protocols, reimbursement structures, and quality assurance for oncology services. Both require affiliated oncology practices to adhere to their guidelines for treatment regimens, documentation, and facility accreditation. Independent Clinical Oncology Network (ICON) publishes a set of guidelines aimed at chemotherapy administration, focusing on reducing medication errors, ensuring the safe handling of ADs, and promoting cost-effective practices. Although these guidelines reference essential pharmacy functions (e.g. mixing, labelling, and transport of ADs), they often frame the compounding role as a nursing responsibility. The lack of explicit, detailed pharmacy-specific requirements leaves gaps in practice oversight, especially concerning workplace monitoring and continuous staff education. The South African Oncology Consortium (SAOC) similarly accredits oncology units and standardises treatment protocols. However, its guidelines for AD handling are not publicly available, and there is limited transparency regarding the specific requirements for pharmacy operations. This can perpetuate inconsistencies in how ADs are prepared and how occupational risks are managed across different facilities. Given that MCOs essentially control access to private health funding, their guidelines and accreditation standards have a substantial impact on oncology pharmacy practice. Nonetheless, neither ICON or possibly SAOC (guidelines are unavailable) currently provides comprehensive oncology pharmacy regulations that match the level of detail found in international standards (ISOPP or QuaPos).

1.4. The Occupational Health and Safety Act

South Africa's Occupational Health and Safety Act (Act No. 85 of 1993) mandates employers to ensure the well-being of workers exposed to potentially hazardous substances. This legislation places responsibility on employers to conduct risk assessments, implement control measures, and provide training to mitigate occupational hazards. In principle, the Act covers individuals handling antineoplastic drugs. However, effective enforcement of its provisions within oncology pharmacies has been uneven.

The Act requires measures such as engineering controls (e.g. biological safety cabinets or a C-PEC), administrative controls (e.g. standard operating procedures, training, job rotation), and personal protective equipment (PPE) to be in place where workers handle hazardous substances. While some large oncology centres invest in state-of-the-art facilities to comply with these legal requirements, smaller or unregistered facilities often lack robust engineering controls and formal safety protocols. Consequently, the level of compliance varies widely, raising concerns about staff exposure and potential health risks.

1.5. Problem statement

It is probable that within the profession of pharmacy in South Africa, no other group of personnel faces a greater occupational risk than those exposed to ADs, since exposure to ADs could lead to serious health effects. The South African guidelines related to pharmacy oncology practices (like the GPP) lack detail compared to those in Europe, America and Asia. The local antineoplastic supply chain is complex, and the risks in South African oncology pharmacies have not been well-described or established.

1.6. Justification

Numerous persons are involved in the supply chain of antineoplastic drugs. Consideration needs to be given to questionable, inadequate and outdated local guidelines and risk control strategies. This study identified potential risks in pharmacies to propose risk control strategies to reduce occupational health risks of pharmacy-related personnel, in consultation with pharmacy SPs. The findings of the study can be used to reform policies, guidelines and monitoring of regulations related to the handling of ADs, and to create awareness amongst pharmacy-related personnel to the extent of occupational health risks related to exposure to ADs. Broadly, the study could promote the advancement of oncology pharmacy in South Africa.

1.7. Study aims and objectives

Aim

To reduce the risk of exposure of pharmacy personnel by identifying alternatives, developing risk control strategies and promoting the advancement of oncology pharmacy in South Africa.

Objectives

- To describe adherence of SA oncology pharmacy facilities and procedures in the supply chain to international and national guidelines.
- To conduct a literature review comparing international to national guidelines and acts to identify shortfalls.
- To identify demographic and work-related factors associated with urine and workplace antineoplastic drug concentrations, e.g. age, sex, job description, pharmacy location, and work practices).
- To develop tailor-made risk exposure control strategies (TMRCS).

Table 1. Summary of objectives, study population, methods, and outcomes

Objective	Adherence to guidelines	Appraisal of guidelines	Potential for exposure to ADs	Recommendations for exposure control
Population	SP1/SP2 Pharmacies (n=6)	ISOPP, QuaPos, GPP, ICON	-	-
Methods	Observational study: work practices, scoring of adherence	Review	Field study, measurement campaign	Identification of intervention options, compilation of performance table interventions
Outcome	Potential skin exposure, ranking according to adherence	Ranking guidelines, completeness and adequacy	Surface contamination of ADs, biological contamination with ADs	Tailor-made recommendations

AD: Antineoplastic drug, GPP: Good Pharmacy Practice, ICON: Independent Clinical Oncology Network, ISOPP: International Society of Oncology Pharmacy Practitioners, SP: Service provider.

1.8. Conceptual framework

The conceptual framework (Figure 3) for this thesis was developed through an integration of the study's objectives, methodologies, and anticipated outcomes, guided by existing international standards and local contexts. Initially, an extensive literature review provided insight into international oncology pharmacy practices, highlighting best practice guidelines (ISOPP, QuaPos), against which South African guidelines (GPP, ICON) were critically appraised. Subsequently, observational data pinpointed gaps in guideline adherence within local oncology pharmacies. Empirical evidence gathered through workplace and biological contamination assessments—surface contamination measurements, biological monitoring via urine analysis, and the DeRmal Exposure Assessment Method (DREAM)—established baseline contamination levels and potential occupational risks. Finally, these findings informed the formulation of tailor-made risk control strategies (TMRCS).

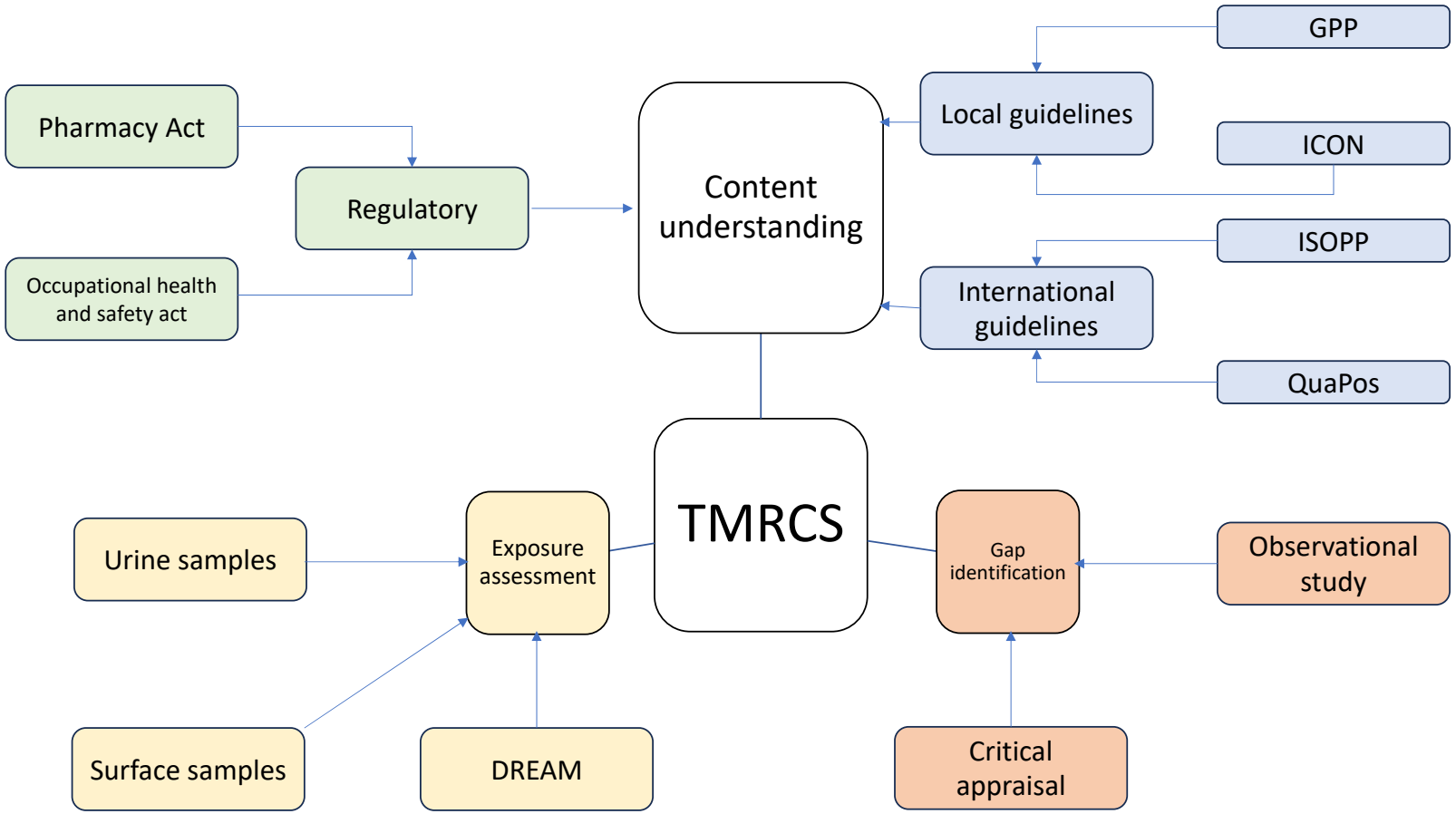


Figure 3. Conceptual framework

GPP: Good Pharmacy Practice, DREAM: Dermal exposure assessment method, ICON: Independent Clinical Oncology Network, ISOPP: International Society of Oncology Pharmacy Practitioners, QuaPos: Quality Standard for the Oncology Pharmacy Service, TMRCS: Tailor-made risk control strategy

CHAPTER 2: LITERATURE REVIEW

2.1. Background

Significant occupational health risks for personnel involved in the preparation and handling of antineoplastic drugs (ADs) have been well demonstrated, and numerous studies describing workplace contamination of antineoplastic drugs have been published.[1-12] Antineoplastic drugs (also called cytostatic or cytotoxic drugs, or simply 'chemo') have been in use for decades in the fight against cancer and some rheumatoid conditions, and today there are hundreds of antineoplastic drugs in clinical use.[13, 14]

Except for a few, the vast majority of ADs in use today are classified by the Centre for Disease Control's (CDC) National Institute for Occupational Safety and Health (NIOSH) as hazardous drugs (HDs).[15] HDs are defined as those being genotoxic, carcinogenic, teratogenic, exhibiting reproductive and organ toxicity at low doses, or any combination of these.[16]

The administration of antineoplastic drugs is usually via parenteral routes (intravenous, intraperitoneal, subcutaneous or intrathecally) and the pharmaceutical formulation of antineoplastic drugs is therefore mostly a solution or powder for reconstitution and then, injection.[17] Because of the pharmaceutical formulation, during preparation before administration to a patient, workplace contamination arises mainly due to the occurrence of droplets, aerosols and/or vapours which, in turn, are mostly absorbed dermally, but also orally or via inhalation. In addition to this, it has been shown that vials containing antineoplastic drugs are also contaminated on the outside of the vial, also placing personnel not involved in preparation at higher risk. [18, 19]

Antineoplastic drugs are severely myelosuppressive and thus, aseptic procedures, which involve the use of containment primary-engineering controls (C-PECs), should be used by qualified pharmacy-related personnel during the preparation of ADs to protect already immunosuppressed patients from microbial contamination and also personnel from exposure to ADs. [3, 20]

2.2. Role of the oncology pharmacist and the burden of cancer

The role of the oncology pharmacist is indispensable in today's clinical oncology environment, and safe work practices are paramount.[21-26] However, in a survey conducted by von Grunigen et al. (2022) a wide variability and major gaps in safe work practices were identified in oncology pharmacies in low- and middle-income (LMIC) countries, including a pharmacy in South Africa.[27] In this study, it is also demonstrated that upper-middle-income countries performed generally better than LMICs. Considerable variation in the content and scope of safe handling guidelines and pharmacy practices was however also observed in a global study representing 24 mainly developed countries which included the United States, Canada, United Kingdom, continental Europe, Japan and Australia.[28]

It is anticipated that the incidence of cancer is set to surge by 70% by 2030 in sub-Saharan Africa, which will, in turn, increase the need for oncology pharmacy services, and it is reported that there will be a shortage of oncology pharmacists shortly.[29, 30] According to the South African Society of Oncology Pharmacists (SASOPh), there are approximately 160 private outpatient facilities in the private sector where ADs are administered. However, there are only 11 such facilities available in the public sector. These facilities need to be staffed by competent oncology pharmacists however, there is currently no official training course for oncology pharmacists in South Africa.[31] The ever-increasing need for an oncology pharmacist is confirmed in a recent study in the United States which recommends the role of the oncology pharmacist be more extensively incorporated into multi-disciplinary teams in the management of cancer care.[25]

In a recent local study by Khan et al. (2022), fourth-year pharmacy students at the University of the Witwatersrand, Johannesburg, were exposed to simulation-based oncology admixing training with favourable results obtained from a questionnaire about the simulation-based experience[31]. This was the first time undergraduate pharmacy students were introduced to an oncology pharmacy environment. In another local study by Keetle (2015) it was found that there is a definite role for the public sector oncology pharmacist exists in South Africa.[24] It must be emphasised that this study was only conducted at pharmacies in the public sector in South Africa and findings at private sector pharmacies could be different.

2.3. Occupational exposure to antineoplastic drugs

Occupational exposure to ADs in oncology pharmacies predominantly occurs during the compounding phase, where ADs are most likely aerosolised, vaporised, or form droplets. This significantly elevated concentrations in the workplace environment, thereby increasing the risk of direct and indirect contamination. Dermal contact is recognised as the primary route of occupational exposure, driven by direct skin deposition and subsequent transfer from contaminated surfaces. Determinants of exposure and the exposure pathway refer to factors that influence the magnitude, frequency, duration, and route of contact between a chemical and receptor (like the stratum corneum).

The conceptual model by Schneider et al. (2000) provides a robust framework to understand the mechanisms involved in dermal exposure.[32, 33] According to this model, exposure occurs via a series of interconnected compartments and transport processes. These compartments include the contaminant source (e.g. drug vials), the air compartment, surfaces, clothing layers, and the skin contaminant layer itself. The movement of contaminants across these compartments is governed by processes such as emission (e.g. splashing, aerosolization), deposition (from air to surfaces and skin), resuspension or evaporation, direct transfer (contact between contaminated surfaces and skin), and penetration or permeation through barriers like protective clothing and the skin's stratum corneum.

Schneider's model highlights that the risk from dermal exposure is directly related to the concentration gradient of contaminants on the skin surface, driving absorption through the stratum corneum into the body. The complexity of assessing dermal exposure arises from the variability in these transport processes, the physicochemical characteristics of the contaminants, and the differing absorption rates through the skin. Consequently, traditional sampling methods—such as surface wipes and biological monitoring—must be interpreted cautiously, acknowledging that they measure contamination rather than direct uptake.

The number of antineoplastic drugs and the number of pharmacy-related personnel occupationally exposed to antineoplastic drugs are steadily increasing as more patients are diagnosed with cancer every year.[16]

2.4. Workplace and biological contamination of antineoplastic drugs in oncology pharmacies

Falck et al. (1979) were the first to demonstrate high levels of mutagenic substances in the urine of nursing personnel involved in the preparation of ADs compared to their non-exposed peers.[34-36] Many studies have since been published describing the adverse effects of occupational exposure of pharmacy-related personnel exposed to antineoplastic drugs.[37-49] Chromosomal aberrations, sister chromatid exchanges and other genetic abnormalities were detected in subsequent studies involving not only nursing personnel but also pharmacy-related personnel. Adverse health effects range from minor to severe and include new tumours, leukaemia, congenital malformations of children born to exposed personnel, foetal loss, infertility, ectopic pregnancies, low birth weight, skin rashes, and other effects on body tissues with rapidly dividing cells (e.g. gastrointestinal tract, hair, nails).[39, 50-59]

Apart from this, studies demonstrating contamination with ADs in hospital pharmacy environments are well-established and have been comprehensively discussed in the literature.[60-88] The need for bio-monitoring and surface wipe contamination monitoring has been emphasised numerous times and is an ongoing matter in the oncology pharmacy fraternity.[49, 85, 89] However, monitoring for ADs is expensive and has never been performed before in South Africa. Recently, modern technologies like closed-system transfer devices (CSTDs), which are designed specifically to contain antineoplastic drugs during mixing and preparation, have demonstrated positive results, but this technology only provides limited protection as contamination was still detected despite its use.[90-95]

It is not possible to set an occupational exposure limit (OEL) for an oncology pharmacy environment because current OELs are based in an environment at a manufacturing plant recorded in an SDS.[10, 96-98] Exposure of antineoplastic drugs to personnel in the oncology pharmacy must thus be kept as low as reasonably possible (ALARA).[44]

2.5. Development of oncology pharmacy safety guidelines

Davis et al. (2011) provide a concise, elegant overview of the development of oncology pharmacy from 1985 to the present and emphasise the need for continuous occupational monitoring and development.[99] In 1986, the American Society of Hospital Pharmacists (ASHP) published the 'Guidelines for Handling Cytotoxic Drugs' for the preparation of ADs. Today, there are numerous comprehensive international publications with guidelines aimed at reducing the occupational risk emanating from exposure to ADs and also improving pharmaceutical services in preparing antineoplastic drugs. These guidelines include, but are not limited to:

- ISOPP 'Safe handling of cytotoxics' – first published in 2007[100]
- QuaPos 6 (Quality standard for the oncology pharmacy service) – first published in 2010[101]
- USP Chapter 800 – updated 2019[102]
- The American Society of Clinical Oncology (ASCO) – published 2011[103]
- The American Society of Health-system Pharmacists (ASHP) – first published in 1986[104]
- The NIOSH Alert – published 2004[15]

Implementation of these guidelines which include standard operating procedures (SOPs), the implementation of techniques designed to contain antineoplastic drugs effectively, the use of engineering controls, training of personnel and the wearing of personal protection equipment (PPE) has significantly reduced the level of exposure/uptake and occupational health risks to pharmacy-related personnel to ADs. However, the development of guidelines is an ongoing process and in addition to the mentioned guidelines, there have been several publications extrapolating on these guidelines.[105, 99] Many developed nations have drafted their guidelines, based on these accepted and comprehensive international guidelines, and enforce them as national law. However, despite the implementation of national guidelines, antineoplastic drugs are still detected in both the urine of healthcare workers and their work environments.[106]

Kennedy et al. (2023) make several recommendations in response to being compliant with the latest National Association of Pharmacy Regulatory Authority (NAPRA) requirements.[107] This includes 1) the establishment of an institutional committee responsible for policies and procedures, 2) continuing education and training, 3) updates on new recommendations for the

use of PPE, 4) receiving, unpacking, storage and transport, 5) planning the oncology pharmacy, 6) AD preparation (compounding), 7) management of waste, 8) accidental exposure and spills, 9) cleaning and decontamination procedures and 10) medical surveillance and workplace monitoring. Publications by Easty et al. (2015) and Green et al. (2009) address similar recommendations.[108, 109] In a survey by Mathias et al. (2019) of guidelines and current practices for safe handling of mainly developed countries, it was found that there was considerable variation in the content and scope of safe handling guidelines.[28] This is confirmed in a study by von Grunigen et al. (2022), where safe handling practices were evaluated in LMICs.[27] Considerable variation was found, and upper-middle-income countries (including South Africa) consistently performed better than low-income countries.

Several studies recommend that women who could be pregnant, and who are actively trying to conceive or breastfeeding should be excluded from all AD compounding.[110-112]

Fazel et al. (2022) evaluated barriers and facilitators for safe handling.[113] The most common barriers identified included 1) poor training, 2) poor workplace safety culture and 3) inconsistent policies. Facilitators included 1) adequate safety training, 2) leadership support and 3) consistent policies. In the study, it is recommended that healthcare employers mitigate these barriers by implementing small but meaningful changes to the workplace. In a study by Simegn et al. (2023), it was found that AD handling at a university hospital in Ethiopia was poor and the desirable attitude of health staff toward the handling of ADs was low.[114]

2.6. The Good Pharmacy Practice Guideline

The South African Pharmacy Council (SAPC) is the legal authority of the profession of pharmacy and pharmacy-related personnel, and publishes guidelines detailing the required guidelines of pharmacy practice in South Africa. The Good Pharmacy Practice (GPP)[115] guidelines published in 2010 outline requirements specific to the compounding (Section 2.17.3) of ADs in South Africa. However, some of the statements in the GPP can be considered incorrect. Section 2.17.3(a) erroneously states that 'no adequate means of monitoring or measuring inadvertent absorption have been devised. Other questionable recommendations are made, like the donning of plain latex gloves, which have been proven to offer inferior protection. Some

statements on the preparation and mixing of antineoplastic drugs in the GPP guidelines are non-specific and are not comparable in light of prevailing literature. The GPP guidelines do not provide in-depth specific training requirements and also do not detail the facility design, engineering controls, work arrangements, personal protective equipment (PPE) and occupational hygiene.

It must, however, be borne in mind that the GPP is a general document discussing all aspects of pharmacy practice in South Africa and is not specifically intended as a standard for AD preparation exclusively. Section 2.17.3 of the GPP also stipulates that pharmacies, where ADs are compounded, must develop their own SOPs for the compounding of ADs. The application of GPP in pharmacies in South Africa is limited to facilities which are registered as pharmacies in terms of the Pharmacy Act (53 of 1974). This is of significant relevance as the compounding of ADs is not necessarily performed in registered pharmacies, and thus, GPP is not necessarily enforced (Figure 2).

2.7. Managed care organisation guidelines

In the private sector, the ICON 'chemotherapy administration guidelines and guidelines resource document' aims to reduce the occurrence of errors and improve safety outcomes.[116] The guideline offers a comprehensive overview of oncology practice in the private sector in South Africa. It describes the role of the oncologist, oncology nurse and oncology pharmacist, and it elaborates on the competencies, necessary skills and training of these staff members. The document discusses the compounding of ADs, which includes preparation of ADs, recommended use of personal protective equipment (PPE), reconstitution, labelling, issuing, transport of ADs and record keeping. The South African Oncology Consortium (SAOC) guidelines are not publicly available and thus could not be assessed.

2.8. Summary of literature reviewed

The reviewed literature highlights the significant occupational health risks posed by ADs, primarily to pharmacy-related personnel during preparation and handling. Antineoplastic drugs, classified as hazardous drugs by NIOSH, are genotoxic, carcinogenic, and teratogenic, requiring stringent handling procedures. Workplace contamination arises from AD formulations, often as droplets, aerosols, or vapours. Studies demonstrate that even CSTDs and robotic technologies cannot completely eliminate contamination. Occupational exposure has been linked to severe health issues, including chromosomal abnormalities and cancers. Monitoring such contamination remains expensive and has never been implemented in South Africa. Globally, guidelines such as ISOPP, USP Chapter 800, and NIOSH guidelines aim to mitigate risks. However, their implementation varies, particularly in LMIC, where safety practices often fall short due to limited resources and training. In South Africa, the GPP guidelines provide a framework but lack specificity and enforceability, particularly in non-registered facilities. With cancer rates projected to surge, the role of oncology pharmacists is critical, but the lack of formal training programmes and disparities in practice remain key challenges. Continuous development of safety guidelines and occupational monitoring is imperative.

CHAPTER 3: METHODS

3.1. Introduction

The methodology for each objective is summarised in Table 2. This includes objective 1, the observational study, objective 2, the critical appraisal of guidelines, objective 3, the findings of the workplace surface contamination and exposure to ADs, and the development of a performance table to evaluate the best suitable intervention for pharmacies.

3.2. Study design

This study primarily employed a cross-sectional design (for objectives 1 and 3) and involved a critical appraisal of guidelines. The study comprised both qualitative and quantitative methods.

3.3. Study sites

The study was conducted in six oncology pharmacies, three from each of the two service providers (SPs) in the private sector. in South Africa. SP1's pharmacies were in Pretoria, and SP2's pharmacies were in Cape Town. The participation of pharmacies in SP2 (three of the six) was decided on by the SP without an explanation regarding the selection. All three pharmacies from SP1 participated.

3.4. Study population

The selection of pharmacy-related personnel was based on their function in the pharmacy which must include the mixing, compounding or preparation of ADs. In each pharmacy, there was one participant. There were no specific qualification criteria, and participants could be pharmacists or registered nurses. Participants were recruited from a list of 43 oncology pharmacy personnel provided by the South African Society of Oncology Pharmacy Practitioners

(SASOPh). Despite 18 personnel agreeing to participate, SP restrictions resulted in the inclusion of only six pharmacies.

3.5. Data collection

3.5.1. Observational study

This cross-sectional pilot study was designed to evaluate the oncology pharmacy facilities. The study evaluated six oncology pharmacy facilities operated by two SPs in South Africa against international best practice guidelines. A checklist was developed based on ISOPP and the QuaPos guidelines, encompassing seven assessment categories: engineering controls, administrative controls, personal protective equipment (PPE), education and training, medical and workplace monitoring, cleaning procedures and waste handling, and spills and accidents. Each category contained 4–8 items rated as non-compliant (0), partially compliant (3), or fully compliant (10). This is described in more detail in the first of the series of three papers written as part of this PhD.

Data collection involved workplace observations, document reviews, and personnel interviews conducted between March and September 2023. Compliance (or adherence to recommendations) was categorised as full (>75%), partial (50–75%), or non-compliant (<50%). Descriptive statistics were applied using Microsoft Excel to calculate category-specific and overall compliance scores.

3.5.2. Critical appraisal of guidelines

This study critically evaluated the effectiveness of South African oncology pharmacy guidelines against international best practices. The GPP guidelines and ICON guidelines were compared with the ISOPP and the QuaPos guidelines. The assessment framework focused on ten oncology pharmacy domains: transport of ADs, working arrangements, education and training, engineering controls, PPE, risk management, medical monitoring, cleaning procedures, spill and accident management, and documentation.

The review methodology involved a comprehensive analysis of the content and structure of the guidelines. This entailed identifying and mapping each domain across the guidelines to evaluate their scope, specificity, and alignment with international benchmarks. Documents were examined for clarity, consistency, and the presence of actionable protocols.

The selection of ISOPP and QuaPos guidelines as benchmarks were based on their global recognition, detailed guidelines specific to oncology pharmacy and recognised by SASOPh. The analysis aimed to identify gaps, contradictions, and areas requiring enhancement within the South African guidelines to align with international best practices. This critical appraisal sought to provide a foundation for future revisions and the development of robust oncology pharmacy practice guidelines.

3.5.3. Potential for dermal exposure

Antineoplastic drug contamination of nine surfaces was assessed using wipes, as described by Botha et al. (2024), the third in a series of papers published as part of this PhD. For each surface, samples were collected at three time points: before cleaning (pre-decontamination), immediately after the pharmacy's routine cleaning procedure (post-decontamination), and at the end of the workday (end-of-day). Surfaces included the surface inside the C-PEC, the floor beneath the unit, and the adjacent surface (next to the C-PEC) where reconstituted ADs are placed after reconstitution. The wipe samples measured the amount of cyclophosphamide (CP), ifosfamide (IF), methotrexate (MTX), 5-fluorouracil (5-FU), gemcitabine (GEM), paclitaxel (PAC), docetaxel (DOC), doxorubicin (DOX) and etoposide (ETO), some of the most commonly used antineoplastics. Surface wipes were collected following the specifications of Exposure Control Sweden (ECS – the contracted laboratory for analysis). A pre-packaged surface wipe sample kit was included and sent to the Netherlands according to ECS specifications. Samples were immediately frozen in a dedicated freezer. The surface wipe kits allow areas of 0.5 m^2 each to be recovered per sampling. Wipe sample collection areas were marked to sample the same area every time to enable consistent sample collection. Surface wipe samples were collected by the principal investigator. Any spills or accidents were recorded by pharmacy personnel. The pharmacy was photographed for reference. A sketch was made of the pharmacy floor layout. The analytical method used by the laboratory at Radboud University,

Nijmegen, the Netherlands is high-pressure liquid chromatography-tandem mass-spectrometry (HPLC-MS-MS) using specialised columns.

Urine samples are accepted matrices to determine the amount of uptake and excretion of antineoplastic drugs or their metabolites. Urine samples were collected by ECS specifications and were tested for the same ADs described in the surface contamination analysis. ECS provided pre-packaged urine sample collection kits for collection. Each urine sample kit contained 10 vacuum tubes, a measuring cup and a transfer device. Participants recorded the volume of urine passed each time, and a sample was taken by using the vacuum tube and transfer device where after the urine sample was frozen. Up to 10 urine samples could be collected over 24 hours by each participant. Samples were shipped overnight on dry ice via a courier company that complied with ECS requirements.

The DeRmal Exposure Assessment Method (DREAM) was used to estimate potential dermal exposure. This is a structured observational method consisting of an inventory and an evaluation component. The inventory component was completed by the researcher, involving a hierarchically structured questionnaire/list of observation items designed to assess determinants and routes of exposure. It is divided into six modules: company, department, agent, job, task, and exposure. Each response within the questionnaire is allocated a specific score. The results of the DREAM analysis were captured in a freely available Microsoft-Excel-based tool in the language, Visual Basic for Applications.[117] In the evaluation component of the DREAM, these scores were processed through a series of algorithms to generate indices of potential exposure, i.e. the amount of contaminant landing on the outer layer of work clothing, and actual exposure, i.e. the amount of contaminant reaching the exposed skin, and dermal exposure in arbitrary units (AU) for nine different body parts and at the task level. This approach enables the detailed characterisation of the agent, the probability and intensity of potential exposure, and the assessment of hygiene practices, including the use of PPE in the workplace.

3.5.4. Tailor-made risk control strategy

To develop a tailor-made risk control strategy (TMRCS), potential interventions were identified from previous studies. Interventions included: training on safe work practices, the use of AD-resistant PPE, improved surface decontamination procedures, i.e. an alternative decontamination agent to replace the current 70% ethanol, and the implementation of CSTDs. Four performance criteria were identified, which included cost and effectiveness (which are quantifiable). In contrast, the feasibility of implementation and worker acceptance were scored using a Likert scale ranging from 1(very low) to 10 (very high). The cost was quantified using data obtained from supplier quotations and by calculating additional labour (if applicable). This approach provided an estimate of the costs of implementing each intervention. The effectiveness of the interventions in terms of the reduction of the potential for dermal exposure values of the decontamination chemicals was extracted from the reviewed literature, using several observations-weighted mean. For papers where exact percentages of reduction were not available, the effectiveness was estimated based on descriptions such as "substantial improvement" or "statistical significance”. Feasibility and worker acceptance were evaluated using SP input from a panel of seven participants with practical experience or knowledge of oncology pharmacy practices. The results, either as mean or median and the minimum and maximum, were compiled in a performance table.

Table 2. Overview of study design, population and data collection tools per objective

Objective	Study design	Study population	Method/data collection tool(s)
1 – Adherence to guidelines	Cross-sectional observational study	Pharmacies, pharmacy personnel (participants)	Checklist
2 – Critical appraisal of guidelines	Literature review	N/A	Critical review
3 – Potential for exposure to ADs	Field study workplace contamination , biological monitoring and potential for skin exposure (Cross-sectional)	Pharmacies, pharmacy personnel (participants)	Urine and surface wipe sample, DREAM estimates
4 - Tailor-made risk control strategy	Desktop review	Pharmacies, Pharmacy personnel and SPs	Performance table

AD: Antineoplastic drug, DREAM: Dermal exposure assessment method, SP: Service Provider

3.6. Data analysis

3.6.1. Observational study

Data from facility observations, document reviews, and interviews were analysed to assess adherence to engineering controls, administrative controls, PPE usage, education, medical and workplace monitoring, cleaning and waste handling, and spills and accident management. Data analysis involved capturing responses from the seven-category checklist into Microsoft Excel. Descriptive statistics were applied to calculate each facility's category and overall compliance scores. Each category score was converted to a percentage, with compliance levels defined as: full compliance (>75%), partial compliance (50%–75%), and noncompliance (<50%), which

were set arbitrarily by expert opinion for evaluation purposes. Mean compliance scores were calculated for each category and compared between the two service providers.

3.6.2. Critical appraisal of guidelines

The data analysis involved critically evaluating South African oncology pharmacy guidelines (GPP and ICON) against international benchmarks (ISOPP and QuaPos) across 10 domains, including risk management, personal protective equipment, and medical monitoring. The analysis identified gaps, inconsistencies, and outdated practices in local guidelines, highlighting the need for updates to enhance safety and compliance with international best practices.

3.6.3. Potential for dermal exposure

Surface contamination data were analysed using the traffic light model of Sessink et al. (2023), indicating contamination levels based on national reference values for ADs. Categories included low (<0.1 ng/cm²), medium-low (0.1–<1.0 ng/cm²), medium-high (1.0–<10 ng/cm²), and high (≥10 ng/cm²).[118] Descriptive statistics combined pre-decontamination and end-of-day concentrations, considering the latter as pre-decontamination for the following day. Non-detect values were imputed using NDExpo, employing regression on order statistics (ROS).

The Wilcoxon signed rank test evaluated decontamination effectiveness on C-PEC and adjacent surface samples, while Spearman's rank correlation assessed relationships between DREAM estimates, observational study scores, and the number of 5-FU surface samples with concentrations ≥1 ng/cm². Statistical analysis utilised JASP (v0.18.3), with a significance threshold of $p < 0.05$.

3.6.4. Tailor-made risk control strategies

Firstly, the effectiveness of the interventions based on different outcomes, i.e. reduction of surface contamination for decontamination procedures and the use of CSTD, reduction of dermal exposure or training and adherence to safe work practice guidelines, were adjusted

according to their intervention position in the exposure pathway. The estimated adjustment factors were 0.6, 0.8, 0.9 and 1, for surface decontamination, PPE, training and CSTD, respectively. The effectiveness was adjusted to the position of the intervention in the exposure pathway (from source to receptor). For example, intervention at the source (directly reducing splashes to the skin, and spills to surfaces) were not adjusted. However, decontamination of surfaces (for example) as an intervention, was adjusted with a factor 0.6 based on expert opinion as the effectiveness of exposure (due to reduction of surface contamination) was more indirect. Next, the results (or performance) of all alternatives for the four criteria were normalised into a 0-1 range to allow for comparison. Finally, the weighted sum was calculated for each intervention of the four criteria.

3.7. Ethical considerations

The research protocol was submitted to the Human Research Ethics Committee for review. Before commencing the study, written consent to conduct research at participating pharmacies was obtained from the relevant SPs and personnel. All collected information was treated with strict confidentiality, and data collection only began once ethical approval had been granted. The research was approved unconditionally on 29 March 2019 – certificate no M190312.

Urine and surface wipe samples were collected exclusively after authorisation had been received from the appropriate SPs. Although there were no legally binding Occupational Exposure Limits (OELs) for ADs in pharmacy settings, pharmaceutical companies that manufactured the drugs under investigation published OELs in their respective Safety Data Sheets (SDS). Any participant who tested positive for any antineoplastic drug was advised to consult a medical oncologist, by the guidelines outlined in the manufacturer's SDS.

Photography of the pharmacy premises was undertaken only after written permission had been obtained from SPs, head pharmacists, and/or other relevant parties.

CHAPTER 4: RESULTS

4.1. Introduction

For the fulfilment of this PhD study, four papers were drafted and provided an overview of the results obtained. The published papers can be found in Appendices B-E.

4.2. Deficiencies in oncology pharmacy safety practices

This was a pilot study that evaluated compliance with international best practice guidelines of six South African oncology pharmacy facilities, using a seven-category checklist[119]. Facilities under SP1 averaged a compliance score of 40.2% (range: 33.1%–49.9%), while SP2 facilities averaged a score of 78.2% (range: 76.4%–79.3%). In the engineering controls category, compliance averaged 46.2% for SP1 and 61.0% for SP2. None of the facilities achieved full compliance. All facilities had containment primary engineering controls i.e. C-PECs, with service records and external extraction fans, but lacked pressure differentials and anterooms. Personal protective equipment compliance was 21.7% for SP1 and limited to latex gloves, while SP2 facilities achieved 88.3%, utilising chemotherapy-grade gloves, masks, and body coverings. Education and training scores differed significantly, averaging 47.1% for SP1 and 85.7% for SP2. Service provider 1 personnel lacked continuous professional development (CPD) participation and training records, while SP2 personnel had comprehensive training and professional affiliations. Medical and workplace monitoring was a poorly performing category, with SP1 scoring 0% and SP2 scoring 66.7%. No pharmacies conducted workplace monitoring, while only SP2 pharmacies performed medical monitoring. Cleaning and waste handling compliance averaged 70.0% for SP1 and 90.0% for SP2. Service provider 2 facilities consistently demonstrated cleaning schedules and proper waste-handling protocols. In the spills and accident management category, scores averaged 40.0% for SP1 and 86.0% for SP2. Documented procedures and corrective measures were lacking in SP1 facilities.

4.3. Misalignment between South African and international oncology pharmacy standards

The evaluation of South African oncology pharmacy guidelines highlighted significant gaps when compared to international benchmarks.[120] The GPP guidelines, which are outdated and general, lacked oncology-specific guidance, particularly in risk management and the use of PPE. Errors included the endorsement of inadequate PPE, such as surgical masks, and a statement incorrectly claiming that no adequate AD monitoring methods exist. The ICON guidelines were found to be more comprehensive than the GPP guidelines and addressed all 10 oncology pharmacy domains. However, they lacked the depth and detail provided by international guidelines such as ISOPP and QuaPos. The ICON guidelines included more information on the transport and receipt of ADs, distinguishing between mixed and unmixed ADs, and recommended robust transport containers. International guidelines like ISOPP and QuaPos provided detailed frameworks, including specific training content, engineering controls, medical monitoring, and comprehensive cleaning and spill management. Both local guidelines require updates to align with international best practices, including structured training programmes, risk management frameworks, and robust monitoring protocols. Updating these guidelines would have improved the safety and effectiveness of oncology pharmacy practices in South Africa.

4.4. Antineoplastic contamination and exposure risks in South African oncology pharmacies

Surface contamination was assessed for nine ADs in six South African oncology pharmacies, divided between two service providers (SP1 and SP2).[121] A total of 36 wipe samples were collected at the beginning and end of the workday across six pharmacies (six samples per site). Each sample was analysed for the presence of seven ADs, resulting in 252 possible “detects”. Of these, 65.1% were positive, i.e. concentrations of one or more AD exceeded the level of detection (LoD). Etoposide and DOX were excluded from the statistical analysis; 5-FU was the most frequently detected AD, followed by CP. Contamination levels were higher in SP1 pharmacies across all measured surfaces. The highest concentration observed was 83.9 ng/cm²

for 5-FU in an SP1 pharmacy. Surface contamination decreased on average by 17.4% following decontamination procedures, although the reduction varied by drug and surface. Service provider 1 pharmacies exhibited less effective decontamination than SP2, particularly for floors. Some instances of increased contamination post-cleaning were attributed to cross-contamination or procedural inconsistencies. Urine analysis revealed detectable concentrations of ADs in two SP1 pharmacy staff members, with IF and CP detected. No ADs were found in urine samples from SP2 personnel. This aligns with observational findings, which reported inadequate PPE and its use in SP1 compared to better compliance in SP2. The DeRmal Exposure Assessment Method (DREAM) estimated higher dermal exposure risks in SP1 pharmacies. Task-weighted potential exposure values for SP1 were nearly double those for SP2. Observational compliance scores were inversely correlated with DREAM exposure estimates, underscoring the impact of suboptimal practices on exposure risk in SP1. Service provider 1 pharmacies showed higher surface contamination, less effective decontamination, and greater occupational exposure to ADs compared to SP2 pharmacies. Service provider 2 pharmacies demonstrated better adherence to safety protocols and PPE usage, which likely contributed to their lower contamination levels and absence of biological uptake in staff. These findings highlight the need for improved contamination control measures in SP1 pharmacies.

4.5. Tailor-made risk control strategies to mitigate antineoplastic drug exposure in South African oncology pharmacies

The consolidated results are summarised in Table 3. A 10^{-2} M sodium-dodecyl-sulphate (SDS) or sodium lauryl sulphate (SLS) isopropanol 80:20 mixture is the strongest alternative, closely followed by CSTDs; PPE and training are ranked third and fourth.

SDS-decontamination combines the high effectiveness of surface decontamination (99.6%) with excellent feasibility for implementation and acceptance at a low cost. The presently widely implemented decontamination with 70% ethanol, had limited effectiveness, whereas decontamination with sodium hypochlorite (NaOCl), though being effective, has low feasibility for implementation as it requires additional removal of the NaOCl to protect devices from corrosion. Closed-system transfer devices, despite having no direct financial burden on pharmacies, exhibited high effectiveness (88.3%), indicating their place as a complementary

measure. Donning and doffing chemotherapy-grade PPE was statistically significant effectiveness but carried substantial costs. Theoretical and practical training, although the most cost-effective option, has demonstrated statistical significance in several studies, especially in behaviours, highlighting the necessity for training to be integrated with other interventions (such as donning and doffing of PPE) rather than serving as a standalone measure.

These findings underline the trade-offs between cost, feasibility, and surface decontamination The overall 'appreciation' of the interventions, expressed as a weighted sum, supports deciding which interventions to implement. Since, in the present case, the overall appreciation does not differ much, and the interventions are complementary to each other, the recommendation would be to consider implementing all four alternatives, excluding the NaOCl-decimation option.

Table 3. Intervention performance matrix

Intervention	Effectiveness (%)	Annual Cost (Rand)	Feasibility (1–10)	Acceptance (1–10)	Weighted sum
CSTDs	Min: 53.6 Mode: 88.3 Max: 100	R0† (Medical aid covers ~R600,000)	Median: 7 Min: 4 Max: 9	Median: 7 Min: 6 Max: 9	0.3849
Decontamination: NaOCl	Min: ~58.0 Mode: ~59.4 Max: ~60.0	~R17,418	Median: 6 Min: 5 Max:9	Median: 5 Min: 4 Max: 6	0.3435
Decontamination: SDS-Based	Min: ~49.2 Mode: ~50.8 Max: ~58.7	~R4,889	Median: 10 Min: 8 Max: 10	Median: 9 Min: 8 Max: 10	0.3867
Decontamination: 70% Ethanol	Lab-adjusted: Min: ~29.4, Mode: ~36.8, Max: ~58.1 Field: ~17.4	~R4,552	Median: 10 Min: 10 Max: 10	Median: 10 Min: 10 Max: 10	N/A
PPE	Min: ~60.8 Mode: ~64.0 Max: ~67.2	~R112,000	Median: 9 Min: 7 Max: 10	Median: 8 Min: 7 Max: 10	0.3478
Training	Min: ~17.4 Mode: ~35.4 Max: ~54.6	~R4,000	Median:7 Min: 4 Max: 9	Median: 8 Min: 7 Max:10	0.3550

CTSDs: closed-system transfer devices, NaOCl: sodium hypochlorite, PPE: personal protective equipment, SDS: sodium dodecyl sulphate solution.

CHAPTER 5: DISCUSSION

5.1. Introduction

The increasing cancer burden in sub-Saharan Africa has heightened the demand for oncology pharmacy services; however, significant safety and regulatory gaps remain. South African oncology pharmacies face particular challenges, including outdated guidelines, inconsistent compliance, and insufficient monitoring of antineoplastic drug (AD) contamination, exposing pharmacy staff to occupational hazards.

Studies of six pharmacies revealed marked differences between SP1 and SP2. Service provider 1 pharmacies consistently showed higher surface contamination with AD residues, persisting despite decontamination efforts. Biological monitoring further indicated occupational exposure in SP1 personnel, evidenced by the presence of drugs like CP and IF in their urine.

Parallel investigations uncovered deficiencies in safe practice adherence, highlighting inconsistent PPE use and inadequate engineering controls. Although SP2 pharmacies showed better compliance, both groups failed to meet international safety guidelines, emphasising the need for comprehensive improvements.

A critical appraisal of local guidelines found substantial inadequacies. The GPP guidelines lack specific oncology-focused recommendations, while the ICON guidelines, although more robust, fall short compared to international standards like ISOPP and QuaPos. This misalignment underlines the urgent need for updated, comprehensive regulations.

Integrated findings from multiple studies confirmed extensive AD contamination, particularly in SP1 pharmacies. Residual contamination on floors and surfaces persisted after cleaning, and statistical analysis confirmed significant decontamination gaps. Service provider 1 personnel demonstrated higher dermal exposure risks, with ADs detectable in urine samples, underscoring the inadequacy of current preventative measures.

Consequently, targeted interventions for SP1 facilities, including improved PPE protocols, enhanced decontamination methods, and consistent training, were recommended to strengthen oncology pharmacy safety standards and safeguard pharmacy personnel.

In this chapter, the key findings are addressed according to each objective which stems from the four papers published for this PhD study. Additionally, recommendations like work-related procedures, policy reform, regulation and/or recognition of oncology pharmacies in South Africa and mitigating strategies are proposed. The chapter concludes by underlining the scholarly contribution of this PhD study.

5.2. Key findings

This PhD contributes significantly to the realm of oncology pharmacy in South Africa and explores topics never investigated before which could make a substantial contribution to the speciality and regulation of oncology pharmacy in South Africa. It draws from key findings and is organised according to objectives and papers published as follows:

5.2.1. Deficiencies in oncology pharmacy safety practices

- Differential compliance by SP: The study revealed a stark contrast between service providers: facilities managed by SP2 achieved compliance levels near 80%, whereas those under SP1 scored consistently below 50%. This suggests that larger or corporately managed organisations may have more robust systems to implement and monitor best practices.
- Inadequate engineering controls: Despite installing some basic measures (e.g. extraction fans), none of the facilities reached full compliance with engineering controls. The absence of dedicated anterooms and nonconforming containment devices underscores persistent infrastructural and financial constraints that hinder adherence to international guidelines.
- Variability in PPE use: The findings highlight that the use of PPE was not uniform across facilities. Service provider 1's reliance solely on disposable latex gloves contrasts with SP2's comprehensive provision of chemotherapy-approved PPE, indicating a gap in understanding or prioritisation of occupational safety.

- Challenges with administrative controls and training: While administrative measures such as centralised preparation were universally applied, only the facility that implemented staff rotation (SP2) achieved compliance. This points to a need for better-designed workflow processes and continuous professional development to support safe practices.
- Critical gaps in monitoring practices: Both groups scored very low in medical and workplace monitoring. This shortfall is concerning because it suggests that personnel may not be adequately protected from the long-term health risks associated with exposure to antineoplastic drugs.
- Implications for regulatory and organisational practice: The overall disparity in compliance levels emphasises the necessity for stricter regulation and standardisation. The study calls for national guidelines, improved training protocols, and enhanced infrastructure investment—especially for smaller organisations—to ensure a safer working environment in oncology pharmacies.

5.2.2. Misalignment between South African and international oncology pharmacy standards

- Alignment with international guidelines: The ICON guidelines for oncology pharmacy in South Africa, although falling short, align with the ISOPP and QuaPos international guidelines, offering relatively comprehensive coverage across important safety and practice domains. However, the GPP guidelines, required by pharmacies registered with the SAPC, fall significantly short of providing adequate protection and guidance for oncology pharmacists.
- Inadequacy of local guidelines: The GPP guidelines are significantly outdated (last revised in 2010) and contain inaccuracies, such as incorrect guidance on the use of surgical masks (ineffective for AD protection) and the erroneous assertion that no adequate methods exist for monitoring exposure to ADs.
- Gaps in administrative and risk management guidance: Administrative controls and detailed risk management protocols are insufficiently addressed in both local

guidelines, particularly the GPP guidelines. Essential components such as clear operational procedures, staff risk management, hazard identification, and risk control strategies, which are extensively covered in international guidelines, are notably absent or inadequately detailed locally.

- Lack of specific engineering controls: The local guidelines (especially GPP) inadequately describe necessary engineering controls, such as detailed cleanroom specifications, airflow management, pressure differentials, and appropriate C-PEC guidelines, all of which are thoroughly articulated in ISOPP and QuaPos guidelines.
- Limited guidance on PPE: The GPP guidelines provide minimal and, at times, incorrect PPE guidance, contrasting sharply with international best practices, which prescribe precise requirements for AD-resistant gloves, FFP3 masks, gowns, shoe covers, and detailed use protocols. While ICON guidelines offer improved coverage compared to GPP, they still lack the full specificity and clarity found in international guidelines.
- Neglect of medical and workplace monitoring: The GPP guidelines incorrectly suggest that adequate monitoring methods do not exist, reflecting outdated knowledge. In contrast, international guidelines and ICON guidelines explicitly recommend comprehensive medical monitoring, baseline assessments, and routine examinations to detect and mitigate exposure effects.
- Insufficient training and educational guidelines: Both local guidelines (GPP and ICON) inadequately specify educational and training content, frequency, and evaluation requirements. International guidelines delineate robust training programs, including theoretical knowledge, practical skills, certification, re-certification processes, and documentation requirements.
- Documentation and incident management shortcomings: The study highlights that detailed protocols for documenting operational activities, spill incidents, workplace monitoring, and employee exposure records—clearly defined in ISOPP and QuaPos—are inadequately addressed locally, posing risks to safe handling and regulatory compliance.

- Recommendations for improvement: There is a clear need for revising and updating South African guidelines—both ICON and especially the GPP guidelines—to align comprehensively with internationally established best practices. Incorporating SP input, adopting clear operational SOPs, detailed risk management processes, precise PPE and engineering control requirements, robust medical monitoring, and comprehensive educational guidelines are critical steps towards safeguarding oncology pharmacy personnel in South Africa.

5.2.3. Antineoplastic contamination and exposure risks in South African oncology pharmacies

- Significant variability in contamination levels: The study identified substantial disparities in antineoplastic drug (AD) contamination between two oncology pharmacy service providers (SP1 and SP2). Facilities associated with SP1 demonstrated consistently higher levels of surface contamination compared to SP2 facilities, indicating less effective control measures and compliance with safety protocols.
- Prevalence of specific drug contaminants: 5-FU was the most frequently detected contaminant across all sampled surfaces. Cyclophosphamide (CP) and gemcitabine (GEM) were also commonly found. Notably, contamination levels of these agents were markedly higher at SP1 facilities (except for GEM), raising concerns about occupational exposure risks at these sites.
- Limited effectiveness of decontamination procedures: Routine decontamination procedures yielded inconsistent outcomes. While overall contamination decreased post-cleaning (17.4% reduction), there remained notable contamination, particularly in SP1 pharmacies, suggesting the cleaning methods (using 70% ethanol and sterile gauze for surfaces and soap, chlorine, and water for floors) were not entirely effective. The detection of higher post-decontamination concentrations in certain instances implies possible issues such as contaminated cleaning equipment.
- Occupational exposure evidenced by biological monitoring: Biological monitoring indicated clear occupational uptake of ADs among pharmacy personnel, as evidenced

by detectable levels of CP and IF in urine samples from two SP1 employees. This finding underscores significant exposure risks related to inadequate PPE usage and compliance issues at SP1 pharmacies.

- Discrepancies in PPE adherence: Observational findings from a linked study highlighted substantial variations in PPE guidelines and safety compliance. Service provider 1 pharmacies employed suboptimal PPE (e.g. standard latex gloves, non-disposable gowns, and surgical masks), while SP2 pharmacies adhered more closely to international PPE recommendations (e.g. chemotherapy-rated gowns, FFP3 respirators), correlating with lower surface contamination and absence of biological uptake in SP2 employees.
- Dermal Exposure Assessment Method (DREAM) and risk estimates: Application of the DREAM exposure estimation method revealed significantly higher potential and actual dermal exposure risks at SP1 facilities. These estimates correlated negatively with observational compliance scores, highlighting that lower adherence to safety guidelines at SP1 pharmacies likely contributed to increased dermal exposure risks.
- Implications and recommendations for practice: The study indicates the necessity for urgent improvements in SP1 pharmacy practices, specifically regarding contamination control measures and PPE compliance. SP2 pharmacies, exhibiting lower contamination and no detectable biological uptake, could potentially serve as practical models for enhancing oncology pharmacy safety practices within South Africa.

5.2.4. Tailor-made risk control strategies to mitigate antineoplastic drug exposure in South African oncology pharmacies

- Intervention effectiveness varied by type: CSTDs showed high theoretical effectiveness (weighted average 88.3%) in reducing surface contamination. SDS-based decontaminants and chemotherapy-grade PPE also demonstrated strong effectiveness in reducing dermal exposure risks. In contrast, training alone had lower standalone effectiveness but was recognised as essential when integrated with other measures.

- The superior performance of SDS-based decontamination: SDS decontamination agents achieved markedly higher effectiveness (82–97.9% in laboratory conditions) compared to commonly used methods like 70% ethanol, which only reduced contamination by approximately 17.4% in real-world settings. This suggests that transitioning to SDS-based cleaning solutions would significantly enhance safety practices.
- Cost implications and feasibility: Although CSTDs had no direct cost to pharmacies, medical aid absorbed substantial indirect costs. SDS-based decontamination was notably cost-effective compared to alternative methods (NaOCl), and its implementation had high stakeholder feasibility and acceptance ratings. PPE had the highest direct pharmacy cost but was strongly supported by stakeholders due to its proven effectiveness.
- Importance of comprehensive training: Training was identified as the least effective standalone intervention, achieving modest improvements in knowledge and behavioural outcomes. However, training significantly amplified the effectiveness of other interventions, reinforcing the importance of its integration into a holistic exposure reduction strategy.
- Stakeholder perceptions and implementation challenges: Stakeholder assessments revealed variability in the perceived feasibility and acceptance of interventions, particularly CSTDs.
- Integrated risk management approach recommended: A multifaceted strategy combining chemotherapy-grade PPE, SDS-based decontamination, structured training programmes, and selective use of CSTDs is strongly recommended. No single intervention emerged as universally effective, emphasising the need for tailored, comprehensive risk management strategies adapted to local operational contexts.
- Real-world implementation concerns: The effectiveness observed in controlled or laboratory conditions differed considerably from real-world application, emphasising the necessity of regular monitoring and adherence evaluations to maintain effectiveness.

5.3. Strengths and limitations

The four studies comprehensively assess oncology pharmacy practices in South Africa, combining diverse methodologies to address contamination risks, workplace safety, and regulatory frameworks.

The study's biggest strength lies in the consistency of the methodology applied to the various parts of this PhD study. The observational study employed a systematic checklist based on international guidelines, allowing for a detailed evaluation of adherence and compliance across multiple categories, including engineering controls, PPE, and medical monitoring. Additionally, the critical appraisal of local guidelines offered a valuable comparison with international benchmarks, highlighting specific areas requiring improvement. Next, the results of the surface contamination assessment and the biological monitoring in the same pharmacies could be associated with the compliance scores of the observational study. Together, these studies provide a holistic perspective on occupational exposure to ADs and gaps in oncology pharmacy practices.

However, the study also has limitations as it focused primarily on private-sector pharmacies, leaving public-sector practices unexplored. In addition, the sample size was very small, with only six pharmacies and a limited number of personnel participating, which may restrict the generalisability of the findings. However, the sample was taken from two out of the four private SPs in the SA private oncology pharmacy sector, which limits a selection bias. The observational study relied partly on self-reported data and direct observations, which could introduce bias or variability depending on the evaluator. While the critical appraisal effectively highlighted gaps in local guidelines, it did not evaluate the practical feasibility of implementing international guidelines in resource-constrained settings. Another limitation is that both the surface contamination and the DREAM estimates provide an indication of the potential dermal exposure, but skin exposure itself is not assessed. Moreover, the inhalation exposure route was considered negligible. Last, we were unable to access prescription books and/or invoices to determine the quantities of ADs processed in each pharmacy.

Despite these limitations, the studies collectively provide critical insights into South African oncology pharmacy practices, serving as a foundation for developing targeted interventions to improve safety, compliance, and regulatory alignment.

5.4. Recommendations

5.4.1 Policy recommendations

The research findings of this PhD study may be utilised by authorities such as the SAPC or MCOs to enhance the occupational health of pharmacy personnel exposed to ADs and prevent long-term harm that can be caused by these agents.

- Strengthen PPE usage: Mandate the consistent use of appropriate PPE, including gloves, gowns, and respiratory protection such as N95 or FFP3 masks (which offer more protection than N95 masks) by MCOs and the SAPC. Training on proper PPE usage should be mandatory to prevent exposure during AD handling.
- Update local guidelines by MCOs and the SAPC and revise and expand the GPP and ICON guidelines to include detailed, oncology pharmacy-specific provisions and align these with international guidelines such as ISOPP and QuaPos to provide a robust framework for safe AD handling.
- Include ADs in the Hazardous Chemical Agent Regulations under the Department of Employment and Labour.

5.4.2 Future research recommendations

- Expand sample size and scope: Future studies should include a larger number of oncology pharmacies across both the private and public sectors in South Africa to improve the generalisability of findings. This should encompass rural and urban settings to capture a comprehensive view of oncology pharmacy practices nationwide.
- Longitudinal studies on exposure and health outcomes: Conduct longitudinal research to evaluate the long-term health effects of occupational exposure to ADs. These studies should correlate contamination levels with specific health outcomes among pharmacy personnel to strengthen evidence on exposure risks.
- Assess the practicality of international guidelines: Research should focus on the feasibility and cost-effectiveness of implementing international oncology pharmacy

guidelines (e.g. ISOPP, QuaPos) in South Africa. This includes assessing resource needs and adaptations required for local contexts.

- Develop and test interventions: Pilot and evaluate targeted interventions, such as enhanced decontamination protocols, advanced engineering controls, and specialised training programmes, to determine their effectiveness in reducing contamination and exposure in real-world practice.
- Explore contamination sources: Investigate the specific sources and pathways of AD contamination, including preparation, handling, and waste disposal processes, to develop focused strategies for mitigation.
- Interdisciplinary research: Collaborate with occupational health specialists, engineers, and policymakers to explore innovative technologies, such as automated AD handling systems and advanced containment strategies, to enhance safety in oncology pharmacies.
- Incorporate economic analyses: Future research should include cost-benefit analyses of safety interventions and guideline implementations to provide actionable recommendations for resource allocation in both private and public sectors.

5.4.3. Recommendations for practice

- Expand training and education: Develop formal oncology pharmacy training programmes and continuous professional development courses to address gaps in knowledge and skills.
- Improve infrastructure and engineering controls: Invest in engineering controls, including properly maintained C-PECs.
- Adopt comprehensive monitoring practice: Implement routine workplace and biological monitoring to identify and mitigate AD exposure risks. This should include workplace sampling and periodic health assessments of pharmacy personnel.
- Enhance decontamination protocols: Establish standardised, evidence-based cleaning protocols to reduce surface contamination, particularly on floors and adjacent surfaces, where residues were found to persist despite current decontamination efforts practice Regular audits by MCOs should ensure compliance with these protocols.

CHAPTER 6: SUMMARY AND CONCLUSION

The research presented in this thesis addresses a critical occupational health concern by examining the exposure risks faced by oncology pharmacy personnel handling ADs within South African oncology pharmacies. Through a multi-faceted methodological approach, including observational assessments, critical appraisal of guidelines, and empirical contamination monitoring, this work has elucidated significant gaps between existing local practices and internationally recognised guidelines. Consequently, it offers substantial contributions to understanding occupational health risks and provides evidence-based strategies for mitigating these risks.

The observational study highlighted disparities in adherence to best practice guidelines across different SPs. Pharmacies associated with SP1 showed markedly lower compliance levels compared to those affiliated with SP2, particularly in critical areas such as engineering controls, use of personal protective equipment (PPE), medical surveillance, and adherence to documented procedures for spills and accidents. This variability underscores a concerning reality within the private oncology pharmacy sector, where inconsistent practices could potentiate occupational hazards. Rigorous compliance with international guidelines and regular audits should be mandatory to protect personnel effectively.

A critical comparative analysis of South African guidelines against international guidelines further illuminated these deficiencies. The local guidelines, particularly the GPP, lack detailed oncology-specific recommendations and contain outdated or incorrect information. These inadequacies significantly compromise the occupational safety framework, reflecting a fragmented regulatory landscape that demands urgent attention. Upgrading these guidelines to align with robust international practices is necessary to enhance pharmacy safety guidelines comprehensively.

Empirical monitoring of surface and biological contamination further emphasised the extent of occupational risk. Surface wipe tests conducted in participating pharmacies indicated widespread contamination with antineoplastic drugs, notably higher in SP1 facilities. Decontamination procedures currently employed showed limited efficacy, evidenced by the

minimal reduction in contamination levels post-cleaning. Biological monitoring provided additional confirmation of occupational exposure, with detectable levels of cyclophosphamide and ifosphamide found in urine samples from SP1 personnel. These findings underscore an alarming exposure scenario, reinforcing the critical need for enhanced decontamination strategies and stringent adherence to protective measures.

The analysis of potential dermal exposure using the DeRmal Exposure Assessment Method (DREAM) corroborated these findings, indicating significantly higher exposure potential among SP1 personnel. The inverse correlation observed between compliance scores from observational studies and DREAM exposure estimates accentuates the impact of inadequate compliance on occupational safety. This provides compelling evidence advocating for systematic changes in practices and processes to protect pharmacy staff from exposure-related health consequences.

Consequently, this thesis has proposed several targeted interventions, synthesised through structured decision-making analyses. The most recommended intervention identified was the adoption of SDS as a decontamination agent, surpassing traditional ethanol-based solutions in effectiveness. The implementation of CSTDs improved PPE usage, and comprehensive staff training was also identified as a crucial strategy. While CSTDs demonstrate moderate effectiveness, their role should be complementary rather than standalone. Personal protective equipment, although effective, incurs a considerable cost, necessitating balanced financial considerations. Staff training, while essential, requires integration with other strategies to achieve meaningful occupational risk reduction.

This thesis underscores the broader implications of inadequate safety protocols, which extend beyond occupational health risks to potentially impact patient safety and healthcare quality. Effective handling and preparation of ADs are critical to ensuring accurate dosing and avoiding medication errors, thus safeguarding patient outcomes. The observed disparities in pharmacy practices highlight a fundamental vulnerability within the healthcare delivery system that must be urgently addressed through systemic improvements in pharmacy operations and regulatory oversight.

This research also critically evaluated the role of MCOs, such as ICON and SAOC, in regulating oncology pharmacy practices. Despite their significant influence in standardising oncology care

protocols, these organisations currently provide limited specific guidance on pharmacy operations concerning AD handling. Enhancing transparency, detail, and enforceability within MCO guidelines would significantly strengthen pharmacy practice guidelines, particularly within the private healthcare sector. Collaboration between regulatory bodies, professional societies, and MCOs is essential for harmonising guidelines and ensuring consistent implementation across oncology pharmacies.

Additionally, the research identified critical gaps in educational resources and ongoing professional development opportunities for oncology pharmacy personnel. Unlike many developed countries, South Africa currently lacks formal training programmes dedicated explicitly to oncology pharmacy practice. This absence of structured educational pathways compromises the ability of pharmacy personnel to maintain and enhance competencies necessary for safely handling hazardous drugs. The establishment of accredited educational programmes and continuous professional development initiatives, aligned with international guidelines, would significantly contribute to enhancing occupational safety and professional expertise within the oncology pharmacy sector.

The thesis also recognises the potential for technological innovations to reduce occupational exposure risks. Automation technologies, such as robotic compounding devices, represent promising alternatives that have shown substantial efficacy in reducing workplace contamination and occupational exposure internationally. Although initial implementation costs may be substantial, these technologies offer long-term benefits, including improved safety, increased operational efficiency, and enhanced accuracy in medication compounding. Exploring the feasibility and practical implementation of these advanced technologies within South African oncology pharmacies could be pivotal in advancing occupational health protection.

Given the increasing prevalence of cancer diagnoses anticipated in sub-Saharan Africa, addressing occupational exposure risks among oncology pharmacy personnel has become an imperative public health issue. The findings of this research provide a robust foundation for advocating necessary reforms in policy, regulation, and practice. Such reforms must prioritise comprehensive updating of national guidelines, stringent enforcement of safety protocols, enhanced educational guidelines, and exploration of advanced technological solutions to mitigate exposure risks effectively.

Finally, the study highlights substantial opportunities for future research. Expanding monitoring programmes to include more pharmacies and longitudinal tracking of contamination and biological uptake would enhance understanding of chronic exposure risks. Investigating additional decontamination agents, PPE technologies, and automation solutions such as robotic compounding devices could also present novel approaches to mitigating occupational exposure.

In conclusion, the findings underscore the necessity for comprehensive action to address occupational exposure to ADs in South Africa. Key recommendations include updating national guidelines to align with international guidelines, implementing mandatory training and compliance protocols, enhancing monitoring of workplace and biological contamination, and adopting more effective decontamination methods. Such interventions are critical to safeguarding the health of pharmacy personnel, thereby ensuring a safer occupational environment and improving overall healthcare service delivery in oncology pharmacy practice.

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APPENDICES

Appendix A: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Mr Ruan Botha

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190312

NAME: (Principal Investigator)	Mr Ruan Botha
DEPARTMENT:	Public Health Oncology Pharmacies Gauteng
PROJECT TITLE:	Occupational exposure to antineoplastic drugs and the development of tailor-made risk control strategies in South African oncology pharmacies
DATE CONSIDERED:	29/03/2019
DECISION:	Approved unconditionally
CONDITIONS:	Approval issued to cover sites: Alberts, Bouwer, Jordaan Pretoria
SUPERVISOR:	Prof DH. Brouwer and Prof G. Nelson
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/08/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Original Research

European Journal of ONCOLOGY PHARMACY

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A pilot study of South African oncology pharmacy facilities: Comparison with best practice guidelines

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Abstract

Introduction: Exposure to antineoplastic drugs can lead to adverse health effects such as fetal loss and DNA damage. Oncology pharmacy facilities should implement best pharmacy practice guidelines to protect pharmacy personnel. The objective of this study was to assess South African oncology pharmacy facility workplace and personnel work practices, guided by internationally accepted best practice guidelines.

Methods: A cross-sectional pilot study was conducted in 6 oncology pharmacy facilities (one personnel member per facility) of 2 South African oncology pharmacy service providers. Using a simple checklist, comprising 7 assessment categories and 43 questions derived from best practice guidelines, work and workplace practices were scored as compliant, partially compliant, or noncompliant. Each facility and service provider were also given an overall score.

Results: Overall scores for the 6 facilities ranged from 33.1% to 79.3%. Service provider 2 pharmacy facilities (which were assessed as being compliant overall) scored higher at 78.0% ± 1.5 (76.4%–79.3%) than service provider 1 pharmacy facilities, which were noncompliant overall at 40.2% ± 21.5 (33.1%–49.9%). Categories in which performance was poor included the presence of engineering controls, use of personal protective equipment, and medical monitoring.

Conclusion: The complexities of South African oncology pharmacy facilities highlight the need for stricter regulation. Despite operating under the auspices of managed care organizations, some facilities' work practices were poor. It is recommended that service providers implement international best practice guidelines.

Keywords: oncology pharmacy, occupational survey/checklist, antineoplastic drugs

Introduction

Health risks for oncology pharmacy personnel have been described in numerous studies on workplace contamination.[1–3] Currently, there are hundreds of antineoplastic drugs (ADs) in use, globally.[4] Most ADs are classified as hazardous drugs by the US Centre for Disease Control's (CDC) National Institute for Occupational Safety and Health (NIOSH).[5] Adverse health effects from exposure to ADs range from minor to severe and include skin rashes, low birth weight, infertility, ectopic pregnancies, tumors and leukemia, and reproductive effects, such as fetal loss and congenital malformations.[6]

Published guidelines on best oncology pharmacy practices include the International Society of Oncology Pharmacy Practitioners (ISOPP) "Safe Handling of Cytotoxics,"[7] the "Quality Standards for Oncology Pharmacies (QuaPos),"[8] the United States Pharmacopoeia Chapter 800,[9] and the American Society of Clinical Oncology (ASCO) "Chemotherapy administration safety standards."[10] These guidelines extensively discuss best oncology pharmacy practices and serve as resources for oncology pharmacy personnel to develop their own guidelines.

Some managed care organizations in South Africa regulate medical oncology facilities, including the South African Oncology Consortium (SAOC) and the Independent Clinical Oncology Network of South Africa (ICON). The ICON developed a "chemotherapy administration standards and guidelines resource document" guideline in a bid to provide oncology pharmacy facilities with a pragmatic assessment approach, as described by Eedes et al[11] who noted that South African oncology pharmacy facilities did not provide input to survey.

The role of the oncology pharmacist is indispensable in today's clinical oncology environment,[12,13] and safe work practices are paramount. However, in a survey conducted by von Grunigen et al,[14] a wide variability and major gaps in safe work practices were identified in oncology pharmacies in low- and middle-income countries(LMICs), including a pharmacy in South Africa.

The authors wish to declare no conflict of interest.

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The study was presented at the South African Society of Medical Oncology (SASMO) 2024 conference at the Cape Town International Convention Centre, South Africa.

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The objective of this study was to assess South African oncology pharmacy facility workplace and work practices, guided by international best practice guidelines.

Methods

This was a cross-sectional pilot study. On request, the South African Society of Oncology Pharmacy Practitioners (SASOPh) provided a list of 43 oncology pharmacy personnel and their contact details. All were invited to participate in the study through email. A simple checklist (Annexure A) was developed from the ISOPP[7] and QuaPos[8] guidelines. The checklist was divided into 7 assessment categories including, engineering controls, administrative controls, use of personal protective equipment (PPE), education and training, medical, and environmental monitoring, cleaning procedures and waste handling, and spills and accidents. Each category comprised several questions (4–8 per category, 43 in total). Each question was designed to obtain a rating: noncompliant (rating = 0), partially compliant (rating = 3), or fully compliant (rating = 10). Information was obtained from the facilities by observing the workplace, perusing relevant documents, and interviewing personnel. The pilot study was conducted from March to September 2023.

Data analysis

Data were captured into Microsoft Excel 2023 (Microsoft Corporation, Redmond, WA) thereafter descriptive statistics were used for analysis. The total score for each category was converted into a percentage; and the mean score (percentage) was then calculated for all 7 assessment categories. A score >75% represented full compliance, partial compliance was assigned for scores of 50%–75%, and a score below 50% indicated noncompliance. The individual assessment category and overall scores were compared between service providers.

Ethics approval

Ethics clearance was obtained from the University of the Witwatersrand's Human Research Ethics Committee (HREC) (clearance certificate no. M190312) on September 14, 2019. Consent was obtained from all service providers and pharmacy personnel before commencing the study.

Results

Of the 43 pharmacy personnel contacted, 23 did not respond (53.5%), 2 refused (4.7%), and 18 (41.9%) expressed willingness to participate in the pilot study. However, permission to participate was required from 3 of the service providers. One service provider refused to allow their oncology pharmacy facilities to participate; 2 agreed. Consequently, only 6 pharmacy personnel (one personnel member at each facility) participated in the pilot study. Three facilities were in Gauteng province and 3 in the Western Cape province of South Africa.

All 6 oncology pharmacy personnel who were interviewed were female; 5 were pharmacists and one was a registered nurse (Table 1). The mean age of the participants was 51.1 ± 6.7 years (45–64 years). The mean duration of employment (experience) of personnel was 11.7 ± 5.7 years (4–20 years). The mean daily exposure to ADs was 6.00 ± 1.79 hours (4–8 hours).

Table 2 shows that service provider 1 facilities were "noncompliant" for 5 of the 7 assessment categories and partially compliant for 2, whereas service provider 2 facilities were fully or partially compliant for all 7 categories. Based on the mean scores, none of the service provider 1 facilities was compliant overall (with scores of 33.0%–49.9%). All facilities affiliated with service provider 2 were fully compliant overall (with mean scores of 77.0%–79.3%).

Table 1

Sociodemographic profile of oncology pharmacy staff.

Characteristic	n (%)
Sex	
Male	0 (0)
Female	6 (100)
Age (years)	
45–54	3 (50.0)
55–64	3 (50.0)
Experience (years)	
0–5	1 (16.7)
6–10	2 (33.3)
11–15	1 (16.7)
16–20	2 (33.7)
Role	
Pharmacist	5 (83.3)
Registered Nurse	1 (16.7)
Exposure (hours/day)	
4–5	2 (33.3)
6–7	2 (33.3)
8 +	2 (33.3)

None of the 6 facilities was fully compliant regarding engineering controls, that is, all scores were <75% (Table 2). Three of the 4 facilities that were partially compliant were affiliated with service provider 2. Points were lost for not having an "anteroom" next to the mixing room in the facilities and for having containment primary engineering controls (C-PEC) that did not comply with international guidelines. Nevertheless, service records for the C-PEC were present in every facility, and all were equipped with an external extraction fan (although none had pressure differentials between the anteroom and the C-PEC as recommended in the ISOPP and QuaPos guidelines).

Only the facility that implemented staff rotation (service provider 2) was compliant regarding the implementation of administrative controls. All facilities lost points for inappropriate facility design. Although all used centralized preparation, none was designed to optimally handle ADs (i.e., movement of ADs did not follow the shortest route through the facility). In one facility (service provider 1), the consumables, for example, syringes and needles, were not appropriately placed to facilitate efficient use.

The scores for PPE compliance for the facilities affiliated with service providers 1 and 2 differed by a factor of 4 (21.7% and 88.3%, respectively). Personnel at service provider 1 facilities used disposable latex gloves but no other PPE. The 3 facilities affiliated with service provider 2 were rated as fully compliant for the use of PPE, which was specifically designed for use when mixing and preparing ADs.

Personnel associated with service provider 2 were fully compliant (85.7%) regarding education and training. A lower score was obtained by service provider 1 personnel (47.1% ± 25.1) as 2 of the 3 were noncompliant. One personnel member from service provider 1 scored higher than the other 2, for attending workshops/conferences and/or masterclasses, being affiliated with a professional body, and having training records available.

Of the 7 categories, all 6 facilities scored lowest for medical and environmental monitoring. All 3 pharmacy facilities from

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Table 2

Facility scores per assessment category.

Assessment category	Service provider 1 scores (%)				Service provider 2 scores (%)			
	Facility 1	Facility 2	Facility 3	Mean ± SD	Facility 4	Facility 5	Facility 6	Mean ± SD
Engineering controls	31.4	41.4	65.7	46.2 ± 17.6	65.7	65.7	51.5	61.0 ± 8.2
Administrative controls	52.0	66.0	52.0	56.7 ± 8.1	52.0	66.0	86.9	68.3 ± 17.6
PPE	21.7	21.7	21.7	21.7 ± 0.0	88.3	88.3	88.3	88.3 ± 0.0
Education and training	28.6	37.1	75.7	47.1 ± 25.1	85.7	85.7	85.7	85.7 ± 0.0
Medical and environmental monitoring	0.0	0.0	0.0	0.0 ± 0.0	66.7	66.7	66.7	66.7 ± 0.0
Cleaning procedures and waste handling	60.0	60.0	90.0	70.0 ± 17.3	90.0	90.0	90.0	90.0 ± 0.0
Spills and accidents	38.0	38.0	44.0	40.0 ± 3.5	86.0	86.0	86.0	86.0 ± 0.0
Overall score (%)	33.0	37.8	49.9	40.24 ± 8.7	77.0	78.4	79.3	78.2 ± 1.2

service provider 1 facilities scored zero. All service provider 2 facilities conducted medical monitoring and were partially compliant because environmental monitoring was not conducted.

Four of the 6 facilities scored 90% for cleaning procedures and waste handling (one from service provider 1 and 3 from service provider 2). Two facilities from service provider 1 scored 60% because they had no training records for cleaning procedures and waste handling and no cleaning schedules or records of cleaning. For waste handling, all 3 facilities affiliated with service provider 2 scored 86.0% in contrast with those affiliated with service provider 1, which scored 38.0%–44.0% because no training records or written procedures were available. One facility affiliated with service provider 1 was able to provide documentation of accidents; however, no corrective measures were recorded.

Discussion

Response rate/participation

The initial response to the invitation to participate in the study was relatively positive; only 2 of 43 oncology pharmacy personnel contacted declined. This indicates a general interest and willingness among oncology pharmacy personnel to contribute to research about their work practices. However, this positive response was thwarted by the requirement for permission to participate in the study from service providers, and limited the number of pharmacies that ultimately participated. Service provider 1 permitted all 3 of its pharmacies to participate in the study while service provider 2 permitted participation by 3 of its many oncology pharmacies, without indicating how they selected them.

Demographic and work characteristics

The mean duration of employment was 11.7 years, indicating a relatively experienced group of participants in oncology pharmacy practices. All 6 pharmacy personnel interviewed were female, and the majority were pharmacists; one was a registered nurse. In South Africa, oncology pharmacy personnel are not required to be registered pharmacists, although the majority of AD mixing is performed by pharmacists.

Overall performance

The 3 facilities from service provider 1 performed inconsistently and relatively poorly overall, while those from Service Provider 2 performed more consistently and achieved higher scores overall for each of the 7 assessment categories. Service provider 1 did not have all the recommended controls in place. DeJoy et al[15] found that the "recommended use of engineering controls and PPE were variable" in a study among 1800 nurses who administered ADs in the United States. Another survey of nurses and pharmacy practitioners in the United States, published in 2015, revealed a lack of universal adherence to recommended national safe handling guidelines.[16]

Engineering controls

The facilities did not perform as well as expected in this category as engineering control measures recommended in international guidelines can be expensive in LMICs. However, less expensive but effective measures (such as extraction fans) were in place in all the oncology pharmacy facilities.

Although no facility's C-PEC complied with international best practice, all facilities had a vertical flow class II C-PEC device installed with a service schedule that complied with ISOPP and QuaPos requirements. Each facility was equipped with an external extraction fan, although pressure differentials were not installed. The absence of anterooms, which are necessary for the donning of PPE and preparation of vials and ampoules containing ADs for mixing in the C-PEC, was probably due to the significant capital investment required.

International and local guidelines specify that the C-PEC should be in a separate room to avoid environmental contamination. However, only 3 of the facilities conformed to this recommendation. Unfortunately, the air-conditioning provided was unable to reduce the heat generated by the C-PEC to a level that was comfortable for the pharmacy personnel who were mixing ADs. Unlike the installation of external extraction fans and anterooms, it is easy and cost-effective to isolate the C-PEC in a separate room. Discomfort due to high temperatures could lead to reduced concentration on the task at hand and an increased risk of errors.

Administrative controls

There were mixed results regarding administrative controls. Although all facilities used centralized preparation (where the pharmacy is located within an oncology out-patient department), some facilities were not ideal for handling ADs. In some facilities, for example, ADs did not follow the shortest route through the facility, increasing the risk of contamination. The facility with the highest score for this assessment category had the advantage of having 2 oncology pharmacy personnel employed. This allowed for staff rotation and, consequently, a higher score.

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PPE

One service provider felt that the use of PPE was unnecessary, while the other implemented and enforced PPE requirements. The lack of use of PPE in the facilities of service provider 1 was possibly due to poor understanding of good oncology pharmacy practice. Some oncology pharmacy personnel renounced the use of PPE, stating that the risk of exposure was of no concern to them. Those who renounced the use of PPE were also unaware of the requirements for PPE when mixing ADs. The only PPE that service provider 1 supplied was latex gloves, which have been proven to be inferior in the mixing of ADs when compared with those approved for use in chemotherapy, such as EN374 gloves.[7] In comparison, service provider 2 employed recommended chemotherapy approved gloves (EN374 gloves), masks, overcoats, and coverings.

Education and training

The difference between the 2 facilities in their scoring in the "education and training" category was in line with findings in the other categories in that service provider 2 facilities scored higher than service provider 1 facilities, mainly because service provider 1 personnel did not attend continuous professional development (CPD) courses. None of the facilities had comprehensive details about training on record. Anecdotally, on-the-job training was provided by experienced oncology pharmacists. Two participants from service provider 1 were not affiliated with a professional or other relevant body such as the South African Pharmacy Council (SAPC) or the SASOPh (which provides training and education through seminars and workshops). Although this is not a requirement, affiliation with such organizations could potentially improve work practices. The training provided by the SAPC (not oncology pharmacy specific) and the SASOPh (oncology pharmacy specific) is accredited for CPD purposes. In-house CPD-accredited training is also provided by company representatives employed in the pharmaceutical industry.

Medical and environmental monitoring

Medical and environmental monitoring in oncology pharmacies is essential. Medical monitoring includes baseline blood tests when employment commences and routinely thereafter as well as liver function and other tests to screen for adverse health effects for exposure to ADs, as recommended internationally. Only service provider 2 did medical monitoring despite the relatively low cost compared with environmental monitoring. The high cost of environmental monitoring, which includes checking for AD contamination of surfaces, may have been the reason that none of the service providers adhered to this international requirement.

Waste management

Waste management companies remove medical waste from facilities such as oncology pharmacies, including PPE. Although all the facilities in this study had contracts with pharmaceutical waste management companies, build-up of AD waste was observed in all of them. Nevertheless, all facilities were fully compliant in this category because they had the required cleaning/disinfectant chemicals/materials, waste management and containers, cleaning procedures, and waste handling. The scores for this category were thus the highest of all the categories. Training on cleaning procedures and waste handling is paramount but no such training was documented. This was in line with the observations made regarding the education and training assessment category.

Spills and accident management

Similarly, training on spills and accident management was not documented in service provider 1 facilities. This is a concern because spills increase exposure to ADs and therefore the risk of adverse health effects.

Facilitators of safe handling of ADs

Robust policies (SOPs) and stakeholder knowledge of service provider 2 led to better outcomes than the service provider 1 facilities. This is possibly due to service provider 2 being a corporate service provider with many oncology pharmacy facilities, which may result in a more thorough scrutiny of processes.

Barriers to safe handling of ADs

Service provider 1 did not have appropriate controls in place to ensure the safe handling of ADs. Fazel et al, in a Canadian study, found that organizational factors (such as poor training, safety culture, and inconsistent policies) were substantial barriers to the safe handling of ADs.[4] These and other factors contributed to the overall poor performance of service provider 1. Service provider 1 is a small business (in contrast to service provider 2, which is a multipharmacy business) and is therefore less likely to comply to occupational health and safety requirements.[17]

Study limitations

The study had several limitations. The sample size was very small and the poor response rate, as a consequence of the facilities needing permission from the service providers to participate, potentially led to response bias, thereby reducing the validity of the results. Facilities with good health and safety practices might have been more willing to participate in the study. These issues raise questions about the representativeness of the participants and the generalizability of the findings. Although, the facilities did not allow direct observation of work practices, which could have led reporting bias, it was possible to assess the implementation of engineering and administrative controls, and the use of PPE. The participating pharmacies were in large urban areas, where work practices may be very different to those in smaller towns and rural areas. Another limitation is that the checklist was not validated or piloted. However, it was based on checklists previously used in similar studies and experts were consulted to ensure that it captured relevant issues pertinent to the study.

Recommendations

At the very least, all oncology pharmacists should be provided with PPE to minimize exposure to ADs, including gloves specifically designed to prevent dermal absorption, masks to prevent exposure through inhalation, and body coverings such as impermeable long-sleeved aprons and overshoes. Policies regarding the provision and use of PPE should be developed and enforced. The use of PPE is at the bottom of the hierarchy of controls for health and safety but is a cost-effective and affordable control.[18]

One level up in the hierarchy of controls is administrative controls, which include training. Oncology pharmacy personnel must be encouraged to actively participate in continuous professional development courses, workshops, and conferences to stay updated on best practices to protect their health. Guidelines for medical and environmental monitoring must be implemented to ensure a proactive approach to health and safety. As not all facilities are registered with the SAPC, Good Pharmacy Practice (GPP) is not necessarily enforced. The registration of all oncology facilities with the SAPC will improve practices to safeguard pharmacy personal. Section 2.17.3 of the GPP, concerning cytotoxic preparation and reconstitution services, should be reviewed and revised to specify the need for regulation of oncology pharmacy. This section is consulted by organizations like SAOC and ICON to develop guidelines and standard operating procedures (SOPs).

Engineering controls are third in the hierarchy of controls. In the case of oncology pharmacies, engineering controls such as anterooms and cleanrooms (ventilation controls) are prohibitively expensive in LMICs. However, the placement of the C-PEC in a separate room is easy and cost-effective. All oncology pharmacies should ensure that they are fitted with optimal ventilation (e.g., effective air-conditioning) and extraction systems that are regularly inspected and maintained by ventilation experts. Records of checks and maintenance should be appropriately filed.

Recommendations for further research

It is recommended that societies like the SASOPh, private oncology service providers, and the SAPC should assist in encouraging participation in future, larger studies on the health and safety of oncology pharmacists and the facilities to improve response rates. Future studies should be extended to other provinces in the country and should include oncology facilities in rural areas. Direct observations should be included in such studies, to reduce information bias.

Conclusion

Some of the gaps identified in this pilot study included the lack of training for oncology pharmacists the lack of best practice guidelines and inadequate controls to minimise exposure. This study highlights the need for stricter regulation of South African oncology pharmacy facilities and the implementation of national guidelines and standardization of workplaces and procedures. The findings contribute to the discourse on the complexities of South African oncology pharmacy facilities, shedding light on organizational factors. Differences in performance between service providers identified issues to be considered for the health and safety of oncology pharmacy personnel, particularly engineering controls and PPE usage. Although all the facilities were, in theory, subject to scrutiny by South African managed care organizations, work practices in some of the facilities were found to be poor. The reason for this requires further investigation. Work practices in South African oncology pharmacies should be investigated to protect employees from adverse health effects.

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A critical appraisal of South African oncology pharmacy standards: A comparison with international best practice standards

Ruan Botha[1], Derk Brouwer[1] and Gill Nelson[1,2]

Abstract

Introduction: The demand for oncology pharmacy services is set to increase as the burden of cancer rises in sub-Saharan Africa. Oncology pharmacists may be exposed to antineoplastic drugs (ADs) and need comprehensive health and safety guidelines. The objective of the study was to assess the effectiveness of the local oncology pharmacy practice standards, by critically evaluating them against international best practice standards.

Methods: We compared the Independent Clinical Oncology Network (ICON) administration of ADs standards resource document (ICON standards) and Good Pharmacy Practice (GPP) standards with the International Society of Oncology Pharmacy Practitioners (ISOPP) Standards for the safe handling of cytotoxics, and the Quality standard for the oncology pharmacy service (QuaPos), using 10 domains: transport of ADs, working arrangements, education and training, engineering controls, use of personal protective equipment, risk management, medical monitoring of personnel, cleaning procedures, accident management and documentation, labelling and checking procedures.

Results: The ICON standards align closely with international best practice standards, but the GPP standards focus only briefly on the compounding of ADs.The GPP standards are outdated and some of the stipulations are erroneous. Oncology pharmacists would do better to adhere to the more comprehensive ICON standards, although these standards also need to be updated in line with best practice.

Conclusion: Revising and improving both these local standards in consultation with key role players in the oncology pharmacy industry will go a long way in protecting the health and safety of oncology pharmacists in South Africa.

Keywords

Hazardous drugs, anti-neoplastic drugs, oncology pharmacy standards/guidelines, critical literature appraisal

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Introduction

With the incidence of cancer expected to increase by 70% in sub-Saharan Africa by 2030,[1] the role of the oncology pharmacist is more important than ever, in correlation with the high demand for oncology pharmacy services in the region. In South Africa, there are no formal training programmes for oncology pharmacists or official guidelines. Special registration as an oncology pharmacist with the South African Pharmacy Council (SAPC) is not required.[2] With a 2024 market revenue of US$ 0.57 billion (projected to increase to US$ 0.78 billion by 2029), the South African oncology drug market is rapidly expanding.[3] This will lead to higher volumes of anti-neoplastic drugs (ADs) passing through the health care system and greater numbers of individuals involved in the mixing of the drugs being exposed.

In 2022, von Grunigen, Geissbuhler[4] reported that there were major gaps in the safe handling of AD drugs in low- and middle-income countries (LMICs) although upper-middle-income countries (like South Africa)

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performed appreciably better than lower-income countries. They used a free online tool (Cyto-SAT) to assess 134 items grouped into 10 domains and 28 sub-domains in oncology pharmacy. Considerable variation in the content and scope of safe handling guidelines and pharmacy practices was also observed in a study in which 24, mainly developed countries, including the United States, Canada, United Kingdom, continental Europe, Japan and Australia, participated.[5] Authors of a study from Ethiopia (another LMIC) reported that, in their setting, only 37.6% of health professionals who handled ADs had good cytotoxic handling practices.[6] Fazel et al. (2022) reviewed studies of barriers to the safe handling of cytotoxic drugs in Canada, which included poor handling (46% of reviewed papers), poor safety culture (41%) and inconsistent policies (36%), while also showing that implementing certain facilitators such as adequate safety training (41%), leadership support (23%), and consistent policies (21%) can have a positive impact on oncology pharmacy practice.[7]

In 2018, the Independent Clinical Oncology Network (ICON) "Chemotherapy standards and guidelines" were published, with a focus on safety, competency, and error reduction. The document specifically mentioned the lack of nationally recognised guidelines for AD administration in South Africa.[8]

All pharmacies (community and institutional) in the private sector in South Africa, in which ADs are prepared, are affiliated with one of two managed care organisations, viz. the Independent Clinical Oncology Network (ICON) or the South African Oncology Consortium (SAOC). Both organisations have guidelines to which the respective oncology practices must adhere. While the ICON standard on the compounding of ADs is available publicly, the SAOC standard is not.

In addition to the ICON or SAOC standards, all pharmacies that are registered with the SAPC are legally obliged to adhere to the Good Pharmacy Practice (GPP) standards in terms of the South African Pharmacy Act No. 53 of 1974.[9] However, not all ICON- and SAOC-affiliated pharmacies are registered with the SAPC. Those that are not registered are not legally required to apply the GPP standards.

Although oncology pharmacy is not a recognised speciality in South Africa, some individuals who have experience in mixing ADs belong to the South African Society of Oncology Pharmacists (SASOPh). Membership is voluntary and only around 60 'oncology pharmacists' in the country belong to the society. The SASOPh recommends the use of international best practice standards, which include the International Society of Oncology Pharmacy Practitioners (ISOPP) standards for the safe handling of cytotoxics, and the Quality standard for the oncology pharmacy service (QuaPos) published by the European Society of Oncology Pharmacy (ESOP). According to the SASOPh, there are approximately 160 private 'oncology pharmacies' in South Africa. The few that are registered with the SAPC are registered either as institutional or community pharmacies as there is no option to register as an oncology pharmacy. Most are not registered with the SAPC because the compounding ADs is not seen as an act exclusively designated to a registered pharmacy and is thus not considered to be one of the three steps in the process of dispensing medication. These unregistered oncology pharmacies are, nonetheless, considered to be 'de-facto' pharmacies as the compounding of ADs takes place in these facilities even though they are not registered with the SAPC.

The objective of this study was to assess the effectiveness of the ICON and GPP standards in protecting the health and safety of those handling ADs in private pharmacies in South Africa, by critically reviewing and evaluating the two local standards against the international best practice ISOPP standards and the QuaPos standard.

Methods

The GPP, ICON, ISOPP and QuaPos standards were reviewed, using 10 oncology pharmacy-related domains derived from two international best practice standards recommended by the SASOPh, to identify gaps and contradictions in the local guidelines. The standards as well as the determination of the comparisons were reviewed by the first author (RB). The domains used were the transport of ADs, working arrangements, education and training, requirements for facilities and engineering controls, use of personal protective equipment (PPE), risk management, environmental monitoring and medical monitoring of personnel, cleaning procedures, accident management and documentation, labelling and checking procedures.

Results

The GPP standards

The GPP standards are aimed at pharmacy practice in general and are not specific to oncology pharmacy. One relatively short section of the GPP standards (5 of 222 pages) is dedicated to the practice of the mixing of ADs and was last updated in 2010. Nine of the 10 domains are covered; no mention is made of risk management. Some of the statements made in the GPP are inaccurate. These include: "no adequate means of monitoring and measuring inadvertent adsorption [of cytostatics] have been devised", and "protective clothing must include … a single-use surgical mask" (which does not provide adequate protection against exposure to ADs). In addition, the recommendations are not written in a logical sequence.

The ICON standards

The ICON standards, last updated in 2018, are more comprehensive than the GPP standards, regarding the

compounding of ADs. While the functions and roles of the oncology nurse and the oncologist are comprehensively described in separate sections, no specific details are provided about the role of the oncology pharmacist; the compounding of ADs is assigned to the oncology nurse. All 10 oncology pharmacy-related domains are covered.

The ISOPP standards

The ISOPP standards for the safe handling of cytotoxics, which are specific to oncology pharmacy, were first published in 2007. Refinement of safe handling practices led to the latest 2022 edition of the standards. They provide a comprehensive, structured approach to the practice of oncology pharmacy and all 10 oncology pharmacy-related domains are discussed in detail.

The QuaPos standard

The globally recognised QuaPos standard was developed by the European Society of Oncology Pharmacy. The most recent edition was published in 2021. The standard is specifically aimed at the oncology pharmacist and the practice of oncology pharmacy, and cover all 10 domains.

Comparison of the GPP, ICON, ISOPP and QuaPos standards

The GPP standards, with their 32 items, are outdated and inadequate regarding oncology pharmacy practice. They mention oncology pharmacy practice only briefly in one of 49 sections, with limited focus on the compounding of anti-neoplastic drugs. They do not provide the detailed and in-depth guidance that the ICON, ISOPP and QuaPos standards do. These three standards are structured, using appropriate and relevant headings, and address the various aspects of oncology pharmacy practice systematically.

Even though recommendations for good oncology pharmacy practice are mentioned in the section in which the function of the oncology is described in the ICON standards, rather than in a section about the oncology pharmacist, the recommendations themselves compare favourably with the ISOPP and QuaPos standards. However, the ICON standards do not discuss the practice of oncology pharmacy as extensively as the other two standards, nor do they provide the same level of detail.

Oncology pharmacy-specific domains: performance of the South African standards

The differences between the four standards regarding the 10 oncology pharmacy practice domains, are provided in Table 1.

Table 1. List of abbreviations.

AD	Antineoplastic drug
GPP	Good Pharmacy Practice
ICON	Independent Clinical Oncology Network
ISOPP	International Society of Oncology Pharmacy Practitioners
LMIC	Lower- middle-income countries
QuaPos	Quality Standard for the Oncology Pharmacy Service
SAOC	South African Oncology Consortium
SAPC	South African Pharmacy Council

Transport of anti-neoplastic drugs

Although the GPP standards mention the safe transport of ADs, additional details that are provided in the ISOPP and QuaPos standards are missing. The GPP standards state that ADs must be transported in protected syringes (to prevent accidental spillage) that are individually labelled with essential information such as the name and strength of the medication, and the patient details. The ICON standards are more comprehensive than the GPP standards and provide more details regarding the transport and receipt of ADs. They compare well with the ISOPP and QuaPos standards as they include recommendations regarding the use of unbreakable, liquid-tight containers, staff training, and documentation and procedures in the event of an accident or 'spill'. The ICON standards specifically distinguish between mixed and unmixed ADs, advocating the use of high-impact moulded foam during transport for added protection of AD containers. The ISOPP and QuaPos standards both recommend that the admixtures be delivered directly to the ward/infusion lounge and that all staff involved in the transport be appropriately trained on procedures relating to accidental spillage. The ISOPP and QuaPos standards also provide more details than the ICON standards about the labelling of containers to identify that they contain ADs.

Work arrangements, warnings and work techniques

Work arrangements, warnings and work techniques are only briefly mentioned in the GPP standards. The ISOPP and QuaPos standards include the effectiveness of work arrangements (administrative controls) in the hierarchy of exposure control. The ICON standards state that, in the absence of an oncology pharmacist/pharmacy, compounding can be done by a registered nurse, but omit detailed mixing techniques. The ISOPP and QuaPos standards emphasize the importance of administrative controls, including clear signage to warn staff about exposure to ADs, designated areas, and detailed aseptic work techniques, reconstitution and compounding of ADs, cytotoxic waste, and spills. The ISOPP and QuaPos standards also comprehensively describe safe work techniques, including compounding ADs in a biological safety cabinet (BSC), sterile mixing, and pharmaceutical microbiology. All four standards recommend the use of luer-lock

syringes for compounding ADs. Reference is made to personnel who wish to conceive or who are pregnant in all except the GPP standards.

Education and training

The GPP standards state, in several places, that staff should receive "adequate training", but do not provide any details about the content or other issues related to the training. The ICON standards mention adequate training in basic principles of ADs, protocols, adverse effects, safe handling, preparation storage, and transport, but does not elaborate on any of these aspects. The ISOPP and QuaPos standards, however, do provide comprehensive guidance about course content, education providers, certification and recertification requirements, and documentation of training. The QuaPos standard also provides a practical example of continuous education.

Requirements for facilities and engineering controls

The GPP standards require that facilities are suitable for the preparation of ADs but provide no additional details regarding engineering controls. The ICON standards specify the requirements for the preparation of ADs in the mixing room, receipt and storage, management of expired ADs, and electronic prescribing of chemotherapy. In contrast, the ICON and ISOPP standards offer comprehensive requirements, including cleanroom specifications, air changes, pressure differentials, and the use of vertical flow BSCs. The QuaPos standard further details the monitoring, validation, and microbial safety of cleanrooms, underscoring the importance of meticulous engineering controls in maintaining a safe environment.

Personal protective equipment

Personal protective equipment includes masks, gowns, gloves, head and shoe coverings. There are variations regarding the use of other PPE in all the standards. The only types of PPE mentioned in the GPP standards are surgical masks, eye protection, single-use plastic aprons, and "appropriate" gloves (undefined). The ICON standards comprehensively describe the use of PPE. For example, they emphasize the importance of using EN 374 gloves, gowns that meet international standards, N95 masks, and head and shoe coverings. All relevant PPE is comprehensively discussed in the ISOPP and QuaPos standards. Both standards recommend the use of FFP3 type masks. The ISOPP standards make extensive reference to the United States Pharmacopoeia Chapter 800 for the requirements of the use of PPE,[10] including AD-resistant gloves. The QuaPos standard describes the use of EN standards/requirements related to the use of PPE, as well as the design of gloves and the frequency with which they should be changed.

Risk management

The GPP standards do not specifically address risk management, but the ICON standards provide a comprehensive framework for incident reporting, and management and implementation of quality assurance improvements. Risk management receives special attention in both the ISOPP and QuaPos standards. The ISOPP standards emphasize hazard identification, risk assessment, and the implementation of a risk control plan, including medical surveillance and incident management. The QuaPos standard provides an extensive evaluation of risks, with detailed requirements for standard operating procedures (SOPs), including a template of an SOP that can be used for risk management. In addition, incident reviews are discussed and procedures for documenting accidents are provided.

Medical monitoring

The GPP standards provide no details about environmental and medical monitoring. However, it erroneously states that "no adequate means of monitoring or measuring inadvertent absorption has been devised". The ICON standards, in comparison, discuss medical monitoring in detail – in line with the ISOPP and QuaPos standards. All three state that blood tests (including full blood counts and liver function tests) and medical examinations should be part of routine examinations. The QuaPos standard recommends annual examinations. Included is the recommendation to record 'baseline' measurements for new employees and 'exit' medical examinations when employees leave the company.

Cleaning and decontamination procedures

The GPP standards state that surfaces should be "thoroughly cleaned immediately after use according to local procedures" but do not provide details about the cleaning methods. The ICON standards state that N95 masks and protective eye wear should be used during the cleaning process but do not go into detail about that process. They do, however, refer to an internal SOP about cleaning, which is not included in the standards themselves. Cleaning and decontamination procedures are, however, extensively described in both the ISOPP and QuaPos standards, which specify the use of PPE during decontamination, and the cleaning agents and materials (such as gauze) that should be used. Cleaning procedures for specific areas in the pharmacy are provided, including the anteroom and storage areas, the BSC, and devices used in oral and/or topical formulations. The ISOPP and QuaPos standards also require cleaning procedures to be documented.

Spills and accidents

The GPP standards state that "correct action is taken following any accidental spillage or contamination of the person",

but do not stipulate what those "correct actions" are. They also state that "accidental spillage or contamination of the operator must be dealt with immediately and procedures must be established for the treatment of the skin, eyes and other surfaces". Again, the specific procedures are not described. The importance of training and documentation regarding spills is included in the ICON standards, without the provision of practical steps for handling spills. Although the ICON standards do not describe the required contents of a spill kit, they do require that such a kit is available in the workplace. They also recommend that all staff receive training on procedures following a spill and that all such events be documented. The ISOPP and QuaPos standards offer comprehensive instructions, including the contents of spill kits and detailed procedures for managing spills in various environments, such as the BSC, cleanroom, storeroom, and during transport. The contents of a spill kit, and procedures that need to be followed after an accidental spill in the BSC, cleanroom, storeroom, or during transport are comprehensively discussed.

Documentation, labelling and checking procedures

The GPP standards briefly mention the necessity for ADs to be "adequately labelled" but lack comprehensive guidance. In contrast, the ICON standards extensively detail the labelling requirements, particularly for take-home medications, and outline the necessary documentation for various processes, including transport of ADs, an AD mixing register, adverse reactions register, spills register, history of medical monitoring of staff, incident reporting, and training. Both the ISOPP and QuaPos standards provide detailed documentation protocols for the maintenance of operational records, labelling requirements, policies, SOPs, electronic documents, medical monitoring, education and training, exposure records, accidents, microbial monitoring, environmental monitoring, cleaning records, maintenance records, and BSC servicing records.

Discussion

Of the thousands of pharmacies registered with the SAPC, only five have the word 'oncology' in their names (as per the SAPC website, August 2024). All five are private pharmacies and are registered as either institutional (hospital) or community (retail) pharmacies as there is no option to register with the Council as an oncology pharmacy.

All registered pharmacies are obliged to adhere to the GPP standards. Only a few of the approximately 160 private oncology pharmacies in South Africa are registered with the SAPC; the others are affiliated with one of the two managed care organisations (the ICON or the SAOC), and adhere to their specific practice standards.

The objective of this study was to assess the effectiveness of the locally-used GPP and ICON standards against international oncology pharmacy best practice standards in protecting the health and safety of those handling ADs in private pharmacies in South Africa. The ICON standards proved to be more comprehensive than the GPP standards and compared well with the two international best practice standards recommended by the SASOPh.

While the GPP standards provide a basic framework for the transport of ADs, they lack the details included in the ICON, ISOPP and QuaPos standards. The GPP standard's lack of specificity, especially regarding labelling of containers and training of staff about spills during transport, could compromise the safety of employees.

There are also major gaps in the GPP standards regarding work arrangements, warnings, and work techniques when handling ADs, although these are adequately covered in the ICON standards. While both the GPP and ICON standards emphasise the necessity for adequate education and training, neither of these locally used standards define 'adequate', nor do they provide sufficient detail about the content.

Regarding the use of PPE, the GPP standards' stipulation for the use of surgical masks when mixing ADs is incorrect. Surgical masks have been proven to provide ineffective protection during the compounding of ADs.[11] The appropriate masks to use are FFP3 masks (recommended in the ISOPP and QuaPos standards). The latter provide superior protection from AD exposure than do surgical masks.

Risk management, which incorporates risk identification, risk measurement and assessment, risk mitigation, and risk reporting and monitoring, is an important aspect in protecting health and safety, in all industries.[12] Therefore, it is concerning that it is not mentioned in the GPP standards with respect to oncology pharmacy practice.

The GPP standards inaccurately state that no adequate monitoring methods for AD exposure exist. This may be because the standards were published more than a decade ago. Many developments have been made in this area since 2010, and there are now well-established methods that can be used to measure and monitor biological and environmental contamination of ADs in oncology pharmacies.[13,14] The medical monitoring stipulated in the international standards should be included in the GPP standard, including blood tests to measure baseline liver function tests, annual medical examinations, etc.

The GPP standards provide minimal guidance for cleaning and decontamination, While the ICON standards underscore the importance of staff training and the use of PPE, they fall short in stipulating specific cleaning methods. Both standards need to be updated to incorporate the guidance provided by the ISOPP and QuaPos standards, i.e., PPE use, cleaning agents, specific area procedures, and documentation requirements.

The GPP and ICON standards provide general recommendations regarding what to do in the event of an

Table 2. Comparison of the GPP, ICON, ISOPP and QuaPos standards regarding the 10 oncology pharmacy-related domains.

DOMAIN	GPP	ICON	ISOPP	QUAPOS
Transport of ADs	Procedures should be in place for the transport of syringes to patients.	Patient details must be visible. Delivery items must be documented. POD must be signed in good order. Labelling of contents and prescription must accompany. Thermolabile labels are discussed. Designated hard containers or bags should be leak proof and labelled 'ADs' or 'hazardous/cytotoxic'. Transport staff must be trained. Intrathecals transported separately.	Discuss the use of high-impact, moulded foam in cardboard boxes that can contain accidental breakage. ADs must be identifiable and demarcated. The handling of a spill is described. Receiving and inventory control is described. Distinction is made between mixed and unmixed ADs.	Discuss the use of unbreakable (protection against impact), liquid tight containers labelled as 'ADs or similar'. Discuss the handling of thermolabile products that are packaged and labelled accordingly. Containers should be lined with absorbent material.
Work arrangements, warnings and work techniques	Work technique is not defined. Requirements for equipment and procedures are not provided. Required "standard of quality" is not defined/ discussed.	Where no pharmacist is available, the mixing of ADs can be performed by a nurse. No reference to work arrangements or mixing techniques are made; assumed that this is in a company SOP. Mixing facility should be marked as "cytotoxic". "No eating/drinking" sign visible. Designated mixing area. Requirements for prescription standards and checks are described. Guidelines are provided for nurses who are pregnant/want to conceive/ breastfeeding.	A designated person should accept responsibility, certain personnel exclusions from working with ADs include family planning and illness, hygiene, staffing and work breaks. Special signage and demarcated areas must be indicated for storage, mixing area, transport, administration areas and AD waste. Provides guidelines regarding reproduction and breastfeeding and suggests alternative employment.	Details the requirements of pharmaceutical, non-pharmaceutical, transport and cleaning staff. Describes aseptic work technique including preparation phases, workflow for aseptic preparation, disinfecting and hygiene plans. Workflow of aseptic production setting including the correct use of ampoules and vials and injection into bags, drawing of a solution, using of a syringe and the filling of elastomeric pumps are provided. Provides guidelines for personnel attempting to conceive or could be pregnant
Education and training	Recommends special training of personnel but provides no details. It is not certain what is meant by "regular monitoring" to "comply with all procedures".	"Oncology pharmacist must have adequate knowledge". Education and training must be documented and repeated annually. Refers to training on safe handling, disposal and proper use of PPE but details are only available in SOPs. States that the aim is to access competency – duty of the head of facility. Staff should have adequate training in basic principles of ADs, protocols, adverse effects, safe handling,	Content of educational course is extensively described in 20 different elements. Discusses the requirements for educational providers. Documentation, certification, evaluation and re-education is discussed in detail.	Goal is to provide theoretical knowledge and practical skills and provides details. Contents of a training program are provided. Provides an example of continuous education. An example of training of new personnel in mixing ADs is given.

(continued)

Table 2. Continued.

DOMAIN	GPP	ICON	ISOPP	QUAPOS
		preparation, storage and transport, and special requirements for mixing but no details are provided. Assume that details are in company SOPs.		
Requirements for facilities and engineering controls	Recommends that facilities should be suitable but provides no details. Recommends the use of vertical flow BSC but provides no specifics on the requirements of the BSC.	Temperature logs must be used. Fridge alarm bells must be used. Luer-lock syringes must be used. The preparation in the mixing room is described. Receipt of ADs are described. Storage of ADs are described. Management of expired and/or damaged ADs containers are described. The requirements of an electronic system for prescribing are described.	Extensively discuss centralised preparation and facilities, the requirements for a clean room including a discussion on the ISO requirements and the requirements for pressure differentials between rooms (including storage room) to purge any AD fumes. Air changes and the requirements for an external exhaust is discussed. Moreover, the requirements for "pass-through" hatches and microbial monitoring, certification and validation of facilities are described. Extensively discuss the requirements for BSCs including the class of BSC required, airflow using HEPA filters, monitoring of the unit and discuss newer technologies such as "RABS"	Provides an extensive overview of facilities and engineering controls and includes design of the room, the gowning area (or anteroom) and mixing room. Details the requirements for the receiving area of ADs, the use of an airlock, storage area, cleanroom classification and ISO requirements, air changes and pressure differentials. Provides specifics for the requirements of a BSC and how to use it. Provides details of clean areas and pressure differentials. Discuss the monitoring of cleanrooms for air particulate contamination.
PPE (personal protective equipment)	Does not provide the specific requirements for gloves and aprons. The recommendation of the use of surgical masks have been proven to be ineffective and needs revision.	Describes the requirements for gloves and states that only gloves validated for chemotherapy preparation should be used, double gloving should be applied, specifies the DIN requirements for gloves and the frequency of changing. Gowns must meet ISO and EN standards for mixing ADs. The use of N95 masks and protective eyewear are recommended. Liquid repellent shoe covers should be worn.	The use of gowns including their characteristics and donning and well as USP <800> requirements are cited [10,15] requirements. The use of protective eyewear is described. Gloves must be AD resistant and replacement frequency is described.	A comprehensive overview of personal protective measures is given. The specifications for gowns (design, materials and characteristics), gloves must comply to EN standards and quality tests are provided. The materials, design, changing of gloves and double gloving is also described. Masks (breathing protection) includes EN requirements. Protective eyewear is described. Hair and shoe covers are described.
Risk management	No mention	Extensively discuss incident reporting, recording and management.	Discuss hazard identification and the compilation of a hazardous drug	Extensively discuss risk evaluation in terms of hazard definition,

(continued)

Table 2. Continued.

DOMAIN	GPP	ICON	ISOPP	QUAPOS
		Provides a general framework and examples of incidents. Implementation of quality assurance improvements are provided.	list, details on a risk assessment on the route that ADs travel through the facility. Recommends the implementation of a risk control plan which includes work operations, medical surveillance, management of spills, review of incidents and the implementation of corrective measures.	ascertainment, evaluation, measures, control and documentation. The requirements for SOPs are discussed in detail.
Medical monitoring	The statement that "no adequate means of monitoring or measuring inadvertent absorption has been devised" is questionable as biological and environmental monitoring have been performed in several studies.	Extensively discuss staff medical surveillance. This includes routine surveillance (baseline blood count) and regular medical examination. Guidance related to suspected exposure related health changes and post contamination surveillance is provided.	To identify health reversable effects due to AD exposure as early as possible. Proposes pre-employment baseline blood tests, periodic monitoring, acute after-accident event and exit-employment medical assessment. Remarks that some medical surveillance in certain countries could be unavailable or prohibitively expensive.	Annual medical assessments which include chest x-ray and full blood counts. Biological monitoring is recommended. Exposure of staff must be documented.
Cleaning and decontamination procedures	Does not provide the specifics on cleaning procedures. Recommend the use of "local procedures" which is undescriptive.	Recommends that cleaning staff be trained on cleaning procedures and that PPE must always be worn. All AD waste is to be disposed of by a licenced contractor. Details the requirements for disposal bins and sharps disposal containers. Additional recommendations are made concerning contaminated disposable equipment, PPE and cleaning equipment, contaminated non-disposable items and unused oral ADs.	Cleaning procedures are extensively discussed and includes the use of PPE, cleaning agents, materials and timing. The procedure for cleaning a BSC is provided step by step. It also addresses cleaning procedures like alternating germicides and residues left by disinfectants. It also provides extensive guidelines for cleaning of the anteroom and cleanroom. It provides details on the cleaning of devices used in oral or topical formulations. Discuss the validation process of cleaning procedures.	Provides details on the design of a cleaning plan which includes cleaning agents and materials. Discusses scheduling (timing) of disinfection/ decontamination. Provides extensive detail on the cleaning and disinfecting procedures for the BSC, preparation area (anteroom) and pass-through hatch.
Spills and accidents	Does not provide any specifics on procedures that should be followed after a spill occurred.	Provides the definition of a spill. Recommends that all employees receive training on spills. Recommends that events be	Describes the procedures for handling spills when occurring inside the BSC, the cleanroom, storeroom and during transport.	Provides the contents of a spill kit. Describes how a spill should be handled and cleaned up after a spill. Details on the disposal of

(continued)

Table 2. Continued.

DOMAIN	GPP	ICON	ISOPP	QUAPOS
		documented. Does not provide the recommended contents of a spill kit.	Describes minimum 13 items that should comprise a spill kit. Describes the clean-up of a spill in detail.	contaminated consumables post-decontamination.
Documentation, labelling and checking procedures	"Adequately labelled" should be elaborated on. This section provides no details but only recommends the use of documentation, labelling and checking procedures.	Describes 10 elements that are the minimum requirement for labels. Also discuss in detail the labelling of "to take home" ADs. Extensively discuss documentation required which includes transport, ADs mixing register, adverse reactions, facilities, awareness of staff, use of PPE, spillages, medical surveillance, incident reporting and training.	Extensively discuss documentation required for policies and SOPs, electronic documents, medical monitoring, education and training, exposure records and accidents, validation, microbial monitoring, contamination monitoring, cleaning logs, maintenance logs, pressure differentials, temperature and particle counts. Also elaborates on operational records. The labelling of ADs is discussed as well as relevant warning labels.	Discuss documentation for risk assessment, training, exposure, documentation areas, shipment of ADs and microbial monitoring. The documentation of final preparation and labelling requirements are discussed. Documentation for research and development and clinical trials are discussed in detail.

AD: antineoplastic drug, BSC: Biological safety cabinet, DIN: Deutsches Institut fur Normung, EN: European norm, GPP: good pharmacy practice, ICON: Independent Clinical Oncology Network, ISO: International Organization for Standardization, ISOPP: International Society of Oncology Pharmacy Practioners, PPE: Personal protective equipment, POD: Proof of delivery, QuaPos: Quality standard for the oncology pharmacy service, RABS: Restricted access barrier system. SOP: Standard operating procedure.

accidental AD spill, but neither provides details about what procedures to follow if a spill occurs or the required contents of spill kits. The contents of a spill kit are provided in the ISOPP standards, viz. written instructions, warning signs and PPE, a spill mat for small spills, a pillow for large spills, use of alkaline detergent solutions, etc., all of which should be added to the GPP and ICON standards.

There are significant differences in the standards, regarding documentation, labelling, and checking procedures for ADs. Again, it is the GPP standards that need to be expanded to include issues such as labelling requirements – particularly for take-home medications – and relevant documentation related to the transport of ADs, reporting of adverse reactions, maintenance of operational records, and medical and environmental monitoring.

Recommendations

It is crucial to update and revise local standards such as the GPP to align with international practices like ISOPP and QuaPos. Implementing comprehensive training programs, mandating advanced engineering controls in pharmacy facilities, and promoting the use of personal protective equipment (PPE) is essential steps to safeguard healthcare professionals. All pharmacies should be registered with the SAPC. The benefits of registration include, amongst others, professional recognition, which enhances credibility and trustworthiness among patients and healthcare providers; access to resources, guidelines, and updates provided by the SAPC that help them to stay informed about best practices and regulatory changes; access to Continuous Professional Development programmes, which ensure that the pharmacy and staff remain up-to-date with the latest developments in the field; and opportunities to network with other professionals and organizations within the SAPC. The GPP standards state only that facilities should be suitable for AD preparation, without specifying details about engineering controls Chemotherapy is transported long distances across the country on a daily basis, so it is essential that appropriate protocols are followed to ensure the safe transport of ADs and the of protection of those involved.

Conclusion

The adverse health effects that are related to occupational exposure to ADs are potentially serious, and revision of the standards related to the compounding of ADs in all pharmacies – whether registered with the SAPC or affiliated with the managed care organisation – is long overdue. The GPP standards (published in 2010) are very outdated. Additionally, some of the stipulations in the standards are erroneous, which could compromise the health and safety of oncology pharmacists (i.e., government employees) if followed. Until a concerted effort is made to revise the GPP standards, they remain redundant with regard to oncology pharmacy practice. All oncology pharmacists would do better to adhere to the more comprehensive ICON standards, although these standards also need to be updated in line with best practice, having last been revised in 2018. Revising and improving both these local standards in consultation with key role players in the oncology pharmacy industry will go a long way in protecting the health and safety of oncology pharmacists in South Africa Table 2.

Author contributions

RB conceptualised the study, designed the methodology, collected the data, contributed to the interpretation of the results, wrote the first draft of the manuscript. DB supervised the study, contributed to the design, critically reviewed the final draft of the manuscript. GN supervised the study, contributed to the design of the study, methodology and interpretation of results, critically reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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Ethical considerations

Not applicable.

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Assessing antineoplastic drug contamination in South African oncology pharmacies: Workplace and biological monitoring

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Abstract

Introduction: Antineoplastic drugs (ADs) are hazardous substances commonly used in medical oncology, posing health risks to pharmacy personnel through occupational exposure. Despite safety guidelines, contamination of surfaces in oncology pharmacies remains prevalent. In this study, we assessed surface contamination and biological uptake of ADs in selected South African oncology pharmacies.

Methods: Six pharmacies (three from each of two medical oncology service providers, SP1 and SP2) participated. Surface wipe samples were collected from three areas in each pharmacy (containment-primary engineering control (C-PEC), floor, adjacent surface) before and after decontamination procedures. Nine ADs were quantified, using high-pressure liquid chromatography tandem mass spectrometry (HPLC-MS/MS). 24-h urine samples were collected from six pharmacy personnel. The DeRmal Exposure Assessment Method (DREAM) was used to estimate exposure risks. The results were compared with those from an observational study that assessed compliance with safety protocols in the same six pharmacies.

Results: Surface contamination was higher in SP1 than in SP2 pharmacies, with 5-fluorouracil (5-FU) being the most frequently detected AD. Post-decontamination samples showed a 17.4% reduction in 5-FU contamination, although SP1 pharmacies still had higher post-decontamination concentrations than SP2 pharmacies, especially on floors. Cyclophosphamide and ifosphamide were detected in the urine of two participants from SP1.

Conclusion: We demonstrated higher contamination and occupational exposure risks in SP1 than in SP2 pharmacies, indicating a need for strict decontamination protocols and better use of personal protective equipment in the SP1 pharmacies. The SP2 pharmacies may serve as a model for oncology pharmacy safety in South Africa.

Keywords

Antineoplastic drugs, occupational exposure, oncology pharmacy, surface contamination, biological monitoring

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Introduction

Health effects of exposure to antineoplastic drugs

Much research has been conducted, describing exposure to antineoplastic drugs (ADs) in hospitals and medical oncology centres.[1–5] Contamination is also common in oncology pharmacies worldwide.[6] The genotoxic effects of ADs, such as sister-chromatid exchanges and chromosomal aberrations, were first described more than 40 years ago.[7,8] Adverse health effects of AD exposure range from minor to severe and include tumours, leukaemia, congenital malformations, foetal loss, infertility, ectopic pregnancies, low birth weight, skin rashes, and other effects on body tissues with rapidly dividing cells (e.g., gastrointestinal tract, hair and nails).[4,9] In response to the negative health effects associated with the handling of chemotherapy agents, the American Society of Health-System Pharmacists (ASHP) issued its first recommendations for oncology pharmacy staff on the safe handling of

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ADs in 1985.[10] Many other guidelines regarding the safe handling of ADs have since been published.[11–14]

Routes of exposure

Exposure can occur during drug preparation, handling, or cleaning activities. The most common route of exposure to ADs is through the skin due to direct contact or contact with contaminated surfaces. Thus, effective decontamination protocols, regular monitoring, and strict safety measures, including the use of personal protective equipment (PPE), are essential to protect those working with ADs.[15–17] Exposure to ADs may also occur through inhalation if pharmacy staff are exposed to aerosols or dust particles containing ADs. Other routes of exposure include accidental ingestion and accidental injection during preparation.

Several studies have detected ADs in the urine of oncology pharmacy personnel.[18,19] However, some researchers have found no evidence of AD uptake in oncology pharmacy personnel,[20–22] which could be ascribed to good oncology pharmacy practice.

Oncology pharmacy practices in South Africa

Parkin et al. estimated that the incidence of cancer would increase by 70% in sub-Saharan Africa from 2012 to 2030.[23] The role of the oncology pharmacist in providing oncology care is thus more important than ever,[24] including in emerging low- to middle-income countries (LMICs) like South Africa and other African countries where oncology pharmacy practice is evolving.[25] Oncology pharmacy is not an officially recognised pharmacy speciality in South Africa; no registration as an oncology pharmacist is required, and no official or accredited training programmes are available.[26] There are also no official oncology-specific guidelines in South Africa, and legislation about the preparation of ADs is outdated.[27] Although many pharmacies where parenteral ADs are administered adhere to high standards,[28] not all follow guidelines like the International Society of Oncology Pharmacy Practitioners (ISOPP) 'Safe Handling' of Cytostatics, and the European Society of Oncology Pharmacy (ESOP) Quality Standard for the Oncology Pharmacy Service (QuaPos), which include using PPE and conducting environmental and biological monitoring.[11,12] The risk of exposure of oncology pharmacists and others who mix ADs thus remains a concern.

The objective of this study was to assess the potential for exposure of oncology pharmacy personnel to ADs based on contamination of pharmacy workspace surfaces.

Methods

Participating sites

Four service providers (SPs), representing four oncology pharmacy chains in the private sector in South Africa were approached to participate in the study; two refused without providing reasons. We successfully recruited six pharmacies located in urban areas: three in Gauteng province (SP1) and three in the Western Cape province (SP2).

Antineoplastic drugs measured

The concentrations of nine ADs were measured on surfaces in the six pharmacies and in the urine of six pharmacy personnel (one from each pharmacy), viz. ifosphamide (IF), cyclophosphamide (CP), docetaxel (DOC), paclitaxel (PAC), gemcitabine (GEM), and 5-fluorouracil (5-FU), methotrexate (MTX), etoposide (ETO) and doxorubicin (DOX). These are some of the most commonly ADs used in South African medical oncology treatment protocols.

Workplace surface wipe sampling

Using wipes (described in detail below), ADs were measured on the surface inside the containment primary engineering control (C-PEC) – the device in which ADs are mixed, the floor in front of the unit, and a surface adjacent to the C-PEC (e.g., a desk or trolley), from March to September 2023. In this way, three measurements of ADs were taken from each of the three surfaces on a single day: one in the morning before the mixing of ADs began (pre-decontamination measurement), one after the surface decontamination (cleaning) (post-decontamination measurement), and the third at the end of the day (end-of-day measurement). Thus, nine surface wipes were collected from each pharmacy. All pharmacies used standardised methods for decontamination, viz. 70% ethanol and sterile gauze for cleaning the C-PEC and adjacent surfaces, and soap, chlorine and water for cleaning the floor with a mop.

The sample wipe kits - provided by Exposure Control Sweden (ECS) - contained gloves, tissues, diluent (formic acid, CH_2O_2 solution), labels, and containers for storage. Surfaces of 0.5 m^2 were drip-wetted with 17 ml of formic acid (CH_2O_2) solution, after which two dry wipes were used to dry the surface in a zigzag (Z) pattern. The method for sample collection followed ECS's procedures.[29] The wipes were stored in airtight containers, frozen at −20 °C for preservation, and transported to the ECS laboratory at Radboud University in the Netherlands for analysis of ADs.

Biological monitoring

Twenty-four hour urine samples were collected from each of the six participants on the same day as the surface wipe sample collection. Study participants collected their own urine samples in 10 ml vacuum tubes (similar to those used for blood samples), using a measuring cup and transfer device. Each participant recorded the volume of urine passed. Using this method, it was not necessary to collect all urine passed in the 24-h period. Ten vacuum

tubes were provided to each participant for the collection of a maximum of 10 urine samples, which were frozen at −20° C on-site at the pharmacy in a dedicated freezer, or at the participants' homes, immediately after collection (in which case, the samples were collected the following day and stored at −20°C).

Each urine sample from each participant was analysed for ADs independently (samples from the same individual were not pooled). The concentrations of ADs were measured in each individual urine sample and the mean concentrations were calculated for each participant. The limits of detection (LOD) and limits of quantification (LOQ) for each AD are provided in Table 1.

The samples were analysed using high-pressure liquid chromatography with tandem mass-spectrometry (HPLC-MS/MS).

The DeRmal Exposure Assessment Method

The DeRmal Exposure Assessment Method (DREAM) was used to estimate exposure risks. This is a structured observational method consisting of an inventory and an evaluation component. The inventory component is completed by an occupational health professional and involves a hierarchically structured questionnaire/list of observation items designed to assess determinants and routes of exposure. It is divided into six modules: company, department, agent, job, task, and exposure. Each response within the questionnaire is allocated a specific score. The results of the DREAM analysis are captured in a freely available Microsoft-Excel-based tool in the language, Visual Basic for Applications.[30] In the evaluation component of the DREAM, these scores are processed through a series of algorithms to generate indices of potential exposure, i.e., the amount of contaminant landing on the outer layer of work clothing, and actual exposure, i.e., the amount of contaminant reaching the exposed skin, and dermal exposure in arbitrary units (AU) for nine different body parts and at the task level.[31] This approach allows for the detailed characterisation of the agent, the probability and intensity potential of exposure, and the assessment of hygiene practices, including the use of personal protective equipment in the workplace.

Table 1. Limits of detection and quantification for nine antineoplastic drugs for surface and urine samples.

	Surface concentration ng/cm^2		Urine concentration ng/ml	
AD	LOD	LOQ	LOD	LOQ
5-fluorouracil	0.007	0.020	-	-
Gemcitabine	0.002	0.002	-	-
Ifosphamide	0.002	0.004	0.003	0.01
Cyclophosphamide	0.002	0.004	0.003	0.01
Methotrexate	0.001	0.002	-	-
Docetaxel	0.002	0.004	-	-
Paclitaxel	0.002	0.004	-	-
Etoposide	0.013	0.040	-	-
Doxorubicin	0.001	0.020	-	-

AD: antineoplastic drug, LOD: limit of detection, LOQ: limit of quantification.
Source: Exposure Control Sweden (www.exposurecontrol.net).

Observational study

A cross-sectional pilot study was conducted in the same six oncology pharmacies in 2023 to assess work and workplace practices, and the findings were published.[28] In brief, a 43-item checklist developed from international best practice guidelines was used to evaluate compliance in seven categories: engineering controls, administrative controls, personal protective equipment (PPE), education and training, medical and workplace monitoring, cleaning procedures, and waste handling. Data were collected through direct observations, document reviews, and personnel interviews. Compliance was scored as full, partial, or non-compliant for each category; total scores were calculated for each pharmacy and service provider. These scores were compared with the DREAM analysis risk estimates (described above) and the proportion of wipe samples with 5-FU concentrations ≥ 1 ng/cm^2. 5-FU was selected because it was the AD for which the concentrations were highest in most of the pharmacies, and for which the number of measurements above the LOD was highest.

Data analysis and interpretation of the results

Surface contamination data, including the 90th percentiles of the distributions, were displayed, using the traffic light model of Sessink et al.[29] This provided a visual indication of the extent of contamination for the areas sampled (traffic light model). Red indicates high contamination (≥10 ng/cm^2), green low contamination (<1 ng/cm^2) and orange and yellow as medium-high (1.0-<10 ng/cm^2) and medium-low contamination (0.1-<1.0 ng/cm^2), respectively. This is per German, Dutch and American national substance reference values as an indication of surface contamination with ADs.[32,33]

Descriptive statistics are provided for pre-decontamination and end-of-day concentrations combined (paired) since the end-of-day sample can be considered to be a 'pre-decontamination' sample of the following day. An imputation of non-detect values was conducted, using the online tool, NDExpo (www.expostats.ca), which uses regression on order statistics (ROS). An independent t-test was used to test differences between the mean numbers of patients for whom AD treatments were prepared in each SP as the exact numbers of AD preparations were not available. The Wilcoxon signed rank test, using C-PEC and adjacent surface pre- and post-decontamination data, was applied to evaluate the reduction of decontamination and to check for statistical significance. Spearman's rank correlation analysis

was used to assess the strength and direction of the relationship between the mean C-PEC and adjacent surface, 5-FU concentrations (pre-decontamination and end-of-day measurements), the DREAM estimates, the observational study scores, and the total number of samples with concentrations ≥ 1 ng/cm^2 (six correlations). Jeffery's Amazing Statistics Programme (JASP) version 0.18.3 (Amsterdam, the Netherlands - https://jasp-stats.org/) was used for statistical analysis. A p-value of <0.05 was considered to indicate statistical significance.

Ethics approval

Ethics approval for the collection of surface wipes and urine samples was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC); certificate no. M190312.

Results

Surface contamination of antineoplastic drugs

None of the samples was positive for ETO, and only one sample was positive for DOX; both ADs were therefore omitted from the statistical analyses. The pre- and post-decontamination sample concentrations, and the end-of-the-day concentrations are displayed as "traffic-light models" in Tables 2 and 3, respectively. One hundred and sixty-four of the 252 (65.1%) wipe samples (beginning and end-of-day) were positive for at least one AD, i.e., concentrations were above the LOD. The surface contamination in 10 (6.1%) of the wipe samples was classified as 'high', in 42 (25.6%) it was classified as 'medium-high', in 65 (39.6%) as 'medium-low', and in 135 (82.3%) as 'low' or below the LOD. The highest concentration was observed for 5-FU from the C-PEC surface in pharmacy 2 (SP1), at 83.9 ng/cm^2. Overall, 5-FU was the most frequently detected AD (n = 29), followed by CP (n = 28). There were 41 non-detect samples from SP1 and 48 from SP2.

Comparison of antineoplastic drug concentrations between service providers

The summary statistics of the AD concentrations in the SP1 and SP2 pharmacies are shown in Table 4. There were notable discrepancies in surface concentrations between the two service providers. Pre- and end-of-day contamination concentrations were consistently higher in SP1 than in SP2 pharmacies, particularly for 5-FU. The proportions of AD concentrations in the highest contamination category (≥ 10 ng/cm^2) were 2.8% and 1.2% in SP1 and SP2 respectively. Similarly, a higher proportion of samples in the SP1 than in the SP2 pharmacies fell into the "medium-high" concentration category (10.3% and 6.0%, respectively). The proportion of SP1 samples in the "medium-low" concentration category (13.5%) was also higher than that of SP2 samples (11.9%). There was a higher proportion of samples in the "low" concentration category (< 0.1 ng/cm^2) in SP2 pharmacies (31.0%) than in SP1 pharmacies (22.8%). For the 90th percentile, SP1, 5-FU and CP were high (≥ 10 ng/cm^2) compared to SP2 which had none. In SP1, the 90th percentile for MTX was low (< 0.1 ng/cm^2). There was no significant difference between the mean number of patients processed in SP1 and SP2.

Effectiveness of decontamination

The number of wipe samples that were positive for at least one AD decreased from 88 to 66 from the pre- to the post-decontamination sampling (17.4% reduction). Only two of the 126 post-contamination concentrations (1.6%) - one for 5-FU and one for CP (both in SP1 pharmacies) were classified as 'high,' compared to seven (5.8%) of the pre-decontamination concentrations. Sixteen measurements (12.7%) were in the 'medium-high' category - a 6.3% reduction in the number of samples in this concentration category; 24 measurements (19%) fell into the 'medium-low' category, 8.8% fewer than in the pre-decontamination period. The proportion of concentrations that was classified as 'low' increased by 19.1% (42 samples showed no detectable contamination). The differences between the pre- and post-decontamination mean concentrations were statistically significant for 5-FU (p = 0.002), GEM (p = 0.021), DOC (p = 0.024), and PAC (p = 0.021). None of the pharmacies had a cleaning protocol.

The 90th percentiles and mean concentrations of most of the ADs were higher in the SP1 than the SP2 pharmacies (Table 4). The 90th percentile concentrations for 5-FU and CP in SP1 pharmacies were above the threshold of 10 ng/cm² ("high" concentration category), indicating a risk of exposure to these ADs for pharmacy personnel in the SP1 pharmacies. Specifically, the concentrations of 5-FU, MTX, IF, and CP were higher in the SP1 than the SP2 pharmacies. However, concentrations of GEM were slightly higher in SP2 than in SP1 pharmacies. Concentrations of DOC and PAC were similar in the pharmacies of both providers.

Antineoplastic drugs detected in urine samples

Two of the six participants' urine tested positive for IF and CP; both were from SP1 pharmacies. The mean concentrations in the first participant's urine were 3.77 ng/ml and 0.21 ng/ml for IF and CP, respectively. The mean concentrations in the second participant's urine were between the LOD and LOQ and could not be quantified.

Comparison between DREAM estimates and observational study scores for 5-FU surface concentrations

The DREAM estimates and the scores calculated in the observational study are summarised in Table 5. Variations were observed in the task-weighted dermal exposure

Table 2. Traffic light model of surface concentrations of antineoplastic drugs per pharmacy, pre- and post-decontamination, including no. of patients per pharmacy per day (N = 252) and participant experience.

	Patients per day (n)	Participant experience (years)		5FU	GEM	MTX	IF	CP	DOC	PAC	DOX	ETO
Pharmacy			**C-PEC**									
1 (SP1)	25	9	PRE	6.56	ND	ND	ND	2.80	0.09	0.06	ND	ND
			POST	0.02	0.01	ND	ND	0.42	ND	ND	ND	ND
2 (SP1)	20	4	PRE	83.78	3.80	ND	11.06	10.52	0.10	0.01	ND	ND
			POST	41.52	1.50	ND	3.58	4.18	ND	ND	ND	ND
3 (SP1)	32	18	PRE	5.68	1.16	2.70	0.52	0.60	0.38	0.54	ND	ND
			POST	0.44	0.24	0.24	0.72	0.38	0.06	0.04	ND	ND
1 (SP2)	20	10	PRE	0.70	7.12	0.01	0.01	0.01	0.06	0.16	ND	ND
			POST	0.07	1.04	ND	0.00	ND	0.02	ND	ND	ND
2 (SP2)	20	20	PRE	21.38	5.74	ND	0.26	1.32	0.32	0.96	ND	ND
			POST	2.16	0.62	ND	0.11	1.12	0.05	0.52	ND	ND
3 (SP2)	30	13	PRE	19.44	2.04	0.16	0.26	0.48	0.01	0.20	ND	ND
			POST	3.22	0.44	0.02	0.05	0.03	ND	0.04	ND	ND
			Floor									
1 (SP1)	25	9	PRE	12.28	0.16	ND	ND	0.50	0.11	0.01	ND	ND
			POST	ND	ND	ND	ND	0.01	ND	ND	ND	ND
2(SP1)	20	4	PRE	ND	ND	ND	0.34	0.54	ND	ND	ND	ND
			POST	1.58	ND	ND	53.82	5.54	0.04	ND	ND	ND
3 (SP1)	32	18	PRE	0.18	0.08	0.09	5.80	2.10	0.01	0.50	ND	ND
			POST	ND	ND	ND	ND	0.01	ND	ND	ND	ND
1 (SP2)	20	10	PRE	0.44	0.16	ND	0.22	0.64	ND	ND	ND	ND
			POST	0.16	0.06	ND	0.16	0.48	ND	ND	ND	ND
2 (SP2)	20	20	PRE	1.88	0.16	ND	0.09	1.28	0.01	0.02	ND	ND
			POST	4.42	0.11	ND	ND	1.38	ND	ND	ND	ND
3 (SP2)	30	13	PRE	0.64	0.13	ND	ND	ND	ND	ND	ND	ND
			POST	0.08	0.03	ND	0.04	0.01	ND	ND	ND	ND
			Adjacent surface									
1 (SP1)	25	9	PRE	ND	ND	ND	ND	2.48	ND	0.00	ND	ND
			POST	ND	ND	ND	ND	0.12	ND	ND	ND	ND
2 (SP1)	20	4	PRE	13.76	0.44	ND	1.88	1.66	ND	ND	ND	ND
			POST	6.02	0.52	ND	2.26	1.42	0.01	ND	ND	ND
3 (SP1)	32	18	PRE	4.84	3.14	3.68	0.90	0.94	0.56	1.08	ND	ND
			POST	3.54	0.96	1.18	0.68	0.48	0.30	0.32	ND	ND
1 (SP2)	20	10	PRE	ND	0.02	ND	ND	ND	ND	ND	ND	ND
			POST	ND	ND	ND	ND	ND	ND	ND	ND	ND
2 (SP2)	20	20	PRE	5.62	0.88	0.02	0.28	1.12	0.01	0.01	ND	ND
			POST	0.30	0.08	ND	0.07	0.80	ND	ND	ND	ND
3 (SP2)	30	13	PRE	3.64	0.28	ND	0.01	0.06	0.02	ND	ND	ND
			POST	0.07	0.13	ND	0.03	ND	ND	ND	ND	ND

5-FU:5-fluorouracil, CP: cyclophosphamide, C-PEC: Containment-primary engineering control, DOC: docetaxel, DOX: doxorubicin (excluded from analysis), ETO: etoposide (excluded from analysis), GEM: gemcitabine, IF: ifosphamide, MTX: methotrexate, PAC: paclitaxel.

Concentration: high medium high medium low low

Table 3. Traffic light model of end-of-day AD concentrations per pharmacy (N = 126).

Pharmacy	Area	5-FU	GEM	MTX	IF	CP	DOC	PAC	DOX	ETO
		Concentration of antineoplastic drugs (ng/cm^2)								
1 (SP1)	C-PEC	ND	ND	ND	ND	0.60	0.08	0.21	ND	ND
	FLOOR	0.96	0.26	ND	ND	3.56	ND	0.74	ND	ND
	AS	ND	ND	ND	ND	ND	ND	ND	ND	ND
2 (SP1)	C-PEC	22.90	1.22	ND	1.64	28.48	0.03	0.01	ND	ND
	FLOOR	0.62	0.07	ND	0.72	1.82	ND	ND	ND	ND
	AS	7.04	0.38	ND	1.38	1.76	0.02	ND	ND	ND
3 (SP1)	C-PEC	ND	0.24	0.07	0.76	5.20	0.04	0.10	ND	ND
	FLOOR	3.66	0.92	0.10	2.86	9.72	ND	0.04	ND	ND
	AS	1.10	0.07	0.24	0.44	0.86	0.10	0.13	ND	ND
1 (SP2)	C-PEC	0.10	0.66	ND	ND	ND	0.03	ND	ND	ND
	FLOOR	0.05	0.03	ND	0.09	0.26	ND	ND	ND	ND
	AS	ND	ND	ND	ND	ND	ND	ND	ND	ND
2 (SP2)	C-PEC	4.02	0.58	ND	0.17	10.88	0.38	0.98	ND	ND
	FLOOR	0.42	0.07	ND	0.06	0.70	0.01	ND	ND	ND
	AS	1.04	0.12	ND	0.01	1.26	ND	ND	ND	ND
3 (SP2)	C-PEC	5.76	1.54	0.03	0.04	0.07	0.01	0.98	0.05	ND
	FLOOR	0.20	0.02	ND	ND	ND	ND	ND	ND	ND
	AS	0.07	0.02	ND	ND	ND	ND	ND	ND	ND

AS: Adjacent surface, C-PEC: Containment-primary engineering control, ND: not detected. 5-FU:5-fluorouracil, CP: cyclophosphamide, DOC: docetaxel, DOX: doxorubicin (excluded from analysis), ETO: etoposide (excluded from analysis), GEM: gemcitabine, IF: ifosphamide, MTX: methotrexate, PAC: paclitaxel SP: service provider.

Concentration: high medium high medium low low

estimates across the six pharmacies. Pharmacy 1 and Pharmacy 2 (both SP1) exhibited the highest task-weighted potential dermal exposure estimates - both at medium-high levels of 38.3 AU. The estimate was slightly lower in pharmacy 3, at 37.4 AU. In contrast, service provider 2 pharmacies had significantly lower estimates (21.5 AU). This is reflected in the task-weighted actual dermal exposure estimates. SP2 pharmacies also scored higher than SP1 pharmacies in the work and work-related practices observational study (higher than 70% and lower than 50%, respectively).

Table 6 shows the correlation between 5-FU surface concentrations and DREAM estimates for dermal exposure. The correlation was poor and not statistically significant ($\rho = 0.154$, $p = 0.770$). The DREAM estimates were moderately but also non-significantly correlated with the number of surface wipe samples with concentrations > 1 ng/cm^2. ($\rho = 0.344$, $p = 0.504$). The observational study scores were significantly negatively correlated with the DREAM estimates ($\rho = -0.926$, $p = 0.008$). There was no correlation between the number of surface wipes with AD concentrations >1 ng/cm^2 and the observational study scores ($\rho = -0.087$, $p = 0.87$).

Discussion

The ADs measured in this study were 5-FU, GEM, DOX, ETO, MTX, IF, CP, DOC and PAC. Initially, 5-FU, IF, CP and MTX were selected as these are some of the most commonly used ADs in patient treatment protocols. However, in addition to this, the laboratory also analysed the samples for GEM, DOX, ETO, DOC and PAC. The ADs most frequently detected in the analysis of the surface wipes were 5-FU, CP, and GEM. Previous studies in oncology pharmacies have also reported 5-FU, CP, and GEM to be among the most frequently detected ADs.[5,34]

The surface concentrations of 5-FU, CP, and IF were higher in the SP1 than in the SP2 pharmacies; GEM was the only AD with a lower mean concentration in SP1 than in SP2 pharmacies. In one of the SP1 pharmacies the pre-decontamination concentration of 5-FU on the C-PEC surface was 83.78 ng/cm^2 – almost four times higher than the maximum concentration in any of the SP2 pharmacies (21.38 ng/cm^2). Although this suggests that the contamination control measures used in the SP1 pharmacies were less effective than those used in the SP2 pharmacies, this is based on only one "high" 5-FU value.

Table 4. Summary statistics for pre-decontamination and end-of-day antineoplastic drug wipe concentrations, combined, for all surfaces (N = 126).

	Antineoplastic drug surface concentrations (ng/cm^2)													
	Service provider 1							Service provider 2						
				Percentile							Percentile			
AD	Mean	SD	Maximum	25th	50th	75th	90th	Mean	SD	Maximum	25th	50th	75th	90th
5-FU	9.08	19.65	83.78	0.07	2.38	6.92	16.50	3.64	6.40	21.38	0.12	0.67	3.93	9.87
GEM	0.76	1.02	3.80	0.03	0.20	0.80	1.80	1.09	2.04	7.12	0.04	0.16	0.83	3.15
MTX	0.38	1.04	3.68	2.00×10^{-6}	1.36×10^{-5}	0.09	0.98	0.01	0.04	0.16	2.72×10^{-4}	0.001	0.004	0.02
IF	1.57	2.77	11.06	0.002	0.62	1.58	3.74	0.09	0.10	0.28	0.01	0.03	0.15	0.26
CP	4.12	6.79	28.48	0.67	1.79	3.37	10.96	1.01	2.51	10.88	0.02	0.16	1.02	1.29
DOC	0.09	0.15	0.56	7.95×10^{-4}	0.03	0.19	0.19	0.05	0.11	0.38	0.004	0.01	0.02	0.14
PAC	0.19	0.3	1.08	6.78×10^{-4}	0.03	0.2	0.60	0.19	0.37	0.98	0.004	0.01	0.13	0.97

SD: standard deviation, 5-FU:5-fluorouracil, CP: cyclophosphamide, DOC: docetaxel, GEM: gemcitabine, IF: ifosphamide, MTX: methotrexate, PAC: paclitaxel.
Concentration: high medium high medium low low

Similar concentrations for 5-FU and CP to those measured in our study have been reported by others. Sottani et al. measured CP, 5-FU, GEM and platinum-containing ADs over a five-year period in Italy; 55% of samples were above the LOD.[35] Chabut et al. measured nine ADs, including CP, 5-FU, GEM, IF, MTX and PAC in a longitudinal study in Canada.[36] Surfaces were frequently contaminated with CP (34% of the positive samples were above the LOD) and GEM (16% were above the LOD). In a study by Sessink et al.[29] in Belgium, the highest concentration recorded for 5-FU was 2.38 ng/cm^2. The detection of 5-FU across all pharmacies in our study, even after decontamination (although at higher concentrations in SP1 pharmacies) points to a potentially higher risk of dermal exposure to this AD. Concentrations of other ADs such as CP were also more frequently higher in SP1 than in SP2 pharmacies on the three surfaces sampled.

Concentrations of ADs were also higher on adjacent surfaces in SP1 than in SP2 pharmacies, with 5-FU concentrations exceeding 13 ng/cm^2 pre-decontamination in SP1, compared to a maximum of 5.62 ng/cm^2 in SP2. The 90th percentiles of 5-FU and CP were higher than 10 ng/cm^2 in SP1 only, again suggesting that decontamination procedures were probably ineffective and work practices poor.

We did not detect a reduction in concentrations of all ADs across all surfaces after decontamination. Post-decontamination concentrations of 5-FU, IF, CP and DOC were higher than pre-decontamination concentrations in one of the SP1 pharmacies. One explanation for this could be the use of already contaminated cleaning equipment (mops).

Decontamination effectiveness will be more variable in real life workplace situations than in well-controlled studies as reported by Simon et al.[37] and Palamini et al.[38] In the latter study it was demonstrated that a sodium hypochlorite solution (NaOCl – 5.25%) removed 96.62% and 99.94% of IF and MTX, respectively on surfaces. They found that using 70% ethanol (EtOH), range 47.5–95.1% (mean 73.7%) was less effective. In a decontamination study by Hon et al. concentrations of ADs remained detectable in a controlled experiment, regardless of the cleaning agent used or the method of decontamination.[39] Regardless, it is critical to thoroughly and appropriately decontaminate cleaning equipment daily.

The urine analysis results also indicated that contamination was higher in SP1 than in SP2 pharmacies. Only personnel from SP1 pharmacies had detectable concentrations of ADs (IF and CP) in their urine. Ndaw and Remy[40] reported similar findings in a study in France, published in 2023: 53% of urine samples tested positive for CP, IF, MTX and α-fluoro-β-alanine (F-BAL - a metabolite of 5-FU) or any combination thereof. The positive urine results in SP1 personnel likely reflect inadequate PPE usage, as was documented in the observational study.[28]

Personnel in SP1 pharmacies used substandard PPE, such as plain latex gloves, single-use surgical masks, and woven, non-disposable gowns which did not cover the forearms. SP2 pharmacies were fully compliant in terms of the types of PPE used, including non-permeable, disposable gowns and other appropriate masks (such as FFP3 masks). As SP1 used substandard PPE, the gowning

Table 5. Comparison of DREAM estimates and observational study compliance scores.

Pharmacy	DREAM estimate (AU)		Observed Compliance score (%)
	Potential dermal exposure[a]	Actual dermal exposure[a]	
1 (SP1)	38.3	22.8	33.0
2 (SP1)	38.3	21.9	37.8
3 (SP1)	37.4	22.8	49.9
1 (SP2)	21.5	0.8	77.0
2 (SP2)	21.5	0.8	78.4
3 (SP2)	21.5	0.8	79.3

atask-weighted, AU: arbitrary units, DREAM: DeRmal Exposure Assessment Method, SP: service provider.

Table 6. Correlation between 5-FU concentrations, DREAM estimates, observational study scores, and number of surface wipe samples with 5-FU concentrations ≥ 1 ng/cm^2.

Variable		5-FU concentration (ng/cm^2)	DREAM estimate[a]	No. wipe sample concentrations ≥ 1 ng/cm^2
5-FU concentration (ng/cm^2)	ρ	—		
	p-value	—		
DREAM estimate[a]	ρ	0.154	—	
	p-value	0.770	—	
No. surface wipe sample concentrations ≥1 ng/cm^2[b]	ρ	0.899[a]	0.344	—
	p-value	0.015	0.504	—
Observational study score	ρ	0.143	−0.926	−0.087
	p-value	0.803	0.008	0.87

afor potential dermal exposure; ρ: Spearman's rank correlation coefficient; DREAM: DeRmal Exposure Assessment Method [b]all antineoplastic drugs.

procedure was not correctly followed and forearms were exposed. Both SP1 and SP2 also did not comply entirely with donning and doffing of PPE as none had an ante-room in any of the pharmacies.

Although we did not measure dermal exposure, the DREAM allowed us to estimate this exposure, and supported our conclusion that working in an SP1 pharmacy poses a higher risk of dermal exposure than working in an SP2 pharmacy. The differences between the two SPs indicate variability in dermal exposure to ADs, which is likely due to differences in pharmacy practices, including PPE use. The task-weighted skin exposure estimates in two of the SP1 pharmacies were almost twice as high as those in the SP2 pharmacies, supporting the post-decontamination surface concentration findings.

The significant negative correlation between the DREAM estimates and the observational study scores indicates that poor implementation of, and adherence to safety protocols (specifically in SP1 pharmacies) potentially leads to higher dermal exposure levels.

Limitations

The main limitation of this study was the small sample size. This was largely due to the unwillingness of some large service providers to participate in the study, and partly due to the high costs of transport and chemical analysis of the samples. Consequently, the findings cannot be generalized to all oncology pharmacies in South Africa. Moreover, it was impossible to estimate the quantities of the different ADs used in each pharmacy due to restrictions under the Protection of Personal Information (POPI) Act, and electronic prescription and invoice data could not be obtained.

Conclusion

This is the first study to investigate workplace contamination and biological uptake of ADs in oncology pharmacies on the African continent. The study highlighted significant differences in surface contamination, decontamination effectiveness, and the potential for occupational exposure between the two medical oncology service providers. Concentrations of ADs were consistently higher in SP1 than SP2 pharmacies and the dermal exposure risks were higher, as evidenced by both surface concentrations and biological monitoring results. The findings suggest that decontamination protocols and PPE practices in SP1 pharmacies require improvement to reduce occupational exposure to ADs. Although the lower surface concentrations and absence of ADs in urine samples in SP2 pharmacy personnel suggest more effective implementation of safety protocols and better use of PPE, additional research is needed if the SP2 practices could serve as a model for improving oncology pharmacy practices in South Africa and protecting the health of oncology pharmacists.

Author contributions

Conceptualization, RB; methodology, RB, DB; Data collection and curation, RB; formal analysis, RB, DB; writing - original draft preparation, RB; writing - review and editing, GN, PS, DB. All authors have read and agreed to the final version of the manuscript.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

This study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M190312) on 29-03-2019. All participants and stakeholders provided written informed consent prior to enrolment in the study. This research was conducted ethically in accordance with the declaration of Helsinki.

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Recommending tailor-made risk control strategies to mitigate dermal exposure to antineoplastic drugs in South African oncology pharmacies

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Abstract

Introduction: South African oncology pharmacies face, due to rising cancer incidence amongst the population, an increased risk of occupational hazards, particularly related to dermal exposure to hazardous antineoplastic drugs (ADs). This study evaluates intervention strategies aimed at mitigating such exposure by examining their effectiveness, cost, feasibility, and acceptance.
Methods: A literature review was conducted across PubMed, Scopus, Web of Science, and Google Scholar for studies published within the last 10 years. Data on interventions—including closed-system transfer devices (CSTDs), decontamination protocols (using sodium hypochlorite - NaOCl, sodium dodecyl-sulphate based agents - SDS, and 70% ethanol), personal protective equipment (PPE), and training programs—were extracted. Effectiveness

was quantified through a reduction in surface contamination and skin exposure using weighted sum approaches and triangular distributions, while cost and stakeholder ratings on feasibility and acceptance were also assessed.

Results: CSTDs demonstrated high theoretical effectiveness (weighted average ~88.3%) in source containment, though they incur significant indirect costs. Among decontamination methods, SDS-based agents provided superior contaminant removal and favourable feasibility and acceptance ratings compared to NaOCl and 70% ethanol. PPE exhibited consistent effectiveness in both laboratory and field settings, while training, although less impactful as a stand-alone intervention, enhanced overall safety when integrated with other measures.

Conclusion: A multifaceted strategy integrating chemotherapy-grade PPE, SDS-based decontamination, the use of CSTDs and structured training is recommended to effectively reduce dermal exposure to antineoplastic drugs in South African oncology pharmacies.

Keywords: closed-system transfer devices, training, personal protective equipment, decontamination, risk management.

Introduction

South African oncology pharmacies operate within a challenging and evolving healthcare landscape, where rising cancer incidence and expanding treatment demands intersect with persistent gaps in occupational safety.[1] Within these settings, pharmacy personnel are routinely engaged in related activities—such as compounding, reconstitution, handling, and cleaning—which inherently carry the risk of exposure to hazardous antineoplastic drugs (ADs).[2] These activities, particularly during drug preparation and cleaning, can lead to significant dermal exposure.[3] Employing the Schneider framework as a guiding model, the dermal exposure pathway is delineated from the initial source (i.e., drug handling and potential spills) through intermediary stages (such as surface contamination and transfer via contaminated clothing) to the final receptor—the skin.[4] This framework underscores the dual importance of mitigating both direct contact with ADs through spills and indirect exposure through contaminated surfaces.

Our previous studies provide critical insights into the current state of oncology pharmacy practices in South Africa and justify the need for targeted interventions.[5-7] The pilot study revealed that pharmacies under service provider 1 (SP1) exhibit markedly lower adherence to international safety guidelines compared to those under service provider 2 (SP2).[7] Specifically, SP1 pharmacies were deficient in key areas such as the proper use of appropriate personal protective equipment (PPE) and consistent application of effective surface decontamination protocols. This non-adherence was not merely theoretical: biological monitoring demonstrated detectable levels of ADs in the urine of SP1 pharmacy personnel, directly linking inadequate PPE use with measurable AD intake.

Our workplace monitoring efforts showed that SP1 pharmacies had a significantly higher number of positive surface contamination sites relative to SP2 facilities.[6] A moderate correlation was identified between potential for skin exposure—quantified using the DREAM method—and the frequency of detected surface contamination, emphasizing the relationship between poor safety practices and an increased potential for dermal exposure. Another striking finding was the high variability in surface decontamination outcomes. Despite the widespread use of a 70% ethanol protocol, our data revealed that it only achieved an average reduction of 17.4% in surface contamination.[6] In contrast, alternative cleaning agents such as sodium-dodecyl sulphate containing decontaminants (SDS) and hypochlorite (NaOCl) have

been reported to perform substantially better, achieving reductions of 90–98% [8-11], however, these were observed under controlled conditions.

Drawing on the dermal exposure pathway and the empirical observations outlined above, the primary objective of our proposed interventions is to reduce the potential for dermal exposure to ADs during compounding activities and cleaning, specifically in SP1. To this end, we propose a multifaceted strategy: the implementation of the use of PPE, which is certified for AD compounding (like AD-resistant certified gloves and impermeable gowns with tight fitting cuffs, and N95/FFP3 masks), optimising decontamination practices by transitioning to more effective cleaning agents, implementing structured training programs to reinforce safe handling behaviours during compounding, and incorporating closed system drug-transfer devices (CSTDs) as an adjunct measure. It is essential to recognise that the overall effectiveness of these interventions will not depend on their reported effectiveness under ideal conditions but on their implementation and use in real-world conditions. The latter factors are influenced by cost, the feasibility of implementation, and the acceptance by the intended users.

Methods

A systematic literature review was conducted to identify studies published within the last 10 years that reported quantitative outcomes related to interventions for reducing potential for AD exposure. Searches were performed in PubMed, Scopus, Web of Science and Google Scholar using the keywords “antineoplastic drugs”, “decontamination”, “cleaning”, “surface contamination”, “closed-system devices”, “personal protective equipment” and “training”. Studies were included if they provided extractable quantitative data; those outside the 10-year timeframe or lacking measurable outcomes were excluded.

For CSTDs, the primary outcome was the reduction of spills onto skin, clothing or surface. Data were extracted as “initial” (pre-intervention) and “residual” (post-intervention) contamination levels from studies reporting on CSTDs. When direct effectiveness percentages were not provided, the reduction was calculated using Equation 1:

$$Equation\ 1: \qquad Effectiveness = 1 - \left(\frac{Residual\ contamination}{\text{Initial contamination}}\right) \cdot 100$$

The extracted data were then grouped and aggregated using a weighted sum approach, whereby each study's contribution was weighted according to its number of observations (N). The consolidated effectiveness distribution was represented as a triangular distribution (minimum, mode, maximum), with the total N indicated.

For decontamination interventions, studies were specifically selected if they reported "initial" (pre-cleaning) and "residual" (post-cleaning) surface contamination levels. The effectiveness of the decontamination process was calculated using Equation 1. This calculation standardised the reported results to a percentage reduction in surface contamination, irrespective of the original metric. The decontamination data were then aggregated using a weighted sum approach, like that applied for CSTDs, with each study's contribution proportionate to its number of observations (N).

For PPE and training interventions, outcomes were grouped by type. For PPE, two distinct clusters of studies were identified. The first cluster consists of laboratory-based assessments by Nalin et al.[12] and Krzeminska et al.[13], which focused on glove permeation and material resistance. The second cluster is derived from field-based outcomes, notably the Cochrane systematic review by Verbeek et al.[14], which evaluated skin and respiratory protection in actual healthcare settings. For the laboratory studies, effectiveness was calculated as the percentage reduction in contaminant permeation; for the field-based data, relative risks (RR) were converted into percentage effectiveness equation 2:

$$Equation\ 2: \qquad Effectiveness\ (\%) = (1 - RR) \cdot 100$$

For training interventions, outcomes were derived from studies reporting changes in knowledge, attitude and performance (KAP). Quantitative data were extracted from studies by Hojati et al.[15] and Ozakin et al.[16] Additionally, the Robson systematic review[17] – considered the most relevant for oncology-related training – provided standardised mean differences (SMDs) for observed behaviour and health outcomes. In contrast to previous approaches where SMDs were viewed as non-convertible, we applied a conversion (using the U3 statistic or an equivalent method) to translate SMD values into percentage effectiveness, thus yielding an intuitive estimate of the training impact. The training data were then aggregated manually, with individual study N values recorded in the summary table. Data extraction was facilitated by a combination of manual review and assistance from the OpenAI o3 tool for initial retrieval. However, for the straightforward effectiveness calculations – particularly for CSTDs and

decontamination – aggregation was performed manually to ensure accuracy and transparency.

Since the extracted effectiveness of the various types of intervention was not directly related to our aim, i.e. reduction of the potential for skin exposure, and the interventions act in different parts of the exposure pathway, we adjusted the aggregated data by applying adjustment factors. To determine the cost criteria for each intervention, quotations from suppliers and internal documents were obtained.

Finally, for 'soft' criteria such as the (technical and organisational) feasibility of implementation of the intervention and its acceptance mainly by intended users, a panel of seven decision makers (including oncology pharmacy managers, oncology pharmacists, supplier management personnel and members of the SASOPh management committee) was recruited. Each panel member rated these criteria for each intervention on a Likert scale from 1-10. For 'soft' criteria, a triangular distribution using the median (due to the nature of the data), minimum and maximum was also calculated and included.

Finally, the performance of each intervention according to the four criteria was consolidated in a performance matrix, and the performance data were normalised into a 0-1 scale to enable comparison of their aggregated weighted sum scores.

Results

The performance matrix is given in Table 1 and the intervention effectiveness extraction Tables are given in supplementary Tables 2-5 (Appendix A). Studies evaluating CSTDs produced effectiveness values ranging from 53.6% to 100% in reducing surface contamination. Aggregating these data using a weighted sum approach (total $N \approx 358$) resulted in a weighted-average effectiveness of approximately 88.3%. An adjustment factor of 1 is applied because the proxy effectiveness measure—reduction in surface contamination—directly reflects the intervention's ability to reduce spills to both skin and surfaces, requiring no further adjustment. In terms of cost, CSTDs incur no direct expense to the pharmacies, although medical aid covers an estimated R600,000 per annum (assuming 25 patients per day). Panellists' assessments provided a mean median feasibility rating of 7(min 4, max 9) and a median acceptance rating of 7 (min 6, max 9), indicating moderate feasibility and user approval.

The effectiveness of surface decontamination measures was evaluated for two cleaning agents. Laboratory studies reported effectiveness values ranging from 96.7% to 100% for NaOCl. An adjustment factor of 0.6 is used as it only reduces surface contamination at the start of the workday, and its effect on the surface-to-skin transfer pathway is uncertain. The adjusted triangular distribution parameters for NaOCl were a minimum of approximately 58.0%, a mode of 59.4% and a maximum of 60.0%. The annual cost for NaOCl is estimated at R17,418. The stakeholder's panel ratings for feasibility and acceptance were 6 (min 5, max 9) and 5 (min 4, max 6) respectively. The alternative SDS (also known as sodium lauryl-sulphate) showed effectiveness values in the range of 82% to 97.9% before adjustment. After applying the 0.6 adjustment factor, the resulting triangular distribution has a minimum of 49.2%, a median of 50.8% and a maximum of 58.7%. This solution is more cost-effective, with an annual cost of R4,889, and received high median expert ratings of 10 (min 8, max 10) for feasibility and 9 (min 8, max 10) for acceptance. The currently used 70% ethanol showed that although laboratory calculations yielded an adjusted triangular distribution with parameters of approximately 29.4% (min), 36.8% (mode) and 58.1% (max), field observations indicate a markedly lower effectiveness, around 17.4%.[6] The currently used 70% ethanol protocol costs R4,552 per annum. For PPE interventions, two clusters of data were identified: laboratory-based assessments and field-based outcomes. Laboratory studies by Nalin et al. (92% effectiveness, N = 15) and Krzeminska et al. (88% effectiveness, N = 10) yielded a weighted average effectiveness of approximately 90.4%. In contrast, field-based data from the Cochrane review by Verbeek et al.[14] indicated an effectiveness of about 75% (N = 50). Aggregating these clusters using a weighted sum approach yielded a triangular distribution with a minimum of 76%, a median of 80% and a maximum of 84%. An adjustment factor of 0.8 was applied because of field challenges, such as improper donning and doffing and diminished laboratory-measured efficacy in reducing both direct and indirect skin exposure. The final consolidated PPE effectiveness is represented by a triangular distribution with a minimum of 60.8%, a mode of 64.0% and a maximum of 67.2%. The annual cost for PPE is approximately R112,000. For the 'soft' criteria, the panel assigned high scores for feasibility (median 9, min 7, max 10) and acceptance (median 8, min 7, max 10). Training effectiveness was evaluated based on changes in knowledge, attitude and performance (KAP), as well as health outcomes. Two studies (Hojati et al.[15] and Ozakin et al.[16]) reported an average KAP improvement of about 34%, with observed ranges from 9% to 61%. Additionally, the Robson[17] systematic review provided standardised mean differences for health outcomes converted into effectiveness of roughly 50% (range 40–60%).

Table 1. Performance matrix

Intervention	Effectiveness (%)	Annual Cost (Rand)	Feasibility (1–10)	Acceptance (1–10)	Weighted sum
CSTDs	Min: 53.6 Mode: 88.3 Max: 100	R0† (Medical aid covers ~R600,000)	Median: 7 Min: 4 Max: 9	Median: 7 Min: 6 Max: 9	0.3849
Decontamination: NaOCl	Min: ~58.0 Mode: ~59.4 Max: ~60.0	~R17,418	Median: 6 Min: 5 Max:9	Median: 5 Min: 4 Max: 6	0.3435
Decontamination: SDS-Based	Min: ~49.2 Mode: ~50.8 Max: ~58.7	~R4,889	Median: 10 Min: 8 Max: 10	Median: 9 Min: 8 Max: 10	0.3867
Decontamination: 70% Ethanol	Lab-adjusted: Min: ~29.4, Mode: ~36.8, Max: ~58.1 Field: ~17.4	~R4,552	Median: 10 Min: 10 Max: 10	Median: 10 Min: 10 Max: 10	N/A
PPE	Min: ~60.8 Mode: ~64.0 Max: ~67.2	~R112,000	Median: 9 Min: 7 Max: 10	Median: 8 Min: 7 Max: 10	0.3478
Training	Min: ~17.4 Mode: ~35.4 Max: ~54.6	~R4,000	Median:7 Min: 4 Max: 9	Median: 8 Min: 7 Max:10	0.3550

†No direct cost to pharmacy

Aggregating these results produced an unadjusted triangular distribution with a minimum of 19.3%, a mode of 39.3% and a maximum of 60.7%. An adjustment factor of 0.9 is applied to adjust for uncertainty regarding the conversion of improvements in knowledge and behaviour into actual reductions in dermal exposure. The final training effectiveness is represented by a triangular distribution with a minimum of 17.4%, a mode of 35.4% and a maximum of 54.6%. For the ‘soft’ criteria, acceptance scored slightly higher (median 8, min 7, max 10) than feasibility (median 7, min 4, max 9).

Aggregation of the performance of the interventions as a weighted sum reveals that SDS-based decontamination has a slightly higher 'overall score' compared to CSTD, with training in the third position.

Discussion

This study evaluated a suite of interventions to mitigate the risk of dermal exposure to hazardous antineoplastic drugs in South African oncology pharmacy settings by providing a tailor-made risk control strategy. By synthesizing data from both laboratory and field studies, we compared the effectiveness of CSTDs, various decontamination protocols, personal protective equipment (PPE), and training interventions. Aggregated effectiveness measures and their place of intervention in the exposure pathway revealed substantial variability across these interventions. To compare the various interventions concerning their potential to reduce dermal exposure, so-called adjustment factors were introduced.

While CSTDs emerged as the most effective intervention in terms of contamination reduction, their high performance must be interpreted in light of the intervention's specific role in the exposure pathway. CSTDs function as a source-containment measure; hence, their high theoretical effectiveness suggests a strong potential to interrupt contamination at its origin.

The effectiveness of NaOCl and SDS for decontaminating surfaces is very high. However, since surface contamination builds up during the day, a direct effect on the reduction of skin exposure due to contact with the contaminated surfaces is uncertain. Therefore, the highest adjustment factor of 0.6 was applied for this type of intervention. Although NaOCl practically eliminates AD contamination, its use is impractical due to the potential for damage to equipment, fumes, and additional labour required to remove the NaOCl. SDS decontaminants have an effectiveness slightly less than NaOCl but do not require the additional removal step, do not produce harmful fumes and are several factors more effective than the currently used 70% ethanol, which in our previous field study had an effectiveness of only 17.4%.

The effectiveness of PPE had a very small range, indicating less variability with min/max close to the mode. The mode for PPE was also the highest of all the interventions, except for the use of CSTDs. With an adjustment factor of 0.8, the extracted data from the literature reveals a compelling case for the use of appropriate PPE. It is a sensible recommendation to make for SP1 as they were non-compliant as found in a previous study.[7] The training intervention effectiveness yielded the lowest-performing intervention, however, training cannot be

considered a stand-alone intervention and must form part of the implementation of the other interventions. This suggests that the most effective strategy may not be to rely on a single intervention but rather to integrate multiple measures that complement one another and compensate for each method's limitations.

The absorption of the cost of oncological pharmacy services is complex and is covered by certain entities for specific services, labour, and consumables. Our cost analysis reveals that while CSTDs impose no direct expense on pharmacies, they still represent a considerable financial commitment to the healthcare system, as evidenced by the annual cost borne by medical aids. However, several factors influence decision-makers. The advantages of using an SDS decontaminant rather than 70% ethanol and given that the cost of SDS is similar to the currently used 70% ethanol, is of enormous benefit. Still, the use of SDS has never been considered in South African oncology pharmacies, and no cost estimates were ever conducted because of this oversight. The implementation of chemotherapy-grade PPE, which was compliant in SP2 but lacking in SP1, is the pharmacy's highest expense. Funding for PPE is provided by medical aids to pharmacies through a dispensing fee. This should also cover the labour of the pharmacist at the oncology pharmacy and any other operational costs of the pharmacy. Conversely, the low cost of training—despite its moderate effectiveness—is not a stand-alone intervention, but rather augments all other interventions and is (excluding the potential cost of CSTDs, which is R 0) the cheapest intervention.

As stated, the feasibility of using CSTDs is determined by panellists, and the influence they have on its feasibility is not always well understood, hence the wide range. However, CSTDs performed the same as training for this criterion, yet it is a more effective intervention. This further underlines the possible discord regarding knowledge and perceptions of CSTDs in general among decision-makers. The difference in the feasibility of implementing a decontaminant is an obvious choice due to the limitations of NaOCl and the advantages of SDS (as previously discussed), especially when considering the effectiveness compared to the currently used 70% ethanol. The feasibility of implementation of chemotherapy-grade PPE was scored high among panellists. This contrasts with the findings made in our previous study, where decision maker(s) and participants in SP1 denounced the use of PPE as ineffective despite the majority of panellists agreeing on the feasibility and acceptance of the implementation of PPE.[7] It is not clear why SP1 had this view about the use of PPE, but it could be attributed to 'small business enterprise attitude' and/or ill-informed influence by their applicable decision maker(s). The decision maker(s) in SP1 did not respond to partake in the panel.

The results of the feasibility are echoed in the acceptance, where SDS was superior to NaOCl for reasons stated previously. PPE and training scored identically with high median scores, indicating a positive view of these interventions by panellists. As all acceptance scores were rated highly by panellists, the acceptance of all these interventions (except for NaOCl) is an indication that decision-makers are proactive in implementing new interventions in general.

The overall 'appreciation' of the interventions, expressed as a weighted sum, supports decision-making on which interventions to implement. Since, in the present case, the overall appreciation does not differ much, and the interventions are complementary to each other, the recommendation would be to consider implementing all four alternatives, excluding the NaOCl-decimation option.

Limitations

This study is limited by the heterogeneity of the available data, which necessitated the use of adjustment factors to account for differences in the point of intervention along the exposure pathway. Although these factors were selected based on the specific stage at which each intervention acts, they introduce additional uncertainty into the effectiveness estimates. Furthermore, our cost calculations are based on patient volume and treatment frequency assumptions that may not be consistent across all South African oncology pharmacies. The use of surface contamination as a surrogate measure for dermal exposure may also overlook other exposure routes, such as inhalation. Future studies should aim to validate these estimates through targeted evaluations and refine the intervention strategies using direct measurements of exposure. One key limitation is that the panel's composition may introduce conflicting viewpoints on feasibility and acceptance, thereby affecting the consensus and overall recommendations.

Conclusion

The integration of effectiveness, cost, feasibility, and acceptance into a comprehensive evaluation framework suggests that no single intervention can serve as a panacea. This strategy should prioritise the implementation of chemotherapy-grade PPE alongside structured training programmes to ensure correct donning and doffing procedures. Given the limited effectiveness of 70% ethanol for decontamination, a transition to an SDS-based

cleaning solution is recommended, as it offers superior contaminant removal with greater feasibility and acceptance. While closed-system drug-transfer devices (CSTDs) demonstrate high effectiveness in source containment, their implementation should be considered as a complementary measure rather than a primary intervention. Instead, a multi-faceted approach—incorporating enhanced PPE compliance, optimised decontamination protocols, and targeted training—represents a more practical and sustainable solution for SP1.

Key Messages

1. Closed-system drug-transfer devices (CSTDs) and chemotherapy-grade personal protective equipment (PPE) demonstrated high theoretical effectiveness in mitigating dermal exposure to antineoplastic drugs (ADs), although real-world implementation challenges must be considered.
2. Sodium dodecyl sulphate (SDS)-based agents significantly outperform the commonly used 70% ethanol for surface decontamination, offering superior effectiveness, lower costs, and higher stakeholder acceptance in South African oncology pharmacies.
3. A multi-intervention approach integrating CSTDs, chemotherapy-grade PPE, SDS-based decontamination, and structured staff training is recommended for optimal reduction of occupational exposure risks in oncology pharmacy settings.

Author Contributions

Conceptualization, RB; methodology, RB, DB; Data collection and curation, RB; formal analysis and interpretation, RB, DB; writing - original draft preparation, RB; writing - review and editing, GN, DB. All authors have read and agreed to the final version of the manuscript**.**

Declaration of conflicting of interests

The authors declare that this is their own work; all the sources used in this paper have been duly acknowledged and there are no conflicts of interest.

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Appendix A: Supplementary tables

Table 2. Effectiveness of training

Author (Year)	Training Intervention	Outcome Measure	Effectiveness (%)	Notes
Robson et al. (2010)	Systematic review of OHS training/education programs (health outcomes only)	Health outcomes converted from SMDs using the U3 statistic	50	Only health outcomes were used; effectiveness was derived by converting SMDs into a percentage using the U3 method.
Hojati et al. (2023)	Smartphone app–based training on chemotherapy safety standards	Knowledge, Attitude, and Performance (KAP) scores (pre vs post)	34	Direct pre–post test comparisons among oncology nurses; average score improvement is 34% with a range of 9% to 61%.
Ozakin et al. (2019)	Comprehensive safe handling and cytotoxic drug preparation training program	Theoretical knowledge test scores (pre vs post)	34	Retrospective analysis of pre–post test results among oncology pharmacy practitioners yielded an average improvement of 34%.

OHS: occupational health and safety, SMD: standard mean deviation

Table 3. Effectiveness of personal protective equipment

Author (Year)	PPE Type	Effectiveness (%)	Observations (N)	Calculation/Notes
Nalin et al. (2021)	Gloves	92	15	(1 – [Residual Contamination/Initial Contamination]) × 100 from glove permeation tests
Krzeminska et al. (2018)	Gloves	88	10	(1 – [Residual Contamination/Initial Contamination]) × 100 from glove resistance assessments
Verbeek et al. (Field data)	Skin and Respiratory PPE	75	50	(1 – Relative Risk) × 100 from field-based outcomes in the Cochrane review

PPE: personal protective equipment

Table 4. Effectiveness of decontamination

Author (Year)	Decontaminants Used	Effectiveness (%)	N (Observations)	Calculation / Notes
Queruau Lamerie et al. (2012)	NaOCl, IPA	98; 80.7	10; 10	NaOCl: Directly reported 98% removal on 10 antineoplastic agents spread on two surface types. Alcohol: IPA/water mixture effectiveness directly reported as 80.7% on the same set of observations.
Gohma et al. (2015)	NaOCl	~96.7	4	Reported degradation for four drugs: 86.6% for cyclophosphamide and 100% for the other three drugs; these were averaged to yield approximately 96.7% effectiveness.
Federici et al. (2018)	NaOCl, SDS, alcohol (0.2% ethanolic NaOH solution)	98.3; 97.9; 96.9	12; 12; 12	Efficacy values were aggregated across three antineoplastic drugs tested on four different surface types; each cleaning solution, performance was computed (N approximated as 12 per agent) and reported as 98.3% for NaOCl, 97.9% for the SDS formulation, and 96.9% for the ethanolic NaOH solution.
Simon et al. (2020)	NaOCl; SDS; IPA	100; 92.5; ~85.8	12; 12; 12	NaOCl: solution had a median effectiveness of 100% over 12 observations. SDS reported 85.4% (single wipe) and 99.6% (vigorous), averaged to 92.5%. Alcohol: approximately ~85.8%
Palamini et al. (2021)	NaOCl	~99.9	4	Reported decontamination achieved nearly 100% removal (99.6% for ifosfamide and 100% for the other antineoplastics); these values were averaged to approximately 99.9%
Anastasi et al. (2015)	SDS, IPA	82; 49	98; 98	Directly reported overall decontamination efficacies based on 98 repeated observations: the SDS cleaning solution yielded 82±6% efficacy, whereas the commercial IPA solution achieved 49±11% efficacy.

IPA: 70% Isopropyl alcohol, NaOCl: Sodium hypochlorite, SDS: Sodium dodecyl sulphate

Table 5. Effectiveness of closed-system transfer devices

Author (Year)	Effectiveness (%)	N (Observations)	Calculation / Notes
Bishay et al. (2022)	100	90	All 90 post-intervention wipe samples were negative
Valero et al. (2018)	~94.1	~28*	From median cyclophosphamide levels (baseline: 1.01 ng/cm² to 0.06 ng/cm² gives (1–0.06/1.01)×100 ≈ 94.1%
Siderov et al. (2010)	68	22	At 12 months, total surface contamination was reduced by 68% in 22 sampled sites
Simon et al. (2016)	53.6	~40*	Overall contamination dropped from 26.39% to 12.24%, i.e. (26.39–12.24)/26.39×100 ≈ 53.6%
Sessink et al. (2011)	95	22	Reported median reduction for cyclophosphamide was 95% across 22 hospital pharmacies
Bartel et al. (2018)	91.3	156	Contamination rate reduced from 66.7% to 5.8%; computed as (66.7–5.8)/66.7×100 ≈ 91.3%

Appendix F: Observational study questionnaire

	WEIGHT	YES	NO
Facilities: Engineering Controls	15	/8	SCORE=13
There is a suitable vertical flow laminar flow unit or BSC			
The unit complies to ISO standards as specified in ISOPP and QuaPos guidelines			
There is an 'ante-room'			
Overall, the engineering controls mitigates contamination significantly			
Pressure differentials between rooms are appropriate			
The unit is serviced by schedule			
The room containing the laminar flow unit is in a negative pressure			
The room is air-conditioned and is comfortable to work in			
TOTAL			
Facilities: Administrative Controls	10	/6	SCORE =
The pharmacy uses centralized preparation			
The design of the pharmacy is ideal to handle chemotherapy compounding			
Work breaks are taken after 2 hours of mixing			
Handling is reduced to a minimum			
Staff are rotated			

Consumables are replaced accordingly not to cause contamination			
TOTAL			
Facilities: PPE	10	0/6	SCORE =
Acceptable masks are provided			
Acceptable gowns are provided			
Acceptable overshoes and caps are provided			
Personnel use PPE correctly who mix and prepare chemotherapy			
Personnel use PPE correctly when performing other functions like cleaning			
PPE is disposed of correctly			
TOTAL			
TOTAL FACILITIES	35 (weight for facilities	/20 questions	TOTAL SCORE=
TOTAL			
Procedures: Personnel education and training	25	/7	SCORE=
Personnel underwent formal/informal training			
All personnel were trained by a pharmacist familiar in oncology pharmacy			
Professional staff (like pharmacists and assistants) undergo CPD			
Conferences on oncology pharmacy is attended by some personnel members			
Some personnel members are affiliated with a local or international oncology pharmacy association (like ISOPP or ESOP)			

Training records are available			
SOP`s and required literature is available			
TOTAL			
Procedures: Contamination and medical monitoring	10	/4	SCORE =
All personnel are subject to continuous liver function tests			
All personnel have a baseline liver function test			
Urine samples are collected and monitored routinely			
Surface wipe samples are collected and monitored routinely			
TOTAL			
Procedures: Cleaning procedures and waste handling	15	/7	SCORE =
Personnel have received training in cleaning procedures			
Personnel have received training in waste handling			
Suitable disinfectant/decontaminant and consumables are available			
A contract is in place with a waste management company disposing chemotherapy			
Suitable waste containers are provided			
There is no build-up of chemotherapy waste			
Cleaning is performed by schedule on a daily basis			
TOTAL			
Procedures: Spills and accidents	5	/5	SCORE =
At least some personnel members can by international consensus contain a spill			
A spill kit containing the required equipment is available			

There are procedures in place on spill management			
Major accidents are infrequent (<1/year)			
Spills are documented and corrective measures are taken			
TOTAL			
TOTAL PROCEDURES	55	/30 questions	SCORE=
OVERALL RANKING	100	/50 questions	/100

Appendix G: Informed consent and information leaflet

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

PARTICIPANT INFORMATION LEAFLET

5 October 2022

Dear prospective study participant,

Occupational (work) exposure of antineoplastic drugs (chemotherapy) to pharmacy related personnel has the ability to cause adverse health effects even in very small quantities. There are several ways that can reduce harmful exposure to chemotherapy which can include certain exposure source isolation, engineering controls, work arrangements, and the use of personal protective equipment. By investigating the existing control measures of a pharmacy, and monitoring exposure levels of these drugs, new ways could possibly be found to reduce these harmful health effects, which our study is focussing on.

The researcher is currently enrolled at the University of the Witwatersrand School of Public Health for a Ph. D in Public Health – Occupational Hygiene Titled "Occupational exposure to antineoplastic drugs and the development of tailor made risk control strategies in South African oncology pharmacies" The study is approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. During the course of the study which will be conducted over one week, participants will be requested to partake in an interview and/or questionnaire which will take approximately 20-30 minutes. Surface wipe samples will be collected in the pharmacy. Participants will also be requested to provide urine samples to detect the presence of certain chemotherapy drugs which will be self-collected by participants over 24 hours. Six urine samples will be collected. The potential benefit of your participation in the study could lead to improved occupational hygiene in oncology pharmacy in South Africa.

Participation in this study is wholly voluntary and no incentives will be offered for participation. In addition, you and your institution will remain anonymous and although you cannot be identified the content of the observations and field notes will be handled with confidentiality. You are free to withdraw from the study at any given point of the data collection. Please note that pictures of the process may be taken and be used in research reports, but care will be taken that your identification will not be revealed. Agreement to sign this letter serves as consent to participate in the research and that the sampling results will be used for publication in a thesis, research articles and conference proceedings. Feedback on the results and findings of the study will be provided to you.

Yours sincerely,

Ruan Botha – Principal investigator and candidate
Tel: 083 578 1714 email: botha82@gmail.com (primary) or 303008@students.wits.ac.za
Supervisor: Prof Derk Brouwer: (011-717-2387) email derk.brouwer@wits.ac.za
Co-supervisor: Prof Gill Nelson: (011-717-2138) email gill.nelson@wits.ac.za

PARTICIPANT INFORMED CONSENT

- I hereby confirm that I have been informed by the principal investigator, Ruan Botha, about the nature, conduct, benefits and risks of the study titled Occupational exposure to antineoplastic drugs and the development of tailor made risk control strategies in South African oncology pharmacies.
- I have also received, read and understand the above written information regarding the study of which any uncertainties have been clarified to me and I have been offered the opportunity to consider an unsigned copy pending my satisfaction with participation.
- I am aware that the results of the study, including personal details regarding my sex, age, role, experience and level of education will be anonymously processed in a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerized system by relevant SPs or on their behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and, of my own free will, declare myself to participate in the study.

PARTICIPANT:

PRINT NAME:_____
SIGNATURE:_____
SITE:_____
DATE:_____

I, Ruan Botha, herewith confirm that the above participant has been fully informed about the nature, conduct and risk of the study.

PRINCIPAL INVESTIGATOR:

PRINT NAME:_____
SIGNATURE:_____
DATE:_____

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

SP INFORMATION LEAFLET

The collection of surface wipe samples, urine samples, a walk-through survey is necessary for SPs to identify alternatives. The data collected in a pharmacy will be confidential and will only be revealed to its SPs. The data obtained from Study objectives 1-3 will be subject to a decision making algorithmic analysis, also known as multi-decision criteria analysis (MCDA).

MCDA is an objective decision analysis process, often used in environments like business analytics, government, military or ecology such as deciding where the best place is to build a new dam for example. It is a systematic transparent decision making process, overcoming unstructured (subjective) decision making. SPs are given the opportunity to assign weighted specific criteria to alternatives as identified. The result is an objective 'tailor-made' control strategy that provides a pharmacy with the best possible control outcome based on major SPs preferences and discretion.

The findings of the study will be used to present at conferences or as poster-presentations or for publication in an academic journal. In addition, these findings will also be published in a PhD thesis for submission to the University of the Witwatersrand.

It must however be emphasized with SPs that the data obtained from this study will be completely confidential, no pharmacy will be named, and the data from your own pharmacy will only be privy to you.

SPs can thus partake with confidence and the possibility to develop a 'tailor-made' risk control strategy is highly advantageous. It is probable that cost will play a significant role in SPs criteria selection which is fortunately very compatible with MCDA.

Thank you for your consideration - Yours sincerely,

Ruan Botha – Principal investigator and candidate
Tel: 083 578 1714 email: botha82@gmail.com (primary) or 303008@students.wits.ac.za

Supervisor: Prof Derk Brouwer: (011-717-2387) email derk.brouwer@wits.ac.za

Co-supervisor: Prof Gill Nelson: (011-717-2138) email gill.nelson@wits.ac.za

SP INFORMED CONSENT

- We hereby confirm that we have been informed by the principal investigator, Ruan Botha, about the nature, conduct, benefits and risks of the study titled Occupational exposure to antineoplastic drugs and the development of tailor made risk control strategies in South African oncology pharmacies.
- We have also received, read and understand the above written information regarding the study of which any uncertainties have been clarified to us and we have been offered the opportunity to consider an unsigned copy pending our satisfaction with participation.
- We are aware that the results of the study, including personal details of participants such as sex, age, role, experience and level of education will be anonymously processed in a study report.
- In view of the requirements of research, we agree that the data collected during this study can be processed in a computerized system by relevant SPs or on their behalf.
- We may, at any stage, without prejudice, withdraw our consent and participation in the study.
- We have have had sufficient opportunity to ask questions and, of free will, declare our participation in the study.

SP PROXY:

PRINT
NAME:_____POSITION_____

SIGNATURE:_____
SITE:_____
_____
_____
DATE:_____

I, Ruan Botha, herewith confirm that the above SP have been fully informed about the nature, conduct and risk of the study.

PRINCIPAL INVESTIGATOR:

PRINT NAME:_____

SIGNATURE:_____
DATE:_____

Appendix H. Turnitin report

turnitin.docx

ORIGINALITY REPORT

8%	5%	6%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Ruan Botha, Gill Nelson, Derk Brouwer. "A pilot study of South African oncology pharmacy facilities: Comparison with best practice guidelines", European Journal of Oncology Pharmacy, 2024 Publication	1%
2	www.ncbi.nlm.nih.gov Internet Source	<1%
3	Padayachee, Neelaveni. "Utilization of Over-The-Counter Medicines in Medical Schemes in South Africa", University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	<1%
4	www.researchgate.net Internet Source	<1%
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7	Moonsamy, Marlene Rose. "Correlation Between Tertiary Education and Pharmaceutical Industry Requirements for Regulatory Affairs Pharmacists", University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	<1%

approved  Date: 31 March 2025