

**TITLE: Closed-System Transfer Devices for the Handling of Hazardous Drugs: A Review of the Clinical and Cost-Effectiveness and Guidelines**

**DATE:** 07 May 2015

**CONTEXT AND POLICY ISSUES**

Exposure to chemotherapy and other hazardous drugs during preparation and administration can present a health risk to health care staff.<sup>1</sup> Closed-system transfer devices (CSTDs) are devices designed to prevent the transfer of contaminants into the environment during drug transfer between the vial and syringe by maintaining a closed connection, and have been successful in reducing occupational exposure to hazardous drugs.<sup>1</sup>

According to the National Institute for Occupational Safety and Health (NIOSH), a closed-system transfer device is defined for use in compounding and administering sterile doses of chemotherapy and other hazardous drugs, as a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drugs or vapor concentrations outside the system.<sup>1,2</sup> Although absolute containment is ideal, it may not be possible and there is still a risk of exposure for staff regularly handling hazardous drugs due to user technique or unpredictable spills.<sup>2</sup> Occupational exposure may be measured by biological monitoring of staff using urine samples or cytogenetic testing, or environmental monitoring of the workplace using wipe and air sampling of marker drugs.<sup>1,2</sup> Although the clinical significance of long-term, low-level exposure to chemotherapy drugs is not fully known, potential hazards include rash, infertility, birth defects, miscarriages, and a possible increased risk of cancer.<sup>2,3</sup> Current CSTDs on the market include PhaSeal (BD Medical), ChemoClave Genie and Spiros (ICU Medical), Texium (CareFusion), OnGuard (B. Braun Medical), and Equashield (Equashield Medical).

The purpose of this review is to assess the clinical and cost-effectiveness of CSTDs for the handling of hazardous drugs, and to identify guidelines regarding the use of CSTDs for the handling of hazardous drugs.

**RESEARCH QUESTIONS**

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1. What is the clinical effectiveness of closed-system transfer devices for the handling of hazardous drugs?
2. What is the cost-effectiveness of closed-system transfer devices for the handling of hazardous drugs?
3. What are the evidence-based guidelines regarding the use of closed-system transfer devices for the handling of hazardous drugs?

**KEY FINDINGS**

Only evidence pertaining to the PhaSeal closed-system transfer device was identified. Evidence from non-randomized studies suggests that the PhaSeal closed-system transfer device decreases the exposure of pharmacists to hazardous drugs such as cyclophosphamide. One cost study found that the use of PhaSeal resulted in cost savings by extending the usage of single-dose vials by maintaining sterility of the medication. One evidence-based guideline recommends that CSTDs not be used as a substitute for biosafety cabinets.

**METHODS**

**Literature Search Methods**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and March 26, 2015. Internet links were provided, where available.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

**Selection Criteria and Methods**

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<b>Table 1: Selection Criteria</b>	
<b>Population</b>	Adults receiving or administering hazardous drugs
<b>Intervention</b>	Closed-system transfer device (CSTD)
<b>Comparator</b>	No comparator, other CSTDs, biohazard safety cabinet
<b>Outcomes</b>	Clinical effectiveness (e.g., drug contamination, safety and harms, etc.), comparative clinical effectiveness, cost-effectiveness, guidelines for use
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

## Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2005. Guidelines that did not report the literature search strategy and evidence-base for their recommendations were excluded.

## Critical Appraisal of Individual Studies

Included non-randomized studies were critically appraised using the Downs and Black checklist,<sup>4</sup> economic studies were assessed using the Drummond checklist,<sup>5</sup> and guidelines were assessed with the AGREE II instrument.<sup>6</sup> Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

A total of 305 citations were identified in the literature search. Following screening of titles and abstracts, 300 citations were excluded and five potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, three publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

### Summary of Study Characteristics

Details of individual study characteristics can be found in Appendix 2.

#### Non-randomized studies

Three non-randomized studies were included.<sup>3,7,8</sup> Two studies were conducted in Japan,<sup>7,8</sup> and one study was conducted in the United States.<sup>3</sup>

One Japanese study compared personnel exposure to cyclophosphamide before and after the implementation of the PhaSeal CSTD.<sup>7</sup> Four pharmacists (3 male, 1 female) that compounded cyclophosphamide in the chemotherapy preparation room of a community hospital pharmacy were included in the study. At the hospital, a class II type B2 biological safety cabinet (BSC) was employed in the compounding room, and each pharmacist was required to wear two layers of gloves, a disposable polypropylene gown with long sleeves and closed fronts, a disposable cap and a disposable surgical mask. Urine samples were taken over a 24 hour period from prior to compounding drugs to the next morning and samples were analyzed using gas chromatography-mass spectrometry to detect levels of cyclophosphamide (limit of detection 0.01 ng/mL). Urine samples were taken during a time period prior to the implementation of the PhaSeal CSTD, and seven months after the implementation of PhaSeal.

One Japanese study compared personnel exposure to cyclophosphamide when a conventional method was used versus when the PhaSeal CSTD was used.<sup>8</sup> Six pharmacists that

compounded cyclophosphamide in the antineoplastic drug preparation room of a hospital were included in the study. At the hospital, pharmacists were required to wear disposable polychloroprene gloves, a disposable polypropylene gown which had long sleeves and closed fronts, a disposable cap and a disposable surgical mask. All pharmacists compounded cyclophosphamide using the conventional method, and then received two weeks of training to use the PhaSeal CSTD. The conventional method involved placing antineoplastic drugs and infusion solutions on a stainless steel tray, which was then placed into a BSC for mixing before transferring the tray to a working table and packing the drug solutions in plastic zipper bags to be transferred outside. Urine samples were taken over 24 hours up to a maximum of five days over an interval of 2 weeks. Urine samples were taken from the pharmacists when they were using the conventional method first, and then two weeks after they had received training to use PhaSeal. Urine samples were analyzed using gas chromatography-mass spectrometry to detect levels of cyclophosphamide (limit of detection 0.1 ng/mL).

The study from the US was conducted at a new cancer hospital (56 beds) that exclusively used the PhaSeal CSTD after six months of operation.<sup>3</sup> Results from this study were compared to another study conducted at the institution's oncology outpatient infusion clinic where PhaSeal was introduced. Eleven hospital employees (4 pharmacists, 4 pharmacy technicians, 3 nurses) who volunteered to participate were included in the study. Standard practice for hospital personnel preparing or administering hazardous medications included the use of gloves, gowns, and masks or goggles. All antineoplastic drugs were prepared in a cleanroom with a class II type B2 BSC vented to the outside. Urine samples were taken over 24 hours towards the end of the work week from the volunteers, and high-performance liquid chromatography-mass spectrometry was used to identify the presence of cyclophosphamide and ifosfamide (limit of detection 0.1 ng/mL).

### Economic evaluation

One economic evaluation conducted in the United States was identified.<sup>9</sup> This study was a cost-savings analysis of the PhaSeal CSTD using a single institution perspective (335-bed teaching medical center) and a time period of 50 days (April 30 to June 18, 2012). The oncology pharmacy in the institution prepared an average of 52 parenteral doses per day and filled an average of 17 outpatient prescriptions per day. The PhaSeal CSTD was assumed to maintain the sterility of medications in a vial for 7 days based on results from recent studies. Medications supplied as injectable solutions were assumed to be stable for 7 days. Cost savings was calculated by determining the number of vials not used due to the reuse of the original vial, assuming that single-use vials would not be reused without PhaSeal.

### Guideline

One evidence-based guideline from Canada was included in this review.<sup>10</sup> Cancer Care Ontario (2013) provided recommendations on the handling of parenteral cytotoxics by health care workers. No official grading system was used, but the evidence base was mainly from non-randomized before and after studies and technical reports.

## **Summary of Critical Appraisal**

A summary of critical appraisal of individual studies can be found in Appendix 3.

All of the non-randomized studies were conducted in hospital settings reflecting real-world use, but differing practices between institutions may limit the generalizability of results.<sup>3,7,8</sup> All of the studies examined a small number of individuals (range 4 to 11), which limits representation from hospital staff. In addition, the number of urine samples taken per person was low for one study (2 to 3 samples).<sup>8</sup> None of the non-randomized studies reported baseline characteristics of the included pharmacists or hospital employees.<sup>3,7,8</sup> None of the non-randomized studies employed a control group.<sup>3,7,8</sup> One non-randomized study attempted to use previous studies as a control, which would not control for variables such as protocols used to prepare the drugs and facility set-up.<sup>3</sup>

The cost savings analysis clearly reported the costs and assumptions used in their study.<sup>9</sup> However, the assumption that the PhaSeal system could maintain the sterility of medications in a vial for seven days was not validated in the study, and only medications compounded in the hematology-oncology pharmacy were considered. Cost savings may be underestimated in this study as only antineoplastic agents were considered and not other hazardous drugs, and not all agents were dispensed during the study period.

The guideline clearly stated its objectives and target population and reported methods used to generate evidence and develop recommendations. The guideline was based on a systematic search of the literature with clearly defined inclusion criteria, and recommendations were derived directly from this evidence. The recommendations themselves were not graded according to any scale.

## Summary of Findings

Individual study findings are summarized in Appendix 4.

### What is the clinical effectiveness of closed-system transfer devices for the handling of hazardous drugs?

In the before-after non-randomized study by Miyake et al., the mean amount of cyclophosphamide that was compounded during the 24-hour period that urine samples were taken from the four pharmacists was 3525 mg before the implementation of PhaSeal and 3945 mg after the implementation of PhaSeal.<sup>7</sup> The mean amount of cyclophosphamide detected in the urine samples was 47.4 ng/24 h before PhaSeal, and 3.6 ng/24 h after PhaSeal. Before PhaSeal, cyclophosphamide was detected in 26 of the 34 urine samples collected from the four pharmacists. After PhaSeal, cyclophosphamide was detected in 2 of 31 urine samples collected from the four pharmacists.

In the non-randomized study by Yoshida et al., the mean amount of cyclophosphamide compounded by the six pharmacists using the conventional method was  $2.76 \pm 1.50$  g/24 h.<sup>8</sup> The mean amount of cyclophosphamide compounded by the six pharmacists using the PhaSeal CSTD was  $2.36 \pm 1.46$  g/24 h. The mean amount of cyclophosphamide detected in the urine samples of the pharmacists using the conventional method was 39 ng/24 h. The mean amount of cyclophosphamide detected in the urine sample of the pharmacists using the PhaSeal CSTD was 4.9 ng/24 h.

In the non-randomized study by Nyman et al.,<sup>3</sup> a mean of 6.8 doses per day of intravenous antineoplastic medications were prepared by the hospital pharmacy. Of those, 0.4 doses/day

cyclophosphamide and 0.5 doses/day ifosfamide were prepared. Other intravenous antineoplastic drugs were not of interest in this study. In the 15 days preceding collection of urine samples, two doses of cyclophosphamide and eight doses of ifosfamide were prepared. One of the eleven hospital personnel tested (a pharmacy technician) tested positive for cyclophosphamide or ifosfamide (levels detected above the limit of detection).

*What is the cost-effectiveness of closed-system transfer devices for the handling of hazardous drugs?*

In the cost savings analysis, the cost savings accrued using PhaSeal over 50 days was \$96,348.70 USD.<sup>9</sup> After a single use of vials, a mean of 43.45% of the drugs were used, leaving a mean of 57.03% of the drug potentially salvageable. Overall, a mean of 51.35% of the waste was avoided (range 0% to 93.94%, depending on the drug). When extrapolated to a year, the annual cost savings was \$703,047.67. The cost of PhaSeal in this study was \$106,566.55. All figures are as reported in the source publication.

*What are the evidence-based guidelines regarding the use of closed-system transfer devices for the handling of hazardous drugs?*

Cancer Care Ontario<sup>10</sup> (2013) recommends that for cytotoxic drug preparation, “a class II type B biological safety cabinet is required with preference for the type B2”. Closed-drug transfer systems (e.g., PhaSeal®) are not a substitute for class II type B biological safety cabinets. There is evidence from studies that closed-drug transfer-systems can reduce contamination during preparation. Further emerging evidence suggests that when these devices are not used as specified, they could become open to the environment. Further research is needed to evaluate this possibility.” (p. 10-11) [no grading]

### **Limitations**

All of the included non-randomized studies were generally of poor quality and included few patients. There were no studies included that examined health outcomes of the hospital personnel exposed to hazardous drugs. Although urine samples may give an idea of exposure, it does not necessarily extrapolate to harms. All of the included studies looked at the PhaSeal CSTD and no other CSTDs, which may limit generalizability to other devices. The cost study was performed in the United States and may not be generalizable to the Canadian context.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

Two non-randomized studies demonstrated that the PhaSeal CSTD was able to decrease the exposure of cyclophosphamide to pharmacists compounding this drug in chemotherapy preparation rooms. A third study suggested a decrease in antineoplastic drug exposure with PhaSeal compared with previously reported results. CSTDs appear to reduce environmental contamination of hazardous drugs (see Appendix 5) and consequently worker’s exposure to these drugs, but it is not clear whether or not this translates to a reduction in clinical harms to the health care staff preparing these medications.

One study reported considerable cost savings with the PhaSeal CSTD due to extending the usage of single-dose vials by maintaining sterility. This study did not confirm sterility using

microbial tests, but other studies have suggested that PhaSeal is able to maintain the sterility of medication in a vial for at least seven days.<sup>11,12</sup>

Cancer Care Ontario recommends that CSTDs not be used as a substitute for biological safety cabinets and warns that if these devices are not used as specified, they could become open to the environment and expose personnel to hazardous drugs.

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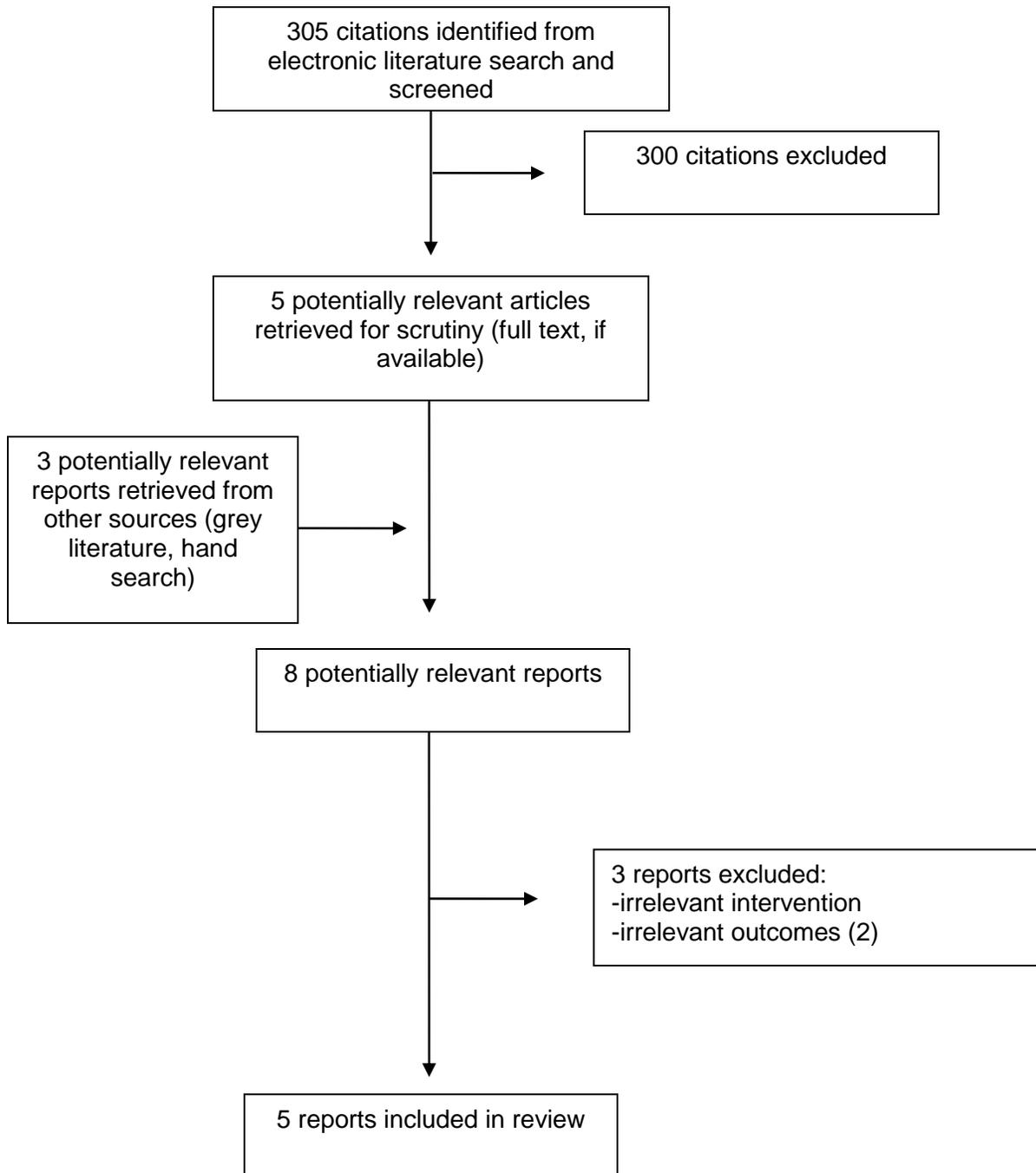
[www.cadth.ca](http://www.cadth.ca)

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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

**Table A1: Characteristics of Included Clinical Studies**

First Author, Publication Year, Country	Study Design, Setting	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Miyake (2013) <sup>7</sup> Japan	Non-randomized before-after single-arm study  Chemotherapy preparation room of a community hospital pharmacy – 655 beds for inpatient treatment of cancer	4 pharmacists (3 male; 1 female) that compounded cyclophosphamide (mean 3525 mg prior to PhaSeal; mean 3945 mg 7 months after PhaSeal)  Pharmacists were required to wear 2 layers of gloves, a disposable polypropylene gown with long sleeves and closed fronts, a disposable cap and a disposable surgical mask	PhaSeal (Carmel Pharma)	No comparator	Cyclophosphamide exposure measured by urine test with GC-MS/MS to detect CP (limit of detection 0.01 ng/mL) – taken from prior to compounding drugs to the next morning over 24 h (prior to PhaSeal, and 7 months after PhaSeal)
Yoshida (2009) <sup>8</sup> Japan	Non-randomized before-after study  Antineoplastic drug preparation room of a hospital	6 pharmacists that compounded cyclophosphamide  Pharmacists were required to wear disposable polychloroprene gloves, a disposable polypropylene gown with long sleeves and closed fronts, a disposable cap and a disposable surgical mask	PhaSeal (Carmel Pharma) – 2-week training	Conventional method – drugs and infusion solution mixed in biosafety cabinet carried on a tray, cabinet was cleaned with 70% ethanol after mixing operation	Cyclophosphamide exposure measured by urine test with GC-MS/MS to detect CP (limit of detection 0.1 ng/mL) – taken over 24 hours, collected on 5 days over an interval of 2 weeks
Nyman (2007) <sup>3</sup> USA	Non-randomized study  Specialty cancer hospital (56 beds)	11 hospital employees working in the pharmacy or on the patient care floor (4 pharmacists, 4 pharmacy technicians, 3 nurses)	PhaSeal (Carmel Pharma) used exclusively at new cancer hospital – opened 6 months at time of analysis	Conventional methods conducted at a separate outpatient infusion clinic (separate study) – gloves, gowns, masks/goggles, ISO 6 cleanroom with class II type B2 BSCs vented to the outside	Antineoplastic exposure measured by urine test with HPLC-ESI-MS/MS to detect CP or IF (limit of detection 0.1 ng/mL) – taken over 24 hours towards the end of the work week

BSC = biosafety cabinet; CP = cyclophosphamide; ESI = electrospray ionization; GC = gas chromatography; HPLC = high-performance liquid chromatography; IF = ifosfamide; MS/MS = tandem mass spectrometry

**Table A3: Characteristics of Included Cost Studies**

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Time Period	Main Assumptions
Edwards (2013) <sup>9</sup> USA	Cost savings analysis, hospital perspective (335 bed teaching medical center)	PhaSeal	50 days (Apr 30 – June 18, 2012)	PhaSeal was able to maintain the sterility of medication in a vial for 7 days and allow for multiple uses of single-use vials  Medications supplied as injectable solutions were assumed to be stable for 7 days  Medications whose stability following reconstitution is greater than 7 days were listed as stable for 7 days  Cost savings was calculated by determining the number of vials not used due to reuse of the original vial.

**Table A3: Characteristics of Included Guidelines**

Objectives			Methodology		
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
Easty (2013) <sup>10</sup> – Cancer Care Ontario					
Health care workers, pharmacy workers, hospital administrators, educators and managers, occupational health and safety services	Handling of parenteral cytotoxics	Contamination of surface and workers during cytotoxic drug preparation, general health outcomes, pregnancy outcomes	Systematic review of the literature, used existing guidelines and adapted them	Non-randomized before and after studies (poor quality), technical reports	Working group was assembled including representation from a research scientist, human factors specialist, pharmacist, occupational health physician, nurse, medical oncologist, and a methodologist. The working group worked together to adapt recommendations from another guideline. Guideline was internally reviewed and peer reviewed.

APPENDIX 3: Critical Appraisal of Included Publications

<b>Table A1: Strengths and Limitations of Non-Randomized Studies using Downs and Black<sup>4</sup></b>	
<b>Strengths</b>	<b>Limitations</b>
<b>Miyake (2013)<sup>7</sup></b>	
<ul style="list-style-type: none"> <li>Study setting was representative of a real-life community hospital setting</li> </ul>	<ul style="list-style-type: none"> <li>Small sample size (n = 4) of only pharmacists, limiting generalizability of results to other staff.</li> <li>Characteristics of pharmacists (e.g., age, BMI) were not reported</li> <li>Method of training pharmacist to use PhaSeal not reported</li> <li>No control group was present</li> </ul>
<b>Yoshida (2009)<sup>8</sup></b>	
<ul style="list-style-type: none"> <li>Study setting was representative of a real-life hospital setting</li> <li>A control group was used</li> </ul>	<ul style="list-style-type: none"> <li>Small sample size (n = 6) of only pharmacists, limiting generalizability of results to other staff.</li> <li>Characteristics of pharmacists (e.g., gender, age, BMI) were not reported</li> </ul>
<b>Nyman (2007)<sup>3</sup></b>	
<ul style="list-style-type: none"> <li>Study setting was representative of a real-life hospital setting</li> </ul>	<ul style="list-style-type: none"> <li>Volunteers were used in the study, which may not be representative of the entire hospital staff.</li> <li>Small sample size (n = 11)</li> <li>No control group within study – used a different study for comparison which would not control for variables</li> <li>Limited information quantifying the amount of cyclophosphamide and ifosfamide was provided</li> </ul>

<b>Table A2: Strengths and Limitations of Economic Studies using Drummond<sup>5</sup></b>	
<b>Strengths</b>	<b>Limitations</b>
<b>Edwards (2013)<sup>9</sup></b>	
<ul style="list-style-type: none"> <li>Costs and assumptions were clearly reported</li> </ul>	<ul style="list-style-type: none"> <li>Microbial testing of vials was not performed – unsure of actual sterility</li> <li>This study focused only on antineoplastic agents compounded in a hematology-oncology pharmacy, which limits generalizability to other agents</li> </ul>

<b>Table A3: Strengths and Limitations of Guidelines using AGREE II<sup>6</sup></b>	
<b>Strengths</b>	<b>Limitations</b>
<b>Easty (2013)<sup>10</sup> – Cancer Care Ontario</b>	
<ul style="list-style-type: none"> <li>There was a clear overall objective and specified target population</li> <li>Methods used for the literature search and recommendations development were clearly reported</li> <li>The working group represented key stakeholders</li> </ul>	<ul style="list-style-type: none"> <li>Recommendations were not graded according to a tool</li> <li>Patient's preferences and views were not explicitly taken into consideration</li> <li>Cost of implementing these guidelines were not evaluated or reported</li> </ul>

**APPENDIX 4: Main Study Findings and Author’s Conclusions**

**Table A1: Summary of Findings of Included Studies**

Main Study Findings		Author’s Conclusions																																													
<p><b>Miyake (2013)<sup>7</sup></b></p> <p><u>Before PhaSeal (between Aug 30 and Sept 11, 2007)</u>                      Mean amount of cyclophosphamide compounded by pharmacists on the day of the urine test: 3525 mg</p> <p>34 urine samples were collected from 4 pharmacists, cyclophosphamide was detected in 26 samples.</p> <p>Mean cyclophosphamide concentration: 47.4 ng/mL</p> <p><u>After PhaSeal (between Nov 7, 2008 and Mar 17, 2009)</u>                      Mean amount of cyclophosphamide compounded by pharmacists on the day of the urine test: 3945 mg</p> <p>31 urine samples were collected from 4 pharmacists, cyclophosphamide was detected in 2 samples.</p> <p>Mean cyclophosphamide concentration: 3.6 ng/mL</p> <table border="1"> <thead> <tr> <th rowspan="2">Pharmacist</th> <th colspan="2">Before PhaSeal</th> <th colspan="2">After PhaSeal</th> </tr> <tr> <th>Amount CP prep (mg/day)</th> <th>CP urine (ng/24 h)</th> <th>Amount CP prep (mg/day)</th> <th>CP urine (ng/24 h)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>2900</td> <td>34.9</td> <td>3000</td> <td>ND</td> </tr> <tr> <td>2</td> <td>2810</td> <td>27.0</td> <td>4600</td> <td>ND</td> </tr> <tr> <td>3</td> <td>3530</td> <td>56.5</td> <td>3700</td> <td>6.4</td> </tr> <tr> <td>4</td> <td>4860</td> <td>71.3</td> <td>4480</td> <td>7.8</td> </tr> <tr> <td><b>Mean</b></td> <td>3525</td> <td>47.4</td> <td>3945</td> <td>3.6</td> </tr> </tbody> </table> <p>CP = cyclophosphamide; ND = not detected</p>		Pharmacist	Before PhaSeal		After PhaSeal		Amount CP prep (mg/day)	CP urine (ng/24 h)	Amount CP prep (mg/day)	CP urine (ng/24 h)	1	2900	34.9	3000	ND	2	2810	27.0	4600	ND	3	3530	56.5	3700	6.4	4	4860	71.3	4480	7.8	<b>Mean</b>	3525	47.4	3945	3.6	<p>“In combination with cleaning according to the Japanese guidelines, PhaSeal further reduces surface contamination and health care provider exposure of cyclophosphamide could be achieved at almost undetectable levels.” (p. 6)</p>											
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<p><b>Yoshida (2009)<sup>8</sup></b></p> <p><u>Conventional method</u>                      Mean amount of cyclophosphamide compounded during period of study: 2.76 ± 1.50 g/day</p> <p><u>PhaSeal</u>                      Mean amount of cyclophosphamide compounded during period of study: 2.36 ± 1.46 g/day</p> <table border="1"> <thead> <tr> <th rowspan="2">Pharmacist</th> <th colspan="2">Conventional method</th> <th colspan="2">PhaSeal</th> </tr> <tr> <th>Samplin g days</th> <th>Mean CP prep (ng/day)</th> <th>Sampling days</th> <th>Mean CP prep (ng/day)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>3</td> <td>20</td> <td>4</td> <td>5.5</td> </tr> <tr> <td>2</td> <td>2</td> <td>170</td> <td>3</td> <td>15</td> </tr> <tr> <td>3</td> <td>2</td> <td>26</td> <td>1</td> <td>ND</td> </tr> <tr> <td>4</td> <td>2</td> <td>12</td> <td>2</td> <td>2.0</td> </tr> <tr> <td>5</td> <td>2</td> <td>8.5</td> <td>3</td> <td>3.0</td> </tr> <tr> <td>6</td> <td>2</td> <td>ND</td> <td>1</td> <td>4.0</td> </tr> <tr> <td><b>Mean</b></td> <td></td> <td>39</td> <td></td> <td>4.9</td> </tr> </tbody> </table> <p>CP = cyclophosphamide; ND = not detected</p>		Pharmacist	Conventional method		PhaSeal		Samplin g days	Mean CP prep (ng/day)	Sampling days	Mean CP prep (ng/day)	1	3	20	4	5.5	2	2	170	3	15	3	2	26	1	ND	4	2	12	2	2.0	5	2	8.5	3	3.0	6	2	ND	1	4.0	<b>Mean</b>		39		4.9	<p>“The closed system device tested was able to significantly reduce cyclophosphamide contamination of surfaces in the preparation area and gloves which the pharmacists used during the mixing operation. Using the closed system device also reduced the amount of urinary cyclophosphamide of the pharmacists.” (p. 160)</p>	
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<p><b>Nyman (2007)<sup>3</sup></b></p> <p><u>Outpatient infusion clinic (pre and post-PhaSeal)</u></p> <ul style="list-style-type: none"> <li>- Different study from a previous publication was used as a comparator.</li> </ul> <p><u>Cancer hospital (PhaSeal)</u>                      At the time of the study (6 months of hospital operation), 1,130</p>		<p>“We demonstrated a lower percentage of ifosfamide- or cyclophosphamide-positive surface samples in our new cancer hospital after 6 months of operation than we had observed in our outpatient oncology infusion clinic after 6 months of switching to the PhaSeal System. However, some</p>																																													

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<p>doses of IV antineoplastic medication had been prepared by the pharmacy, mean 6.8 doses of IV antineoplastic medications/day; 73 (0.4 doses/day) cyclophosphamide, 92 (0.5 doses/day) ifosfamide. In the 15 days preceding collection of samples, 2 doses of IV cyclophosphamide and 8 doses of IV ifosfamide were prepared.</p> <p><b>Patients with urine samples positive for cyclophosphamide or ifosfamide</b></p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th>Hospital</th> <th colspan="2">Outpatient Infusion</th> </tr> <tr> <th>PhaSeal (n = 11)</th> <th>Pre-PhaSeal (n = 7)</th> <th>6m Post-PhaSeal (n = 7)</th> </tr> </thead> <tbody> <tr> <td><b>Pharmacists</b></td> <td>0/4 (0%)</td> <td>2/2 (100%)</td> <td>0/2</td> </tr> <tr> <td><b>Pharmacy technicians</b></td> <td>1/4 (25%)</td> <td>1/3 (33%)</td> <td>0/3</td> </tr> <tr> <td><b>Nurses</b></td> <td>0/3</td> <td>2/2 (100%)</td> <td>0/2</td> </tr> <tr> <td><b>Total</b></td> <td>9%</td> <td>71%</td> <td>0</td> </tr> </tbody> </table>			Hospital	Outpatient Infusion		PhaSeal (n = 11)	Pre-PhaSeal (n = 7)	6m Post-PhaSeal (n = 7)	<b>Pharmacists</b>	0/4 (0%)	2/2 (100%)	0/2	<b>Pharmacy technicians</b>	1/4 (25%)	1/3 (33%)	0/3	<b>Nurses</b>	0/3	2/2 (100%)	0/2	<b>Total</b>	9%	71%	0	<p>contamination with the antineoplastic agents tested was still present." (p. 223)</p>	
	Hospital		Outpatient Infusion																							
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Table A2: Summary of Findings of Included Economic Evaluations	
Main Study Findings	Author's Conclusions
Edwards (2013) <sup>9</sup>	
<p>The numbers are shown as reported in the publication.</p> <p>Mean initial use of vials: 43.45% (Mean 57.03% of drug potentially salvageable)</p> <p>Actual waste avoided (range): 0% (dacarbazine, erubulin) to 93.94% (vincristine)</p> <p>Overall waste avoidance: 51.35%</p> <p>Cost savings: \$96,348.70 over 50 days (study period)</p> <p>Annual cost savings: \$703,047.67</p> <p>Cost of PhaSeal: \$106,556.55 (2012 USD)</p>	<p>"Significant reductions in drug waste and cost savings were realized through the use of the Phaseal closed system transfer device to extend the beyond-use date of single-dose vials of selected antineoplastic medications." (p. 345)</p>

Table A2: Summary of Findings of Included Economic Evaluations	
Recommendations	
Easty (2013) <sup>10</sup> – Cancer Care Ontario	
<p><b>Cytotoxic drug preparation</b></p> <p>"A class II type B biological safety cabinet is required with preference for the type B2, because it ensures that there is no recirculation of air within the cabinet</p> <p>Closed-drug transfer systems (e.g., PhaSeal®) are not a substitute for class II type B biological safety cabinets. There is evidence from studies that closed-drug transfer-systems can reduce contamination during preparation. Further emerging evidence suggests that when these devices are not used as specified, they could become open to the environment. Further research is needed to evaluate this possibility." (p. 10-11)</p>	

**APPENDIX 5: Additional References of Potential Interest***Environmental Contamination*

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Harrison BR, Peters BG, Bing MR. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. *Am J Health Syst Pharm*. 2006 Sep 15;63(18):1736-44.

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