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REPORT

PHASEAL SYSTEM FOR CHEMOPREPARATION

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

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EXECUTIVE SUMMARY

Cytotoxic drugs used in the treatment of cancer as well as some non-neoplastic diseases are of immense benefit to patients. However, they present serious risks to those routinely handling them, namely, the doctors, oncology nurses and pharmacy staff. Long term effects of exposure to cytotoxic drugs leads to complications like foetal malformations in the offspring of female workers, and spontaneous abortions, amongst others.

The PhaSeal system is a disposable closed system for the preparation, administration and disposal of parenteral hazardous drugs by reducing environmental contamination and employee exposure[1]. The system is said to prevent leakage of the drug into the environment, thus protecting health care workers from potential exposure to the drug being handled.

The PhaSeal system is used in the United States as well as parts of Europe and Asia.[2,3,5-12] Its unique design is meant to prevent environmental contamination and help protect healthcare employees through the preparation, administration and waste handling of hazardous drugs.

Available evidence shows that the PhaSeal system is safe and effective in reducing contamination when used in the preparation and administration of cytotoxic drugs. However, there is the issue of incompatibility of the PhaSeal system with several cytotoxic drugs, particularly products in ampoules and drug vials of certain sizes. Training of personnel involved in chemotherapy preparation, administration and waste disposal is important to ensure the correct technique of using the device.

Available evidence also indicates that the PhaSeal system creates an additional yearly expense to the cost of every chemotherapy infusion. [redacted].

There is no available evidence on the setting in which the PhaSeal system is to be used. Available studies have been carried out in existing chemopreparation rooms at hospital pharmacies or oncology centres.

Given the local situation where in many Malaysian government hospitals chemotherapy is still being prepared without the presence of biological safety cabinets (BSC) or clean rooms, the use of the PhaSeal system can be considered until these hospitals are equipped with clean rooms or BSCs (personal communication with representatives from the Pharmaceutical Services Division, MOH and Radiotherapy and Oncology Pharmacy unit). However, the issue of incompatibility of PhaSeal with certain drug vials or ampoules limits its application.

When a decision to use the PhaSeal system is made, emphasis should be given on the training of personnel concerned in the preparation, administration and waste disposal of cytotoxic drugs. This is to ensure correct use of the device to minimise leakage of the cytotoxic drugs.

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PHASEAL SYSTEM FOR CHEMOPREPARATION

1. INTRODUCTION

Cytotoxic drugs used in the treatment of cancer as well as some non-neoplastic diseases are of immense benefit to patients. However, they present serious risks to those routinely handling them, namely, the doctors, oncology nurses and pharmacy staff. These health care workers are the ones responsible for the drug preparation, handling of waste products and administering the cytotoxic drugs.

Traditionally, cytotoxic drugs are prepared in biological safety cabinets (BSC). These health care workers are, in some ways, exposed to low levels of these drugs produced from the drug preparation. Long term effects of exposure to cytotoxic drugs leads to complications like foetal malformations in the offspring of female workers, and spontaneous abortions, amongst others.

Safety guidelines and protective measures have been implemented to protect health care workers when preparing, handling and administering cytotoxic drugs. Despite this, health care workers continue to be exposed to these hazardous agents.

PhaSeal is a disposable closed system for the preparation, administration and disposal of parenteral drugs by reducing environmental contamination and employee exposure[1]. The system is said to prevent leakage of the drug into the environment, thus protecting health care workers from potential exposure to the drug being handled.

2. TECHNICAL FEATURES

PhaSeal comprises of two safety features ensuring leakage prevention. One is the dry connection system which contains a needle, enclosed within a protective sleeve sealed by a membrane cover to ensure leak-free transfer of drugs. Transfer is made via a specially cut injection cannula and when the elements are separated after transfer of drugs the membranes act as a tight seal, preventing cytotoxic drugs from coming into contact with the atmosphere.[1]

The PhaSeal Concept

PhaSeal utilizes an in-built pressure equalization technique. The expansion chamber makes sure that neither overpressure nor vacuum can occur during drug preparation. This effectively prevents aerosol and vapour leakage.

PhaSeal also uses a double membrane system to ensure leak-free transfer of drugs. Cytotoxic hazardous drugs do not come into contact with the atmosphere and all connections remain dry. Extensive scientific documentation shows that no leakage occurs when using PhaSeal.

Injector™

The Injector ensures a closed transfer of the drug by means of double, tightly sealed, elastomeric membranes.

The second feature is the expansion chamber for pressure equalisation. The chamber neutralises over- and under-pressure (vacuum) in the drug vial during drug preparation, the primary causes of release of drug aerosols or vapour.[1]

Protector™

The Protector is a pressure equalization device, which is permanently attached to the vial and is used in the preparation of drugs from either powder or liquid form.

It effectively ensures that there is neither overpressure nor vacuum when air or fluid is injected into or aspirated from the vial.

3. POLICY QUESTION

Is PhaSeal system safe and effective for chemotherapy preparation in hospitals in Malaysia?

4. OBJECTIVE

To determine the safety, effectiveness and cost-effectiveness of the PhaSeal system for chemotherapy preparation.

5. METHODOLOGY

Electronic databases like PUBMED, OVID, Cochrane Library, and CINAHL were searched. So were Guidelines databases, HTA databases and Google. The following keywords were used either singly or in combinations: *PhaSeal, chemotherapy, chemopreparation, chemoprotection, safety, hazard*, effectiveness.* The search was limited to publications between 2000 and 2007.

In addition, cross-reference searching was carried out from reference lists and bibliographies of the full text articles retrieved.

From the initial search, a total of 17 articles were obtained based on the keywords. Of these, only 12 titles were considered to be relevant gauged from the abstracts. Data from these articles, whether available in full text or abstract only, were studied. Each article was graded for the level of evidence according to the Catalonian Agency for Health Technology Assessment (Appendix 1).

6. RESULTS AND DISCUSSION

Safety and Effectiveness

Studies carried out on the PhaSeal system have demonstrated similar outcomes; the PhaSeal system is effective in reducing leakage during chemopreparation.

A study by Nygren et al. investigated the difference in airborne emission and surface leakage when using the traditional open technique and the PhaSeal system. The PhaSeal closed system resulted in significantly less leakage than using the traditional open technique. It was also found that airborne emission was less than surface leakage when the PhaSeal system was put into use. However, the difference in airborne emission between the techniques was small and not statistically significant. It was concluded that airborne emissions do not occur in the same way as surface leakage. In this study it was concluded that when using the traditional technique even skilled nurses will encounter large spills, whereas with the PhaSeal system even inexperienced nurses can, after a short introduction, use this with little spills.[2, level 8]

Nyman et al., similarly, concluded that when used properly the PhaSeal system can help reduce exposure to antineoplastic contamination. In this study wipe and urine samples were analysed for cyclophosphamide and ifosfamide contamination.[3, level 8]

The American Society of Health-System Pharmacists (ASHP) Guidelines on Handling Hazardous Drugs reported that studies have shown that preparing and administering hazardous drugs with PhaSeal resulted in less environmental contamination when compared to using standard techniques. However, not all hazardous drugs can be prepared using PhaSeal components. It was also concluded that closed system drug-transfer devices, e.g. the PhaSeal system (or any other ancillary devices) are not substitutes for using a ventilated cabinet, the biological safety cabinet (BSC).[4, level 9]

Wick et al. looked at wipe samples of different sites of the preparation area and urine samples of the personnel involved, including 2 pharmacists responsible for entering and checking chemotherapy drug orders, 2 nurses involved in administration, 2 pharmacy technicians working in the pharmacy, 1 pharmacy technician preparing the chemotherapy doses and 1 control. Samples were taken before the implementation of the PhaSeal system and 6 months after implementation. Results suggested that the PhaSeal system is effective in reducing leakage during chemopreparation.[5, level 8]

A study was conducted to determine the long-term effectiveness of PhaSeal in reducing or preventing environmental contamination by cytotoxic drugs in the drug preparation room of an active outpatient oncology clinic. In this study the PhaSeal system was used consistently for a year without the use of a biological safety cabinet. All cytotoxic drug preparations were done on a table top with a disposable plastic/paper cover. Samples were taken at the end of the working day, prior to cleaning the preparation room. Environmental contamination was effectively reduced with the use of the PhaSeal system. The combination of physical membrane seals and air pressure equalisation chamber prevents movement of the cytostatic drug into the preparation room environment.[6, level 8] The same was found in another study which compared the levels of surface contamination with cyclophosphamide following preparation with standard technique and the closed-system drug transfer device (PhaSeal).[7, level 8]

Likewise, another study reported that the PhaSeal system effectively confined antineoplastic agents during preparation and kept the working environment free from surface contamination when used in conjunction with BSC and conventional cleaning methods.[8, level 8]

Consistent with the findings above, a 4-phase study reported less contamination with the PhaSeal system compared to the classical system using Luer lock syringes and needles. Cytotoxic drugs were prepared by well-trained technicians with vast experience in the field. Wipe and urine samples were taken during each phase and analysed for contamination.[9, level 8]

In a study by Spivey & Connor, fluorescein was used as the contamination detection agent. Like others, this study compared the two techniques, namely the PhaSeal system and conventional method, to determine which is mostly likely to release drug particles into the environment during drug preparation and administration. The findings were that with the PhaSeal system there was no demonstrable contamination into the work environment – no fluorescein drops were detected on the equipment or the gloves following any of the operations. On the other hand, using the conventional procedures resulted in fluorescein leakage from a number of activities:

1. Withdrawing a needle from an over-pressurised vial resulted in the largest spots;
2. Withdrawing a needle from the port of IV bag resulted in the formation of a drop of contamination on the port;
3. Simulated drug administration and IV push of drug into IV port resulted in release of the fluorescein into the environment;
4. There was contamination on the gloves of the workers.[10, level 9]

Tans & Willems, however, did not find the PhaSeal system effective in reducing surface contamination. The results may have been influenced by a big spill due to an incorrect use of the system. Nevertheless, there was an improvement in the glove contamination with the use of the PhaSeal system.[11, level 8]

It was reported that there was no difference in the handling time per dosage unit for PhaSeal on a table top and the traditional preparation in a biological safety cabinet. It was also found that from an ergonomic point of view the table top is much better than a biological safety cabinet. In addition, the turnover is higher for preparation and administration of drugs with the PhaSeal system as there were less personal protective measures, which are rather time-consuming, need to be taken. On using the system, the interviewed staff reported it as ‘easy to use’.[6, level 8]

One issue concerning the use of the PhaSeal system worthy of mention is the fact that the PhaSeal system is not compatible with all cytotoxic drugs, especially products in ampoules (e.g. arsenic trioxide). It is also not compatible for use with 28mm neck drug vials (e.g. wide-mouth cisplatin). However, a PhaSeal protector is apparently due out in the market soon. Moreover, PhaSeal can also be complicated to use with vials containing more air that the PhaSeal reservoir can contain. Nevertheless, but the majority of antineoplastics products can be obtained in packaging compatible with the PhaSeal system.[3, level 8]

Miyamatsu et al. concluded that the PhaSeal system safe to use in chemopreparation. It was also concluded that this system would be useful in the preparation of cytotoxic drugs given that those handling the device is familiar with its operating procedures.[12, level 8]

Cost-effectiveness

Only a few studies addressed the issue of cost, not cost-effectiveness, of the PhaSeal system in chemopreparation.

A local study was conducted to evaluate the cost of preparing and administering chemotherapy using the PhaSeal system at one of the hospitals in the Ministry of Health, Malaysia.[13, level 9] It was found that in the months of November and December 2006 the total direct cost of the PhaSeal system was approximately RM30,000. This averaged out to approximately RM141 for each of the 216 patients in the study. Each of these patients was receiving either single chemotherapy or in a combination.

Wick et al. reported that by using the system may increase the cost of each chemotherapy infusion by $6 to $15. The system also adds to yearly expense, different from the biological safety cabinet which creates only a one-time expense.[5, level 8] Similarly, another study showed that the system added $10 - $15 to the total cost of each infusion.[3, level 8]

Sessink et al., on the other hand, found the cost to be less when the PhaSeal system is used as it involves fewer personal protective measures. It also does not require a biological safety cabinet or a cleanroom facility with a ventilation system.[6, level 8.]

Setting

There is no available evidence on the setting in which the PhaSeal system is to be used. Available studies have been carried out in existing chemopreparation rooms at hospital pharmacies or oncology centres.[1-12, level 8-9]

7. CONCLUSION

The PhaSeal system is used in the United States as well as parts of Europe and Asia.[2,3,5-12; level 8-9] Its unique design is meant to prevent environmental contamination and help protect healthcare employees through the preparation, administration and waste handling of hazardous drugs.

Available evidence shows that the PhaSeal system is safe and effective in reducing contamination when used in the preparation and administration of cytotoxic drugs. There is, however, the issue of incompatibility of the PhaSeal system with several cytotoxic drugs, particularly products in ampoules and drug vials of certain sizes. Training of personnel involved in chemotherapy preparation, administration and waste disposal is important to ensure the correct technique of using the device.

Available evidence indicates that the PhaSeal system creates an additional yearly expense to the cost of every chemotherapy infusion. Locally, the direct cost of the PhaSeal System for chemotherapy preparation and administration is approximately RM141 per patient.

8. RECOMMENDATION

Given the local situation where in many Malaysian government hospitals chemotherapy is still being prepared without the presence of biological safety cabinets (BSC) or clean rooms, the use of the PhaSeal system can be considered until these hospitals are equipped with clean rooms or BSCs (personal communication with representatives from the Pharmaceutical Services Division, MOH and Radiotherapy and Oncology Pharmacy unit). However, the issue of incompatibility of PhaSeal with certain drug vials or ampoules limits its application.

When a decision to use the PhaSeal system is made, emphasis should be given on the training of personnel concerned in the preparation, administration and waste disposal of cytotoxic drugs. This is to ensure correct use of the device to minimise leakage of the cytotoxic drugs.

9. REFERENCES

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APPENDIX 1

LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH, (CAHTAR) SPAIN)

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

(SOURCE: MODIFIED FROM SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK [SIGN])

APPENDIX 2

HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

PhaSeal System

BACKGROUND

Cytotoxic drugs used in the treatment of cancer as well as some non-neoplastic diseases are of immense benefit to patients. However, they present serious risks to those routinely handling them, namely, the doctors, oncology nurses and pharmacy staff. These health care workers are the ones responsible for the drug preparation, handling of waste products and administering the cytotoxic drugs.

Traditionally, cytotoxic drugs are prepared in biological safety cabinets (BSC). These health care workers are, in some ways, exposed to low levels of these drugs produced from the drug preparation. Long term effects of exposure to cytotoxic drugs leads to complications like foetal malformations in the offspring of female workers, and spontaneous abortions, amongst others.

Safety guidelines and protective measures have been implemented to protect health care workers when preparing, handling and administering cytotoxic drugs. Despite this, health care workers continue to be exposed to these hazardous agents.

PhaSeal is a closed system for the preparation, administration and disposal of parenteral drugs. The system is said to prevent leakage of the drug into the environment, thus protecting health care workers from potential exposure to the drug being handled.

POLICY QUESTION

PhaSeal system for chemotherapy preparation.

OBJECTIVE

To determine the safety, effectiveness and cost-effectiveness of the PhaSeal system for chemotherapy preparation.

SCOPE

Include

Use of PhaSeal system

Long term side effects of cytotoxic drugs in health care workers involved in preparation, administration and disposal of cytotoxic drugs.

Exclude

Other methods of cytotoxic drug preparation, administration and disposal.

Long term side effects of cytotoxic drugs in patients on chemotherapy

ASPECTS TO BE CONSIDERED

Safety
Risks of exposure

Effectiveness
As a fully closed system in cytotoxic drug preparation and administering system

Cost implications
If evidence in favour of safety and effectiveness

Legal implications
Duty to warn
Informed decision-making

Organisational implications
Training to be provided to those involved in using the PhaSeal system

STRATEGY

Adopt/adapt existing HTA reports
New HTA

METHODOLOGY

Systematic review of existing HTA
Retrieve and analyse evidence – HTA reports and literature
Draw up evidence table
Synthesis of evidence
Draft up report – merge
Feedback on report draft
Final report
Present final report to HTA Advisory Committee
Present final report to HTA Council

APPENDIX 3

Evidence table: PhaSeal
Question: Is PhaSeal effective when used in preparation of chemotherapy?

Bibliographic citation	Study type / Methodology	LE	No. of patients & Patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
Nygren O, Gustavsson B, Strom L, Eriksson R, Jarneborn L, Friberg A. Exposure to anti-cancer drugs preparation and administration. Investigations of an open and a closed system. J Environ Monit. 2002;4:739-42.	Cross-sectional study. This study looked at drug leakage during preparation and administration. Comparisons were made with respect to surface contamination and airborne emission. Airborne emission was determined using platinum as a tracer, employing air sampling on membrane filters and adsorptive voltammetry for the platinum analysis. (Pt-AdV) Surface leakage was measured using the radio-isotope 99m-technetium as a tracer, using gamma-ray detection for technetium determination. (Tc-method) Air sampling was done at 6 places around the set-up. Air was sampled at flow rates of about 10L min^{-1} using vacuum pumps. Test subjects carried a personal sampling device, sampling air at a flow rate of 2L min^{-1}. Gloves, bench covers and filters were tested for ^{99m}Tc and Pt.	8	10 Nurses at Östra Hospital, both experienced and inexperienced, female, non-smoking, aged 20-55 years – all made 6 preparations and administrations using both the traditional open technique and the new closed system.	Closed system (PhaSeal)	Open system (traditional pump technique)		The difference in airborne emission between the techniques was small and not statistically significant. Airborne emission is less than surface leakage. =>Airborne emissions do not occur in the same way as surface leakage. In measuring spillage and leakage, Pt-AdV method was preferred over Tc method since the Tc method had not yet been validated for determination of filter samples. Using the Pt-AdV method, the following were found: -Using the traditional open technique, leakage was significantly more than using the new closed system. The closed system resulted in leakage of 3-4 orders of magnitude lower. -With the open technique, the preparations resulted in a less leakage (56µL) as compared with administrations (72µL). -With the closed system, the opposite was true – leakage during preparation was more (0.009µL) than during administration (0.001µL). **Conclusion**: The traditional technique results in significant leakage; even skilled nurses will encounter large spills with the technique. The closed system results in less leakage and even inexperienced nurses can, after a short introduction, use this with little spills.	This study was given financial support by The Swedish Council for Work Life Research.

ASHP Council on Professional Affairs. ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2006 June 15; 63:1172-93.	Guideline	9		Closed system (PhaSeal)	Standard techniques		Studies have shown that compounding and administering hazardous drugs with PhaSeal resulted in less environmental contamination when compared to using standard techniques. However, it was stated that PhaSeal components cannot be used to compound all hazardous drugs. It was concluded that closed system drug-transfer devices (or any other ancillary devices) are not substitutes for using a ventilated cabinet.	Recommendations are evidence-based where possible. In the absence of published data, professional judgement, experience and common sense were used.
Wick C, Slawson MH, Jorgenson JA, Tyler LS. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. Am J Health-Syst Pharm. 2003 Nov 15; 60:2314-20.	Cross-sectional	8	8 personnel from the University of Utah Hospitals and Clinics 2 pharmacists involved in entering and checking chemotherapy drug orders, 2 nurses involved in administration, 2 pharmacy technicians working in the pharmacy, 1 pharmacy technician preparing the chemotherapy doses, 1 control subject	PhaSeal system (After implementation – AI) – 6 months after	Before implementation of PhaSeal (BI) – traditional method		**<u>Wipe samples</u>** **17 samples taken BI** - all had detectable levels of cyclophosphamide (5 had a value above the linear range of the assay) - 11 had detectable levels of ifosfamide (1 had a value above the linear range of the assay) **21 samples taken AI** - 14 samples had undetectable cyclophosphamide levels; 7 had detectable levels. - 6 samples had undetectable levels of ifosfamide; 15 had detectable levels (5 samples had levels that were above the range of the assay) **<u>Urine samples</u>** **52 samples collected BI** - 10 had detectable levels of ifosfamide - 18 had detectable levels of cyclophosphamide **54 samples collected AI** - All samples were below the limits of detection for cyclophosphamide and ifosfamide	Supported by Carmel Pharma Weaknesses of the study were highlighted by the authors.

Sessink PJ, Rolf ME, Ryden NS. Evaluation of the PhaSeal hazardous drug containment system. Hosp Pharm. 1999;34(11): 1311-7.	Cross-sectional study To determine the long-term effectiveness of PhaSeal in reducing or preventing environmental contamination by cytostatic drugs in the drug preparation room of an active outpatient oncology clinic.	8	3 female nurses with 10, 12 and 27 years of experience	PhaSeal system All cytostatic drug preparations were done on a table top with a disposable plastic/paper cover, and **not** using the biological safety hood (according to standard safety guidelines)	-	May 1996 – June 1997	Wipe samples were taken once at 17 sites in and around the drug preparation room at the end of working day, prior to cleaning (at the end of each working day all work surfaces were cleaned first with soapy water, then with alcohol). Samples were analysed for presence of fluorouracil and cyclophosphamide. Results: Cyclophosphamide and fluorouracil were not detected in any wipe samples taken in the drug preparation room. Cyclophosphamide was detected in a single wipe sample taken from the floor in the corridor outside the preparation room. The interviewed staff judged PhaSeal as 'easy to use' product. Handling time per dosage unit is the same for PhaSeal on a table top as for traditional preparation in a biological safety cabinet, but from an ergonomic point of view, a table top is far better than a biological safety cabinet. Overall turnover is higher for preparation and administration of cytostatic drugs with PhaSeal system because fewer personal protective measures, which are rather time-consuming, need to be taken. Under the conditions evaluated in this study, the PhaSeal system effectively prevents environmental contamination. The combination of physical membrane seals and air pressure equalisation chamber prevents movement of the cytostatic drug into the preparation room environment.	

Vanderbroucke J, Robays H. How to protect environment and employees against cytotoxic agents, the UZ Ghent experience. J Oncol Pharm Practice. 2001;6(4):146-52.	Cross-sectional study **Phase 1 (Classical system)** BSC was moved to new preparation room; work with CS for 3.5 months **Phase 2 (Cleaning procedure)** Clean BSC and preparation room; wipe sample for baseline PS. The BSC and preparation room was cleaned 3 times **Phase 3 (PhaSeal system)** Use of use of PhaSeal for 6 months. It was discovered that there were 6 areas of leakages of the external exhaust pipelines, one of which was on the left side of the room near the entrance of the air-conditioning unit. **Phase 4 (Classical system)** Use of classical system for 3 months after the exhausts were replaced with sealed pipelines	8	10 well-trained pharmacy technicians with broad experience in preparing sterile and cytotoxic preparations. When using the classical system, procedures followed were in accordance with their internal 'safety handbook for cytotoxics'. The technicians involved in using the PhaSeal system had followed an additional training in manipulating the system. **Wipe samples** of class II BSC and **urine samples** of technicians involved in preparatory activities and pharmacists present in the same room to control the activities.	PhaSeal system (PS) (closed)	Classical system (CS) (open) using Luer lock syringes and needles		The study was divided into 4 phases: **Phase 1 – Classical system (CS)** Traces of cyclophosphamide was found immediately after installation of BSC in new room, both inside BSC and in direct surroundings – suggests that BSC itself is a cause of contamination. **Phase 2 – Cleaning procedure** After first two cleaning sessions the contamination was not lowered in the BSC and the floor in front of it. After third cleaning, results showed a decrease to a level of contamination lower than the first baseline at the start of study. **Phase 3 – PhaSeal system** Results showed a decrease in contamination in all spots except inner side and airfoil of left BSC (NB. There were 6 areas of leakages of the external exhaust pipelines, one of which was on the left side of the room near the entrance of the air-conditioning unit. The air pushed the vapours down directly into the aspiration zone of the left BSC's airfoil.) **Phase 4 – Classical system** Results showed an increase of the contamination, but to a lower level than in the first period of CS. **Urine samples** PhaSeal – only one positive urine test of an assistant preparing cytotoxic drugs. Classical system – four positive urine tests of technicians, one positive of pharmacist present in same room.	

Connor TH, Anderson RW, Sessink PJ, Spivey SM. Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture area. Am J Health Syst Pharm. 2002 Jan;59(1):68-72.	Cross-sectional study 24 weeks	8	Pharmacy technicians trained in the use of PhaSeal system and had been using the system for several months before study started. Study was conducted in a high-usage ambulatory pharmacy following a complete renovation of the work area.	PhaSeal – used to prepare cyclophosphamide and ifosfamide	Standard method – used to prepare fluorouracil		Wipe samples and blanks were assigned a random number for a blinded analysis. **Fluorouracil contamination** Some areas on the floor, after which levels of contamination increased for most locations (2 BSCs, floor). High levels were found in the area outside pharmacy where returned chemotherapy pumps were routinely stored. **Cyclophosphamide contamination** One location by the window, an area on the floor (most likely resulted from the breakage of a 2g vial early in the study – levels declined over time **Ifosfamide contamination** Initially some areas of the floor had residual contamination – levels declined with time. On final day of sampling, high levels found in one of BSCs (may be due to improper use or failure of PhaSeal system, an unreported breakage or contamination by some other means). Conclusion – PhaSeal system effectively confined antineoplastic agents during preparation and kept the working environment free from surface contamination when used in conjunction with BSC and conventional cleaning methods.	Supported in part by Carmel Pharma The authors admitted that fluorouracil may not be an ideal control in this study due to possible differences in stability and in the ease with which it may be effectively removed by cleaning procedures. However, data from their earlier study suggest that it is suitable as a control.

Spivey S, Connor T. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV drug preparation with a closed system. Hosp Pharm. 2003;38:135-9.	Experimental	9	Drug (fluorescein) preparation was done by experienced pharmacy technician, trained in the use of the PhaSeal system. Administration of drug was done by an oncology nurse with minimal previous experience with PhaSeal. All manipulation was done in a BSC, simulating actual working conditions as closely as possible, using room lighting. A sterile plastic-backed drape was placed in the BSC before the start of each set of operation and scanned with UV light to detect an interfering fluorescence which might have originated from the pad.	PhaSeal system (closed system)	Conventional needle/syringe procedures		**Conventional procedures** Fluorescein leakage resulted from several activities: 5. Withdrawing a needle from an over-pressurised vial resulted in the largest spots; 6. Withdrawing a needle from the port of IV bag resulted in the formation of a drop of contamination on the port; 7. Simulated drug administration and IV push of drug into IV port resulted in release of the fluorescein into the environment; 8. There was contamination on the gloves of the workers. **PhaSeal system** No demonstrable contamination into the work environment – no fluorescein drops were seen on the equipment, the gloves or the drape following any of the operations.	Supported in part by Carmel Pharma TH Connor (co-author) is a member of the Scientific Advisory Board of Carmel Pharma.

Nyman HA, Jorgenson JA, Slawson MH. Workplace contamination with antineoplastic agents in a new cancer hospital using a closed-system drug transfer device. Hosp Pharm. 2007;42:219-25.	Cross-sectional study	8		PhaSeal system at the new cancer hospital – PhaSeal is used exclusively =>current study	Outpatient infusion clinic (samples were collected before and 6 months after PhaSeal system was implemented) – results used as benchmark against which to compare levels of contamination found in current study		Wipe sample analysis for cyclophosphamide and ifosfamide contamination: A few areas in the pharmacy were contaminated – the distribution indicates that one source of contamination in hospital pharmacies may be contamination on the outside of the vials arriving from the manufacturer or distributor. Less samples collected from current study tested positive for contamination compared with those collected at the outpatient infusion clinic. Highest level of ifosfamide contamination was lower in the cancer hospital than at outpatient infusion clinic. Urine samples of participants: Current study – one participant tested positive for both drugs (pharmacy technician who worked filling oral prescriptions and did not prepare iv antineoplastics). It is thought that the positive urine test may be due to environmental contamination in the general pharmacy area and/or contact with oral cyclophosphamide. Conclusion – when used properly the PhaSeal system can help reduce exposure to antineoplastic contamination.	The authors highlighted the fact that the PhaSeal system is not compatible with all chemotherapy, especially products in ampoules (e.g. arsenic trioxide). It is also not compatible for use with 28mm neck drug vials (wide-mouth cisplatin). However, a PhaSeal protector should soon be available. PhaSeal can also be complicated to use with vials containing more air that the PhaSeal reservoir can accommodate (but the majority of antineoplastics products can be obtained in packaging compatible with the PhaSeal system.
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;63:1736-44.	Cross-sectional study Oct 2002 – Aug 2003	8		Closed-system drug transfer device (CSTD) in conjunction with	Standard preparation techniques		The use of PhaSeal in the biological safety cabinet in the preparation of hazardous drugs reduced cyclophosphamide surface contamination as compared with standard techniques alone. Data from this study was inconclusive with regards to fluorouracil contamination.	Supported by an unrestricted education grant from Carmel Pharma.

Tans B, Willems L. Comparative contamination study with cyclophosphamide, fluorouracil and ifosfamide: standard technique versus a proprietary closed-handling system. J Oncol Pharm Practice. 2004;10:217-23.	Cross-sectional study 24 months To investigate the contribution of the PhaSeal system on the reduction of glove and surface contamination with hazardous drugs (HD) during preparation. Samples were taken on 5 occasions: 1. Just before PhaSeal system was implemented 2. 2 months after introduction of PhaSeal for the preparation of cyclophosphamide and fluorouracil 3. 4 months after introduction PhaSeal 4. 2 months after PhaSeal was discontinued 5. 18 months after re-starting the use of PhaSeal for preparations of cyclophosphamide and ifosfamide. Only contamination due to cyclophosphamide was measured on the gloves.	8		PhaSeal system All personnel were well trained in using the PhaSeal system prior to commencement of the study	Conventional method		Conclusion The use of the PhaSeal system did not seem to reduce the surface contamination in this study. This is probably because of a big spill due to an incorrect use of the system, which may have influenced the results. There was an improvement in the glove contamination with the use of the PhaSeal system.	Mayne Belgium and Carmel Pharma supposedly provided 'support' for the research.

Note: LE= Level of Evidence

Evidence table: PhaSeal
Question: Is PhaSeal safe when used in preparation of chemotherapy?

Bibliographic citation	Study Type / Methodology	LE	No. of patients & Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Miyamatsu H, Sakamoto M, Azuma K, Ishii F, Mae A, Satou K, Koura C, Kouno K, Saito K, Abe M, Akashi T. Evaluation of operability of the PhaSeal system, a sealed handling device for anticancer agents. Jap J Pharmaceutical Health Care and Sciences. 2006;32(12): 1211-21.	Cross-sectional study. 10 pharmacists and 10 nurses were recruited for the study. The PhaSeal system was tested with regards to suitability and ease of operation. The PhaSeal system was compared to the conventional system in terms of time required for preparation and aspiration of drugs.	8		PhaSeal system (PS-s)	Conventional system (C-s)		Time required for preparation: C-s 42.6 +/- 11.15s PS-s 63.3 +/- 14.99s ($p<0.01$) Time required for aspiration: C-s 27.2 +/- 9.08s PS-s 17.7 +/- 5.53s ($p<0.01$) It was concluded that PhaSeal was safer to use for the medical professionals. However, it was not conclusive on the ease of operation of the device. The PhaSeal was thought to be useful in the preparation of cytotoxic drugs provided the personnel handling it are more familiar with its operating procedures.	Abstract. Article in Japanese.

Note: LE= Level of Evidence

Evidence table: PhaSeal
Question: Is PhaSeal cost-effective when used in preparation of chemotherapy?

Bibliographic citation	Study Type / Methodology	LE	No. of patients & Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Wick C, Slawson MH, Jorgenson JA, Tyler LS. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. Am J Health-Syst Pharm. 2003 Nov 15; 60:2314-20.	Cross-sectional	8	8 personnel from the University of Utah Hospitals and Clinics 2 pharmacists involved in entering and checking chemotherapy drug orders, 2 nurses involved in administration, 2 pharmacy technicians working in the pharmacy, 1 pharmacy technician preparing the chemotherapy doses, 1 control subject	PhaSeal system (After implementation – AI)	Before implementation of PhaSeal (BI)		PhaSeal creates an added yearly expense, unlike the biological safety cabinet, which poses a one-time capital expenses which can be depreciated. The PhaSeal system may add between $6 and $15 to the cost of each chemotherapy infusion.	Supported by Carmel Pharma
Sessink PJ, Rolf ME, Ryden NS. Evaluation of the PhaSeal hazardous drug containment system. Hosp Pharm. 1999;34(11): 1311-7.	Cross-sectional study To determine the long-term effectiveness of PhaSeal in reducing or preventing environmental contamination by cytostatic drugs in the drug preparation room of an active outpatient oncology clinic.	8	3 female nurses with 10, 12 and 27 years of experience	PhaSeal system All cytostatic drug preparations were done on a table top with a disposable plastic/paper cover, and not using the biological safety hood (according to standard safety guidelines)	Standard technique	May 1996 – June 1997	Fewer personal protective measures resulted in lower costs. There is also no need to invest in and maintain a cleanroom facility with a ventilation system with a ventilation system and a biological safety cabinet when PhaSeal is used.	

Nyman HA, Jorgenson JA, Slawson MH. Workplace contamination with antineoplastic agents in a new cancer hospital using a closed-system drug transfer device. Hosp Pharm. 2007;42:219-25.	Cross-sectional study	8		PhaSeal system at the new cancer hospital – PhaSeal is used exclusively	Outpatient infusion clinic (samples were collected before and 6 months after PhaSeal system was implemented) – results used as benchmark against which to compare levels of contamination found in current study		The PhaSeal system was found to add, on average, $10 to $15 to the total cost of an infusion.	

Note: LE= Level of Evidence