PhaSeal® Evidence

A summary of the published evidence of the effectiveness of the PhaSeal closed-system drug transfer device
Introduction

The PhaSeal Closed-System Drug Transfer Device (CSTD) is a containment device that has been evaluated extensively in laboratory studies and in clinical use.

Simulation studies show that the PhaSeal system prevents leakage of liquids, aerosols and vapors. It is therefore considered as being both leakproof and airtight.

‘In clinical use’ evaluations in Europe and North America show that the introduction of the PhaSeal system is proven to reduce environmental contamination with cytotoxic drugs and reduce the occupational exposure of health care personnel to cytotoxic drugs.

In addition, reports show that PhaSeal can be introduced into routine use without compromising efficiency.

PhaSeal is the only product on the market today that satisfies the NIOSH definition of a Closed-System Drug Transfer Device (CSTD) required by the American Society of Hospital Pharmacy (ASHP) and by the 2007 International Society of Oncology Pharmacy Practitioners (ISOPP) guidelines.
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Evaluation of PhaSeal

The performance of PhaSeal has been evaluated in numerous studies. Both fluid leakage (leakproof) (see Table 1) and vapour leakage (airtight) (see Table 2) have been evaluated. Some studies have compared PhaSeal with traditional (syringe and needle methods) or transfer devices.

Studies of a different type have examined the performance of PhaSeal in clinical usage. These can conveniently be categorized into two types – those that examine the impact of PhaSeal on environmental contamination and personnel exposure (see Table 3) and those that evaluate the implementation of PhaSeal (see Table 4).

Evaluations for fluid leakage
The potential for fluid leakage has been examined in several laboratory studies comparing the PhaSeal system with the traditional (needle and syringe) technique and with other drug transfer devices (see Table 1).

Early studies relied on indirect methods, using radioactive technetium and platinum, to demonstrate leakage. Recent studies using either fluorescein or acidic liquid to detect leakage. All studies have shown that the PhaSeal system effectively contains fluids and prevents leakage during manipulations designed to simulate normal use.
Table 1: Studies evaluating fluid leakage during preparation and administration

<table>
<thead>
<tr>
<th>First author and date of publication</th>
<th>Comparator</th>
<th>Method</th>
<th>Detection method</th>
<th>Result</th>
<th>Conclusions/Implications</th>
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<tr>
<td>Gustavsson 1996 *</td>
<td>Traditional technique.</td>
<td>Simulated 6 preparations and 6 administration by each of 12 participants.</td>
<td>Technetium.</td>
<td>Traditional technique: More than 50 % manipulations were associated with leakage of more than 1000 nanolitres. PhaSeal system: all but two manipulations were associated with leakage of less than 10 nanolitres. The traditional system for preparation and administration is associated with a high level of leakage, even for skilled nurses. The PhaSeal system resulted in almost non-detectable leakage even when handled by inexperienced subjects.</td>
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<tr>
<td>Gustavsson 1997 * (Abstract)</td>
<td>Traditional technique.</td>
<td>Simulated preparation and administration of 6 doses by each of 10 participants.</td>
<td>Technetium &amp; platinum tracers.</td>
<td>Airborne platinum 2–3 times higher with traditional technique. The traditional system for preparation and administration is associated with a high level of leakage, even for skilled nurses.</td>
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<tr>
<td>Nygren 2002 *</td>
<td>Traditional (pump) technique.</td>
<td>Simulated preparation and administration of 6 doses by each of 10 participants. Experienced and inexperienced nurses.</td>
<td>99m-technetium &amp; platinum tracers.</td>
<td>Average leakage: traditional system, preparation – 56 μL; administration 72 μL. PhaSeal system, preparation – 0.009 μL; administration 0.001 μL. Using the closed system the leakage is 3–4 orders of magnitude lower in comparison with the open system (traditional pump technique). Even inexperienced nurses can, after a short introduction, use this technique without spills above 0.1 μL.</td>
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<tr>
<td>Spivey 2003 *</td>
<td>Traditional technique.</td>
<td>Reconstitution of dry powder; transfer from vial to IV bag; simulated drug administration; IV push of drug solution into IV port.</td>
<td>Fluorescein + UV light.</td>
<td>Visible leakage at each phase of conventional manipulation. No leakage seen with PhaSeal. The PhaSeal system can prevent leakage of hazardous solution into the work environment and could reduce overall exposure of health care workers.</td>
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<td>Spivey &amp; Jorgenson 2007 * (Poster)</td>
<td>Two alternative transfer devices: Tevadaptor, Syringe Adaptor &amp; Luer Lock Adaptor (Teva Medical Ltd), Alaris SmartSite &amp; Texium (Cardinal Health).</td>
<td>Procedure designed to mimic preparation and administration. During procedure system components disengaged, photographed under UV light and touched to a gauze pad.</td>
<td>Fluorescein + UV light.</td>
<td>Visible leaks seen with Tevadaptor and Cardinal Health/Alaris systems on outside of each component during all manipulations. No leakage was observed with the PhaSeal system. The PhaSeal system confined the drug and could be used to help to reduce overall exposure of health care workers.</td>
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<tr>
<td>Jorgenson 2007 * (Poster)</td>
<td>Three alternative transfer devices: The ICU Medical System (Clave® Vial Adaptor &amp; Spiros™ Male Connector), The B. Braun/Tevadaptor™ System (Vial Adaptor &amp; Syringe-Adaptor) by Teva Medical Ltd, The Alaris System (SmartSite® Vented Vial Access Device &amp; Texium™ Male Luer) by Cardinal Health.</td>
<td>Syringes were filled with fluid and injected into vials attached to the transfer devices. After aspirating back and disconnecting, the connections of each device were pressed against litmus paper to detect the presence of any fluid. Each component tested for 10 manipulations.</td>
<td>Acidic liquid and litmus paper.</td>
<td>Visible leakage with all three other systems. No leakage observed with the PhaSeal system. The PhaSeal system satisfies the requirement for transfer devices to be leakproof and could be used to help to reduce overall exposure of health care workers.</td>
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Evaluations for vapor leakage

The potential for vapour leakage in PhaSeal and other drug transfer devices has been examined using titanium tetrachloride (TiCl₄) as the drug simulant. Titanium tetrachloride generates visible ‘smoke’ when in contact with moisture in the air. Thus, if titanium (vapour) particles are able to leak from a transfer device, then smoke will be formed outside the device. In these studies titanium was placed in glass vials that were then attached to five different drug transfer devices (Tevadaptor (On-Guard) Vial Adaptor system (Teva Medical Ltd), Chemo Mini-Spike Plus Dispensing Pin (B Braun Medical Inc), Alaris SmartSite (Cardinal Health), Chemoprotect Spike (Codan US Corporation) and the PhaSeal Protector 50 and Injector Luer Lock).

The formation of titanium smoke outside the transfer device was observed for all the transfer devices except the PhaSeal system.

Particles of TiCl₄ vapour, like those of cyclophosphamide, ifosfamide and 5-fluorouracil, are small enough to pass through 0.2 micrometer filters. The smoke particles are too big to pass through the filter and so if smoke is seen outside the transfer device it is because particles of TiCl₄ have passed the filter and have reacted with moisture in the outside air.

It has been argued that the titanium smoke quickly plugs the filter membranes of the Tevadaptor™, which are then ruptured by the build up of excessive pressure and smoke is then released. This is refuted by the lead advisor of the study J. Jorgenson, who reports that no damage to the filters was detected.
### Table 2: Studies evaluating vapour leakage during preparation and administration

<table>
<thead>
<tr>
<th>First author and date of publication</th>
<th>Comparator</th>
<th>Method</th>
<th>Detection method</th>
<th>Result</th>
<th>Conclusions / Implications</th>
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<tbody>
<tr>
<td>Au 2006* (Poster)</td>
<td>Tevadaptor Vial Adaptor system (Teva Medical Ltd), Chemo Mini-Spike Plus Dispensing Pin (B Braun Medical Inc), Alaris SmartSite (Cardinal Health), Chemoprotect Spike (Codan US Corporation).</td>
<td>Titanium tetrachloride, used to simulate drug vapor. It was placed in glass vials that were then attached to five different drug transfer devices.</td>
<td>Videotaped and photographed observation of appearance of smoke outside the transfer device.</td>
<td>Titanium smoke was observed forming outside all the devices except the PhaSeal system.</td>
<td>The PhaSeal system satisfies the requirement for transfer devices to be airtight and could be used to help to reduce overall exposure of health care workers.</td>
</tr>
<tr>
<td>Jorgenson 2007** (Poster)</td>
<td>Dispensing pin with Clave (ICU Medical), Vial Adapter with Clave (ICU Medical), CyTwo-Fer by Baxter, Chemo-Aide (Baxter).</td>
<td>Titanium tetrachloride, used to simulate drug vapor. It was placed in glass vials that were then attached to the drug transfer devices.</td>
<td>Videotaped observation of appearance of smoke outside the transfer device.</td>
<td>Titanium smoke was observed forming outside all the devices except the PhaSeal system.</td>
<td>The PhaSeal system satisfies the requirement for transfer devices to be airtight and could be used to help to reduce overall exposure of health care workers.</td>
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</table>
Clinical evaluations of the PhaSeal system

Evaluation of impact on environmental contamination and exposure of personnel

Several studies have examined the impact of the PhaSeal system on environmental contamination and exposure of personnel in routine working situations (see Table 2).

The results show that the use of the PhaSeal closed system transfer device is associated with low levels of environmental contamination and low exposure of personnel to cytotoxic drugs.
<table>
<thead>
<tr>
<th>First author and date of publication</th>
<th>Study design</th>
<th>Contamination and exposure measures</th>
<th>Results – environmental contamination</th>
<th>Results – personnel exposure</th>
<th>Conclusions / Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessink 1999</td>
<td>Evaluation of the use of PhaSeal used without a biological safety cabinet in a preparation room in an outpatient oncology unit. Evaluation after 1 year of use.</td>
<td>Surface wipe samples — cyclophosphamide and fluorouracil.</td>
<td>Neither drug detected in any samples (15 locations) inside the preparation room.</td>
<td>N/A</td>
<td>“The PhaSeal system alone is is sufficient to prevent environmental contamination during the preparation of cytostatic drugs”.</td>
</tr>
<tr>
<td>Vandenbroucke &amp; Robays 2001</td>
<td>Evaluation of environmental contamination and personnel exposure during periods of PhaSeal usage before and after thorough cleaning of facility. Evaluation after reintroduction of a traditional system.</td>
<td>Surface wipe samples — cyclophosphamide and fluorouracil. Urine samples — cyclophosphamide.</td>
<td>Both periods of “classical system” were associated with increases (2–10 fold) in cyclophosphamide levels.</td>
<td>Levels markedly lower or not detectable during PhaSeal phase.</td>
<td>Routine use of the PhaSeal system reduce overall exposure of health care workers.</td>
</tr>
<tr>
<td>Connor 2002</td>
<td>Comparison of environmental contamination arising from traditional method and PhaSeal system in renovated iv admixture facility. 24 week study.</td>
<td>Surface wipe samples — fluorouracil for traditional method, cyclophosphamide, ifosfamide for PhaSeal.</td>
<td>Flurouracil levels increased for most locations over study period. Cyclophosphamide — most values &lt;3ng/ml. High levels on floor declined. Ifosfamide — Floor levels declined.</td>
<td>N/A</td>
<td>Routine use of the PhaSeal system in conjunction with BSCs appeared to contain surface contamination and could help to reduce overall exposure of health care workers.</td>
</tr>
<tr>
<td>Wick 2003</td>
<td>Before and after implementation of PhaSeal.</td>
<td>Surface wipe samples — cyclophosphamide and ifosfamide. Infusion center and pharmacy. Urine samples — cyclophosphamide.</td>
<td>Baseline: 17/17 samples positive for cyclophosphamide, 11/17 positive for ifosfamide. After 6 months: 7/21 samples positive for cyclophosphamide, 15/21 positive for ifosfamide.</td>
<td>Baseline: 6/8 positive for cyclophosphamide, 2/8 positive for ifosfamide. After 6 months: None positive for either drug.</td>
<td>Routine use of the PhaSeal system in conjunction with BSCs, clean rooms and protective clothing could help to reduce overall exposure of health care workers.</td>
</tr>
<tr>
<td>Tans 2004</td>
<td>Evaluation of environmental contamination during periods of PhaSeal use, the traditional system and after the reintroduction of PhaSeal.</td>
<td>Surface wipe samples — cyclophosphamide, ifosfamide and fluorouracil.</td>
<td>No differences between periods with and without PhaSeal except for marked reduction in contamination of gloves. NB Levels low without PhaSeal; incorrect use of PhaSeal recorded; Spillage also recorded.</td>
<td>N/A</td>
<td>Routine use of the PhaSeal system in conjunction with correct preparation and cleaning procedures could help to reduce overall exposure of health care workers.</td>
</tr>
<tr>
<td>Harrison 2006</td>
<td>Evaluation of environmental contamination before, during and after introduction of PhaSeal (CSTD phase) During CSTD phase fluourouracil prepared on open counter top. 3 oncology pharmacies, 36-week study.</td>
<td>Surface wipe samples — cyclophosphamide and fluorouracil.</td>
<td>Proportion of positive fluorouracil samples fell significantly during CSTD phase. Median surface contamination with Cyclophosphamide fell significantly during CSTD phase.</td>
<td>N/A</td>
<td>The use of PhaSeal in conjunction with standard hazardous drug preparation techniques can reduce surface contamination and could help to reduce overall exposure of health care workers.</td>
</tr>
<tr>
<td>Nyman 2007</td>
<td>Evaluation of environmental contamination after 6 months exclusive use of PhaSeal in a new hospital.</td>
<td>Surface samples — cyclophosphamide in pharmacy and nursing areas.</td>
<td>Low level of contamination in oncology infusion clinic. Levels lower compared to previous study.</td>
<td>1/11 positive for cyclophosphamide compared to 6/8 without PhaSeal in previous study.</td>
<td>A CSTD (such as PhaSeal) should be part of a comprehensive exposure control program along with containment devices, protective clothing, cleaning, monitoring for contamination and training of staff.</td>
</tr>
</tbody>
</table>
Evaluation of impact on workflow and staffing
Several studies have examined the practicality of implementing PhaSeal in routine working situations (see Table 4). Two conclusions can be drawn from these reports:

- Staff who understand the risks of handling chemotherapy understand the advantages of PhaSeal
- Staff given appropriate training become adept at handling the PhaSeal system without sacrificing efficiency

Table 4: Studies evaluating the impact of PhaSeal on workflow and staffing

<table>
<thead>
<tr>
<th>First author and date of publication</th>
<th>Study design</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferencak 2000(^{20}) (Poster)</td>
<td>Survey of nurses and pharmacy staff after inservice training on the use of PhaSeal.</td>
<td>Perception of increased safety.</td>
<td>Staff who regularly prepared and administered chemotherapy were more likely to perceive PhaSeal as being a safer system than other staff.</td>
<td>Staff who understand the risks of handling chemotherapy readily understand the advantages of PhaSeal.</td>
</tr>
<tr>
<td>Poirier 2004(^{11}) (Poster)</td>
<td>Assessment of preparation (pharmacy technicians) and administration times (nurses) after introduction of PhaSeal.</td>
<td>Differences in preparation and administration times.</td>
<td>Pharmacy technicians returned to pre-trial efficiency levels within hours; nurses within two weeks.</td>
<td>The benefits of PhaSeal can be achieved without sacrificing working efficiency.</td>
</tr>
<tr>
<td>Miyamatsu 2006(^{22})</td>
<td>Comparison of preparation times using a conventional system (CS) and PhaSeal (PS) in pharmacists and nurses.</td>
<td>Total preparation time; aspiration time.</td>
<td>Total preparation time: CS – 42.6 ± 11.15 secs, PS – 63.3 ± 14.99 secs Aspiration time: CS – 27.2 ± 9.08 secs PS – 17.7± 5.53 secs.</td>
<td>Training is needed to handle PhaSeal in the same time as conventional systems.</td>
</tr>
<tr>
<td>Landini 2006(^{22}) (Poster)</td>
<td>Implementation of PhaSeal in pediatric and adult hospitals by a multidisciplinary stakeholder group.</td>
<td>Smoothness of transition; pre-implementation wipe tests for cyclophosphamide.</td>
<td>Transition of PhaSeal into hospital went smoothly. Pre-implementation wipe tests showed levels of contamination &gt; 1 nanogram/cm(^2) in some pharmacy preparation areas.</td>
<td>A multidisciplinary committee is essential to agree on hospital-wide protocols for cytotoxic drug handling.</td>
</tr>
</tbody>
</table>
References

7. Spivey S and Jorgenson JA. Contamination comparison of transfer devices intended for containment of hazardous drugs. Presented at Oncology Nursing Society, 32nd Annual congress, April 24-27, 200, Las Vegas NV.
10. Kraus M. Titanium chloride smoke as a drug simulant — a critique. Hospital Pharmacy Europe 2007; March/April: 34
21. Poirier S, Jones C, & Calvert MJ. Practical implementation of a closed system (PhaSeal) for the preparation, administration and disposal of cytotoxic drugs in a busy ambulatory cancer centre.
**CONCLUSIONS**

- The PhaSeal system is leakproof and airtight and satisfies the NIOSH, ASHP and ISOPP definitions of a closed-system drug transfer device.

- Introduction of the PhaSeal system can prevent three sources of environmental contamination with cytotoxic drugs. These are:
  - Aerosols formed during drug preparation
  - Drug vapors released during drug preparation
  - Droplets released during transfer

- Introduction of the PhaSeal system has been proven to reduce occupational exposure of health care personnel to cytotoxic drugs.

- Staff given appropriate training quickly become adept at handling the PhaSeal system without sacrificing efficiency.