

Table 1: Studies evaluating fluid leakage during preparation and administration

Study or Published Article Name	First author and date of publication	Comparator	Method	Detection Method	Result	Conclusions/ Implications
Contamination comparison of transfer devices intended for handling hazardous drugs.	Jorgenson 2008 ¹	Four alternative transfer devices: the B. Braun/Tevadaptor™ System (Vial Adaptor & Syringe Adaptor) by Teva Medical Ltd., the Alaris System (SmartSite® Vented Vial Access Device & Texium™ Male Luer) by Cardinal Health, the Chemoprotect Spike® by Codan US Corporation and the Chemo Mini-Spike Plus™ Dispensing Pin by B. Braun Medical, Inc.	Two part study simulated preparation and administration manipulations to determine containment of liquids, aerosols and vapors.	Part One: Titanium tetrachloride Part Two: Fluorescein and UV light	Comparator transfer devices: Visible leakage on outside of each component during all manipulations in Parts One and Two. PhaSeal System: No leakage observed in Parts One and Two.	Only the PhaSeal System met the NIOSH and ISOPP definitions of a CSTD.
Leakproof connection integrity test for devices intended for handling hazardous drugs.	Jorgenson 2007 ² (Poster)	Three alternative transfer devices: the ICU Medical System (Clave® Vial Adaptor & Spiros™ Male Connector), the B. Braun/Tevadaptor™ System (Vial Adaptor & Syringe Adaptor) by Teva Medical Ltd. and the Alaris System (SmartSite® Vented Vial Access Device & Texium™ Male Luer) by Cardinal Health.	Simulated aspiration to determine leakproof integrity of device connection points. Each component tested for 10 manipulations.	Acidic liquid and litmus paper	Comparator transfer devices: Visible leakage observed. PhaSeal System: No leakage observed.	The PhaSeal System satisfies the requirement for transfer devices to be leakproof.
Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV preparation with a closed system.	Spivey 2003 ³	Traditional technique	Simulated preparation and administration manipulations: reconstitution of dry powder, transfer from vial to IV bag, IV push of drug solution into IV port.	Fluorescein and UV light	Traditional technique: Visible leakage at each phase. PhaSeal System: No leakage.	A closed system such as PhaSeal has the ability to confine hazardous drugs, substantially reducing or possibly eliminating drug exposures.
Exposure to anti-cancer drugs during preparation and administration. Investigations of an open and a closed system.	Nygren 2002 ⁴	Traditional (pump) technique	Simulated preparation and administration of six doses by each of 10 participants. Experienced and inexperienced nurses.	Technetium and platinum tracers	Traditional technique: Average leakage - preparation 56 µL; administration 72 µL. PhaSeal System: Average leakage - 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 traditional pump technique. Even inexperienced nurses can, after a short introduction, use this technique without spills above 0.1 µL.
Evaluation of technetium assay for monitoring of occupational exposure to cytotoxic drugs.	Gustavsson 1997 ⁵ (Abstract)	Traditional technique	Simulated preparation and administration of six doses by each of 10 participants. Experienced and inexperienced nurses.	Technetium and platinum tracers	Traditional technique: Airborne platinum 2–3 times higher than with PhaSeal System.	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.
Report regarding the Protector project.	Gustavsson 1996 ⁶	Traditional technique	Simulated preparation and administration of six doses by each of 12 participants. Experienced and inexperienced nurses.	Technetium	Traditional technique: More than 50% of the manipulations were associated with leakage of more than 1000 nanoliters. PhaSeal System: All but two manipulations were associated with leakage of less than 10 nanoliters.	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.

Table 2: Studies evaluating vapor leakage during preparation and administration

Study or Published Article Name	First author and date of publication	Comparator	Method	Detection Method	Result	Conclusions/ Implications
Contamination comparison of transfer devices intended for handling hazardous drugs.	Jorgenson 2008 ¹	Four alternative transfer devices: the B. Braun/Tevadaptor™ System (Vial Adaptor & Syringe Adaptor) by Teva Medical Ltd., the Alaris System (SmartSite® Vented Vial Access Device and Texium™ Male Luer) by Cardinal Health, the Chemoprotect Spike® by Codan US Corporation and the Chemo Mini-Spike Plus™ Dispensing Pin by B. Braun Medical, Inc.	Two part study simulated preparation and administration manipulations to determine containment of liquids, aerosols and vapors.	Part One: Titanium tetrachloride Part Two: Fluorosecin and UV light	Comparator transfer devices: Visible leakage on outside of each component during all manipulations in Parts One and Two. PhaSeal System: No leakage observed in Parts One and Two.	Only the PhaSeal System met the NIOSH and ISOPP definitions of a CSTD.
Evaluation of vial transfer devices for containment of hazardous drug vapors.	Jorgenson 2008 ⁷ (Updated Poster)	Four alternative transfer devices: the Dispensing Pin with Clave® by ICU Medical, the Vial Adapter with Clave® by ICU Medical, the CyTwo-Fer by Baxa and the CHEMO-AIDE by Baxter.	Simulated preparation manipulations to determine containment of aerosols and vapors.	Titanium tetrachloride	Comparator transfer devices: Visible leakage on outside of each component during all manipulations. PhaSeal System: No leakage observed.	Only the PhaSeal System prevented the release of titanium smoke out of the closed-system drug transfer device. Only the PhaSeal System met the NIOSH definition of a closed-system drug transfer device.

Table 3: Studies examining the impact of PhaSeal on environmental contamination and exposure of personnel

Study or Published Article Name	First author and date of publication	Study Design	Contamination and Exposure Measures	Results – Environmental Contamination	Results – Personnel Exposure	Conclusions/ Implications
Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device.	Sessink 2010 ⁸	Evaluation of environmental contamination before and after implementation of PhaSeal in 22 US hospital pharmacies.	Surface wipe samples (cyclophosphamide, ifosfamide and 5-fluorouracil).	Following PhaSeal: Contamination levels for all drugs were significantly reduced; median values for surface contamination with cyclophosphamide, ifosfamide and 5-fluorouracil were reduced by 95%, 90% and 65%, respectively.	N/A	Use of PhaSeal significantly reduces surface contamination when preparing cyclophosphamide, ifosfamide and 5-fluorouracil as compared to standard drug preparation techniques.
Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device.	Siderov 2010 ⁹	Evaluation of environmental contamination before and after implementation of PhaSeal in two Australian metropolitan hospitals. Contamination was tested at baseline and then at five and 12 months post-implementation.	Surface wipe samples (cyclophosphamide).	Following PhaSeal at five months: Contamination was reduced at 59% of sites with four sites showing undetectable contamination. Following PhaSeal at 12 months: surface contamination was reduced at 75% of sample sites. Wipes showed evidence of cyclophosphamide contamination on commercial product (vial) exteriors.	N/A	PhaSeal further reduces surface contamination, in some cases to undetectable levels, when used inside a cytotoxic drug safety cabinet (CDSC).
Use of a closed system device to reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment.	Yoshida 2009 ¹⁰	Evaluation of environmental contamination and personnel exposure before and after implementation of PhaSeal.	Surface wipe samples, glove contamination samples and urine samples (cyclophosphamide).	Following PhaSeal: Cyclophosphamide contamination on surface wipe samples and glove samples was significantly reduced compared to conventional mixing method.	Following PhaSeal: Cyclophosphamide contamination in the urine of pharmacists was significantly reduced compared to conventional mixing method.	PhaSeal can reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment.
Workplace contamination with antineoplastic agents in a new cancer hospital using a closed-system drug transfer device.	Nyman 2007 ¹¹	Evaluation of environmental contamination and personnel exposure in pharmacy and nursing areas following six months of exclusive use of PhaSeal in a new hospital.	Surface wipe samples (cyclophosphamide and ifosfamide); Urine samples (cyclophosphamide and ifosfamide).	Following PhaSeal: Low level of contamination in oncology infusion clinic. Levels lower compared to previous study without PhaSeal.	Following PhaSeal: 1/11 positive for cyclophosphamide compared to 6/8 from previous study without PhaSeal.	PhaSeal should be considered as part of a comprehensive exposure control program including the use of containment devices, personal protective equipment, cleaning, monitoring for contamination and training of staff.
Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques.	Harrison 2006 ¹²	Evaluation of environmental contamination before, during and after introduction of PhaSeal. During period of PhaSeal use, fluorouracil prepared on open counter top. Evaluation included three oncology pharmacies over 36 weeks.	Surface wipe samples (cyclophosphamide and fluorouracil).	During period of PhaSeal use: Proportion of positive fluorouracil samples fell significantly; median surface contamination with cyclophosphamide fell significantly.	N/A	The use of the PhaSeal System in conjunction with standard hazardous drug preparation techniques significantly reduced cyclophosphamide surface contamination.

Table 3 (continued): Studies examining the impact of PhaSeal on environmental contamination and exposure of personnel

Study or Published Article Name	First author and date of publication	Study Design	Contamination and Exposure Measures	Results – Environmental Contamination	Results – Personnel Exposure	Conclusions/ Implications
Comparative contamination study with cyclophosphamide, fluorouracil and ifosfamide: standard versus a proprietary closed handling system.	Tans 2004 ¹³	Evaluation of environmental contamination during an initial phase with PhaSeal (four months); an interim phase with traditional technique (two months); and a second phase with PhaSeal (18 months).	Surface wipe samples (cyclophosphamide, ifosfamide and fluorouracil).	No differences between periods with and without PhaSeal except for marked reduction in contamination of gloves. NOTE: Levels low without PhaSeal; incorrect use of PhaSeal recorded; spillage also recorded.	N/A	The PhaSeal System is an important improvement in reducing contamination on gloves.
Using a closed-system protective device to reduce personnel exposure to antineoplastic agents.	Wick 2003 ¹⁴	Evaluation of environmental contamination and personnel exposure before and after implementation of PhaSeal.	Surface wipe samples (cyclophosphamide and ifosfamide); Urine samples (cyclophosphamide).	Before PhaSeal: 17/17 samples positive for cyclophosphamide, 11/17 positive for ifosfamide. After six months with the PhaSeal System: 7/21 samples positive for cyclophosphamide, 15/21 positive for ifosfamide.	Before PhaSeal: 6/8 positive for cyclophosphamide, 2/8 positive for ifosfamide. After six months with the PhaSeal System: None positive for either drug.	The PhaSeal System appeared to reduce surface contamination and exposure of health care personnel to cyclophosphamide and ifosfamide.
Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an IV admixture area.	Connor 2002 ¹⁵	Comparison of environmental contamination arising from use of traditional technique and PhaSeal System in renovated IV admixture facility. Evaluation took place over 24 weeks.	Surface wipe samples (fluorouracil for traditional method; cyclophosphamide and ifosfamide for PhaSeal).	Traditional technique: Fluorouracil levels increased for most locations over study period. PhaSeal System: Cyclophosphamide – most values <3 ng/cm ² ; high levels on floor declined; Ifosfamide – floor levels declined.	N/A	The PhaSeal System, in conjunction with BSCs, appeared to contain surface contamination resulting from the preparation of cyclophosphamide and ifosfamide.
How to protect environment and employees against cytotoxic agents: The UZ Ghent experience.	Vandenbroucke and Robays 2001 ¹⁶	Evaluation of environmental contamination and personnel exposure during periods of PhaSeal use before and after thorough cleaning of facility. Evaluation after reintroduction of a traditional system.	Surface wipe samples (cyclophosphamide and fluorouracil); Urine samples (cyclophosphamide).	Traditional technique: Both periods of this classical system were associated with increases (2–10 fold) in cyclophosphamide levels.	Levels markedly lower or not detectable during period of PhaSeal use.	By using PhaSeal, both personnel and their surroundings are protected.
Evaluation of the PhaSeal hazardous drug containment system.	Sessink 1999 ¹⁷	Evaluation of PhaSeal used without a biological safety cabinet in a preparation room in an outpatient oncology unit. Evaluation after one year of use.	Surface wipe samples (cyclophosphamide and fluorouracil).	No drug detected in any samples (15 locations) inside the preparation room.	N/A	The PhaSeal System alone is sufficient to prevent environmental contamination during the preparation of cytostatic drugs.

Table 4: Studies evaluating microbiological integrity and its impact on pharmacy cost-savings scenarios

Study or Published Article Name	First author and date of publication	Comparator	Study Design	Results	Conclusions/ Implications
Microbiological challenge of four protective devices for the reconstitution of cytotoxic agents.	DePrijck 2008 ¹⁸	Traditional technique plus three alternative transfer devices: the Clave® by ICU Medical, the Chemoprotect Spike® by Codan US Corporation and the Securmix by Eurospital.	Devices were challenged with low and high inocula of micro-organisms and manipulated repeatedly; cells were counted by means of solid-phase cytometry.	Of the four devices, PhaSeal afforded the lowest transfer of micro-organisms.	PhaSeal proved the least susceptible to microbial contamination of the vial; adequate disinfection of the vial prior to connection remains required.
Economic impact of the preparation scenario for cytotoxic drugs: an observational study.	Vandenbroucke 2008 ¹⁹	Three different preparation and conservation scenarios for cytotoxic drugs, all using PhaSeal for the protection of employees and the product.	Analyzed preparation data from July and August 2006 and simulated, for each day, the theoretical use of drug vials belonging to three different preparation and conservation scenarios for cytotoxic drugs. 3,086 preparations were evaluated.	On average, the overall cost of cytotoxic preparation can be decreased by 7% to 15% depending on the applied scenario.	The use of multi-dose vials until their physical and chemical expiry dates can save a substantial amount of money in the range of Euros 300,000 to Euros 700,000 per year for the studied hospital. The possible savings can be a supplementary argument for investing in a better work-setting and devices to ensure the safe and sterile handling of hazardous drugs.

Table 5: Studies evaluating the impact of PhaSeal on workflow and staffing

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 quickly become adept at handling the PhaSeal System without sacrificing efficiency

Study or Published Article Name	First Author and Date of Publication	Study Design	Outcome Measures	Results	Implications
Implementation of a safety device for use in preparing and administering cytotoxic medications in an inpatient setting.	Landini 2006 ²⁰ (Poster)	Implementation of PhaSeal in pediatric and adult hospitals by a multidisciplinary stakeholder group.	Smoothness of transition; pre-implementation wipe tests for cyclophosphamide.	Transition of PhaSeal into hospital went smoothly. Pre-implementation wipe tests showed levels of contamination > 1 ng/cm ² in some pharmacy preparation areas.	A multidisciplinary committee is essential to agree on hospital-wide protocols for cytotoxic drug handling.
Evaluation of operability of the PhaSeal System, a sealed handling device for anticancer agents.	Miyamatsu 2006 ²¹	Comparison of preparation times using a conventional system (CS) and PhaSeal (PS) in pharmacists and nurses.	Total preparation time; aspiration time.	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.	Training is needed to handle PhaSeal in the same time as conventional systems.
Practical implementation of a closed system (PhaSeal) for the preparation, administration and disposal of cytotoxic drugs in a busy ambulatory cancer center.	Poirier 2004 ²² (Poster)	Assessment of preparation times (pharmacy technicians) and administration times (nurses) after introduction of PhaSeal.	Differences in preparation and administration times.	Pharmacy technicians returned to pre-trial efficiency levels within hours; nurses within two weeks.	The benefits of PhaSeal can be achieved without sacrificing efficiency.
Implementation of safer chemotherapy systems utilized in a VA medical center.	Ferencak 2000 ²³ (Poster)	Survey of nurses and pharmacy staff after in-service training on the use of PhaSeal.	Perception of increased safety.	Staff who regularly prepared and administered chemotherapy were more likely to perceive PhaSeal as being a safer system than other staff.	Staff who understand the risks of handling chemotherapy readily understand the advantages of PhaSeal.

Conclusions

- The PhaSeal System is leakproof and airtight and satisfies the NIOSH, ASHP and ISOPP definitions of a closed-system drug transfer device (CSTD).
- 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 healthcare personnel to cytotoxic drugs.
- Staff quickly become adept at handling the PhaSeal System without sacrificing efficiency.
- Use of the PhaSeal System may help facilities realize an economic benefit in pharmacy.

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