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Technical Evaluation of a New Sterile Medical Device to Improve Anticancer Chemotherapy Administration

Nicolas Simon, MSc, PharmD, Bertrand Décaudin, PharmD, PhD, Damien Lannoy, MSc, PharmD, Frédérique Danicourt, PharmD, Christine Barthélémy, PharmD, PhD, and Pascal Odou, PharmD, PhD

Occupational exposure of healthcare workers to antineoplastic agents has been acknowledged for years (Jochimsen, 1992). It can lead to biologic or clinical disorders such as chromosomal aberrations (Cavallo et al., 2005), miscarriages (Valanis, Vollmer, & Steele, 1999), premature deliveries, and low birth weights (Fransman et al., 2007). Since the 1980s, occupational exposure has been described in nurses who handle antineoplastic drugs (Selevan, Lindbohm, Hornung, & Hemminki, 1985). Considerable contamination has been noted in the air in the vicinity of laminar air-flow hoods (Sessink, Friemèl, Anzion, & Bos, 1994; Sessink, Timmermans, Anzion, & Bos, 1994; Sessink, van de Kerkhof, Anzion, Noordhoek, & Bos, 1994). Those authors also revealed the presence of anticancer drugs or metabolites in the urine of pharmacy and nursing staff who prepared cytotoxic drug infusion bags.

The Occupational Safety and Health Administration ([OSHA], 1996) recommended protective measures, including ventilated biologic safety cabinets or isolators to reduce the risk of environmental contamination. OSHA also required that healthcare workers be educated and trained to reduce their risk of exposure and that they wear personal protective equipment when handling hazardous drugs.

In the 2000s, other sources of contamination were found. Drug vial surfaces appeared to be contaminated by cytotoxic drugs (Mason, Morton, Garfitt, Iqbal, & Jones, 2003). Moreover, preparation techniques exposed operators during manipulation, especially when needles were used (Spivey, & Connor, 2003). Chemical contamination was found inside positive- and negative-pressure isolators (Crauste-Manciet, Sessink, Ferrari, Jomier, & Brossard, 2005; Hedmer, Tinnerberg, Axmon, & Jönsson, 2008; Mason et al., 2005). Several decontamination protocols have been assessed to clean workplace surfaces, but none completely removed chemical contamination by anticancer

Purpose/Objectives: To assess the PCHIMX-1® (Doran International), a new sterile medical device intended by its manufacturer to improve the quality and safety of cytotoxic drug infusions, as well as its influence on manipulation times required for pharmacy technicians and nurses and its effect on infusion line outflow parameters.

Design: PCHIMX-1 assemblies were compared to standard infusion sets.

Setting: Pharmacy and oncology units of a French general hospital.

Methods: Reference assemblies (an infusion bag connected to an infusion set) were compared to PCHIMX-1 assemblies (PCHIMX-1 connected to two bags and to an infusion set). Two assessments were performed: (a) comparison of the times of manipulation during both preparation and administration of 5-fluorouracil infusion bags ($n = 40$) and (b) effect of PCHIMX-1 on infusion quality.

Main Research Variables: Manipulation times in the pharmacy (T_p) and in the ward (T_w) were measured, as well as flow rate and infusion efficiency.

Findings: The results showed that T_w was significantly increased, whereas T_p was significantly decreased; total time was unchanged. Results also showed that PCHIMX-1 significantly changed infusion efficiency; flow rate was not affected.

Conclusions: PCHIMX-1 obliges pharmacy technicians and nurses to change their handling procedures. The device does not have any influence on infusion flow rate but considerably improves infusion quality by ensuring that the full quantity of medication prescribed is administered.

Implications for Nursing: PCHIMX-1 guarantees that the complete prescribed dose of chemotherapy is administered without any change in infusion quality and adheres to the latest recommendations concerning occupational exposure protection.

cer drugs (Roberts, Khammo, McDonnell, & Sewell, 2006). More so than in pharmacies, chemical contamination with anticancer drugs was found in oncology wards where

cytotoxic preparations or patients' excreta were handled (Connor, Anderson, Sessink, Broadfield, & Power, 1999; Hedmer et al., 2008; Vermeulen, Heideman, Bos, & Kromhout, 2000; Ziegler, Mason, & Baxter, 2002).

Current recommendations are designed to improve patient management and to reinforce protective measures for operators against occupational exposure (American Society of Health-System Pharmacists, 2006; International Society of Oncology Pharmacy Practitioners [ISOPP] Standards Committee, 2007). OSHA (1996) recommended biologic and environmental monitoring of professionals. The ISOPP Standards Committee (2007) advised curtailing risks by centralizing preparation in a dedicated, sterile room in the pharmacy under a biologic safety cabinet or an isolator. Healthcare workers in the pharmacy and in wards must be trained to handle cytotoxic agents (ISOPP Standards Committee, 2007) and wear personal protective equipment (gloves, masks, gowns, and goggles) when they handle cytotoxic materials (ISOPP Standards Committee, 2007; OSHA, 1996). Specific medical devices can reinforce risk management during preparation and administration (Simon, Décaudin, & Odou, 2008). They are classified into three categories: (a) devices to protect the handler of the vial or ampoule, (b) devices to protect the operator during preparation, and (c) devices to protect the administrator during administration of the cytotoxic drug to the patient (ISOPP Standards Committee, 2007). To improve protective measures, the ISOPP Standards Committee (2007) recommended a preflushed infusion line and an adequate rinse with a nontoxic solution after cytotoxic drug infusion. Healthcare workers are advised to rinse the tube after administration to ensure that the total dose prescribed is administered to the patient (ISOPP Standards Committee, 2007).

In addition to the recommendations, many manufacturers have developed medical devices to reduce the risk of contamination during pharmacy preparation (e.g., Tevadaptor[®], Teva Medical; Phaseal[®], Carmel Pharma). Some devices have been developed to protect against contamination during infusion by adding the possibility of a rinsing step after administration (Cyto-ad-set[®], Codan; Chemoset[®], ICU Medical).

PCHIMX-1[®] (Doran International) is a new sterile medical device marketed in France and soon in the United States (see Figure 1). It is intended by its manufacturer to improve the quality and safety of cytotoxic drug infusions. Infusion quality can be defined as the ability to adhere to medical prescription indications such as drug flow rate, thus infusion duration, and to ensure that the full quantity of medication prescribed is administered. The device consists of a Y-type extension line placed on the infusion line between cytotoxic bag (first arm of Y tube) and infusion device (gravity-fed or electric infusion device). The first arm of the Y tube also is provided with a needle-free closed connector to



Note. The PCHIMX-1 device consists of two tubes connected in a Y configuration. The tubes are made of polymers without 2, 2-diethylhexylphtalate (also known as DEHP) to limit container-content interactions. Two clamps can be used to close the tubes. One of the tubes is connected to the chemotherapy bag. It carries a bidirectional valve, allowing for needle-free access in cytotoxic drug preparation. The other tube is connected to another 100 ml infusion bag containing an inert solution (e.g., sodium chloride 0.9%). The distal extremity can be connected to any infusion device for administration by gravity-fed devices or infusion pumps. Trademark and patent are pending.

Figure 1. PCHIMX-1[®]

be used during cytotoxic drug preparation. The second arm of the Y tube is connected to an inert solution bag intended for flushing and rinsing the infusion line.

PCHIMX-1 seems to follow the latest recommendations for optimizing cytotoxic drug administration while protecting against occupational exposure. No in vitro preclinical data are available to prove the exposure reduction. Nevertheless, in pharmacies, the presence of the needle-free connector means reduced use of needles, which are known to increase the risk of contamination. In wards, the Y configuration makes a rinsing step possible. Thus, theoretically, healthcare workers are exposed less to cytotoxic solutions while disconnecting the catheter after administration. However, assembling an additional medical device on an infusion line obviously modifies

the hydrodynamic conditions of infusion outflow (Elad, Zaretsky, & Heller, 1994). Therefore, an assessment was essential.

The aims of this study were to assess the influence of PCHIMX-1 on the manipulation time required by pharmaceutical technicians and nurses (aim 1) and to evaluate how PCHIMX-1 assembly affects infusion parameters, flow rate, and infusion efficiency during an in vitro standardized simulation of gravity-fed infusion (aim 2).

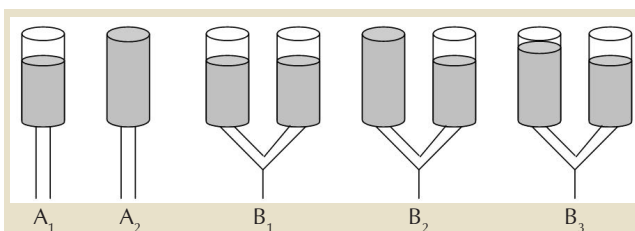
Methods

First Assessment: Impact of PCHIMX-1 on Manipulation Time in Practice

The researchers compared two types of assembly and methods, before and after the introduction of PCHIMX-1 in a hospital. The study focused on the preparation of 5-fluorouracil (5-FU, 400 mg/m²) because of its simplicity (only one transfer operation between drug vial and infusion bag). The preparation is carried out routinely in the pharmacy unit and consists of transferring the primary concentrated solution (50 mg/ml) to the infusion bag. Because the maximum prescribed dose is 800 mg, the concentrated solution was transferred with a 20 ml syringe into a 100 ml infusion bag (0.9% sodium chloride).

The reference assembly (see Figure 2, systems A) consisted of an infusion bag connected to a gravity-fed infusion device (KIS-1[®], Doran International). That was the assembly used routinely before the introduction of PCHIMX-1. In the pharmacy, the manipulation procedure meant connecting and flushing an infusion device (gravity or pump infusion set according to the prescription) before diluting cytotoxic drugs. This step was performed to avoid excessive exposure of nurses to cytotoxic drug solutions. Syringes (20 ml Luer lock) and needles (BD Blunt 18 G 40 mm, Becton Dickinson) were used to transfer the 5-FU solution from vial to infusion bag. Preparations were performed under a negative-pressure isolator. In the ward, nurses simply had to connect the infusion device to a patient's vascular access device and adjust the flow rate by counting the drip rate. Previously, infusion lines were not rinsed after administration and nurses risked exposure when disconnecting infusion lines. The PCHIMX-1 assembly (see Figure 2, systems B) consisted of a PCHIMX-1 connected to a 100 ml infusion bag (0.9% sodium chloride). A syringe (20 ml Luer lock) and spike method (Minispike + Micro, BBraun Medical) were used. Forty assemblies were evaluated in both groups.

A pharmacist trained pharmacy technicians and then nurses to handle the device according to the manufacturer's recommendations. In the pharmacy, before the appropriate infusion bag was connected, the two clamps had to be closed. After the PCHIMX-1 was connected to the infusion bag, the air was completely flushed; the drug then can be diluted with the needle-free access.



Note. The gray areas are 0.9% sodium chloride, and the empty areas are air. Systems A are the references. They correspond to a single infusion bag (0.9% sodium chloride, gray area) connected to a gravity-fed infusion set. The bag is completely flushed with air in system A₂. Systems B are the studied systems. PCHIMX-1 is connected to two 100 ml 0.9% sodium chloride infusion bags, one to dilute the anticancer drug (left), the other to purge and rinse the infusion line (right). B₁ corresponds to a PCHIMX-1 connected to two non-air-flushed infusion bags. In the B₂ assembly, the infusion bag is completely air-flushed. The B₃ system strictly corresponds to the manufacturer's recommendations for use. After the bag was air flushed, 2 ml air was reinjected through the bidirectional valve.

Figure 2. Scheme of the Five Assemblies Studied

Two ml of air were injected through this access (the first Y arm) to "push" the drug completely into the infusion bag. The preparation then was transferred to the ward and a nurse took over.

In the ward, after a nurse connected a 100 ml flush bag to the other infusion Y arm, an infusion device (KIS-1) was connected to the universal outlet. The manipulation of the infusion line was performed in three stages.

- The infusion line was filled completely with a fraction of the flush solution before the experiment started.
- After the flush line was clamped, the chemotherapy line was opened so that administration was at the prescribed flow rate.
- At the end of the infusion, the administration line was clamped and flush line opened for rinsing.

Setting: The experiment was conducted in the pharmacy unit and oncology ward of Dunkerque General Hospital in France.

Main evaluation measures: Times of manipulation (in seconds) were measured in the pharmacy unit (T_p) and in the ward (T_w). Total time of manipulation (T_T) was calculated (T_p plus T_w). T_p corresponded to the time allocated to preparing the chemotherapy infusion bag and T_w to the time required by nurses to prepare and connect the infusion line to the patient.

Second Assessment: Impact of PCHIMX-1 on In Vitro Infusion Quality

To simulate in vitro gravity-fed infusion, the study used routine hospital medical devices: gravity-fed infusion device (KIS-1), infusion and flush bags (100 ml 0.9% sodium chloride), flow-rate regulator (P2LLTF[®], Doran International), and PCHIMX-1. An 18-gauge polyurethane angiocatheter (Sendal) was added to the distal end of

the infusion line. Because of a lack of recommendations for measuring the flow-rate accuracy of gravity-fed infusions, measurements of infused solution mass were performed continuously on electronic scales fulfilling the requirements of the NF S 90–250 standard (XP504, Mettler-Toledo). This standard indicates the methodology to be used to verify the precision of infusion pumps.

Infusion methods: This experiment compared five infusion methods. The reference infusion method consisted of an infusion bag connected to a gravity-fed infusion device. The infusion line was filled completely with the infusion solution before the experiment started. Bags were totally air flushed or not. The PCHIMX-1-based infusion method consisted of a PCHIMX-1 connected to an infusion bag (first arm of Y tube) and a flush bag (second arm of Y tube) with a gravity-fed infusion device below. Assays were performed according to PCHIMX-1 routine use. Three protocols were followed: (a) a completely air-flushed infusion bag, (b) a non-air-flushed infusion bag, and (c) a partially air-flushed infusion bag. Air was flushed by aspiration with a syringe connected to the PCHIMX-1 needle-free access. The B₃ preparation protocol, as recommended by the manufacturer, consisted of a totally air-flushed infusion bag before preparation, followed by a 2 ml reinjection of air through the bidirectional valve. Bags were hooked at a height of 155 cm, and containers collecting the infused solution were laid out on scales at 55 cm above the floor.

Experimental plan: Prior to the experiment, filled infusion bags and empty containers were weighed, and at the end of the experiment, empty infusion bags and filled containers were weighed. Time measurements were started just after the infusion devices were unclamped and stopped when drops stopped falling into the drip chamber. The experience was repeated 10 times for each group at two flow rates: 250 ml and 500 ml per hour. The 250 ml per hour flow rate was checked with a flow-rate regulator, whereas the 500 ml per hour flow rate was hand checked with the drip rate.

Main evaluation measures: Two parameters were used to compare infusion quality between infusion lines with or without PCHIMX-1.

- Flow rate (F, ml per hour) was defined as the volume of solution infused per time unit. This parameter was calculated from the mass of solution collected throughout the experiment according to time.
- Infusion efficiency (IE, %) was defined as the ratio of infused solution volume to the total solution volume to be infused. This parameter was calculated from the mass of solution before and after infusion.

Data Collection

One member of the staff trained the pharmacy technicians and nurses, performed the experiments, and centralized all the data.

Statistical Analysis

Results are expressed as means and standard deviations. A bilateral nonparametric Mann-Whitney test was used to compare parameter values between systems A and B. Statistical significance was set at $p = 0.05$. Analysis was performed with XLSTAT® (Addinsoft).

Results

First Assessment

Table 1 summarizes the results. Statistical comparison of the three manipulation times showed significant differences between the reference and PCHIMX-1 systems. Time of manipulation in the pharmacy unit was decreased significantly, whereas in the ward it was increased significantly. However, no significant difference was found between the two mean total times of manipulation.

Second Assessment

Table 2 summarizes collected data and statistical analysis. For each air-flush status, no difference occurred in flow rate between reference and PCHIMX-1 infusion lines, whereas significant differences occurred between air-flush and non-air-flush protocols. Flow rate proved to be about 10%–25% higher with non-air-flush protocols.

As for IE, values were significantly higher for PCHIMX-1 assemblies than for reference assemblies at the two tested flow rates, whatever the flushing status. For the reference infusion line, IE was significantly inferior for air-flushed systems compared to non-air-flushed systems at 250 ml per hour (non-air-flushed: $85.57 \pm 1.59\%$; completely air-flushed: $81.81 \pm 0.68\%$; $p < 0.05$) and 500 ml per hour (non-air-flushed: $85.49 \pm 0.3\%$; completely air-flushed: $84.09 \pm 0.41\%$; $p < 0.05$). For the PCHIMX-1-based infusion lines, IE values

Table 1. Comparison Manipulation Time in the Pharmacy Unit and the Oncology Ward, and Total Time Between Reference Infusion Line and PCHIMX-1

Time (seconds)	Reference Infusion Line (A)		PCHIMX-1 Infusion Line (B)	
	\bar{X}	SD	\bar{X}	SD
T _p	159.7	69.01	116.13 ^a	23.36
T _w	31.02	8.82	79.23 ^a	15.44
T _t	190.72	68.42	195.35	27.94

^a Significantly different between A and B ($p < 0.05$)

T_p—pharmacy unit; T_t—total time; T_w—oncology ward

Table 2. Comparison of PCHIMX-1® to a Reference Infusion Line

Flow Rate	Reference Infusion Line				PCHIMX-1 Infusion Line					
	Non-Air-Flushed (A ₁)		Air-Flushed (A ₂)		Non-Air-Flushed (B ₁)		Air-Flushed (B ₂)		Air-Flushed + 2 ml (B ₃)	
	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD
250										
F (ml per hour)	275.41	12.94	241.8 ^a	10.61	269.61	25.25	221.33 ^c	11.59	249.43 ^e	7.22
IE (%)	85.57	1.59	81.81 ^a	0.68	102.14 ^b	2.06	98.58 ^{c,d}	1.14	99.56 ^{e,f}	0.34
500										
F (ml per hour)	512.62	49.76	395.13 ^a	46.35	501.57	28.94	398.17 ^c	26.58	393.48 ^g	31.65
IE (%)	85.49	0.3	84.09 ^a	0.41	100.15 ^b	4.73	98.91 ^d	0.55	99.78 ^{e,f}	0.78

^a Significantly different between A₁ and A₂ (p < 0.05); ^b Significantly different between A₁ and B₁ (p < 0.05); ^c Significantly different between B₁ and B₂ (p < 0.05); ^d Significantly different between A₂ and B₂ (p < 0.05); ^e Significantly different between B₂ and B₃ (p < 0.05); ^f Significantly different between A₂ and B₃ (p < 0.05); ^g Significantly different between B₁ and B₃ (p < 0.05)

Note. Infusion efficiency values higher than 100% resulted from experimental errors.

were slightly lower for air-flushed lines compared to non-air-flushed lines (completely air-flushed: 98.58 ± 1.14% and partially air-flushed: 99.56 ± 0.34% versus non-air-flushed: 102.14 ± 2.06%) and for totally air-flushed lines than for partially air-flushed ones. Higher IE values were obtained for all infusion protocols using PCHIMX-1 for both flow rates: 250 ml per hour (non-air-flushed: 102.14 ± 2.06%; completely air-flushed: 98.58 ± 1.14% and partially air-flushed: 99.56 ± 0.34%) and 500 ml per hour (non-air-flushed: 100.15 ± 4.73%; completely air-flushed: 98.91 ± 0.55% and partially air-flushed: 99.78 ± 0.78%).

Discussion

Impact of PCHIMX-1 on Infusion Flow Rate

Anticancer drugs are administered principally via IV by gravity-fed infusion or with electronic infusion devices such as infusion pumps. These techniques do not perform in the same way (Ziser, Feezor, & Skolaut, 1979). Assessing the ability of a new device to maintain flow rate throughout administration is important. Crass and Vance (1985) showed that flow rates often differed from those expected. Pleasants, Sawyer, Williams, McKenna, and Powell (1988) demonstrated that administration technique might influence tobramycin pharmacokinetic data, particularly plasmatic maximum concentration.

Many factors affect the accuracy of gravity-flow infusion systems. Four categories already have been established: factors related to medical devices, factors related to IV fluids, patient-related factors, and others (Crass & Vance, 1985). The current study found no differences between PCHIMX-1 and reference infusion lines, regardless of air-flush status. The data are in accordance with the lack of influence of PCHIMX-1 on flow rate during gravity-fed infusion. Nevertheless, the use of an air-flushed infusion bag was linked to a signifi-

cantly lower flow rate. This result can be explained by pressure variations within the infusion bag as described by Crass and Vance (1985). The manufacturer highly recommends use of air-flushed infusion bags. If bags are not flushed, air might enter tubes through the drip chambers at the end of infusion and hinder the rinsing step if the air volume is too great. Healthcare professionals can correct modifications to flow by using infusion pumps or by readjusting the flow rate regularly. The current study did not determine the effect of PCHIMX-1 on pump infusion flow rate. The comparison between non-air-flushed systems found no significant difference in flow rates, suggesting that PCHIMX-1 does not limit flow rate. Therefore, the device is not expected to limit pump infusion flow rate.

Impact of PCHIMX-1 on Rinsing Step

In some wards, infusion lines are not rinsed after administration; therefore, patients are deprived of a fairly high proportion of prescribed doses because of the dead space volume of infusion devices. Drug loss was estimated to influence the area under the curve of plasmatic drug concentrations (Pleasants, Sawyer, Williams, McKenna, Brown, & Powell, 1988). In the current study, IE was decreased by about 15% when a reference infusion line rather than a PCHIMX-1 infusion line was used. These results are in accordance with the value of the dead space volume of the reference infusion set (16 ml). PCHIMX-1 makes it possible, therefore, to infuse the total prescribed dose, so this study validates the protocol recommended by the manufacturer (partially air-flushed infusion bag).

Other medical devices can be used to improve drug infusion. Chemoset and Cyto-ad-set were conceived with the same rationale as multiaccess infusion devices. An infusion flush bag is connected to cytotoxic infusion bags on several extension lines through an antireflux valve access on the same infusion line. PCHIMX-1 is a

simple extension line with a universal outlet and can be connected to any infusion set.

To the authors' knowledge, no study has examined the role of these devices in reducing occupational exposure. Such study would help operators to choose the best protective devices when manipulating cytotoxic drugs in oncology wards. On the other hand, several studies have shown a reduction in environmental contamination with special devices during preparation, namely PhaSeal® (Nygren, Gustavsson, et al., 2002; Sessink, Rolf, & Ryden, 1999; Spivey & Connor, 2003) and Tevadaptor® (Nygren, Olofsson, & Johansson 2008).

Whatever the conditions of use, the only single parameter that was modified significantly by the addition of PCHIMX-1 to the infusion line (because of the rinsing step) was the volume of fluid administered and, consequently, the amount of delivered drug. The volume of fluid needed to completely rinse the infusion line was estimated to be about 40 ml (unpublished data). The advantage that PCHIMX-1 has over other devices is that a 100 ml bag is sufficient to ensure the preflush and rinsing steps of the infusion line if short infusion devices are used. With other devices, the rinsing step cannot be controlled adequately for two reasons: First, they have a higher dead space volume; second, the flush solution volume cannot be measured precisely with a large-volume infusion bag.

Implications for Nursing

Using PCHIMX-1 requires changes to procedures in pharmacy units and oncology wards. In pharmacies, manipulation time is decreased because of simplification of the preparation steps. In wards, manipulation time is increased because nurses have to connect a flush bag and an infusion device before flushing. This means that the administration method (gravity or pump) can be changed at the last moment. The choice was made to connect the infusion line and flush it with a neutral infusion solution in the ward rather than in the pharmacy. The transfer of infusion flush time from the pharmacy to the ward partly explains the difference between T_p and T_w . The mean values of total manipulation time were not significantly different, indicating better administration quality with no additional time required.

The effect of PCHIMX-1 on total manipulation time depends on preparation and administration times. In the current study, manipulation time in the pharmacy was lower with this device. But the chosen preparation for the study was simple. The overall effect of PCHIMX-1 on preparations must be evaluated for each preparation, including those requiring longer reconstitution times (e.g., cyclophosphamide, ifosfamide, docetaxel, dacarbazine), those that call for multiple transfer operations

between drug vials and infusion bags (e.g., cisplatin, carboplatin, irinotecan, dacarbazine), and preparations for which a needle is required (e.g., vinca alkaloids).

In the ward, the results clearly indicated that, in optimized routine conditions, manipulation time increased. Even if administration time is not modified, the rinsing step leads to an increase in the time a seat or bed is occupied by a patient, which could be inconvenient for ward organization. However, the rinsing step is highly recommended if drug infusion is to be performed correctly and if nurses' exposure to cytotoxic drug solutions is to be reduced.

Conclusion

PCHIMX-1 conforms to the latest recommendations for the preparation of cytotoxic infusion bags because it reduces the use of needles (ISOPP Standards Committee, 2007). It helps decrease contamination during administration, and nurses are less exposed to cytotoxic drug solutions. Nevertheless, its use requires changes to procedures for pharmacy technicians and nurses without modifying total manipulation time. The device does not have any influence on infusion flow but considerably enhances infusion quality through a simple process of flushing and rinsing the infusion line without disconnection. Further research is necessary to compare PCHIMX-1 to other devices in terms of infusion quality and reduction of occupational exposure.

The authors gratefully acknowledge Doran International for scientific and technologic expertise as well as infusion sets (PCHIMX-1 and KIS-1).

Nicolas Simon, MSc, PharmD, is a hospital teaching assistant in the Department of Biopharmacy, Galenic and Hospital Pharmacy, Lille Nord de France University, and a pharmacist at the laboratory of Antitumor Pharmacology, Centre Oscar Lambret, Lille; Bertrand Décaudin, PharmD, PhD, is an assistant professor in the Department of Biopharmacy, Galenic and Hospital Pharmacy, Lille Nord de France University, and a pharmacist at the Lille University hospital center; Damien Lannoy, MSc, PharmD, is a hospital teaching assistant in the Department of Biopharmacy, Galenic and Hospital Pharmacy, Lille Nord de France University, and a pharmacist at the Lille University hospital center; Frédérique Danicourt, PharmD, is a pharmacist at the Dunkerque general hospital in France; Christine Barthélémy, PharmD, PhD, is an assistant professor in the Department of Biopharmacy, Galenic and Hospital Pharmacy, Lille Nord de France University; and Pascal Odou, PharmD, PhD, is a professor in the Department of Biopharmacy, Galenic and Hospital Pharmacy, Lille Nord de France University, and a pharmacist at the Lille University hospital center. No financial relationships to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Décaudin can be reached at bertrand.decaudin@univ-lille2.fr, with copy to editor at ONFEditor@ons.org. (Submitted April 2009. Accepted for publication November 16, 2009.)

Digital Object Identifier: 10.1188/10.ONF.E370-E376

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