

# Evaluation of reflux in intravenous hazardous drugs (HDs) delivery systems. Exposure of nursing staff to hazardous drugs.

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**Abstract:** For the intravenous administration of hazardous drugs, infusion kits are used to administer various drugs using the same system. The system acts as a protection measure for the health workers who are administering the drugs, and reduces the amount of handling required when using the perfusion system, thus minimising exposure to HDs. These systems have been sampled and analysed using ultraviolet (UV) and fluorescence spectrophotometric techniques. It has been observed that they do not prevent contamination of the washing solution that cleans the system prior to disconnection and removal. The system should therefore not be regarded as safe.

**Keywords:** Tree system lines, hazardous drugs, exposure, healthcare worker protection, nursing.

**Resumen:** *Evaluación del reflujo en los sistemas de administración intravenosa de MP. Exposición del personal de enfermería.*

Para la administración intravenosa de medicamentos peligrosos (MP), se utilizan equipos de infusión que permiten administrar varios fármacos en el mismo sistema y sirven como medida de protección para los trabajadores que los administran, pues reducen las manipulaciones del sistema de perfusión y minimizan la exposición. Se han realizado tomas de muestras de estos sistemas, y se han analizado mediante técnicas de espectrofotometría ultravioleta (UV) y espectrofotometría de fluorescencia. Se ha observado, que no evitan la contaminación de la solución de lavado que limpia el sistema antes de su desconexión y retirada. Por tanto, el sistema no debe considerarse seguro.

**Palabras clave:** Sistemas tipo árbol, MP, exposición, protección de los trabajadores, enfermería.

## Introduction

Although historically there has been a division between the safety of patients and healthcare workers, from a material point of view there is no such separation, but rather an interrelationship in a common and complex environment.

The increase in the incidence of pathologies such as cancer, autoimmune diseases, or chronic diseases in our society, in turn, means an increase in the use of hazardous drugs (HDs) by nurses. This situation has made pollution risk control a global occupational priority.

According to the NIOSH document (2016) "list of antineoplastic and other hazardous drugs", HDs are considered to be those drugs with carcinogenic, teratogenic, or genotoxic properties, or that are toxic to the reproductive system or to a specific organ, at low doses. Certain new drugs, considered risky for other reasons, are also included. The groups of medicines considered as dangerous according to the above classification (NIOSH 2016) are:

List 1: Antineoplastic drugs.

List 2: Non-anti-neoplastic drugs that meet one or more NIOSH criteria for consideration as being risky.

List 3: Non-anti-neoplastic drugs that have effects on reproduction.

Occupational exposure to these drugs mainly affects nursing professionals, since the administration of these drugs is a routine daily task in a multitude of healthcare jobs. Professionals could potentially be exposed to different HDs in various ways for many years throughout their working lives.

Classic forms of occupational exposure to HDs are: dermal, inhalation, oral, and injection. Inhalation was initially thought to be the main source of occupational exposure to HDs (Polovich, 2017). Aerosols are generated when HDs are prepared, which led to the worldwide use of Biosafety Cabins (BSCs) in the 1980s. Dermal absorption has now been found to be a common form of exposure which could happen during any activity involving the handling, disconnection, and removal of HDs.

In the early 1990s (Mcdevitt, 1993), cyclophosphamide contamination was first identified on work surfaces in pharmacies and administration areas. Since then, the presence of environmental contamination has been recognised as a source of exposure for healthcare workers who may absorb HD residues upon contact with contaminated work surfaces.

HD residues can be transferred to other elements and surfaces, even resulting in exposure to workers who are not personally involved in the handling of HDs (Polovich, 2017). In a 2014 study (Hon et al., 2014), samples were taken from the hands of workers who were not directly involved in HD management but who were found to have a level of exposure equal to that of nurses who handled HDs regularly. These results suggest that the number of staff exposed to HDs is higher than what was originally thought.

HD residues have been found on various surfaces within biosecurity cabins (BSC), administration areas, sinks, computer terminals, pens, elevator buttons, and the soles of shoes, etc. (Hon, 2011). Several studies have even shown contamination from HDs on the external surfaces of vials shipped from the factory. (Mason et al., 2003).

In addition, since the late 1990s, numerous studies have identified and documented the contamination of wastewater from hospitals. Some HDs can be found in wastewater treatment systems, the residues maintaining pharmacological activity (O'Keefe, 2017) for long periods of time, leading to pollution that can affect the environment in general.

Despite the growing interest in the different factors leading to contamination by HDs, most of the studies published have historically focused on the preparation of HDs and not on their administration.

The absence of studies of contamination in the area of HD administration, and the persistent financial pressure on health systems across Europe, may have limited the studies of contamination resulting from intravenous administration procedures, when it is precisely those procedures that generate the greatest risk of exposure because of the hospital work practices currently employed by nurses (Oncology Nurse Protection, 2017).

The traditional ways in which needles and syringes are used often results in leakage. The materials used in the manufacture of perfusion systems and stopcocks can cause contamination. The use of closed systems of multiple infusion intravenous therapy (MICT), although minimising exposure, do not replace the CBS, nor do they replace the

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personal protection equipment used in hospitals pharmacies because of the different work practices and consequent occupational exposure (Murf, 2012), which contributes to an increased risk to healthcare professionals, and also to patients and their families. Although corrective measures for these risks have been incorporated over time, there are few objective independent studies that demonstrate their efficiency and effectiveness. In fact, in some cases, safety measures may introduce new risks and dangers.

It is precisely for that reason that this study aims to evaluate and quantify the amount of reflux in the administration phase of intravenous therapy when multiple infusion sets of so-called tree systems are used. By this way, data obtained made possible to prove the presence or absence of risk.

This is the first independent study that evaluates, in parallel, how well are sealed the two multi-access infusion systems.

## Material and methods

The following samples have been used:

- 24 Safety intravenous medication delivery systems with 4 connectors (access points) of two commercially available brands (X and Y), 12 standard and 12 modified systems with an anti-reflux device according to patent U201431177.
- One dropper stick, secondary systems, 24 bags of 50ml saline solution (washer), 24 syringes, 24 needles, one 100ml saline solution bag.
- Rhodamine 6G (Aldrich) diluted in 100 ml of 0.9% physiological serum (Grifols) with a secondary system (extension tube).
- 2 intravenous perfusion pumps, one of each brand, for the systems used (X and Y).
- 24 vials for the preservation, transport and handling of samples.

Used for analysing the samples:

UV-VIS Shimadzu UV-2101PC spectrophotometer and Varian Cary Eclipse spectrofluorometer.

### *Infusion and sample collection systems.*

Samples were collected using two types of commercial intravenous medication delivery systems (X and Y).

These are two safety devices for the intravenous administration of HDs, currently marketed and used under two different brand names. Both have four valves for the connection of the hazardous drugs (secondary ports), a central line with a bag spike for the connection of the central washing serum, a drip chamber, and Luer-Lock connections. Both pieces of equipment are manufactured from similar materials, the main difference being the location of the valves for secondary connections.

The modification of the systems consisted of adding two one-way valves with opposite flow directions, and a reflux collection system. The valves function in such a way that one valve facilitates the collection of the reflux mixture containing the drugs without allowing it to contaminate the washing serum released by the other valve.

The infusion systems were purged with saline solution prior to use. Samples were collected by testing the two types of intravenous medication delivery systems (X and Y), with two different modes (A and B) of operation in order to check for differences in the amount of reflux in both modes. Then the modified version, with the incorporation of one-way valves and a reflux collection bag, was studied.

*Mode A:* All systems were purged with physiological serum before coupling the secondary system with the drug, a secondary system was coupled with Rhodamin 6G dye, the washing serum clamp was

closed, the drug clamp was opened, and the infusion of Rhodamin 6G was started in order to recreate what happens when drugs are administered to patients. When the infusion of the drug had been completed, the drip chamber was refilled by closing the secondary system clamp and opening the scrubber serum clamp and also that of the anti-reflux device in the modified systems. In both cases, a sample of the washing serum bag was taken from each of the systems with a new syringe and needle, and placed in a vial for further analysis.

*Mode B:* The same as mode A, but the administration of the drug was stopped halfway through the infusion and the dripper chamber was filled, closing the secondary clamp, and opening the scrubber serum clamp and that of the anti-reflux device in the modified systems.

### *Calibration*

A standard solution of Rhodamin 6G 10<sup>-4</sup> M in Grifols 0.9% physiological saline solution was prepared for the calibration line and diluted accordingly. No precipitate of any kind was observed during the entire measurement time.

Spectrophotometric measurements were made at 520 nm, and fluorimetric measurements were made at 520 nm excitation and 550 nm emission.

The linear range was maintained from 2x10<sup>-6</sup> to 10<sup>-5</sup> M for colorimetric measurements, and from 2x10<sup>-7</sup> to 4x10<sup>-6</sup> for fluorimetric measurements.

The samples were measured directly from the concentration present in the vials except in cases where the measurement was outside the linear range, for which dilution in physiological serum was necessary.

## Discussion of results

Although tree type systems or multi-access infusion systems for the administration of HDs are considered to be closed drug transfer devices (CSTD), it has been observed and quantified that, in commercially available infusion sets, there is a reflux of HDs from the secondary dripper to the primary line or washer serum (LP).

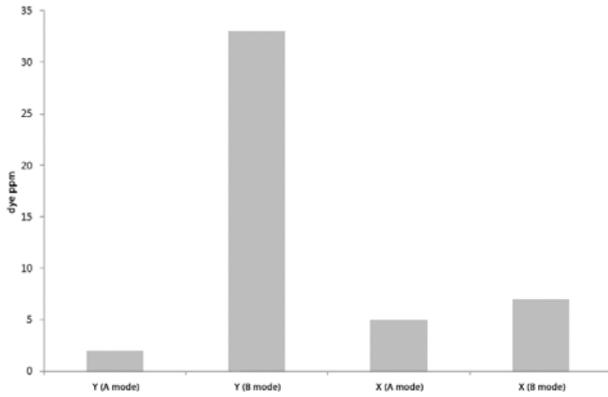
This situation usually occurs during therapy when the dropper chamber is emptied and the system chamber is pressed to be filled again. It is at this point that the reflux of the HDs occurs, thus contaminating the washing serum.

The results obtained using both ultraviolet and fluorescence techniques indicate that, in the two commercially available systems studied, there is a reflux ranging from 2ppm to more than 30ppm of Rhodamine 6G, as shown in Figure 1. It is interesting to note that in the case of device X, the variations observed between mode A and mode B are small, with contamination in mode A being slightly lower than in mode B. In the case of device Y, the change of the working mode produces a large variation in the extent of the contamination. This contamination, in the case of mode B, is more than 15 times higher than that observed in mode A.

On the other hand, it has been found that the contamination produced when using device X in mode A is more than double that observed when using device Y in the same procedure. Taking into account the data obtained, working method A is safer than working method B, and under these experimental conditions, device Y is safer than device X.

The data discussed above show that, in any mode of operation, commercial devices always cause pollution. This contamination is usually generated during therapy by emptying the dropper chamber and compressing the system chamber to refill it. It is at this point that the reflux of the HDs occurs, and the washing serum is consequently contaminated. In order to avoid this problem, a modification of conventional systems has been proposed; see Figure 2.

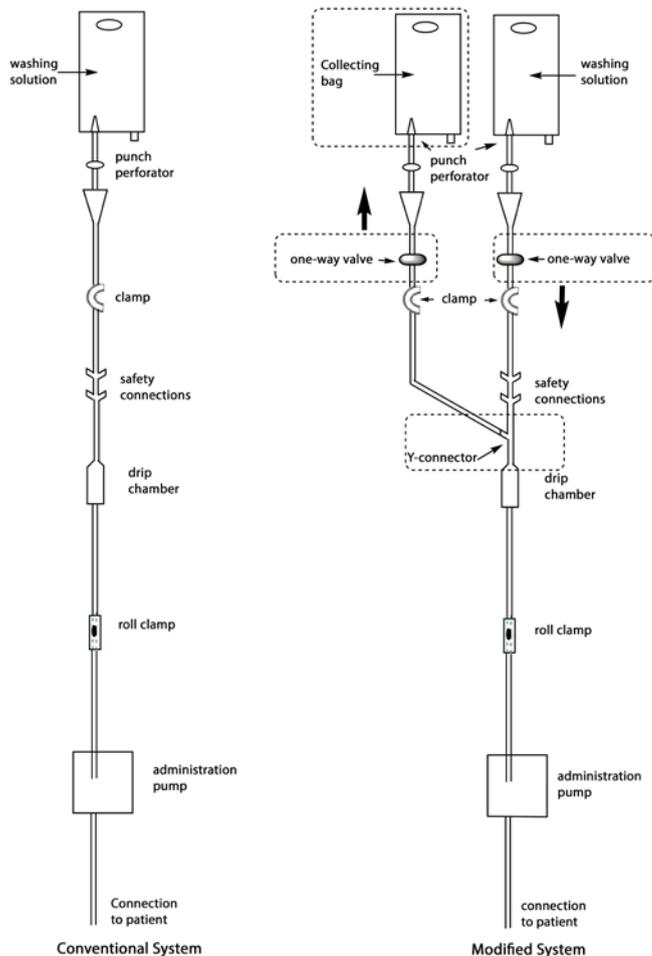
The conventional system is modified by incorporating a one-way valve which is located just below the bag spike of the central serum washer, allowing only the passage of clean serum from the bag into the system, thus preventing the reflux of HDs. In addition, it also



**Figure 1:** Comparative study of commercial systems in the different modes of operation.

includes a "y" type joint for connecting the system to the anti-reflux device that incorporates an empty bag for collecting air and drug residues, a bag spike, a one-way valve that allows passage from the system to the collection bag, a clamp, and a pump with a safety connector.

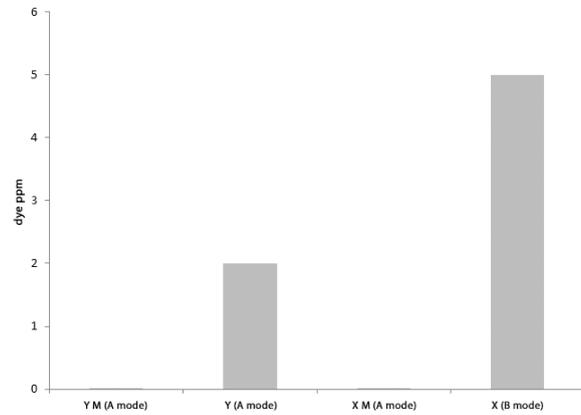
The procedure for refilling the modified system is the same as that for refilling a conventional system, i.e. open the main line clamp and that of the anti-reflux device, and then compress the drip chamber. In this way, by means of the unidirectional valves, the air and drug residues are sent to the collection bag, thus preventing them from refluxing into the clean serum bag, and facilitating their disconnection and removal, leaving the system free of drugs, and avoiding contamination.



**Figure 2:** Diagram of the modification of conventional systems.

The results obtained with the modified system clearly indicate that

contamination in both the X and Y systems is reduced to values below 5 ppm (Figure 3).



**Figure 3:** Comparative study of commercial systems X and Y, and these modified systems (working in all cases in mode A).

The data from this study clearly shows that, although shaft-type systems can avoid contact with HDs during connection, at the end of the treatment, the system changes from a closed system to an open system where leaked liquid may remain in the system. If the washing serum is contaminated, the system may release contaminated serum at the time of disconnection.

**Conclusions**

The tests carried out prove that, in conventional equipment, there is a backflow of liquid from the secondary system to the central washing serum, carrying a danger to the point of disconnection.

The same test performed on a modified infusion set with anti-reflux (VA) valves shows that contamination of the main serum by the secondary serum is virtually eliminated. This is reached through the strategic placement of anti-reflux valves and the addition of an empty bag that collects the reflux produced by the pressing of the chamber, thus avoiding contamination of the washer serum, and thereby eliminating the source of exposure.

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**References**

1. Fahimi F, Sefidani A, Taghikhani S, Saliminejad L. The rate of physicochemical incompatibilities, administration errors. Factors correlating with nurses errors. *Iranian J. Pharm. Res.* 2015; 14(S): 87-93.
2. Guardino X. NTP: 1051. Exposición laboral a compuestos citostáticos: sistemas seguros para su preparación. Instituto Nacional de Seguridad e Higiene en el trabajo. 2015. Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT).
3. Hon CY, Teschke K, Chua P, Venners S, Nakashima L, Venners S. Occupational exposure to antineoplastic drugs: identification of job categories potentially exposed throughout the hospital medication system. *Safe. Health Work.* 2011; 2:273-281.
4. Hon CY, Teschke K, Demers PA, Venners S. Antineoplastic drug contamination on the hands of employees working throughout the hospital medication system. *J Occ. Med.* 2014; 58:761-770.

5. *Mason HJ, Morton J, Garfitt SJ, Iqbal S, Jones K.* Cytotoxic drug contamination on the outside of vials delivered to a pharmacy. *Annals Occ. Hyg.* 2003; 47: 681-5.
6. *Mcdevitt JJ, Lees PS, McDiarmid MA.* Exposure of hospital pharmacists and nurses to antineoplastic agents. *J. Occ. Med.* 1993, 35:57-60.
7. *Müller C.* ¿Wie genau ist die Dosierung?. *Pharma. Zeit.* 1997, 142(11):879.
8. *Murf SJ.* Principal engineering controls. En: Government editor. *Safety and health handbook for cytotoxic drugs.* Lanham, Mariland 2012.p 231-232-
9. NIOSH. Performance test protocol for closed system transfer devices used during pharmacy compounding and administration of hazardous drugs. 2015 [acceso: 25 de noviembre de 2017]. Disponible en: [www.cdc.gov/.../performancetestprotocolclosedsystemtrans](http://www.cdc.gov/.../performancetestprotocolclosedsystemtrans)
10. NIOSH. List of Antineoplastic and other hazardous Drugs in Healthcare Settings. 2016 [acceso 15 de octubre de 2017]. Disponible en: [https://www.cdc.gov/niosh/.../hazardous-drugs-list\\_2016-161.pdf](https://www.cdc.gov/niosh/.../hazardous-drugs-list_2016-161.pdf).
11. NIOSH. Exposición a drogas peligrosas. 2017 [acceso: 27 de noviembre de 2017]. Disponible en: [www.cdc.gov/niosh/topics/hazdrug/default.html](http://www.cdc.gov/niosh/topics/hazdrug/default.html).
12. O'Keefe TL. Cytotoxic drug contamination in hospital and municipal wastewater and its transfer to surface water. *Pharma-Cycle Inc.* 2011 [acceso: 20 de noviembre del 2017]. Disponible en: [www.jaaha.org/doi/abs/10.5326/JAAHA-MS-6471](http://www.jaaha.org/doi/abs/10.5326/JAAHA-MS-6471).
13. Oncology Nurse Protection Is it time for more precise legislation on exposure to hazardous drugs? *Mind. Res.* 2017. <http://www.mindmetreresearch.com/wp-content/uploads/2017/02/MindMetre-Oncology-Nurse-Protection-Report-February-2017.pdf>
14. *Polovich M.A.* Eye-Opener. Understanding invisible Hazardous Drug Exposure. *Oncology Nursing New;* 2017 [acceso: 14 de octubre de 2017]. Disponible en: [www.oncnursingnews.com/.../eye-opener-understanding-invisible-hazardous-drug-exposure](http://www.oncnursingnews.com/.../eye-opener-understanding-invisible-hazardous-drug-exposure).