

ORIGINALS

English

A comparative study of contamination in three closed systems for the preparation of hazardous drugs through simulations with fluorescein

Estudio comparativo de contaminación de tres sistemas cerrados para la preparación de fármacos peligrosos mediante simulación con fluoresceína

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Abstract

Objective: The objective of this study was to compare the environmental contamination generated during the preparation of cytostatic agents using three different methods through simulations using fluorescein, and the time required for preparation of each method.

Method: A comparative study of the processing of fluorescein mixtures using three types of closed systems was conducted at the centralized unit for hazardous drugs of the Pharmacy Department of a General Teaching Hospital. Environmental contamination was detected in critical points of connection, and in splashes produced at any other points. The main variable was qualitative detection of contamination through ultraviolet light when three methods were compared (method A: ChemoClave[®], method B: SmartSite[®] valve and Texium[®] connector, method C: PhaSeal[™] with BD luer extension). A final number of 60 mixtures were prepared to detect differences of at least 5%.

Results: Qualitative contamination at the critical points during preparation, was seen in groups A and B for every mixture that was processed. No contamination at all in critical points was seen in any of the mixtures prepared using PhaSeal[™]. Statistically significant differences were found between arms A and C ($p < 0.001$) and arms B and C ($p < 0.001$); no differences were found between arms A and B.

Conclusions: The combination of PhaSeal[™] system in conjunction with the BD luer extension for administering hazardous drugs from a tree modality system has been shown to be the system with the lowest level of contamination during processing without increasing the time required for preparation of the mixture.

Resumen

Objetivo: El objetivo de este estudio fue comparar la contaminación ambiental generada durante la preparación de fluoresceína y el tiempo de preparación usando tres sistemas cerrados de transferencia diferentes.

Método: Estudio comparativo de elaboración de mezclas de fluoresceína con tres tipos de sistemas cerrados en una unidad de mezclas peligrosas de un Servicio de Farmacia de un Hospital General Universitario. Se consideró contaminación ambiental la detectada en los puntos críticos de conexión y las salpicaduras generadas en cualquier otro punto distinto. La variable principal fue la detección cualitativa mediante luz ultravioleta de la contaminación generada cuando se comparan tres sistemas (sistema A: ChemoClave[®], sistema B: válvula SmartSite[®] y conector Texium[®], sistema C: PhaSeal[™] con alargadera luer BD). Se prepararon 60 mezclas para poder detectar diferencias de al menos el 5%.

Resultados: Se detectó contaminación en los puntos críticos durante la preparación en todas las mezclas de los grupos A y B. No se detectó contaminación en ninguna de las mezclas en las que se usó el sistema cerrado PhaSeal[™]. Se encontraron diferencias estadísticas entre los grupos A y C ($p < 0.001$) y entre los grupos B y C ($p < 0.001$); no se encontraron diferencias entre los grupos A y B.

Conclusiones: La combinación del sistema PhaSeal[™] y la alargadera luer BD para administrar fármacos peligrosos en la modalidad de árbol ha mostrado ser el sistema con el menor nivel de contaminación durante la preparación, sin que esto se traduzca en aumento en el tiempo de elaboración.

KEYWORDS

Hazardous substances; Equipment and supplies;
Antineoplastic agents; Drug compounding; Drug contamination.

PALABRAS CLAVE

Sustancias peligrosas; Equipos y suministros;
Agentes antineoplásicos; Preparación de fármacos;
Contaminación de fármacos.



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Introduction

Occupational exposure to antineoplastic drugs that have carcinogenic, mutagenic, teratogenic and/or reprotoxic properties is a concern for all health care professionals involved in their preparation and administration on a continuing basis¹.

Although antineoplastic agents constitute the largest group of hazardous drugs (HDs), there are at present other very diverse categories of medications currently in use in our country that affect a wide range of health professions and clinical areas².

Several factors can play a role in the environmental contamination generated after the handling of HDs: installations, maintenance, staff training, personal protective equipment, decontamination, handling protocols and closed system drug-transfer devices (CSTDs)³.

In its standard on handling HDs (USP 800), the United States Pharmacopeia (USP) requires the use of CSTDs for administering HDs, and recommends the adoption of CSTDs during HDs compounding as long as the pharmaceutical forms allow for it⁴. Several studies have shown the effectiveness of closed transfer systems in minimizing environmental contamination⁵⁻¹¹.

The USP 800 guidelines recognize the importance of conducting studies for CSTDs and not simply considering them as interchangeable systems. In recognition of these differences, National Institute for Occupational Safety and Health (NIOSH) is developing performance protocols that may be useful for this purpose; however, these protocols are not yet complete¹².

In Spain, as in the rest of Europe, there are no specific regulations regarding closed systems. They are usually considered as medical devices regulated under Royal Decree 1591/2009 and belonging to Class IIa devices. The closed systems currently available are ChemoClave® (ICU Medical Inc., San Clemente, CA), PhaSeal™ (Becton, Dickinson and Company, Franklin Lakes, NJ), the Texium® connector (Becton, Dickinson and Company, Franklin Lakes, NJ), the SmartSite® valve (Becton, Dickinson and Company, Franklin Lakes, NJ), Equashield® (Equashield LLC, Seaview Blvd., Port Washington, NY) and Tevadaptor® (Teva Medical Ltd, HaMerkaz, Israel). At present the systems with the ONB code are PhaSeal™, Equashield® and Tevadaptor®, but they are not in widespread use in our country^{13,14}. This product code is issued by the Food and Drug Administration (FDA) and certifies that the devices allow antineoplastic and other HDs to be reconstituted and transferred while reducing the exposure of health care personnel.

As concerns the handling of HDs, their administration has an important role to play in ensuring the safety of health care professionals as, although the level of exposure is lower than during their preparation, the level of protection is also lower. Two drug administration systems are very extended in our country: the ChemoClave® valve system by ICU Medical and tree modalities, the most common of which is the BD system that uses the SmartSite® valve¹⁵.

The primary objective of this study was to qualitatively compare the environmental contamination generated during the preparation of cytostatic agents using three different methods through simulations using fluorescein:

1. Method A: valve administration system (ChemoClave® by ICU Medical).
2. Method B: administration system using the tree modality (SmartSite® valve and Texium® connector by BD).
3. Method C: administration system using the tree modality (PhaSeal™ by BD).

Secondary objectives were the measurement of the degree of contamination and the time required for preparation of each method.

Table 1. Components used in the reconstitution and dilution/transfer to the infusion

| | Reconstitution | Transfer to bag |
|----------|--|--|
| Method A | <ul style="list-style-type: none">– 20 mm universal spike with vial access CLAVE® connector with a 0.22 µm vent filter– Spiros® syringe closed male connector | <ul style="list-style-type: none">– Bag spike with a 0.22 µm vent and a CLAVE® connector |
| Method B | <ul style="list-style-type: none">– 20 mm anchoring spike with a SmartSite® valve port with a 0.22 µm vent filter– Texium® syringe closed male connector | <ul style="list-style-type: none">– BD luer extension set with a SmartSite® valve |
| Method C | <ul style="list-style-type: none">– 20 mm PhaSeal Protector™ 50 vial access– PhaSeal injector™ | <ul style="list-style-type: none">– BD luer extension set with a SmartSite® valve– PhaSeal™ connector to connect to extension line SmartSite® valve |

Methods

A comparative study of the processing of fluorescein mixtures using three types of closed systems was conducted at the centralized unit for hazardous drugs preparation of the Pharmacy Department (PD) of a General and Teaching Hospital.

Table 1 provides details about the devices that were used.

Saline solutions with luer connections (Fleboflex® luer) were used for methods B and C. For method A, Fleboflex® saline was used as the bag spike with the CLAVE® connector requires using a conventional connection.

Figure 1 shows the various components being compared.

Fluorescein was chosen as the tracer to measure contamination throughout the entire process. Fluorescein allows visual detection as it becomes fluorescent when exposed to ultraviolet light.

Two types of environmental contamination were evaluated¹⁶:

1. Contamination at critical connection points (septum valve of the vial spike, syringe connector and valve of the infusion bag). This was considered to be local contamination, of lesser risk.
2. Splash contamination detected anywhere other than at critical points: on the vial, the handler's gloves, work surface, etc. It is considered to be contamination that is more extensive and variable and as such, more difficult to control.

The sample size was calculated on the basis of the percentage of contamination in each group. Contamination is expected to be found only at the critical points. According to preliminary studies it is expected that contamination in groups A and B will be around at least 50% and that in group C it will reach a maximum of 10%¹⁷. Assuming an alpha risk of 5% and power at 80% in a bilateral contrast, 19 preparations are needed for each group in order to detect statistically significant differences between proportions of at least 5%.

All of the procedures were performed in biosafety cabinets (BSCs), simulating actual work conditions. Two highly qualified nurses with similar



Figure 1. Images of the three types of closed systems used in the study.

experience and an oncology pharmacist who usually work in the cytostatic drug preparation area participated in the simulation.

A total of 60 mixtures were processed using vials of fluorescein in a simulation of the preparation of HDs.

Amber glass vials with 25 mg of fluorescein powder were prepared beforehand. To ensure there was no fluorescein contamination on the outside of the vials, they were scanned with UV light before bringing them into the BSC⁶.

The fluorescein mixtures were processed in the BSC after scrubbing the cabinet with alkaline detergent and disinfecting it with alcohol. A sterile drape with an absorbent upper side and impermeable bottom was then placed. Each nurse then prepared 10 fluorescein mixtures of each of the three methods by performing the following procedures: inserting the spike into the vial of fluorescein, reconstituting the vials using 50 mL of saline solution (0.05% concentration), removing 40 mL of the solution using a 60 mL syringe with the proper connector, transferring the solution to an infusion bag with 250 mL 5% glucose solution using the CLAVE[®] valve of the bag's access spike (Method A), the SmartSite[®] valve of the extension line (Method B) or the PhaSeal[™] connector (Method C)⁶.

A UV light lamp (UV light 365 nm, Cole-Parmer) was used to detect fluorescein. The light of the BSC was turned off after each preparation and any contamination was detected with the UV lamp. From a qualitative perspective, it was deemed that there was contamination at the critical points if it was visually present at any of the 3 points. In addition, secondarily, a further quantitative analysis was made by placing the critical points on filter paper and measuring them at their largest diameter. A cotton swab was inserted into the PhaSeal[™] connector to check for contamination. Figure 2 shows detection of fluorescence through UV light.

Another secondary variable was the measurement of the time required to prepare the mixture for each method.

The pharmacist was responsible for supervising the processing of the mixtures and the measuring of the fluorescence generated by each preparation. To reduce variability in the interpretation of the results, the same person performed all of the assessments and photographs were taken to increase control over the process.

The statistical analysis was performed with IBM SPSS Statistics for Windows software, Version 21.0, Armonk, NY: IBM Corp. Frequencies were used for categorical variables (presence or absence of contamination) and measures of central tendency and dispersion were used for the quantitative variables (size of the drops, local contamination and preparation time). Mean and standard deviation were calculated if they followed a normal distribution and if they did not, median and 25th and 75th percentiles were calculated. Results with p-value <0.05 were considered to be statistically significant.

The statistical analysis of the main variable, the comparison of the qualitative contamination between the three groups, was performed using the chi square exact Fisher's test. An alpha value of 5% (p<0.05) was applied to compare possible differences between variables.

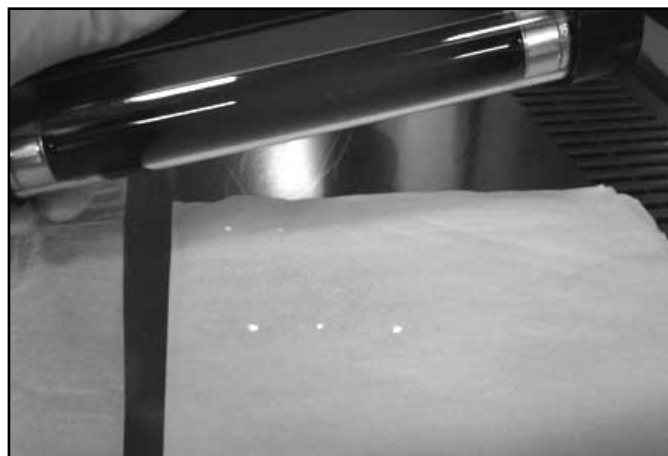


Figure 2. Detection of fluorescence through UV light.

Table 2. Contamination, and time of the different methods. Time of preparation in the three methods are indicated through mean and standard deviations in parentheses

| | Method A | Method B | Method C |
|-------------------------------|-------------|-------------|------------|
| Contamination critical points | Yes (20/20) | Yes (20/20) | No (0/20) |
| Mixture time mean (seconds) | 83.3 (7.5) | 88.6 (9.4) | 85.4 (6.6) |

The dimension of the contamination at the critical points of the three groups was compared with the Mann-Whitney U test, as they do not follow a normal distribution.

The preparation times for the three groups were analyzed using Student's t test for independent samples.

Results

Table 2 gives a qualitative description of the presence of contamination at the critical points during preparation and the time required for preparation of each of the three methods.

Table 3 examines the quantitative local contamination at the various critical points in greater depth.

There was no splashing or spilling in any of the three groups during preparation.

With regard to qualitative contamination at the critical points during preparation, contamination was seen in groups A and B for every mixture that was processed. No contamination at all was seen in any of the mixtures on at any of the critical points prepared using PhaSeal[™]. Statistically significant differences were found between arms A and C (p<0.001) and arms B and C (p<0.001); no differences were found between arms A and B.

However, when we analyzed the size of the contamination at the critical points during preparation, we found greater contamination in arm A than in arm B at the critical points of the connector and the vial spike and these differences were statistically significant (p<0.001). The differences in the bag transfer device between groups A and B were not statistically significant (p=0.100).

The increase in the average time required for the preparation of a mixture in arms B and C with regard to arm A was 5.25 and 2.05 seconds respectively, but these differences did not reach statistical significance (p=0.058; p=0.363). The differences between arms B and C were not statistically significant either (p=0.219).

Discussion

In order to adequately assess closed systems, criteria to determine that a closed system is effective should be established. Although it would be ideal for all contamination to be totally contained, it is quite unlikely that this is feasible and therefore a limit as low as is reasonably achievable should be set⁴.

Since no standard exists for the assessment of closed systems with respect to reducing contamination, there are no recommendations on which one to use⁴. In the absence of a standard, a number of methods have been proposed that have allowed the effectiveness of several devices marketed as closed systems to be assessed. Most of the studies that attempt to demonstrate that there is less environmental contamination when closed sys-

Table 3. Local contamination in critical points. Size of contamination points in the different methods are indicated through median and interquartile ranges 25-75 in parentheses

| | Method A | Method B | Method C |
|--------------------------|------------------|------------------|------------------|
| Syringe connector (cm) | 0.40 (0.20-0.50) | 0.10 (0.06-0.19) | 0.00 (0.00-0.00) |
| Vial spike (cm) | 0.10 (0.06-0.20) | 0.02 (0.00-0.05) | 0.00 (0.00-0.00) |
| Bag spike/bag valve (cm) | 0.08 (0.00-0.20) | 0.02 (0.00-0.05) | 0.00 (0.00-0.00) |

tems are used have assessed surface contamination, employing sampling techniques that allow an assessment of the residual contamination by cytostatic drugs. Other studies have used surrogate markers such as fluorescein, titanium tetrachloride and radioactive technetium¹⁸.

Our study was performed with fluorescein, a marker which, although not considered to be overly sensitive, is useful for detecting contamination and the formation of droplets during handling and provides a simple and inexpensive method that can be used as a first step to easily identify which systems are not closed. In addition, fluorescein, unlike other markers, does not cause any harm to those handling it¹⁸.

The use of drug administration systems with a tree modality, in which the different HDs are connected through safety valves to an administration tree, is very extended in our country. This is considered to be a closed system as the bags are not disconnected after the infusion has ended. The drugs are prepared in the BSC and added to the bag through a safety valve after the extension tube has been purged with clean saline solution. For a system to be considered as being entirely closed, its critical point through which the drug is added must be free of any contamination.

The other type of drug administration system that is used in our country is the ChemoClave[®] valve administration system. In this drug administration system the various mixtures that constitute the patient's treatment are added on one by one, through a series of connections and disconnections. The already processed hazardous drug is sent by the PD in an infusion bag with a spike that does not require purging and which is connected in the nursing unit to an extension via a closed male luer connector (Spiros[®]) to the CLAVE[®] valve of the bag's spike. The extension is then connected to the pump administration set available at the hospital, via its one-way connector to the infusion bag's spike¹⁵. In an earlier study we had already pointed out that such an administration system cannot be considered closed as the connection between the bag's CLAVE[®] valve and the extension's Spiros[®] connector is not dry¹⁷.

The study of contamination at critical points has revealed that there is contamination at said points during preparation both with the ChemoClave[®] system and the system that uses Texium[®] and SmartSite[®]. No contamination was found with PhaSeal[™], whose connections were found to be totally dry and is the only system that leaves the BSC without any visible contamination.

The quantitative analysis showed that the B system is less contaminated at the critical points of the connector and the vial spike than the A system. This is consistent with a previous study performed with fluorescein¹³.

With regard to processing time, the system that took the least time was the A system, which does not require purging of the system. However, no statistically significant differences were found, probably because although methods B and C require purging, their extensions with a luer connector make the connection to the saline bag easier than a conventional spike. A

previous study of handling staff preferences, we found that luer connections were preferred to conventional connections because they reduce the risk of mechanical injury and make handling easier¹⁵. No differences were found in the time required for preparation of the mixture between arms B and C, probably because although the filtration system with Texium[®] and SmartSite[®] is simpler, it has a greater resistance to flow than the PhaSeal[™] system.

The use of filters to equalize pressure when transferring HDs is highly contested with regard to their ability for achieving truly effective filtering of the aerosol gas contained in the air that is passed out of the system¹⁹. In our view, what is even more relevant is the fact that the connections of these filter systems are not dry and this therefore translates into environmental contamination inside the BSC and likely spreads outside of it.

Due to the importance of ensuring that the closed system selected is capable of containing the HDs from reconstitution to administration²⁰, it is of vital importance that systems with dry connections be used during processing, so that the infusion bags with the HD leave the BSC without any contamination and that administration be carried out with a system that is really closed.

In our study, the combination of PhaSeal[™] system in conjunction with the BD luer extension for administering HDs from a tree modality system has been shown to be the system with the lowest level of contamination during processing without increasing the time required for preparation of the mixture.

Funding

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Conflict of interests

No conflict of interests.

Contribution to the scientific literature

The article offers a systematic comparison of different closed systems for handling of hazardous drugs. The main value of the research lies in the testing of compatible closed-system combinations which cover the whole chain of reconstitution, transfer and application of the pharmaceutical compounds.

The constant marketing of closed-system transfer devices for the safe handling of hazardous drugs makes necessary a continuous training of health professionals together with the evaluation of the features of the different systems. The evaluation of closed-systems in relation to contamination decrease has not yet been standardized and there are no recommendations about which closed-system to use.

Bibliography

1. Howard J. Preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. The National Institute for Occupational Safety and Health (NIOSH) Publication Number 2004-165, Cincinnati; 2004 [accessed 30/03/2018]. Available at: <http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>
2. Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT). Medicamentos peligrosos. Medidas de prevención para su preparación y administración. Barcelona; 2016 [accessed 30/03/2018]. Available at: <http://www.insht.es/InshtWeb/Contenidos/Documentacion/FICHAS%20DE%20PUBLICACIONES/EN%20CATALOGO/Higiene/2016%20medicamentos%20peligrosos/Medicamentos%20peligrosos.pdf>
3. Yoshida J, Koda S, Nishida S, Nakano H, Tei G, Kumagai S. Association between occupational exposure and control measures for antineoplastic drugs in a pharmacy of a hospital. *Ann Occup Hyg*. 2013;57(2):251-60. DOI: 10.1093/annhyg/mes061
4. USP. General Chapter 800 Hazardous Drugs: Handling in Healthcare Settings; 2016 [accessed 30/03/2018]. Available at: <http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare>
5. 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;60(22):2314-20.
6. 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(2):135-9. DOI: [org/10.1177/001857870303800213](https://doi.org/10.1177/001857870303800213)
7. 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(18):1736-44. DOI: 10.2146/ajhp050258
8. Nygren O, Olofsson E, Johansson L. Spill and leakage using a drug preparation system based on double-filter technology. *Ann Occup Hyg*. 2008;52(2):95-8. DOI: 10.1093/annhyg/mem067
9. Siderov J, Kirska S, McLauchlan R. Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device. *J Oncol Pharm Pract*. 2010;16(1):19-25. DOI: 10.1177/1078155209352543
10. Sessink PJ, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract*. 2011;17(1):39-48. DOI: 10.1177/1078155210361431
11. Clark BA, Sessink PJM. Use of a closed system drug-transfer device eliminates surface contamination with antineoplastic agents. *J Oncol Pharm Pract*. 2013;19(2):99-104. DOI: 10.1177/1078155212468367

12. National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. A performance test protocol for closed system transfer devices used during pharmacy compounding and administration of hazardous drugs [draft] [accessed 30/03/2018]. Available at: <http://www.cdc.gov/niosh/topics/hazdrug/pdfs/performance-test-protocol-closed-system-transfer-devices.pdf>
13. Gómez-Álvarez S, Porta-Oltra B, Hernández-Griso M, Pérez-Labaña F, Clemente-Martí M. Evaluation of two closed-system drug transfer device in the antineoplastic drug elaboration process. *Farm Hosp.* 2016;40(1):36-43. DOI: 10.7399/fh.2016.40.1.9059
14. Forte Pérez-Minayo M, Castillo Bazán E, Hernández Segurado M, Arias Moya MA, Pelegrín Torres P, Bécáres Martínez FJ. Use of closed systems in the Hospital Pharmacy. *Farm Hosp.* 2016;40(2):102-10. DOI: 10.7399/fh.2016.40.2.9994
15. González-Haba E, Manrique-Rodríguez S, Herranz A, Casado C, Sánchez MN, Sanjurjo M. Evaluation and selection of closed-systems for safe cytostatics handling. *Eur J Clin Pharm.* 2015;17(4):279-88.
16. Favier B, Labrosse H, Gilles-Afchain L, Cropet C, Perol D, Chaumard N, *et al.* The PhaSeal® system: impact of its use on workplace contamination and duration of chemotherapy preparation. *J Oncol Pharm Pract.* 2012;18(1) 37-45. DOI: 10.1177/1078155211401454
17. González-Haba Peña E, Manrique Rodríguez S, Herranz Alonso AM, Pérez Castán P, Moreno Gálvez M, Iglesias Peinado, *et al.* Comparative study of preparation of hazardous drugs with different closed-system drug transfer devices by means of simulation with fluorescein. *Farm Hosp.* 2016;40(6):496-503. DOI: 10.7399/fh.2016.40.6.10607
18. Power L. Closed-System Transfer Devices. For Safe Handling of Injectable Hazardous Drugs. *Pharmacy Practice News.* 2013 [accessed 30/03/2018]. Available at: http://www.pharmacypracticenews.com/download/cstd_ppn0613_wm.pdf
19. Nota técnica de Prevención 1.051: Exposición laboral a compuestos citostáticos: sistemas seguros para su preparación. Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT); 2015 [accessed 30/03/2018]. Available at: <http://www.insht.es/InshtWeb/Contenidos/Documentacion/NTP/NTP/Ficheros/1043a1054/ntp-1051w.pdf>
20. Davis J, McLauchlan R, Connor TH. Exposure to hazardous drugs in Health-care: An issue that will not go away. *J Oncol Pharm Pract.* 2011;17(1):9-13. DOI: 10.1177/1078155210388462