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Risk Management of Cytotoxic Drug Contamination: Evaluation of the Securing of the Cytotoxic Preparation Circuit at Ibn Sina Hospital-CHU Rabat

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Abstract:
Introduction: The cytotoxic drug circuit is a complex process involving numerous healthcare professionals and implementing protective measures. The objective of this study is to control the circuit of cytotoxic drugs and evaluate the risk of contamination to the staff, patients, and environment in order to implement corrective measures to mitigate the risk.
Materials & Methods: We chose the Failure Mode and Effects Analysis (FMEA) method to identify failure modes and estimate the risks associated with the occurrence of these failures, in order to initiate necessary corrective or preventive actions. We selected quinine sulphate as the tracer drug, which has the advantage of being colorless after reconstitution and fluorescent under UV light. We transferred it from the ampoule to a sterile vial to adapt it to closed-system preparation.
Results & Discussions: Simulating the spread of contamination in the chemotherapy circuit using quinine helped identify critical points at risk of contamination in several areas, with a predetermined level of criticality indicated by a Risk Priority Index (RPI) ranging from 9 to 16. The areas with an RPI of 12 included the dispensing room, isolator gloves (16), transport cooler for preparations (9), nursing unit (nurse's gloves (11), patient's bed (9), and workbench (10)), and waste disposal (9). The remaining areas posed a low level of risk. Consequently, we established corrective measures by improving handling techniques for all involved parties, including preparers, nurses, and pharmacists, to minimize cytotoxic projection in accordance with proper preparation and administration practices.
Conclusion: This risk analysis allowed for the establishment of specific measures aimed at optimizing each failure, thereby protecting staff, patients, and the environment from the risks associated with cytotoxic drugs.
Keywords: Risk management, Drug circuit, FMEA, Chemotherapy, Contamination.

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Introduction

The preparation of cytotoxic drugs plays a significant role in hospital pharmacies as well as in healthcare services based on the patient's antimitotic protocol. This compounding, in accordance with Good Preparation Practices [1], takes place within an Inpatient Cytotoxic Preparation Unit of a hospital pharmacy and is delivered to the clinical department for administration to the patient.

Cytotoxic drugs are high-risk medications that present specific dangers. These drugs have a narrow therapeutic index with high toxicity. Consequently, protective measures must be implemented throughout the cytotoxic circuit. This circuit is traditionally divided into three main processes (prescription, preparation, and administration), involving three categories of healthcare professionals (physicians, pharmacists, preparers, and nurses).

Cytotoxic drugs exhibit intrinsic toxicity associated with their mechanism of action on cells. Most of these compounds possess genotoxic, carcinogenic, or reproductive toxic properties [1, 2]. Exposure to these substances occurs at all stages of cytotoxic handling (manufacturing, preparation, transport, administration, and disposal). Hence, the importance of implementing a quality assurance system within hemodialysis centers; several methods are available, with one of the most effective being Failure Mode and Effects Analysis (FMEA), which is a method for a priori risk analysis [3].

The objective of our work was to define the cytotoxic preparation circuit at Ibn Sina Hospital in Rabat and assess the practices for handling cytotoxic drugs. This involved identifying areas of contamination with cytotoxic drugs at various stages of the cytotoxic circuit, as well as ensuring the protection of healthcare personnel, patients, and the environment in order to implement preventive and corrective actions using the FMEA method.

Materials & Methods:

This was a cross-sectional study conducted at Ibn Sina Hospital. To analyze the risk of contamination with cytotoxic drugs, we chose the FMEA method, a preventive, qualitative, and quantitative analysis technique. This analysis requires the application of the Ishikawa diagram, a brainstorming method used to identify and represent the various causes of a problem or effect in the case of FMEA. Starting from the identified effect, brainstorming is conducted around 5 categories of causes (manpower, method, environment, equipment, material), also known as the 5 Ms rule.

The failure mode is defined as a defective or malfunctioning system. The criticality of the failure is quantified using a triple rating (Table 1):

- -"G" rating: severity of the failure, evaluated on a multi-level scale.
- -"F" rating: frequency of occurrence of the failure, representing the number of cases per unit of time.
- "D" rating: detectability of the failure, represented by a coefficient on a multi-level scale, reflecting the mitigation of the severity of the consequences in case of detection weighted by the probability of detection.

The criticality index is obtained by multiplying the three ratings: C= G * F * D.

The higher the criticality, the more concerning the considered failure mode is. FMEA allows for the proactive control of non-conformity risks that could negatively impact the security of the cytotoxic drug circuit before they occur.

In practice, we applied the method according to the following steps:

- Definition of the scope of work.
- Formation of a multidisciplinary working group to incorporate the viewpoints of key stakeholders directly involved in the process under study. One of the group members is a quality specialist.
- Determination and description of the process steps to monitor the cytotoxic drug circuit. The working group drew inspiration from the ISOPP Practice Standard: Safe Handling of Cytotoxic Drugs, established by a working group of the International Society of Oncology Pharmacy Practitioners (ISOPP) [4], for the

sequence of process operations and modeled it as a flowchart (Fig 1).

- Step-by-step analysis to identify potential failure modes, their causes, effects, frequency, and means of detection, using the Ishikawa cause-and-effect diagram. The Ishikawa diagram helps identify causes that could lead to a high risk of contamination by cytotoxic drugs (Fig. 2). The causes are identified and classified into categories:

- Manpower: personnel, skills, workforce, human factors, etc.
- Materials: equipment, computer equipment, software, maintenance, etc.
- Methods: procedures, operational modes, instructions, decision support tools...
- Raw materials: physical entities or information data.
- Environment: facilities, circuits, environment, working atmosphere, etc.

Evaluation and calculation of the criticality of these failures and their severity for the patient and personnel. We chose to work with four levels for frequency, severity, and detectability to align with previous FMEA studies conducted at the hospital [5, 6]. A decision matrix was developed by the working group to define risk levels based on the criticality class (Fig. 2). This work allows for the classification of risks according to their criticality, using established calculation grids that determine criticality ranges (Fig. 3) [5]:

- Low criticality risk: Level 1 (acceptable)
- Intermediate criticality risk: Level 2 (acceptable under control)
- High criticality risk: Level 3 (unacceptable).

Table 1: Risk Rating Grid.

Frequency

Frequency	Score	Frequency Level	Criteria
F1	1	Exceptional	Failure observed less than once a month
F2	2	Rare	Failure observed at least once a week
F3	3	Frequent	Failure observed once per day
F4	4	Very frequent	Failure observed more than once per day

Severity

Severity	Score	Severity Level	Criteria
G1	1	Low	Minor consequences without impact (task intensity: 0→2)
G2	2	Moderate	Moderate consequences with impact (task intensity: 2→5)
G3	3	High	Significant consequences with high impact (task intensity: 5→7)
G4	4	Very High	Significant consequences with high impact (task intensity: 7→9)

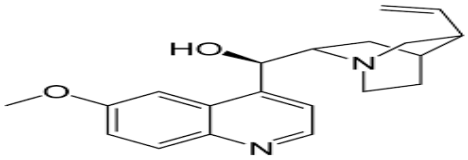
Detectability

Detectability	Score	Level of detectability	Criteria
D1	1	Highly detectable	Automated detection (UV lamp).
D2	2	Detectable	Human detection (Visual observation, smelling odor...)
D3	3	No detectable	No means of detection.

1. **Choice of Tracer Drug**

Tracer Product: In this study, we selected quinine sulfate as the tracer drug, which has the following advantages:

- It remains colorless after reconstitution.
- It is non-fluorescent in sodium chloride (visually undetectable) [7].



The form we found of quinine sulfate is an injectable ampoule that is difficult to transfer into a closed system bag. Therefore, we transferred the medication from the ampoule into sterile vials before proceeding with the actual dilution. This transfer follows the following protocol:

• Cleaning of empty vials:

- Elimination of the majority of microorganisms using a detergent through mechanical, physicochemical, and thermal actions.
- Thorough rinsing to remove any traces of cleaning product.
- Visual inspection is performed at the end of the operation.

• Crimping of the vials using a crimping tool.

• Sterilization of empty vials at the sterilization unit:

- Grouping 4 vials for preparation and 3 vials for microbiological control in a series of three sterilization cycles.
- Sterilization by hot air oven using saturated steam [8].

• Microbiological control of sterilized vials:

The objective of this control is to detect microbiological contamination in the empty sterile vials, which is essential to ensure their sterility. We performed a bacteriological control of the sterilized vials before proceeding with the dilution in the bags. The control is carried out at the microbiology laboratory of Ibn Sina Hospital. Germ identification is done after filtration, and the culture media used are TCS, DCL, Chapman, and Sabouraud:

- TCS (Tryptone Soya Broth): It is a universal medium suitable for a wide range of applications due to its excellent nutritive properties. It can be used for the culture and isolation of aerobic and anaerobic bacteria, as well as for promoting the growth of particularly demanding germs [9].
- DCL (Deoxycholate Citrate Lactose): It is a selective medium designed for the isolation of Salmonella and Shigella (Gram-negative bacilli).
- CHAPMAN: It is selective for Staphylococcus species. The selectivity of this medium is based on the presence of sodium chloride, which inhibits most Gram-positive and Gram-negative bacteria that ferment mannitol and acidify the medium, resulting in a color change from the initial red to yellow [10].
- SABOURAUD: It is a classical medium for the culture, isolation, and identification of saprophytic or pathogenic yeasts and molds [11].

- The process of microbiological control follows these steps:

- Rinsing of empty vials with 0.9% sodium chloride.
- Inoculation onto the culture media.
- Incubation at a temperature between 25°C and 30°C for 72 hours. After an initial reading, the petri dishes are re-incubated at room temperature.
- Identification is done by analyzing the obtained cultures.

• Transfer of quinine from ampoules to sterile vials:

Equipment used:

- 12 ampoules of quinine
- 24 empty vials
- 12 bags of 250 ml 0.9% sodium chloride solution
- Packaging paper.

2. Circuit points :

The cytotoxic drug circuit has been defined as the cytotoxic processFigure 1: Scheme of the chemotherapy circuit at Ibn Sina Hospital

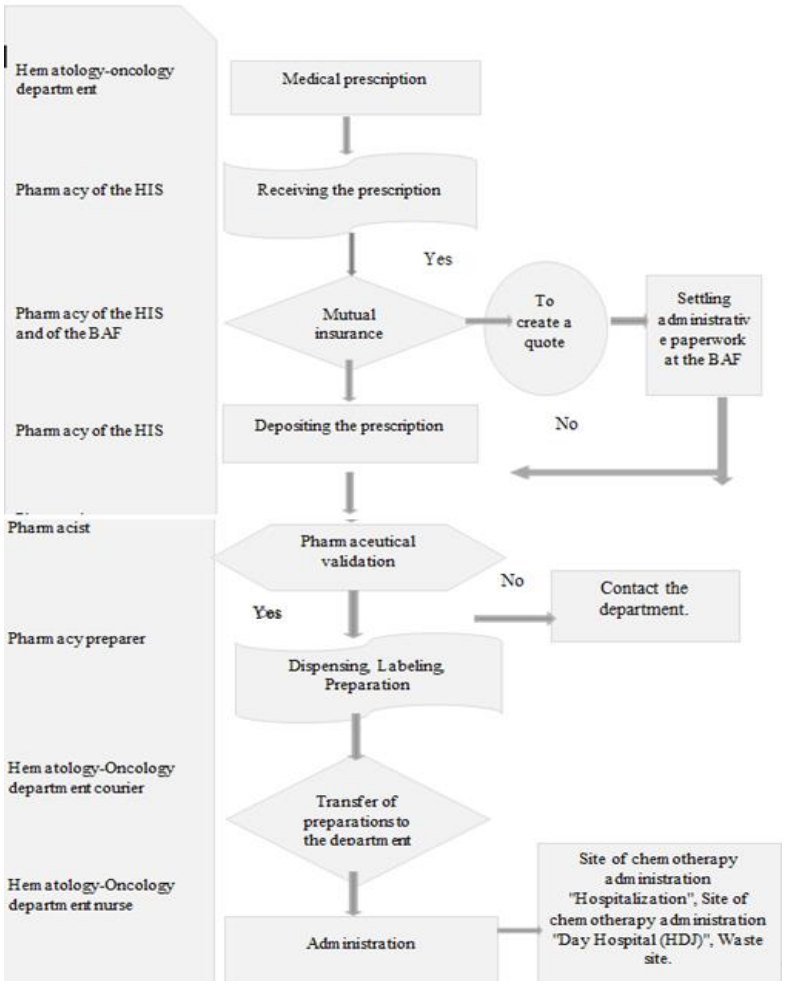


Figure 1: Scheme of the chemotherapy circuit at Ibn Sina Hospital.

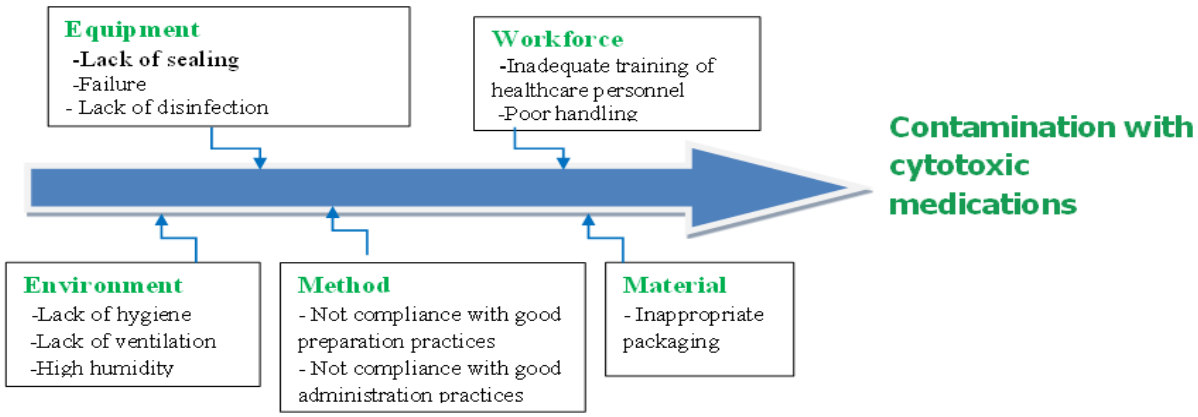


Figure 2 : Analyse des causes- Diagramme « cause/effet » d'Ishikawa

Once the simulations were completed and the preparers left, the lights were turned off, and traces of quinine were observed using a 350nm UV lamp. An observation of the blank areas was conducted before starting the series of preparations by the preparers and the pharmacist to identify any fluorescent contaminants. Additionally, after each observation at the end of the day, all observed traces were cleaned.

The distribution of contamination was thoroughly evaluated in sites with tracer deposits, taking into account the facility's layout and the progression of simulations in different locations within the cytotoxic drug circuit.

In order to address any failures and conclude the study, corrective and/or preventive actions are proposed at various stages of the cytotoxic drug

circuit to reduce the risk of contamination. The solutions are determined based on the levels of criticality obtained after identifying and analyzing the failures. After assessing the levels of criticality, any steps classified as criticality level 3 will require immediate corrective measures. After correction, the process step can undergo a new analysis to reassess its criticality and determine its acceptability.

Results:

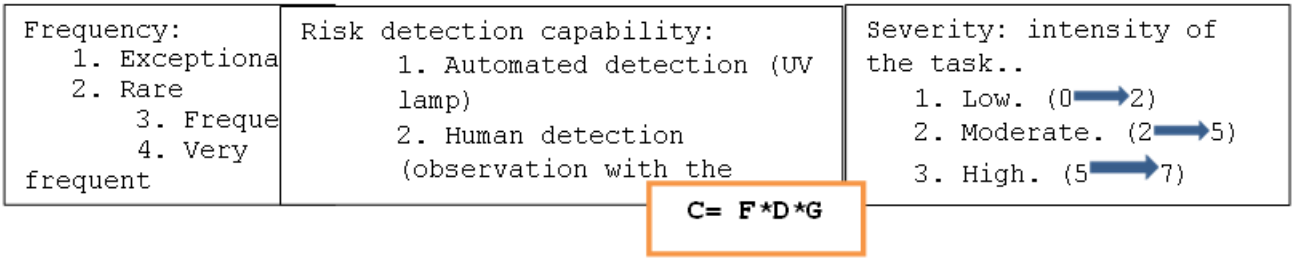
The assessment of the frequency and severity of contamination was conducted by the work team using the predefined scoring system. The risk priority index was calculated for each tested point, and the results are shown in Table 2.

Table 2: Risk Acceptability Levels.

Criticity			
Risk Severity	**Class Score**	**Risk Level**	**Action**
C1	1 à 5	Acceptable	Low Criticité No risk reduction actions required
C2	6 à 10	Tolerable under control	Moderate Criticité Risk reduction actions to be undertaken after addressing priority actions
C3	11 à 16	unacceptable	High Criticité Priority risk reduction actions to be implemented immediately

Table 3: Summary of Critical Contamination Results

Site	Zone	Contamination	Severity	Frequency	CDR	IPR = G*F*D
Supply 1 (before preparation)	Supply Storage	Yes	1	2	1	2
	Placed Bin	Yes	3	4	1	12
	Workstation	Yes	3	3	1	9
	Pouch	Yes	1	2	1	2
	Vial	Yes	1	2	1	2
	Syringe	Yes	1	2	1	2
	Floor	Yes	2	3	1	6
	Pack of gloves	Yes	1	2	1	2
	Alcohol barrel	Yes	3	4	1	12
	Refrigerator	Yes	3	4	1	12
	Average of the step					6.1
PSM3	SAS	Yes	1	2	1	2
	Work Area	Yes	2	3	1	6
	Pouch	Yes	1	2	1	2
	Syringe	Yes	1	2	1	2
	Gloves	Yes	4	4	1	16
	Cuff	Yes	1	2	1	2
	Waste Bag	Yes	1	2	1	2
	Alcohol swab	Yes	1	2	1	2
	Vial	Yes	1	2	1	2
	Floor	Yes	1	2	1	2
	Syringe	Yes	1	2	1	2
	Average of the step					3.6
Supply 2 (after preparation)	Pouch	Yes	1	2	1	2
	Syringe	Yes	1	2	1	2
	Plastic Bin	Yes	4	4	1	16
	Treatment Bag	Yes	1	2	1	2
	Work Area	Yes	3	3	1	9
	Cooler	Yes	3	3	1	9
	Wall	Yes	2	1	1	2
	Door and Handle	Yes	2	1	1	2
	Alcohol barrel	Yes	2	3	1	6
	Average of the step					4.9
Transport	Treatment Bag	Yes	1	2	1	2
	Cooler	Yes	3	3	1	9
	Treatment Cart	Yes	1	1	1	1
	Average of the step					4
HDJ MED B	Cooler	Yes	3	3	1	9
	Glove	Yes	2	3	1	6
	Treatment Bag	Yes	1	2	1	2
	Bed	Yes	2	2	1	4
	Work Area	Yes	1	2	1	2
	Average of the step					4.6
Hematology-Oncology Inpatient	Glove	Yes	2	3	1	6
	Work Area	Yes	2	3	1	6
	Treatment Bag	Yes	1	2	1	2
	Bed	Yes	2	3	1	6
	Cooler	Yes	3	3	1	9
	Average of the step					5.8
Traceability Office	Computer	Yes	3	3	1	9
	Printer	Yes	4	4	1	16
	Calculator	Yes	3	4	1	16
	Average of the step					13.6
Waste Zone	Cytotoxic Waste Bin	Yes	3	3	1	9
	Regular Waste Bin	Yes	2	2	1	4
	Average of the step					6.5
	Overall average of the process					6.1



The use of Failure Mode and Effects Analysis (FMEA) allowed for the systematic and methodical identification and analysis of critical risks at each point in the cytotoxic medication circuit. Failure modes were expressed in observable physical terms as much as possible. The risk level was accepted with a Risk Priority Index (RPI).

In total, we identified 4 critical levels of personnel contamination risk within our cytotoxic preparation circuit, reaching the predetermined critical threshold with an RPI of 16. The average contamination risk level was detected in 11 circuit points with RPIs of 12 and 9. The remaining points represented a low level of risk.

In terms of equipment, we found high levels of criticality in plastic bins, alcohol barrels, refrigerators, and work surfaces. Regarding PPE, we observed very high criticality for gloves and lower criticality for the work area.

In the post-preparation dispensing area, we observed very high criticality in plastic bins, high criticality on the work surface and cooler, and lower criticality in the alcohol barrel.

During transportation, we found high criticality in the cooler, but no traces were detected on the transport cart (RPI=9).

In the administration of cytotoxic drugs:

- In the hospitalization sector, we detected high criticality in the cooler and lower criticality in the nurse's gloves.
- In the HDJ MED B sector, we observed high criticality in the cooler and lower criticality on the patient's bed, nurse's gloves, and work surface.

In the pharmacist's office, we observed very high criticality for the printer and calculator, with high criticality for the computer.

In the waste disposal area, we detected high criticality in the cytotoxic waste bin.

Simulation of the spread of contamination throughout the chemotherapy circuit using quinine as a tracer highlighted the diffusion of the fluorescent substance in several areas: pre-preparation dispensing area, PPE area (PSMIII), post-preparation dispensing area, medication transport, administration area, traceability office, and waste zone.

Tracking the tracer medication "Quinine" throughout the cytotoxic medication circuit allowed us to control the projection of contamination in different areas using the FMEA method. This approach provided clear and actionable qualitative results after identifying the mechanisms of contamination spread. By highlighting the risk of contamination by cytotoxics in our study, we were able to use a structured analysis to identify the failures in our cytotoxic drug circuit and prioritise them in order to focus on the most critical failures. The most appropriate and relevant improvement measures for the preparers, nurses, and pharmacists to minimize cytotoxic projection are as follows:

At the preparation site:

- Preparers must follow good preparation practices.
- Adhere to the specified handling procedures with closed systems.
- Allocate sufficient time during preparation to minimize contamination risks.
- Systematically change the reconstitution field if a closed system leakage occurs.
- Preparation should be done by a single preparer.
- Include two airlocks (SAS) in the isolator.
- Personnel handling cytotoxic medications should receive additional information about the hazards associated with low levels of exposure to these drugs.

- Individuals involved in handling cytotoxic drugs (physicians, pharmacists, preparers, and nurses) should undergo continuous biological monitoring, including evaluation of parameters such as complete blood count, liver function tests, urea, creatinine, and electrolytes.

At the dispensing site:

- Pharmacy personnel should wear gloves before unpacking cytotoxic drugs for placement on the storage shelves.
- Preparers must strictly adhere to the cleaning procedures for the equipment used before preparation.
- Disinfection of preparations coming out of the isolator.

During transportation:

- Disinfection of coolers before placing treatment sachets inside and after each use in the clinical area.
- Containers used for transporting cytotoxic preparations should be sturdy with resistant walls.
- Personnel involved in cytotoxic transport should receive appropriate instructions regarding potential risks, good handling practices, and procedures to follow in case of breakage or leakage.

At the hospitalization and HDJ sites of the clinical hematology service:

- Adherence to good administration practices by nursing staff.
- Mandatory use of personal protective equipment during cytotoxic medication administration.
- Systematic change of work surfaces, gloves, and examination sheets in case of contamination and after each chemotherapy session.
- Systematic change of patient bed sheets after each chemotherapy session.
- Contaminated linens should be labeled as "Hazardous Contamination."
- Linens and clothing should be considered potentially contaminated materials and should be collected in labeled containers.
- Wash contaminated laundry separately from other laundry.

At the pharmacist's office:

- UPC personnel should not move during cytotoxic preparation without taking all necessary precautions.
- Regular cleaning of the office and equipment.

At the waste disposal area:

- Establish a waste management procedure.
- We recommend treating the "DARSI" trash bin as cytotoxic waste and applying the same measures recommended for cytotoxic waste or placing it in a separate location.
- Cytotoxic medication waste generated outside the preparation area should be disposed of in the cytotoxic waste bin located outside the isolator in the preparation room. Avoid compressing the material with hands.
- Personnel involved in cytotoxic waste transportation should receive instructions on transport safety procedures and measures to take in case of leaks.

Conclusion:

The work presented in this report aimed to control and assess the risk of contamination in the cytotoxic medication circuit at Ibn Sina Hospital in Rabat.

We proposed a risk analysis methodology based on the AMDEC method.

To achieve the targeted objectives, the areas of the cytotoxic medication circuit must undergo continuous monitoring, particularly in terms of chemical aspects. It is essential to implement a chemical contamination risk assessment to prevent any contamination. The IPR, as a quality indicator, allows us to identify, prioritize, and eliminate risks in the process of preparing anticancer medications before incidents occur, ensuring the absence of interference in chemotherapy manipulation.

In case of failure in any of the processes in different areas, it is evident that preventive and corrective measures should be implemented and integrated into the procedural documentation system.

During this work, we were able to detect chemical contaminations in the chemotherapy circuit, and consequently, we established specific measures aimed at optimizing each failure.

Personnel remains a crucial factor in contamination risk management. Awareness, sensitization, and continuous training of all staff, regardless of category, are essential to prevent contaminations that can affect patients, products, and the personnel themselves.

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Bibliographic Reference:

1. Bonnes Pratiques de Fabrication. Agence Nationale de sécurité et du Médicament 2011.
2. Institut National Du Cancer. La Situation Du Cancer En France En 2012. Boulogne-Billan court: Inca; 2012. Http://Www.E-Cancer. Fr/Publications/69-Epidemiologie/629-La-Situation -Du-Cancer-En-France-En- 2012
3. « https://cytoprevent.eu/wp-content/uploads/2021/02/2018-Sophie-Ndaw-Exposition-professionnelle-des-personnels-de-sante-hospitaliers-aux-medicaments-cytotoxiques.pdf »
4. SoppIsopp Standards Of Practice, International Society Of Oncology Pharmacy Practitioners, 2007; Ashp Guidelines On Handling Of Hazardous Drugs, American 2005.
5. Marie P, Christophe C, Manon R, Marc M, Charleric B, Patrice V. Environmental monitoring by surface sampling for cytotoxics: a review. Environ Monit Assess. janv 2017;189(2):52.
6. Ndaw S, Denis F, Marsan P, Rémy A, Robert A. Exposition professionnelle des personnels de santé hospitaliers aux médicaments cytotoxiques. Biométrologie et mesure de la contamination des surfaces. Réf En Santé Au Trav. juin 2018; (154):81-92.
7. Https://Www.Doctissimo.Fr/Sante/Dictionnaire-Medical/Traceur
8. Sakudo, « Fundamentals Of Prions And Their Inactivation (Review) », International Journal Of Molecular Medicine, Vol. 27, No 4, 1er Avril 2011.
9. Biokar Diagnostics. Http://Www.Solabia. Fr.
10. Http://Www.Microbiologiemedicale.Fr/Milieuxdisolement/Nonselectifs/Chocolat.Htm
11. Http://Www.Aclyon.Fr/Enseigne/Biotech/Microbio/Milieu_Culture/Sabouraud.Htm.
12. ISOPP. Safe Handling of Cytotoxics. Standards of Practice, 2018

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