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Proposal of An Haccp Plan For Controlling Hazards Associated With The Preparation of Cytotoxic Drugs In Hospital Pharmacy

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Abstract:
Cytotoxic preparations pose three major risks: toxicity for medical staff and patients, microbial contamination of preparations, and environmental pollution. This study proposes the implementation of an Hazard Analysis and Critical Control Point plan in the cytotoxic drug preparation unit of the pharmacy at Hassan II Hospital of the Fez University Hospital Center, as a method to control the inherent hazards in cytotoxic drug preparation.
Daily monitoring within the preparation unit identified four key stages of this plan. At each stage, associated hazards are identified, and their root causes are analyzed to establish preventive measures for risk control. Critical limits are defined for each hazard, along with monitoring procedures. If monitoring detects a loss of control, corrective actions are implemented. This plan only addresses hazards that are both severe and frequent.
Keywords : *Cytotoxic. HACCP. Hazard. Hospital.*

List of Abbreviations :
HACCP: Hazard Analysis and Critical Control Point
ISO: International Organization for Standardization
CCP: Critical Control Point
OPRP: Operational Prerequisite Program
GPP: Good Preparation Practices
MSC: Microbiological Safety Cabinet
HEPA: High Efficiency Particulate Air filter
Pa: Pascal

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I. INTRODUCTION

In order to control the quality, efficacy, and safety of anticancer drugs in accordance with good preparation practices [1-2] and to reduce chemotherapy costs [3-4], one of the measures taken by most countries is the centralization of cytotoxic preparations within an in-house pharmacy under the responsibility of a pharmacist [5].

At Hassan II Hospital of the University Hospital Center of Fez, the preparation of cytotoxic drugs began in the central pharmacy in 2010 following the establishment of a new oncology center. The increase in cytotoxic preparation activities motivated the reorganization of the anticancer drug preparation unit, and the implementation of a quality management approach became essential. This approach is based on hazard analysis and control using the HACCP (Hazard Analysis and Critical Control Point) method. The latter aims to improve pharmaceutical services, prevent, and manage the risks of medication errors. Although this concept was initially established for food safety control [6], it has proven to be applicable to a wide range of human activities.

The objective of this work is to develop an HACCP plan that can be implemented by the pharmacy staff. To achieve this objective, regular monitoring conducted during the preparation of cytotoxic drugs at the hospital pharmacy enabled:

- the development of a chronology of the main steps in cytotoxic drug preparation;
- the proposal of an HACCP plan.

II. METHODS

The study was conducted within the cytotoxic drug preparation unit of the pharmacy at Hassan II Hospital in Fez. The main steps in cytotoxic drug preparation that were suitable for the implementation of an HACCP plan were identified following daily visits to the unit.

Prior to the development of the HACCP plan, the HACCP team members were identified, followed by a description of the product and its use, and finally, the definition of the cytotoxic drug preparation steps.

The HACCP plan was developed by referring to the Codex Alimentarius [7] and adapting it to the specific situations imposed by the preparation of cytotoxic drugs, as well as to ISO 22000 (2005 and 2018 versions) [8].

The English acronym HACCP, which translates to "Hazard Analysis and Critical Control Points" in French, is based on 7 principles. Initially designed to control risks for food safety, this concept has proven applicable to other human activities.

The first principle, which corresponds to hazard analysis, involves identifying the nature of the hazards associated with each preparation step and then determining the causes of their occurrence in order to define control measures. For this purpose, it was considered that a hazard is identified as any situation, condition, or activity related to each preparation step that may constitute a potential source of harm to health (toxic effects on the patient or the preparer), render the drug preparation ineffective, or lead to environmental damage. This definition gives the word "hazard" a meaning that goes beyond harm to human health, as it includes drug ineffectiveness (resulting from defective preparation) or even environmental harm.

When a step or activity is considered essential for hazard control, it becomes a determining point. This notably includes CCPs (Critical Control Points) and OPRPs (Operational Prerequisite Programs), which were introduced by ISO 22000:2005 [8]. Drawing inspiration from and adapting the 2018 version of ISO 22000, an OPRP was defined as a "control measure applied to prevent the occurrence of a hazard or to reduce it to an acceptable level, with an action criterion and monitoring that allows for effective control of drug quality and/or preparation steps, as well as their environment." Similarly, a CCP was defined as a "preparation step or activity at which one or more control measures are applied to prevent a hazard or reduce it to an acceptable level, with defined critical limits and corrective actions."

The determination of CCPs and OPRPs was facilitated by the use of the ISO 22000 Procert decision tree [8].

The two parameters: critical limit and action criterion, are subject to continuous or regular monitoring; this is the fourth principle.

When monitoring reveals that the hazard associated with a given step or activity is no longer under control, the use of corrections and/or corrective actions becomes necessary (fifth principle). A correction, which is usually pre-established, is an action aimed at eliminating a detected nonconformity. It acts on the product (medicinal preparation). A corrective action aims to eliminate the cause of a nonconformity and prevent its recurrence; it acts on the preparation activity.

The sixth principle corresponds to the verification of the effectiveness and efficiency of the HACCP plan.

Finally, documentation comprising all the procedures and records implemented for the application of the HACCP system represents the seventh and last principle.

III. RESULTS AND DISCUSSION

1. Preliminary step to hazard analysis

This step aims to establish a multidisciplinary team responsible for developing and managing the HACCP plan, to describe the product (medicinal preparation) as well as its intended use, and finally, to establish a diagram defining the different preparation steps. This step constitutes a prerequisite for the development of an HACCP plan.

1.1 Formation of the HACCP team

The members of the team must be appointed, their responsibilities defined, and their competencies specified (Table 1).

Table 1 : HACCP Team Composition.

HACCP Team Members	Team Responsibility	Area of Expertise
Lead Pharmacist	-Heads the anticancer drug preparation unit. -Ensures the implementation of proper preparation and hygiene practices. -Oversees the mastery of recording procedures and staff training.	-Extensive experience in the management and handling of chemotherapy preparations. -Long-standing experience in training on cytotoxic drugs and preparations. -In-depth knowledge of the health risks associated with the preparation and use of anticancer drugs.

Deputy Pharmacist	-Ensures the proper implementation of the plan and adherence to its procedures. -Supervises all pharmaceutical preparation operations and approves batch releases. -Maintains traceability records. -Monitors corrective actions.	-Experience in managing a cytotoxic preparation unit. -Experience in preparing chemotherapy treatments.
Quality, Hygiene, and Environment (QHE) Technician	-Ensures the implementation of operational and environmental hygiene measures.	Experience in hospital hygiene and nosocomial infections.
Microbiologist	-Identifie les dangers microbiens, les limites critiques et les méthodes de contrôle et de surveillance du danger.	-Experience in microbiology
A chemotherapy preparation technician.	-Participates in chemotherapy preparation and cleaning/disinfection operations. -Ensures compliance with and implementation of health and safety protocols.	-Good knowledge of cytotoxic drug preparation.

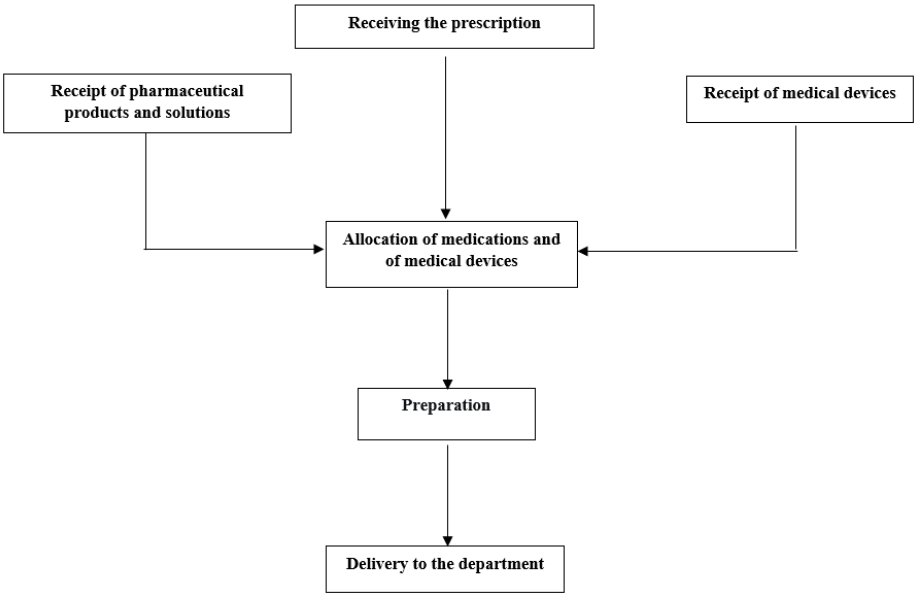
1.2 Description of the product and its intended use

A chemotherapy preparation can be formulated in two presentations: polyvinyl chloride infusion bag or pump for intravenous administration, or injectable syringe for intrathecal or subcutaneous administration; these formulations are packaged in a plastic sleeve. In accordance with good preparation practices, they must contain the correct drug, at the correct dose, the correct dilution volume, the correct reconstitution/dilution solvent, and appear clear and free of sediment, suspended particles, and microbial contamination. They have a short shelf life, hence the need for rapid administration after preparation or refrigeration between 4°C and 8°C if use is delayed.
The preparation of cytotoxic drugs is performed based on a named prescription. They are intended to be administered to well-defined patient profiles, which is why they are carried out under close medical supervision. They are indicated in the treatment of malignant tumors: lymphomas, myelomas, breast cancer, etc.

1.3 Flowchart of chemotherapy preparation operations

Four major steps in the preparation of cytotoxic drugs constitute the manufacturing flowchart. These preparations comply with the standards of Good Preparation Practices (GPP) [9].
The chronology of the different steps is represented in Figure 1.

Figure 1 : Flowchart of cytotoxic drug preparation operations.



Receipt of the prescription and cytotoxic drugs

The prescription is issued by a senior physician in reference to standard protocols and dosages established using software. This does not exclude the analysis upon receipt of the prescription by an authorized pharmacist, which consists of verifying [10]:

- The form of the prescription: identity of the physician, identity of the patient, and prescription date.
- The content of the prescription: diagnosis, conformity of the prescription to reference protocols, treatment cycle number, interval between two successive cycles, dose calculation, drug interactions, infusion duration, route of administration, type of diluent, and associated adjuvants.

The medical devices, solutions, and cytotoxic drugs received in the preparation unit are subject to checks for expiration date, quantities, and their condition (packaging condition, coloration, clarity, suspended particles, and presence of precipitate).

Assembly

This step involves assembling all prescribed medications, solutions (solvent for dilution and reconstitution), and medical devices (preparation syringe, sterile compress, and sterile field) necessary for the preparation in an individual basket corresponding to each treatment cycle, then disinfecting the entire set with a hydroalcoholic solution before introducing them into the transfer airlock of the microbiological safety cabinet. Each solvent bag will be labeled; this label includes the preparation date, the patient's name, the drug name, the route of administration, the dose in active substance, and the storage method.

Preparation

A manufacturing worksheet directly linked to the prescription is created; it informs about the patient (first and last name, diagnosis, body surface area) and provides some details about the protocol (treatment cycle number and day, the protocol's medications and their batch numbers, reconstitution and dilution solvent, prescribed dose and its conversion to volume, and the preparation procedure). This manufacturing worksheet is systematically associated with the basket corresponding to each treatment cycle.

Each medication is reconstituted if necessary and then diluted in the appropriate solvent (saline or glucose solution) in accordance with the manufacturing worksheet. The preparation is performed in a Class III microbiological safety cabinet (MSC), under positive pressure and in an aseptic environment.

Delivery to the department

The prepared chemotherapy treatments undergo a quality control process that includes: verification of the correspondence between the preparations and the manufacturing worksheet, checking of the labeling, detection of any aggregates or suspended particles, verification of the physical integrity of the bags (bag tightness), and verification of the color. The completed drug preparations will be packaged in a plastic sleeve that serves as secondary packaging (protection and information about the preparations) and either stored in the refrigerator (2-8°C) or promptly delivered to the department.The treatments are transported in containers specifically designated for this purpose (rigid, with secure sealing systems and opaque) and adapted to the storage requirements of cytotoxic products, in compliance with environmental and personnel protection standards.

Record Document

All pharmaceutical preparation operations are subject to rigorous traceability through the following registers:
- Prescription validation register: checklist for prescription validation.
- Preparation register: sequential number, preparation labels, date and time of preparation, identity of the preparer (name and signature), and batch number of the drugs used.
- Dispensing register: departure time, list of dispensed drugs, and identity of the transporter (name and signature).
- Anomalies and events register: detected anomalies, product returns, department complaints, and incidents.

2. HACCP plan for controlling hazards associated with chemotherapy preparations

The implementation of the HACCP plan [11] will be carried out on the cytotoxic preparation steps already identified (figure 1).

2.1 Hazard analysis

For each step in anticancer drug preparation, the hazards are identified according to their nature and the causes of their occurrence, which allows for defining control measures for each identified hazard (Table 2).

The receipt of the prescription and the drugs is a crucial step for controlling upstream the toxicity or ineffectiveness of cytotoxic preparations. Thus, a pharmaceutical analysis of the prescription and a check of the expiration date must be systematically performed for each drug listed in the therapeutic protocol.

During the preparation of cytotoxic drugs, the risk of microbial contamination is very likely if the cleaning and disinfection operation of the MSC was not performed effectively before and at the end of each preparation, if the preparation was not used extemporaneously [12], or if the airflow in the MSC is contaminated [13]. Indeed, to control this microbial hazard, the effectiveness of cleaning and disinfection is monitored by sampling at the time of chemotherapy preparation, using swabs and Petri dishes, on critical surfaces. This operation will validate or not the asepsis of the MSC surfaces. As for the HEPA (High Efficiency Particulate Air) filter change, if it is

saturated or disintegrated, verification of the physical integrity of the gloves and cuffs, the pressure differential between the preparation chamber and the transfer airlock of the MSC, and finally verification of its tightness, will condition a sterile atmosphere. These control measures help prevent microbial introduction and thus guarantee the sterility of chemotherapy preparations. Let us recall that using a closed-system preparation device allows better control of these contaminants.

Chemical contamination of preparations occurs during the preparation process, due to the use of a syringe that has already been used for preparing another drug or to the introduction of chemically contaminated air during reconstitution and dilution. Chemical contamination of the environment occurs when the HEPA filter is disintegrated or saturated. In this case, it is appropriate to label each syringe used for preparing each drug or to change the HEPA filter if it is saturated or no longer intact.

To control the toxicity or ineffectiveness of preparations, it is necessary to perform, after the gathering/assembly and during the preparation, a verification of the correspondence between the labeling of the saline bags and the manufacturing worksheet.

After preparation, the dispensing of an ineffective drug is a consequence of the loss of its stability due to delayed administration to patients without prior refrigeration.

The administration of a toxic, ineffective, or unsafe drug to cancer patients presents a potential or confirmed hazard. However, it is possible and necessary to control, prevent, and manage these hazards. Therefore, all steps identified in the preparation flowchart correspond to determining points (CCP, OPRP).

2.2 HACCP plan

After hazard analysis, an HACCP plan is established (Table 3). This plan is developed so that at each preparation step (Figure 1), the hazards are identified and their control measures defined. Critical limits or action criteria are proposed and constitute parameters for monitoring the application of control measures. Finally, when monitoring detects a loss of control, corrective actions are pre-established.

Preparation Steps	Hazards	Causes	Control Measures
Reception of the prescription and the drugs	Preparation of a toxic drug	Error in the prescription (overdose)	Prescription validation
		Expired drug due to exceeding the expiry date	Expiry date check
	Preparation of an ineffective drug	Error in the prescription (underdose)	Prescription validation
		Expired drug due to exceeding the expiry date	Expiry date check
Assembly	Preparation of an ineffective or toxic drug	Gathering error	Double-check of the gathering
Preparation	Microbial contamination of drugs	Ineffective or insufficient cleaning-disinfection of the microbiological safety cabinet	Monitoring of cleaning and disinfection effectiveness
		Microbial contamination of the MSC airflow	Verification of the pressure differential between the preparation chamber and the transfer airlock
			Verification of the condition of the HEPA filters
			Checking the physical integrity of gloves and cuffs
			Verification of the MSC's tightness
	Chemical contamination of drugs and/or the environment	Due to the use of a syringe already employed for preparing another drug	Adherence to Good Preparation Practices (GPP) procedures
		Due to MSC airflow contaminated by cytotoxic vapor	Verification of the HEPA filters' condition
	Preparation of a toxic or ineffective drug	Error in dosage calculation	Verification of the dosage
		Omission of one or more components in the preparation	Double-check: - After gathering/assembly - During preparation
		Labeling error of the preparation	Verification of the correspondence between the manufacturing worksheet and the preparation's labeling
		Confusion between syringes for intravenous or intrathecal use	Temporal separation of syringes according to the route of administration
Delivery to the department	Perte de stabilité du médicament cytotoxique	Non-respect des conditions de transport, de conservation et de la durée de stabilité	Transport des préparations dans de bacs opaques à la lumière et isothermes avec des réfrigérants
			Limiter la durée d'acheminement et d'administration des préparations

Table 2 : Hazard Analysis.

Preparation Steps	Hazards	Control Measures	Critical Limits/Action Criteria	Monitoring		Corrections/Corrective Actions
				Frequency	Method	
Receipt of the prescription and drugs	Preparation of a toxic or ineffective drug	Prescription validation	Prescription compliance	At the time of prescription receipt	Checklist	Rewrite the prescription
		Verification of the drugs' expiry date	Expiry date	Upon receipt of the drugs	Visual inspection	-Reject the drug if the date exceeds the set limit -Use quickly if the expiry date is approaching or exchange the product with the supplier
Assembly	Preparation of a toxic or ineffective drug	Double-check	Adherence to the gathering procedure	At the end of gathering and during preparation	Gathering procedure	Repeat the gathering and activate the preparation
Preparation	Microbial contamination of drugs	Monitoring of cleaning and disinfection effectiveness	Aseptic microbiological safety cabinet	Before and at the end of preparation	By swabbing and applying agar plates	-Repeat cleaning and disinfection. Re-prepare the drugs
		Verification of the pressure differential between the preparation chamber and the transfer airlock	No pressure variation (0 Pa) between the transfer airlock and the preparation chamber	Each day before starting the preparation	witch on the MSC for 15 minutes and then record the pressure displayed on the gauges	-Change the HEPA filter -Change the gloves and/or cuffs -Locate and correct leaks in the MSC.
		Verification of the HEPA filters' condition	Permeability < 0.01%	Once a year	HEPA filter integrity test with dioctyl phthalate	Change the HEPA filter
		Loss of physical integrity of gloves and cuffs	Surface of gloves and cuffs physically intact	Once a month	Gloves are filled with compressed air then immersed in water	Change the gloves and/or cuffs
		Verification of the MSC's tightness	Leak rate of 0.1%	Once a month	Leak test	Locate and correct leaks

Table 3 : HACCP Plan.

Preparation Steps	Hazards	Control Measures	Critical Limits/Action Criteria	Monitoring		Corrections/Actions correctives
				Frequency	Method	
Preparation	Chemical contamination of drugs and the environment	Adherence to the GPP procedure	Syringe not used for preparing another product	Before each preparation	GPP procedure	Re-prepare the drugs (product rejection)
		Verification of the HEPA filters condition	Permeability < 0.01%	Once a year	HEPA filter integrity test with dioctyl phthalate	Change the HEPA filter
	Preparation of a toxic or ineffective drug	Double-check : - at the end of gathering - at the time of preparation	Adherence to the gathering procedure	Double-check of the gathering	Gathering procedure	Repeat the gathering and activate the preparation
		Verification of the dosage	Tolerance of an error of +/- 5% of the dosage (if bag volume ≥ 100 ml)	At the end of preparation	Drug dosage by HPLC/gravimetry	Re-prepare the product (product rejection)
		Verification of the correspondence between the preparation worksheet and the preparation's labeling	Adherence to the gathering procedure	Double-check of the gathering	Gathering procedure	Re-label the preparation

		Temporal separation of intrathecal and intravenous preparations	Adherence to the intrathecal preparation procedure	Before each preparation	GPP procedure	Re-prepare the product
Delivery to the department	Loss of stability of the cytotoxic drug	Limit the waiting time between the prepared product and its dispatch to the department	2 hours	Every half hour	Recording of the preparation time	-Re-prepare the product or review the drug dosage -Raise awareness among the personnel responsible for distribution

Table 3 : HACCP Plan (continuation and end).

IV. CONCLUSION

The HACCP system, initially designed for food safety control, has proven to be applicable to virtually any human activity with certain adaptations. Its application in a hospital setting for controlling the safety of cytotoxic preparations is possible and allows for the formalization of good preparation practices for cytotoxic drugs, as shown by the results of the present study. However, its success depends on the application of other additional and necessary measures. These concern:

- Validation of the HACCP plan by a competent entity.
- Ad hoc training for personnel preparing and handling cytotoxic drugs.
- Implementation of recording procedures that serve as evidence of the proper application of the system.

REFERENCES :

[1]. Anonymous. Good Preparation Practices. Journal Officiel de l'ANSM. 2007.
[2]. Cazin JL, Gosselin P. Implementing a multiple-isolator unit for centralized preparation of cytotoxic drugs in a cancer center pharmacy. Pharm World Sci. 1999;21:177-83.
[3]. Legat C, Limat S, Coutet J, Dattoma F, Jacquet M, Woronoff-Lemsi MC. Economic impact of centralized preparation of anticancer drugs. J Pharm Clin. 2003;22:181-5.
[4]. Favier M, Fliche E, Bressolle F. Economic benefit of a centralized reconstitution unit of cytotoxic drugs in isolator. J Oncol Pharm Pract. 1999;2:182-5.
[5]. Chauvin B, Camus M, Phung-Nguyen, Rieutord A, Brion F. Standardization of the cost of injectable preparations of cytotoxic and antiviral injectable drugs in a centralized unit. Le Pharmacien Hospitalier et Clinique. 2007;42:127-33.
[6]. Council Directive 93/43/EEC on the hygiene of foodstuffs. Official Journal of the European Union. 1993;L175:1-11.
[7]. Codex Alimentarius: Hazard Analysis and Critical Control Point (HACCP) system and guidelines for its application. Food Hygiene Basic Text. 3rd ed. Afnor; 2005.
[8]. ISO 22000: Food safety management systems — Requirements for any organization in the food chain. 3rd ed. Rome: Afnor; 2005.
[9]. ISOP Practice Standard: Safe Handling of Cytotoxic Drugs. International Society of Oncology Pharmacy Practitioners; 2008.
[10]. Specifications for centralized units in pharmacy for the preparation of anticancer agents in network sites. Lorraine Regional Cancer Network; 2009.
[11]. Boehemer G. How to Implement HACCP. BPI; 2004.
[12]. Beaney AM. Preparation of parenteral medicines in clinical areas: how can the risks be managed - a UK perspective? J Clin Nurs. 2010;19:1569-77.
[13]. Khalili H, Sheikh babayi M, Samadi N, Jamalifar H, Dalili D, Samadi N. Bacterial contamination of single- and multiple-dose vials after multiple use and intravenous admixtures in three different hospitals in Iran. Iran J Pharm Res. 2013;12:205-9.