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Strategic Insights and Practical Tips for Establishing the Aseptic Chemotherapy Drug Compounding Unit in a Tehran Hospital: A Comprehensive Guide to Operational Success

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ABSTRACT

Aseptic compounding units are critical in the pharmaceutical field, especially for handling hazardous medications like chemotherapy drugs. These facilities are crucial for safeguarding patients, healthcare workers, and the environment. This article presents a practical roadmap for institutions seeking to establish chemotherapy drug preparation centers, drawing upon the experience of Iran's first GMP-compliant drug preparation unit. It delves into the regulatory framework, encompassing compliance with international standards like USP797 and USP800, and outlines the essential steps involved, including physical space establishment, clean room construction, human resource management, communication protocols, standard operating procedures, documentation, and authorization processes. The article emphasizes the paramount importance of patient safety, personnel safety, and environmental safety, highlighting the risks associated with hazardous drugs and the need for robust protective measures and protocols. It also acknowledges the challenges faced in Iran, including equipment accessibility and adherence to standards, and underscores the urgency for addressing these issues. The article concludes by advocating for the rapid establishment and development of drug preparation units in chemotherapy facilities across Iran, drawing inspiration from the successful implementation of the first GMP-compliant center and advocating for greater legislative support and collaboration.

INTRODUCTION

Aseptic compounding units are essential facilities in the pharmaceutical field, playing a crucial role in ensuring the safety of patients, healthcare workers, and the environment, especially when handling hazardous medications such as chemotherapy drugs (2023). In various countries and regions, including European nations and the United States, the preparation of chemotherapy drugs occurs in pharmacy units under pharmacist supervision (Holle and Michaud 2014, 2018, ESOP 2018). The global trend of using and administering cytotoxic medications has been growing, extending beyond oncology settings to treat non-malignant diseases, leading to an increased risk of potential exposure for a broader range of healthcare professionals and staff (Leso, Sottani et al. 2022). The primary objective of this article is to furnish an operational roadmap tailored for institutions aspiring to establish centers. To streamline the

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discourse and prevent redundancy, readily available information from international guidelines has been omitted.

LITERATURE REVIEW

Patient Safety

In 2012, over half of global cancer cases and deaths were concentrated in low- and middle-income countries, constituting 57% and 65%, respectively, reflecting the dual burden of infectious and non-communicable diseases in these nations (2018, 2023). The Institute of Medicine's report, "To Err is Human," underscores the alarming toll of medication errors in the United States, estimating an annual loss of 44,000 to 98,000 lives, with fatal errors, particularly attributed to chemotherapeutic drugs, ranking as the second most common contributor (Institute of Medicine Committee on Quality of Health Care in 2000, Ashokkumar, Srinivasamurthy et al. 2018). Given the intricate nature of chemotherapy regimens, errors are susceptible at any stage from prescribing to administration (Ashokkumar, Srinivasamurthy et al. 2018). Injectable medication errors in secondary care, especially those involving high-risk injectables like cytotoxic drugs and total parenteral nutrition (TPN) products, have prompted recommendations from the UK's National Patient Safety Agency (NPSA) to compound them in the pharmacy for enhanced safety (Bateman and Donyai 2010). A study in Iran examining drug handling and administration errors during chemotherapy revealed a substantial 32.5% error rate across various stages, emphasizing the critical need to address these issues in healthcare practices (Maria Tavakoli-Ardakani 2013).

Personnel Safety

Hazardous drugs, characterized by various harmful attributes, pose risks to both patients and healthcare workers who handle them (Connor TH 2016). Antineoplastic drugs (ADs), employed in cancer treatment, exhibit selective but partial impact on malignant cells, leading to significant toxic side effects on normal cells (Canal-Raffin, Khennoufa et al. 2016, CDC (accessed on 29 December 2022).). The toxicity of ADs has been documented for over three decades, with the National Institute for Occupational Safety and Health (NIOSH) highlighting adverse health effects in 2004, including skin rashes, reproductive system disfunctions, and hematopoietic issues (Friese, McArdle et al. 2015, Wahlang, Laishram et al. 2017, IARC 2023). Studies, beginning with Falck's pivotal 1979 research, have consistently confirmed the significant health risks associated with occupational exposure to these drugs (Falck, Gröhn et al. 1979, Sotaniemi, Sutinen et al. 1983, Valanis, Vollmer et al. 1997, Bernabeu-Martínez, Sánchez-Tormo et al. 2021). Workers handling ADs, spanning pharmacists, nurses, physicians, and various support staff, are susceptible to exposure through multiple pathways, including skin contact, inhalation, ingestion, and accidental injection (Friese, McArdle et al. 2015, Marie, Christophe et al. 2017). The health and safety of healthcare professionals and the environment must be the top priority at all stages of handling hazardous drugs, including receipt, storage, preparation, dispensing, transportation, administration, cleaning, and disposal. Proper protective measures and protocols help minimize risks from these dangerous substances, allowing healthcare workers to focus on caring for patients without undue concern for their own well-being or the broader impact of their important work.(da Conceição, Bernardo et al. 2015). Despite efforts, challenges persist in safeguarding workers' health, including the lingering contamination of work surfaces with cytotoxic drugs, inadequate protective equipment usage, and a lack of dedicated pharmacy wards in some regions (Acampora, Castiglia et al. 2005, Hedmer, Georgiadi et al. 2005, Roberts, Khammo et al. 2006, Turci and Minoia 2006, Shahrasbi, Afshar et al. 2014, Abbasi, Hazrati et al. 2016). This underscores the urgent need for improvements in safety practices and infrastructure to protect healthcare personnel involved in cytotoxic medication preparation.

Environmental Safety

The documented environmental contamination with hazardous drugs is a key factor in the establishment of guidelines for constructing pharmacy facilities where cytotoxic drugs are managed (Power and Coyne 2018). Numerous articles have reported surface contamination by chemotherapy drugs in both pharmacies and patient care areas (Connor, Anderson et al. 1999, Zock, Soefje et al. 2011, Bussières, Tanguay et al. 2012). The implementation of safe policies for handling hazardous drugs encounters multiple challenges, including issues related to personnel knowledge, attitudes, supervisor encouragement, compliance, logistical constraints, spatial limitations within institutions, and prohibitive costs, despite well-documented benefits (2023). Despite the unanimous emphasis on safety precautions by American, European, and Australian authorities, challenges persist in ensuring adherence to these guidelines (Connor, Anderson et al. 1999, Hedmer, Georgiadi et al. 2005, Connor TH 2016, Marie, Christophe et al. 2017). Iran is currently grappling with challenges in accessing equipment and complying with standards for chemotherapy drugs preparation, necessitating prompt intervention. This article aims to provide insights into the establishment and operation of Iran's first drug preparation unit, approved according to Good Manufacturing Practices (GMP) principles by the country's Food and Drug Organization, while also examining prevalent obstacles in this domain (2018). In this article, we are going to examine the operational steps of this process, and to convey the point concisely, we refrain from mentioning the standards that are accessible in all guidelines.

STRATEGIES

Regulatory Framework

Overview of Pharmaceutical Regulations in Iran in the Field of Compounding

In adherence to clean room standards for the preparation of cytotoxic drugs, the handling of such drugs necessitates strict compliance with safety regulations to mitigate associated risks. This document outlines that these standards, aligning with international guidelines, are designed based on four fundamental principles, as introduced in the earlier section. These principles encompass safeguarding employees working with these drugs, protecting the product from microbial contamination and particulate matter, minimizing environmental pollution, and reducing pharmaceutical product wastage. Notably, the first three principles align with the objectives of establishing drug preparation units in developed countries. The significance of the fourth principle, reducing pharmaceutical product wastage,

becomes particularly evident in specific circumstances, as elaborated in the subsequent section.
The service standard for the preparation of chemotherapy injectable solutions, issued by the Secretariat of the Strategic Council for the Development of Health Guidelines in the summer of 1400, delineates the protocol for preparing chemotherapy drugs in a controlled environment under the supervision of a trained pharmacist. Furthermore, the chemotherapy service management guidelines, published by the Ministry of Health, Treatment, and Medical Education, stipulate the necessity of a preparation unit for facilities housing more than 12 chemotherapy beds.

Compliance with International Standards (GMP)

Generally, the criteria delineated in Section A-1 are formulated in alignment with the USP797 standards. Specifically, the design specifications for spaces dedicated to the compounding of cytotoxic drugs underscore compliance with USP797. It is imperative to note that the construction guidelines for units dedicated to the preparation of chemotherapy drugs also adhere to the principles outlined in USP797. Furthermore, in the compounding of chemotherapy drugs, due consideration must be given to the principles articulated in USP800, which pertain to the handling of hazardous drugs, in accordance with the drug classification.

The Steps of Establishing a Chemotherapy Drug Preparation Unit

Physical space

In accordance with the standard part of the physical space for the compounding of cytotoxic drugs, as outlined in the standardized document governing clean room specifications for cytotoxic drug compounding, the facility for drug preparation may be situated either within the confines of the hospital pharmacy or in close proximity to the cytotoxic drug administration unit. This designated area constitutes a regulated working environment, comprising a minimum of two distinct rooms – namely, the clean room and the anteroom. Supplementary spaces within this regulated working environment may encompass changing rooms designed for donning personal protective equipment during work activities, as well as areas designated for the storage of medications.
The prescribed minimum area for establishing a regulated working environment equipped with a Biological Safety Cabinet (BSC) is 14 square meters. Additionally, an additional 6 square meters of space is mandated for each supplementary hood within the facility.

Clean Room Construction

In adherence to international standards, including USP 797, ISO, and FS209E, the designated location for Biological Safety Cabinets (BSCs) is within the clean room. This clean room must conform to ISO class 7 standards, and its pressure should be maintained at a negative level compared to adjoining rooms. A minimum pressure difference of 2.5 pascals between the clean room and the anteroom is imperative to ensure a consistent inward airflow. Continuous monitoring of room pressure is essential and necessitates the installation of pressure monitors.
The placement of this facility may be proximate to the chemotherapy drug injection unit. The overarching objective of regulating the work environment is to eliminate or mitigate particulate matter within the environment associated with injectable drugs. This is achieved through meticulous environmental cleaning practices, the use of requisite personal protective equipment during transitions from particle-contaminated areas to cleaner zones, and strategic spatial engineering. This designated space comprises distinct components:
1. Anteroom: This area must adhere to the ISO class 8 standards.
2. Clean Room or Buffer Area: This space must meet the ISO class 7 standards.
3. Biological Safety Cabinet: Direct Compounding Area, dedicated to the preparation of medicines, the Biological Safety Cabinet serves as a specialized workbench equipped with fundamental engineering controls. It ensures aseptic conditions for product preparation, achieving a minimum ISO class 5 standard. Various types of biological safety cabinets exist, with the class II type being particularly suitable for the compounding of chemotherapy drugs. It is essential to note that a Laminar Airflow Workbench (LAFW) cannot substitute for a Biological Safety Cabinet due to its lack of requisite engineering characteristics for handling hazardous drugs.

Human Resources

Individuals qualified to provide the requisite service are explicitly identified in the birth certificate and the service standard governing the compounding of chemotherapy injection solutions, encompassing both bulky and non-bulky preparations. Specifically, clinical pharmacists and general pharmacists who have successfully completed a specialized training course in the handling of cytotoxic drugs are deemed suitable. As per the stipulations within the same document, the initiation of operations requires a minimum staffing configuration of one clinical pharmacist and two general pharmacists.

Competent personnel assigned to the cytotoxic drug preparation unit, comprising drug preparation technicians and service personnel, must undergo comprehensive theoretical and practical training in "working with cytotoxic drugs". The presentation of certificates attesting to the completion of these specified courses is obligatory for employment in the chemotherapy drug preparation unit. Recurrent training sessions are mandated on an annual basis. Furthermore, written procedural instructions should be readily accessible within the workplace.

It is noteworthy that none of the internal guidelines proffer recommendations regarding the requisite personnel numbers. Consequently, the determination of personnel and services should be based on a judicious assessment of the average number of center preparations and the internal workflow dynamics. A salient consideration is found in the food and drug standard notification, indicating an average preparation rate of 12 drugs per hour per Biological Safety Cabinet (BSC). This statistical insight aids in estimating the requisite personnel levels.

Intra-organizational Communication

To establish a unit for the preparation of chemotherapeutic drugs, it is imperative to establish a systematic process for communication with various hospital departments, external to the pharmacy, and the chemotherapy administration section.

Among the departments requiring established communication pathways, the followings are noteworthy:

1. Microbiology Laboratory: Conducting periodic microbial monitoring for identification and elimination of microbial contamination within the clean room environment is contingent upon square footage and class specifications of different clean room sections. Trained personnel should undertake sample collection, incubation of culture media, and interpretation of results, which must be confirmed by an accredited microbiology laboratory. Therefore, prior to commencement of operations, the communication pathway and coordination between the drug preparation unit and the hospital's microbiology laboratory or another accredited microbiology laboratory must be established. A comprehensive Standard Operating Procedure (SOP) for microbial monitoring should be drafted, validated by the hospital's infection control unit, and any modifications to this SOP should gain approval from the responsible infection control unit and the laboratory's technical authority.

2. Procurement Unit: Interaction with this department is crucial for the timely procurement of necessary equipment for the clean room. A well-documented plan for acquiring and placing essential clean room equipment, including but not limited to items such as dual-port IV bags, syringes of various volumes, needles (16G to 19G), IV sets, personal protective equipment, disinfectant solutions, needle filters or discs, infusion pumps, waste collection bags, and dedicated sharp and hazardous waste bins (Safety Box) should be in place. Establishing this communication is pivotal, as any delays in obtaining required equipment may impede the functioning of the clean room due to existing market constraints in Iran.

3. Maintenance Department: Establishing communication with the facilities department, staffed by technicians familiar with engineering principles and the maintenance of the clean room, is of paramount importance. Given that many drug preparations in Iran are often completed for immediate injection during the same shift, any issues in the operation of engineering equipment and the structural integrity of the clean room must be promptly identified and rectified. If trained technicians are not available within the hospital's facilities department, it is strongly recommended to provide training for selected personnel by the clean room manufacturer or another reputable training institution before initiating operations. Relying on external services (outside the hospital) is not advisable due to potential time constraints.

4. Validation Partner: Validation of the clean room at the outset of operations (post-construction), after any structural modifications, and periodically, at least every 6 months, is mandatory. Therefore, a third-party company should be selected for this purpose, and necessary contracts should be established for ongoing collaboration. Results of this validation are required for obtaining initial operational approval and its renewal.

5. Pharmacy: If the management of the drug preparation unit is external to the pharmacy, coordination with the pharmacy regarding drug procurement methods and ensuring the effective delivery of drugs directly from the pharmacy to the preparation unit must be predetermined. This includes considerations for the direct delivery of drugs to the patient from the pharmacy to mitigate risks associated with vial breakage, environmental contamination resulting from drug storage at home, and the potential lack of adherence to proper drug storage conditions by the patient.

Establishing Standard Operating procedures

The compounding facility must possess approved Standard Operating Procedures (SOPs) to uphold the environmental quality during the preparation of Compounded Sterile Preparations (CSPs). Recommended procedures for writing SOPs are listed in both USP 797 and the Food and Drug Administration standard. (2023)

Documentation

The comprehensive inventory of requisite documents for the drug preparation unit is meticulously outlined in both the United States Pharmacopeia (USP) 797 and the officially communicated standards of the food and drug regulatory authority, readily accessible for reference.

Seeking authorization to commence operations.

In accordance with the US Food and Drug Administration (FDA) standard, following the establishment of a cytotoxic drug compounding unit, the inspection and certification process must be carried out by the FDA or an authorized regulatory body. Upon the center's declaration of readiness to commence operations, FDA inspectors are dispatched to conduct an inspection. After verifying the presence of all necessary requirements for the center to initiate activities and ensuring the successful completion of required tests, the authorization to commence operations is issued. This authorization needs to be reassessed every six months and following any changes, repairs, or replacement of HEPA filters. In the absence of specified alterations, the conditions of the clean room standard must be re-evaluated every six months, and the activity authorization should be renewed unless otherwise stipulated by the FDA based on specific conditions mentioned in the authorization.

DISCUSSION

The state of hazardous drug preparation in Iran lags significantly behind that of other developing and developed countries. The expeditious establishment and development of drug preparation units in facilities conducting chemotherapy should be pursued with greater intensity and cohesion by legislative bodies in Iran. The continuation of this process under current circumstances could lead to an irreparable catastrophe in the near future. It is hoped that, by sharing our experiences in establishing the first chemotherapy drug preparation center, successfully accredited by the US Food and Drug Administration based on Good Manufacturing Practices (GMP) principles, we can take a significant step towards accelerating the proliferation of similar units in relevant centers nationwide.

CONCLUSION

Aseptic compounding units are essential for ensuring the safety of patients, healthcare workers, and the environment when handling hazardous medications like chemotherapy drugs. The establishment and development of drug preparation units should

be pursued with greater intensity and cohesion by legislative bodies in Iran. Adherence to international standards, proper infrastructure, and comprehensive strategies are crucial for the successful operation of these units. By implementing these measures and sharing experiences, the proliferation of safe and effective chemotherapy drug preparation centers can be accelerated.

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