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Original Article

A United States pharmacopeia chapter 800-centered process improvement proposal for compounding antineoplastic medications in an academic medical center pharmacy

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Abstract. It is well described that handling antineoplastic medications without proper personal and environmental protections leads to malignancy, reproductive toxicity, and organ damage. In December 2019, the United States Pharmacopeia Chapter 800 (USP<800>), which addresses the proper handling of hazardous drugs, will be enforceable for any facility handling these agents. Northwestern Memorial Hospital in Chicago, Illinois has developed a process improvement for the central pharmacy clean room to increase compliance to USP<800> standards. This plan specifically focuses on adjusting the workflow of four antineoplastic agents that are compounded in their central pharmacy clean room.

Keywords: United States Pharmacopeia chapter 800, pharmacy, antineoplastic, National Institute for Occupational Safety and Health, compliance

Introduction

The standards described in United States Pharmacopeia General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings (USP<800>) [1], a detailed addendum to the brief hazardous drugs (HDs) section of General Chapter <797> Pharmaceutical Compounding – Sterile Preparations (USP<797>), will be officially enforceable across all institutions that handle HDs as of December 2019. Prior to the publication of USP <800>, minimal standards existed regarding the preparation, administration, and transportation of HDs; however, this chapter now provides practical standards that must be implemented in order to increase the protection of healthcare workers and patients from unnecessary contact with HDs.

USP<800> was developed in response to publications and alerts from safety organizations and healthcare facilities, such as The National Institute for Occupational Safety and Health (NIOSH). Notably in 2004, NIOSH released their alert entitled "Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings"[2]. It presented compiled data and reports regarding HDs as far back as the 1960s which documented negative outcomes for healthcare workers exposed to HDs. Adverse events included reports of malignancies, reproductive toxicity in both men and women, and overall organ damage. Thus, it was clear that an enforceable standard was needed to protect the safety of those involved with the preparation of HDs.

At Northwestern Memorial Hospital, a 900 bed academic medical center in Chicago, Illinois, the pharmacy staff are working to update the facility's practices and procedures in order to become fully compliant with USP <800>. Like many other hospitals throughout the country, several barriers to achieving full compliance exist ranging from financial barriers, changes to workflow, or staff education. Additionally, improvements must ideally be implemented without affecting the current standard of patient care. Little has been published to date detailing hospitals' efforts toward increasing USP<800> compliance and the barriers involved in doing so.

In order to move forward with the changes needed to improve Northwestern Memorial's compliance to USP<800>, a task force including pharmacists, pharmacy technicians, and pharmacy students was created to amend and improve current practices. More specifically, the task force identified that the manipulation of several NIOSH Class I Hazardous Drugs, or antineoplastic drugs, was being performed in conditions that do not meet the specifications for safe handling of these dangerous compounds [3]. Because of this, Northwestern Memorial has developed a process improvement proposal which addresses these issues. The overall objectives of the task

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force charged with this initiative are to improve the safety of hospital employees and patients as they come into contact with HDs throughout the entire medication delivery process and to increase compliance to USP<800> while maintaining efficient pharmacy workflow.

USP<800> Overview

USP<800> outlines the standards for the handling and preparation of HDs so that pharmacies and other facilities are able to maximize patient, employee, and environmental safety. These standards range from maintaining engineering controls, proper drug storage, disposal protocols, documentation, and other exposure control measures. As the date approaches when USP<800> will be enforceable by pharmacy regulatory agencies, hospitals are working to implement these standards.

In general, facilities that compound or prepare HDs are required to have engineering controls that ensure containment of the HD throughout its normal course of manipulation or in the case of a leak, spill, or error. This includes, but is not limited to, a negative pressure ISO class 7 buffer room and containment primary engineering controls (C-PEC) such as biological safety cabinets (BSC) or compounding aseptic containment isolators (CACI) that are externally vented. As for the storage of HDs, antineoplastic agents that are not in their final dosage forms (i.e. they will be repackaged or manipulated in some way) must be stored separately from non-HDs. Additionally the containment secondary engineering controls (C-SEC) for these drugs involve storage in a negative pressure, externally vented room, with at least twelve air changes per hour. If refrigeration is required, there must be a dedicated hazardous drug refrigerator, which should be stored in a negative pressure environment with twelve air changes per hour. Negative pressure spaces with a refrigerator should have an exhaust near the compressor and the back of the refrigerator.

Disposal of these drugs further complicates the implementation of USP<800>. HDs and contaminated materials must be disposed of according to federal, state, and local regulations. Because of this, those involved in the general disposal processes for the pharmacy must also be trained on how to dispose of HDs. Many facilities also employ separate disposal mechanisms for bulk waste and trace waste, such as personal protective equipment (PPE), further adding to the need for trained personnel.

Because PPE worn during HD manipulation is subject to higher risk in the event of contamination, there are additional requirements for handling it in USP<800>, as compared to USP<797>. Those compounding HDs are required to wear chemotherapy gloves that meet the American Society for Testing and Materials standard D6978, hair and beard covers, gowns that are proven not to be permeable to HDs, two pairs of shoe covers, eye protection, and respiratory protection beyond a surgical mask.

While these PPE requirements are in place to help protect those involved from exposure to the HDs during manipulation or if accidents like spills occur, there are additional standards for the management and cleaning of HD spills. Firstly, facility-mandated standard operating procedures for these situations must be maintained at all times. Whether the spill occurs in a drug storage area or in the direct compounding area, they should be cleaned immediately by trained personnel. Spill kits should be on hand at all times, and those trained to use them must be present any time HDs are being handled.

At the time of the spill and at other regularly scheduled times, cleaning of the USP <800> environment is required. The cleaning process is far more extensive than that required by USP <797>. The sequential cleaning process begins with decontamination. Decontamination is defined by "inactivating, neutralizing, or physically removing hazardous drug residue from non-disposable surfaces and transferring it to absorbent, disposable materials…". Next, the cleaning phase begins which involves removing contaminants from objects and surfaces using specific detergents or other chemicals. The last step of cleaning is disinfection which is the process of destroying microorganisms from the compounding areas or supplies. Together, these steps ensure a safe space for the manipulation of HDs [1].

Assessment of Current Practice

Northwestern Memorial Hospital has several pharmacy locations distributed throughout the different wings of the facility. Of most importance to this initiative are the central pharmacy which houses a large, USP<797> compliant, non-hazardous drug clean room, an inpatient oncology pharmacy with a designated hazardous drug compounding room, and a smaller general satellite pharmacy with a BSC. Early on, it was recognized by pharmacy staff that these facilities had the equipment needed to redistribute the workflow of HDs to optimize employee safety without affecting the quality of patient care.

In order to begin identifying specific areas for improvement for USP<800> compliance, fourth year pharmacy students began reviewing USP<800>, completing Simplifi797® Critical Point training modules, and observing procedures in the pharmacy locations described above [4]. By doing this, they were able to create a list of potential areas for improvement. Next, the students met with clean room technicians and pharmacists to hear and evaluate their specific questions and concerns about HD handling in the pharmacies. It was very apparent that these employees were most concerned about their exposure to antineoplastic drugs in the central pharmacy clean room, a compounding space not designed to handle the preparation of HDs.

Seeing as this was an issue identified by the both the pharmacy students and pharmacy employees, it was decided that this was the best area of focus. From there, the pharmacy students and a clean room pharmacist met to review the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings [3]. From the list of NIOSH Class 1 drugs, they identified the agents which are handled and manipulated in the general clean room. The drugs that raised the most concern were mitomycin, hydroxyurea, the bacillus Calmette-Guerin (BCG) vaccine, and methotrexate.

Mitomycin

USP<800> Standard and Manufacturer Guidance

In the package insert for mitomycin, an alkylating agent, there were vague guidelines for the handling and disposal of this hazardous drug. Therefore, we must turn to the guidance of USP<800> for recommendations, keeping in mind that USP<800> resulted from data and case reports that were made public after mitomycin and other HDs first came to market. Section 5.3 of USP<800> describes in detail the requirements outlined previously pertaining to the compounding environments in which HDs should be handled. These controls can help drastically mitigate the risk of inhalation, contact to mucous membranes, or ingestion of mitomycin [1, 5, 6].

Current Practice

Mitomycin is compounded in the central pharmacy clean room upon request by a surgeon performing an oncologic procedure for bladder irrigation. The drug is reconstituted, drawn up into a syringe, and the final product is placed in an amber bag. A nurse or technician comes to pick up the drug or deliver it to the operating room, respectively. Because the delivery of this medication is extremely time sensitive, it is currently prepared in the central pharmacy to reduce transit time to the operating rooms which are housed in the same wing of the hospital.

Proposed Solution

The inpatient oncology pharmacy operates from 0730 to 2300 during the weekdays. This location has a negative pressure, externally vented HD clean room with two CACI. Typically, only one CACI is used at a time when the scheduled chemotherapy compounding begins in the late morning. Additionally, mitomycin is usually requested starting from 0830 and throughout the day. Therefore, mitomycin can be compounded in the mornings after opening of the inpatient oncology pharmacy, leaving adequate time to clean the CACI at the beginning of the shift. The second CACI may be used if it is open and an additional technician is available to avoid disrupting current workflow. From there, a pharmacy technician not working in the HD clean room would deliver the mitomycin dose to the appropriate operating room.

Hydroxyurea

USP<800> Standard and Manufacturer Guidance

Hydroxyurea is an antimetabolite drug used as chemotherapy. Northwestern Memorial often uses this medication as a compounded oral suspension, which is non-sterile. Thus, Section 5.3.1 of USP <800> was also considered which details the non-sterile HD compounding standards. However, because there is a risk of aerosolization of the hydroxyurea drug particles as it is compounded into a liquid, C-PEC, C-SEC, and PPE used in sterile HD compounding should still be used [1, 7, 8].

Current Practice

Hydroxyurea oral suspension is batched in the central pharmacy cleanroom. Compounding of the suspension involves opening hydroxyurea capsules. Risk for exposure to this drug drastically increases when the capsules are opened and drug powder is mixed with liquid. The suspension is stored with non-HD oral liquids in the main pharmacy area. Scheduled patient specific doses are drawn up into oral syringes each day for the afternoon delivery for administration overnight or in the morning. The patient-specific label states that chemotherapy precautions should be taken, but technicians generally just wear gloves and sometimes a surgical mask while drawing up the dose.

Proposed Solution

Since hydroxyurea is batched for multi-use purposes and is not time-sensitive, the transition of its initial compounding from the central pharmacy to the inpatient oncology pharmacy is logistically viable. The oncology pharmacy usually has rush periods when they make their scheduled inpatient chemotherapy doses beginning in the late morning. Outside of these hours, hydroxyurea can be batched by the technicians handling HDs since it only needs to be done on a weekly basis.

The batched oral liquid can continue to be stored in the central pharmacy where it is to be kept in a bag designated for chemotherapy drugs to prevent unnecessary exposure and as an alert to all staff that handle it.

When working on the patient specific oral syringe doses each day, the technicians will first complete all non-HD orders. They will then don gloves and masks before continuing with the HD oral liquid orders and finish the process by thoroughly cleaning the directly exposed surfaces with 70% isopropyl alcohol wipes. Additionally, pharmacists will wear gloves and a mask when verifying all doses and place each patient-specific set of syringes in a chemotherapy bag as described previously. These steps will reduce personnel exposure to the drugs and also prevent potential, unnecessary contamination of other medications.

An important factor for the implementation of this proposed solution involves further education of all pharmacy staff involved with handling hydroxyurea. Information relevant to the potential hazards presented by contact with HDs and instructions for procedural changes should be highlighted to enhance the safety surrounding the handling of this HD.

Overall, this is only a temporary solution for the compounding of hydroxyurea; the full enforcement of USP<800> will require not only the batching but also the patient specific doses to be drawn up under a negative pressure environment. Further evaluations and alterations of the process will be necessary to reach total compliance in addition to the alterations proposed above.

Bacille Calmette-Guerin Vaccine

USP<800> Standard and Manufacturer Guidance

The BCG (Tice) vaccine is a live vaccine that can be used for tuberculosis prophylaxis and the prevention or treatment of some bladder cancers. Currently, it is believed that the BCG vaccine produces an inflammatory response

that stimulates macrophages to have anti-tumor effects. According to the manufacturer of Tice®, the preparation of the vaccine suspension should be done using aseptic technique and in a separate, designated area. Preferably, the preparation should occur in a C-PEC in order to minimize the risk for inhalation, which could result in an outbreak of tuberculosis. These recommendations align with Section 5.3 of USP<800> [1, 9, 10].

Current Practice

The BCG Tice® vaccine suspension is currently prepared in the central pharmacy cleanroom for patients requiring bladder irrigation. Pharmacy staff know when these patients are coming several weeks in advance. The vaccine is reconstituted into a suspension for irrigation, dispensed in a 60 mL Toomey catheter-tip syringe, and wrapped in foil. A nurse picks up the scheduled dose from the pharmacy window. In addition to preparation, there are existing, informal hospital protocol for cleaning of the direct compounding area after BCG preparation. This process takes approximately 30 minutes. Deactivation, decontamination, and cleaning are performed with 2% sodium hypochlorite (bleach). The sodium hypochlorite is removed with sodium thiosulfate or followed by use of a germicidal detergent in sterile water. Finally, the hood is disinfected with sterile water and 70% alcohol. After this process, the hood must remain unused for 5 minutes to allow the alcohol to dry.

Proposed Solution

Since the timeline for the preparation and administration is known so far in advance, the BCG vaccine can be moved to the inpatient oncology pharmacy for preparation and inserted into the scheduled chemotherapy workflow. Because this is a live vaccine, there is concern for contamination of other products, especially those for transplant patients. Therefore, the existing hospital protocol described above for BCG preparation must be followed and CACI downtime should be added into the workflow. Nursing staff will pick up the dose after preparation at the pharmacy.

Methotrexate

USP<800> Standard and Manufacturer Guidance

Methotrexate is a folate synthesis inhibitor used for a variety of inflammatory conditions and malignancies. The central pharmacy clean room specifically prepares doses for intravitreal injection or for the treatment of ectopic pregnancy. Like the manufacturer guidance for handling of mitomycin, USP<800> Section 5.3 contains the best standards for the conditions in which methotrexate should be handled. The risks for contact to mucous membranes, inhalation, and ingestion to pharmacy employees is similar to that of mitomycin [1, 11, 12].

Current Practice

Methotrexate is compounded in the central pharmacy cleanroom for ectopic pregnancy and intravitreal injections. The stock methotrexate vials are stored in the central pharmacy Talyst® machines. For ectopic pregnancy, the drug is simply drawn from the stock vial into a syringe. The intravitreal injections are prepared by appropriately diluting the stock methotrexate solution and drawing them up into a syringe.

Proposed Solution

Both methotrexate products can be moved to the inpatient oncology pharmacy. In fact, this pharmacy is located in the same wing of the hospital as the Women's Pavilion, actually improving the logistics of delivery of the medication for ectopic pregnancy. However, this becomes an issue if an order for methotrexate for ectopic pregnancy is placed overnight. Fortunately, a remedy for this problem stems from the smaller satellite pharmacy with the BSC. If there is an order overnight, a pharmacy technician can retrieve the drug vials from the inpatient oncology pharmacy and bring them to the small satellite pharmacy for preparation and pharmacist verification since it is open 24 hours a day and is conveniently located in the same wing as the oncology pharmacy. As for the intravitreal injections, they are used during normal business hours, and nurses are already accustomed to picking up these doses from the pharmacy. The oncology pharmacy can insert these into their normal work flow if the ordering physicians are aware that they can expect an hour order time on the medication. The second CACI may also be utilized if it is open to reduce the wait time on the medication.

Discussion

The proposed solutions outlined above are just the beginning of a longer journey to USP<800> compliance and optimal employee and patient safety. An ongoing discussion between pharmacy staff and hospital administration will be necessary to continue implementing changes. In this initiative, changes to the workflow were only made regarding NIOSH Class I Hazardous Drugs, as they posed the greatest, most immediate threat to pharmacy staff exposed to these drugs. Further plans to improve USP<800> compliance should involve a comprehensive address for drugs in all other NIOSH classes to ensure they are being handled and prepared according to the manufacturer's instructions. Additionally, discussion surrounding the remodeling of the central clean room pharmacy to include a USP<800> compliant compounding space should be initiated. This plan would include significant financial and logistical barriers, but as USP<800> becomes enforceable, as the Joint Commission begins to review compliance to the chapter, and as the introduction of new, hazardous drugs to the market continues to rise, remodeling the central pharmacy will be a necessary, long-term solution.

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Conflict of Interest

The authors declare no conflicts of interest.

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