Academic Medical Center | Patient Safety Organization
a component entity of Risk Management Foundation

Patient Safety Alert: Pharmacy Compounding

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Introduction

The Academic Medical Center Patient Safety Organization (AMC PSO) recently held its first Medication Safety Task Force (MSTF) collaborative convening session. Key opinion leaders from member pharmacy departments gathered to offer their expertise and opinions regarding the most current issues in compounding sterile preparations and patient safety. Attendees engaged in active discussions surrounding the most current pharmacy matters related to government and regulatory affairs, local hospital and physician practices, compounding source considerations, and identifying the next steps and challenges for compounding pharmacies, pharmacists, and health care clinicians. The AMC PSO's goal in sponsoring this meeting was to:

- Introduce pharmacy leaders in the AMC PSO to the values of convening sessions held under its auspices
- Openly discuss current issues in the compounding pharmacy sector and what can be done to improve patient safety and quality
- Propagate the natural progression of CRICO's established mission of helping health care providers turn credible patient safety data into effective action

Role of Compounding Pharmacies and Recent Patient Safety Issues

In the past, compounding pharmacies existed to serve the requirements of patients with particular treatment needs. Today compounding pharmacies have expanded the quantities and types of medications that they provide and as a result, have become a crucial part of the health care system in the United States. Among the many customized products they produce are; individualized medication formulations, doses that are not available commercially, preparations free of preservatives, dyes and allergens, and a wide array of specialty therapeutic and diagnostic agents for use by individual practitioners and researchers or by health care institutions (Drazen, Curfman et al. 2012).

Over the last two decades, several incidents of infectious microbes found in products prepared by compounding pharmacies have diminished the vital support that these institutions provide to patients with unique needs (CDC. 2002; Drazen, Curfman et al. 2012; Kainer, Reagan et al. 2012). Most recently, three lots of preservative-free methylprednisolone acetate (80mg/ml for injection), prepared by the New England Compounding Center (NECC) and designated for epidural and joint injections to treat pain syndromes, were found to be contaminated with *Exserohilumrostratum* (CDC. 2012; Kainer, Reagan et al. 2012) and other molds and fungi. Between May and September of 2012, approximately 14,000 patients received injections from the contaminated lots and the first reports of fungal meningitis complications, including basilar strokes, were recorded by the Centers for Disease Control and Prevention (CDC) in August of 2012. Because these cases of *Exserohilum rostratum* meningitis were scattered

across 75 medical centers in 19 states, it was not until late September 2012 that the CDC associated the vials of methylprednisolone acetate from NECC as a common factor among the patients. In early October of that same year, the CDC and Food and Drug Administration (FDA) recommended that all treatment facilities stop the use of any NECC product and on October 6th, NECC issued a voluntary recall of all the products that had been compounded at its Framingham, MA facility. As of March 10th 2013, there have been 48 mortalities attributed to the NECC contaminated methylprednisolone acetate and another 720 individuals who were injected with this drug are being treated for persistent fungal infections (CDC. 2012). As noted above, in addition to fungal meningitis, cases of posterior circulation stroke, spinal osteomyelitis and diskitis, epidural abscess and joint infections were also directly linked to NECC glucocorticoid injections (Kainer, Reagan et al. 2012).

All CRICO member institutions needed to contact and advise all patients who received any NECC injectable product to be on alert for manifestations of latent infections. Incubation periods could be on the order of several weeks which created a large number of patients requiring notification for prolonged periods of observation. Institutions established immediate educational programs for its physicians and staff, website updates, and contact numbers for patients receiving these cautionary letters. Hospital pharmacies increased their internal compounding capacity to offset the drug shortages. Fortunately, no other clinical infections have yet surfaced in Massachusetts. We believe we are beyond the incubation period of the likely pathogens, principally fungal in etiology.

In addition to the closure of NECC, the drug shortage problem was further exacerbated by the sudden, initially voluntary, shut down of Ameridose, a manufacturer and compounding pharmacy upon which many hospitals relied for pharmaceuticals. Contaminants were found in their products as well, and the ownership was the same as NECC's, thus casting concerns over attention to the sterile compounding standards compliance. No known clinical infections have yet emerged as a result of the Ameridose contamination.

These compounding crises also touched a wave of finger pointing accusations as to who had jurisdiction for safety inspection and monitoring: the state pharmacy board under the Department of Public Health or the FDA. The CDC was intimately involved in consulting on the investigations of the contaminated pharmacies and tracking the affected patients nationally with establishment of a patient registry.

To cope with the sudden exacerbation of drug shortages within the hospital industry, Massachusetts hospitals were allowed to apply for a DPH waiver to allow one hospital to compound specifically defined pharmaceuticals for another hospital within a structured system arrangement.

RESOURCES FOR PHARMACISTS, CLINICIANS AND ADMINISTRATORS

http://www.cdc.gov/hai/outbreaks/meningitis.html
See this web page for links to the information below:

- Advice to Patients (MedWatch)
- CDC Clinician Resources
    - CDC Health Alert Network (HAN) Update
    - List of States Affected
    - Information about Voluntary Recall of Ameridose Medical Products
    - http://www.neccrx.com/
- FDA Clinician Resources
    - Update on NECC Products
    - Report on Investigation of Conditions Observed at NECC
    - Patient Notification Letter
    - List of Recalled NECC Products
    - Impact of Ameridose Shutdown on Drug Supply

- American Society of HealthSystem Pharmacists
    - http://www.ashp.org/sterilecompounding
    - http://www.ashp.org/DocLibrary/BestPractices/MgmtGdlOutsourcingSterileComp.asp

COMPOUNDING SOURCE CONSIDERATIONS

As previously mentioned, a review of the published medical literature reveals a number of compounding pharmacy mistakes in recent years that have directly impacted patient safety. While a future AMC PSO convening session scheduled for the summer of 2013 will directly address guidelines for safeguarding against compounding pharmacy medication errors, there are a number of steps that clinicians, administrators and compounders can currently take to reduce the probability of such adverse events.

First, is for IV compounding pharmacy vendors and health care practitioners to be updated on the most current quality and regulatory standards. For example, in response to NECC's release of contaminated methylprednisolone acetate a number of regulatory and enforcement changes were made at both the state and national level, and more are being considered in the future. Both the state and federal regulatory agencies have newly proposed regulations and laws designed to improve oversight over compounding pharmacies at the local, state and federal levels. While certainly the pharmacies themselves need to be aware of these changes to implement them into their day to day workflow and IV compounding process, institutional practitioners should also be vigilant of new regulations because of the potential impact on such issues as medication availability, costs, or changes in formulations and their impact on patient care.

Clinicians and manufacturers should also keep themselves advised of the latest medication error alerts, as well as any exposure and contamination risks related to compounding pharmacies. Clearly, the faster such information is made available and shared among colleagues, the sooner any potential hazards to patients can be removed from the system.

Practitioners, administrators and production facility staff should also be aware of the costs associated with running compounding centers. As newer and better production systems are implemented to protect patients from medication errors, the costs of these special-order ligands and the time it takes to compound them may both increase. In addition, over the last ten years, there has also been an increased demand for products from compounding pharmacies which results in increased capacity demands upon their infrastructure. When compounding centers do expand their production facilities and staff to match increased demand, there have been many industry reports of difficulty recruiting and retaining staff with the high level of technical skills required. Lastly, in cases where expansion is not possible, increased demands have led some compounding pharmacies to greater outsourcing, which also increases cost.

BENEFITS AND RISKS OF OUTSIDE STERILE PRODUCT COMPOUNDING VENDORS

Due to drug shortages and patient-specific needs, many institutional pharmacies have developed greater reliance on outside vendors. For example, as many of the institutional pharmacies are not capable of obtaining products in large enough quantities to meet their needs, and as the impact of drug shortages exacerbates supply issues, these outside IV compounding centers are able to provide products to fill patients' needs. These vendors can also supplement existing sterile product room production capacity needs that are due to a lack of trained staff or space limitations at an institutional pharmacy. Outsource companies also frequently offer services beyond current in-house IV compounding capabilities and in some cases can extend "beyond use" dating which is attractive to most hospital pharmacies.

While it might be necessary to rely on vendors to achieve production goals, clinicians, pharmacists and administrators need to be aware that outsourcing also has risks associated with it. For example, compounding pharmacies and some of their associated regulatory agencies do not always have full control over the standard operating procedures and practices of outsourced production centers. This includes not being able to observe daily testing, cleaning and routine maintenance of vendor's facilities or any assurance that a compounding pharmacy is seeing the raw data from a vendor's quality report results.

COMPOUNDING PHARMACIES AS AN EVOLVING ENVIRONMENT

The primary response to patient adverse events related to compounding pharmacy errors has been an increase in regulations governing production standards and requirements from the appropriate state, local, or federal government agencies. These changes have generally included, but are not limited to, tighter guidelines and higher compliance criterions. Some regulatory branches have also sought improvements in clean room design and control as well as more stringent obligations in process validation and documentation. Operators and technicians at production facilities are also being required to comply with all applicable state and federal requirements.

Perhaps the most widely known is USP 797, a comprehensive set of regulations that govern many policies and procedures surrounding sterile compounding (United States Pharmacopoeia, 2004). USP 797 is endorsed by the The Joint Commission. USP 797 is considered to have an aggressive compliance schedule, and as such, has received great attention from hospital administrative, clinical, and pharmacy staff (United States Pharmacopoeia, 2004; United States Pharmacopeial Convention, 2004). However, its requirements also extend to architectural and environmental areas. Consequently, hospital design, construction, and operations professionals should also become familiar with it. It is designed both to cut down on infections transmitted to patients through pharmaceutical products and to better protect pharmacy staff in the course of their exposure to pharmaceutical manufacturing materials. Issued by U.S. Pharmacopoeia (USP), the regulation governs any pharmacy that prepares "compounded sterile preparations." Many pharmacies fit this description. Moreover, many large hospitals have several pharmacies—a main one and several satellite branches—that all fall under USP 797 domain (United States Pharmacopoeia, 20XX; United States Pharmacopeial Convention, 2004).

THE FUTURE OF COMPOUNDING PHARMACIES: A TIME OF TRANSITION

Several experts on the convening session panel were of the strong opinion that this is only the beginning of a major transition time for compounding pharmacies. Most notably, there is a founded concern that the current infrastructure in the compounding pharmacy sector will not be able to sustain a projected increase in product demand without increased regulatory oversight to insure that quality is maintained at the highest levels. It is believed that this transition will largely be fuelled by a significant increase in demand for special-needs medications over the next few decades. This increased use of special-needs medications is predicted to be driven by advances in science and technology that allow clinicians to prescribe more custom treatments which are individually designed for a specific patient's disease state. Complementing these technological advances are an aging population with a forecasted greater longevity and increased need of medical treatment.

There are already strong indicators of continuing drug shortages in the manufacturing sector (Chabner, 2011). This has been observed most notably in the lack of availability of some common cancer therapeutic agents as well as antibiotics, anesthetic agents, antihypertensive medications and common electrolyte solutions and vitamins

(Food and Drug administration, 2013). Generic chemotherapeutic drug shortages has forced physicians to prioritize patients, improvise standard regimens, choose unproven treatment options for patients with curable disease and threatened research protocols (Chabner, 2012). Generic drugs are usually sold for a very limited profit (regulated by Medicare legislation) and as such, are frequently produced as economically as possible or not at all. This often means using older and less efficient production facilities with limited inventories to reduce carrying costs (Chabner, 2011). In response, the FDA has taken steps to expand the drug supply. These include: hastening its inspection and approval of new or refurbished production facilities and streamlining methods to expedite approval of alternative domestic and foreign manufacturers. These improvements are on the manufacturing rather than the compounding side of the pharmaceutical industry.

SOLUTIONS FOR REDUCING COMPOUNDING PHARMACY ERRORS

With the projected increase demand for compounding pharmacy products, there are several steps that the manufacturing sector and regulatory agencies can take to decrease the probability of adverse events related to their products. As new facilities are built, or current facilities are expanded to meet new demand, ideally, these steps would involve the coordination and cooperation of production houses and government agencies in both their design and implementation. First would be the design and implementation of a well-developed quality management system across the industry. This system would also include elements resulting in the creation of experienced and trained personnel to fill the projected vacancies in the projected increased number of production centers. A second phase would involve the update of current good manufacturing practices for validated clean room design, conditions, procedures and maintenance. Third, in conjunction with this, would be the further refining of controlled production and quality assurance procedures and guidelines that evolve with the latest technological advances.

INFRASTRUCTURE COSTS WITH INTERNAL STERILE PRODUCT COMPOUNDING

To create a system of total internal compounding that will meet current and future demands, while also meeting patient safety standards, there needs to be substantial investment in space, staff, equipment, staff development and training and financial resources to manage the sterile IV compounding program. These costs will be even greater as the industry expands to create new infrastructure, or expands current facilities over subsequent years to meet the projected increased demand. A large portion of the fiscal overhead will be allotted simply for space and capital equipment. A substantial share of the costs will also be dedicated to the initial and ongoing training of staff. Funding will also have to be budgeted for continual environment, staff, and product testing and additional monies are required for the proper cleaning and maintenance of a sterile clean room environment. Many of the costs listed above are related to insure compliance with USP 797 regulations, as the work and ongoing operational costs associated with maintaining a USP 797 compliant facility are significant. Administrators, pharmacists, clinicians and patients can all anticipate that these increases in capital and operations investment will most likely initially result in increased costs for compounding pharmacy products whether done internally or purchased from an outside IV compounding vendor.

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