Considerations for Sourcing Premixed Pharmaceuticals

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Introduction

Healthcare providers want to make the best decisions for patients when sourcing pharmaceuticals. The many options available and variables involved with premix ready-to-administer drugs can be overwhelming, especially with critical care medications. Premix solutions can either be made in-house by the pharmacy cleanroom staff, supplied by a 503B outsourcing facility or supplied by a commercial manufacturer.

Hospital pharmacies supplying vital injections and infusions have a few options if compounding in-house is not appropriate due to the complexity of formulations, availability of resources and expertise, medication shortages, or delays in therapy that could result in negative patient outcomes. The following information highlights key considerations when sourcing premix pharmaceuticals, including quality assurance and safety, availability, accessibility, product labeling and cost considerations.

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Quality Assurance and Safety

Commercially manufactured pharmaceuticals must undergo rigorous testing and abide by Current Good Manufacturing Practice (CGMP) regulations established by the FDA.[1] Pharmaceutical companies invest significant resources in developing and commercializing their products. They have dedicated research and development teams, stringent quality control measures, and a comprehensive understanding of FDA regulations.

Commercially available pharmaceuticals must comply with the FDA review and quality assurance regulations, which is an ongoing process and helps ensure a high level of confidence in the quality of these medications.

Over the past decade the documented risks reported with compounded pharmaceuticals have been brought to light. The FDA has investigated many cases of serious patient injury linked to poor-quality compounded drugs.[2] In 2012, contaminated drugs compounded by a Massachusetts pharmacy led to more than 750 cases of infection and more than 60 deaths of patients in 20 states.[2] Due to this tragedy and many other adverse events including death linked to poor-quality compounded drugs, Congress passed the Drug Quality and Security Act (DQSA). DQSA was enacted on November 27, 2013.[2] The DQSA updated the Federal Food, Drug and Cosmetic Act (FD&C Act) regarding human drug compounding.[2] The DQSA added section 503B to the FD&C Act, establishing a new, voluntary category of compounders, also known as outsourcing facilities.[2] Outsourcing facilities are subject to CGMP requirements. They may distribute compounded drugs with an order for bulk supply (no patient-specific prescription provided) or for a patient-specific prescription.

The FDA recognizes that compounded drug products serve an important role for patients whose clinical needs cannot be met by FDA-approved products.[3] Pharmacies rely on 503B compounded drugs, especially during manufacturer medication shortages. It is important to remember that premixed solutions prepared in a 503B compounding facility do not undergo the FDA approval process like commercially manufactured drugs, so they are not evaluated for safety, effectiveness, or quality by the FDA before they reach patients. However, these facilities are still responsible for ensuring the safety and efficacy of their prepared sterile compounds but don't have the same high level of oversight. Refer to The Pew Charitable Trusts: U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-19 and you will see that incidents have not stopped occurring.[4]

Similar to the way it inspects manufacturing facilities, the FDA inspects outsourcing facilities according to a risk-based schedule.[2] Outsourcing pharmacies must also meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.[2] Drugs compounded in 503B facilities are subject to all provisions of the FD&C Act that apply to conventionally manufactured drugs, except they are exempt from labeling with adequate directions for use, premarket approval requirements and drug supply chain security requirements.[3]

There are many things to consider when choosing the best supplier, and pharmacies need to do their due diligence to ensure their outsourced providers meet the CGMP regulations for outsourcing facilities. If choosing a 503B compound, it is important to understand how the compound is being prepared in the 503B facility. For example, is the drug compounded using bulk ingredients, such as active pharmaceutical ingredients (API), rather than being prepared with commercially manufactured ingredients? And if so, is the final compound filtered or terminally sterilized?

The FDA puts limits on the use of bulk drug substances used in compounding.[5,6]

Outsourced compounding facilities may only use bulk drug substances that meet the following criteria[5]:

- Are used to compound drug products that appear on the FDA's drug shortage list at the time of compounding, distribution, and dispensing; or[5]
- Appear on the FDA's list of bulk drug substances for which there is a clinical need (the 503B bulks list).[5]

You can find more information on the list of bulk drug substances that can be used in compounding under sections 503B of the FD&C Act.[5] For a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), it must not be "essentially a copy of one or more approved drug products."[3] If a compounded drug product is identical

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or nearly identical to an approved drug that is not on FDA's drug shortage list at the time of compounding, distribution, and dispensing, the compounded product is essentially a copy, and an outsourcing facility may not produce it under section 503B.[3]

It is undeniable that 503B facilities are held to a lower standard than pharmaceutical drug manufacturers. Therefore, due diligence when sourcing from a 503B pharmacy is essential to protect our patients.[1]

Availability and Accessibility

Commercially manufactured pharmaceuticals are widely available and have longer storage and stability times than sterile compounds.[6-8] See "Sterile Compounding Versus Outsourcing Premixed Solutions: Making Informed Decisions" for more information regarding storage and stability. Manufactured products are accessible through extensive distribution networks and relationships with group purchasing organizations.

Drugs with longer stabilities allow pharmacies and healthcare facilities to have ready-to-administer drugs on or near nursing units or administration sites. Extended stability is crucial in critical care areas such as the emergency room, operating room, progressive care, and intensive care units where delays in critically needed medications may result in harm.

In a 2022 article published by the Institute for Safe Medication Practices (ISMP) titled Analysis Identifies Multiple Common Causes of Norepinephrine Errors, it was reported that many preparation and dispensing errors associated with norepinephrine, an essential and commonly used critical care medication, were related to high pharmacy workloads, hidden norepinephrine labels due to light-protective bags, and the pharmacy staffs' lack of knowledge about the urgency of dispensing norepinephrine.[9]

Product Labeling

503B outsourcing facilities are exempt from some of the labeling required of commercial drug manufacturers.[3,10] Commercially manufactured pharmaceuticals and 503B compounded drugs can be available in a range of strengths. Multiple strengths allow healthcare professionals to tailor medications to individual patients' needs. However, given that 503B outsourcing facilities are not held to the same requirements as manufacturers, this can be a problem.

According to the Institute for Safe Medication Practices (ISMP), "All of the hazards that had not yet resulted in errors were reported to ISMP and involved look-alike labels or drug names. Most reports noted that the packaging and labeling on various concentrations of norepinephrine infusions compounded by 503B outsourcers looked nearly identical."[9]

Different drug concentrations should have visually distinctive labels to help reduce dispensing and administration errors.[10]

Based on reports sent to ISMP and the FDA, ISMP reported that these providers inconsistently follow label guidelines required of manufacturers under FDA and USP standards.[10]

Cost Considerations

The costs of premixed compounds from 503Bs or commercially manufactured premixes may be offset by the savings related to decreased personnel expenses associated with time and effort, decreased equipment expenses and reduced risk of problems identified by the board of pharmacy or FDA, or expenses related to compounding errors or contamination issues. The extensive research, development and manufacturing processes that go into making a commercially available premix will ease the financial burdens pharmacies may face with compounding.

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Conclusion

Healthcare providers face numerous considerations when sourcing premix pharmaceuticals for their patients. One of the key considerations is quality assurance and safety. Commercially manufactured pharmaceuticals undergo rigorous testing and adhere to FDA regulations, providing a high level of confidence in their quality. On the other hand, compounded drugs have been associated with serious patient injuries and even deaths due to poor quality. The Drug Quality and Security Act (DQSA) was enacted to address these risks and establish outsourcing facilities subject to CGMP requirements. However, it is important to note that compounded drugs, including premixed solutions from 503B facilities, do not undergo the FDA approval process like commercially manufactured drugs. Pharmacies must also consider availability, accessibility, product labeling, and cost when sourcing premix pharmaceuticals. Outsourcing facilities can be a valuable resource, especially during medication shortages, but due diligence is necessary to ensure they meet CGMP regulations. Understanding the preparation process, such as the use of bulk ingredients and sterilization methods, is crucial in evaluating the safety of the compounded drugs. It is important to remember that commercially manufactured pharmaceuticals are FDA-approved and offer wider availability and longer storage and stability times compared to sterile compounds, making them the ideal option when insourcing.

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