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Improving Compounding Safety: New Regulations and Options for Institutional Insourcing

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In the wake of the New England Compounding Center tragedy, calls for greater controls over compounding pharmacies has spurred legislative activity in both the US Senate and the House of Representatives. State boards of pharmacy and the US Food and Drug Administration (FDA) have also increased regulatory scrutiny of these operations, resulting in the closure of additional compounding pharmacies in multiple states.[1-3] Growing concern over the continued supply of quality products have many hospital pharmacies either evaluating "insourcing" sterile compounding operations or already actively engaged in these processes. By controlling the supply, production, and quality themselves, hospital pharmacists feel more assured of safer and consistent patient care surrounding the use of these compounded sterile preparations.

Legislative Activity: Deciding Which Agency Has Oversight

Nationally, the Senate's Health, Education, Labor, and Pensions Committee (HELP) recommended that the FDA should be granted greater authority to regulate compounding pharmacies. The HELP Committee subsequently approved the Pharmaceutical Compounding Quality and Accountability Act (PCQAA).[4]

Under this proposed legislation 3 categories for sterile compounding would be created. The first category would cover traditional compounding by pharmacies, wherein products are prepared pursuant to individual patient prescriptions. This category would include hospitals and hospital systems where anticipatory compounding occurs for products in advance of a prescription for use solely within the hospital system. This type of traditional pharmacy compounding would continue to be regulated by state boards of pharmacy. The second category clearly establishes that drug manufacturers would "continue to be regulated by the FDA." The third category presents a new approach to regulate large-scale drug compounders. The PCQAA terms these operations to be "compounding manufacturers" and defines them as businesses that produce "sterile compounded drugs in advance of a prescription and sells them across state lines." Under the proposed Senate legislation, the door would be open for pharmacies to expand inhouse sterile compounding operations consistent with the requirements of the individual state boards of pharmacy.

Not surprisingly, the House of Representatives has adopted a different approach to this issue. The House Energy and Commerce Committee does not support giving the FDA more authority in this area, stating that it already has full authority to act to improve oversight and quality of compounded sterile products. To date, the House subcommittee seems more focused on continuing to analyze what went wrong with the New England Compounding situation and why the FDA did not respond more aggressively to previous quality and compliance issues that were documented for this compounding center.[5] In view of this approach to the problem, hospital pharmacies would still be open to moving forward with expanding their internal sterile compounding operations.

United States Pharmacopeia Chapter 797

Detail of the procedures and requirements for compounding sterile preparations are delineated in the United States Pharmacopeia (USP) in Chapter <797> Pharmaceutical Compounding: Sterile Preparations. It also establishes standards that are applicable to all practice settings in which sterile preparations are compounded. USP <797> seeks to protect patients from harmful large content errors and microbial contamination of compounded sterile products.[6] All of the USP chapters that fall below 1000

PRACTICAL IMPLICATIONS

Insourcing sterile compounding allows hospitals to gain greater control of this process. However, organizations embarking on this path should have a clearly defined plan to ensure compliance with all applicable regulations and standards to operate the safest possible program. The most efficient operational and physical options must also be selected to ensure that the best return on investment is realized. Done correctly, insourced sterile compounding can result in:

- Direct accountability for quality, product safety, and regulatory compliance
- Enhanced supply of products
- Expanded patient care options
- Improved institutional financial performance

can be enforced by the FDA, adopted by state boards of pharmacy, and surveyed against by The Joint Commission. In fact, a 2011 survey found only 17 states directly referenced USP <797> in part or in its entirety as part of their individual state practice requirements.[7] Many states are in various stages of retooling their regulations and how they will reference USP <797> as concern continues to escalate sterile compounding. It is also important to recognize that USP <797> is not a static document. The USP Sterile Products Expert Committee is continuously monitoring research and practice to suggest improvements to chapter <797> and revised chapters are periodically issued by the USP.

Pharmacies considering insourcing sterile products should be ready to adopt USP <797> as their minimum practice standard. This includes compliance with its recommended facility requirements, training, documentation, process control, and quality requirements.

One of the key elements for consideration by pharmacies is the risk level of the products that they will be compounding. USP <797> has established standards for low-, medium-, and high-risk compounding.

Low-Risk Level

- Simple admixtures compounded using closed system transfer methods
- Prepared in International Organization for Standardization (ISO) Class 5 Primary Engineering Control (PEC)
- ISO 5 PEC is located within an ISO 7 Buffer Room with an ISO 8 ante area
- In the absence of a sterility test, the maximum beyond-use dates (BUDs) are 48 hours room temperature, 14 days refrigerated, and 45 days frozen

Low-Risk Level With <12 Hour BUD

- Simple admixtures compounded using closed system transfer methods
- Prepared in ISO Class 5 primary engineering control (PEC)
- Compounding area is segregated from non-compounding areas but is not an ISO 7 Clean Room
- Administration must start no later than 12 hours after preparation

Medium-Risk Level

- Admixtures compounded using multiple additives and/or small volumes
- Batch preparations (eg, syringes)
- Complex manipulations (eg, total parental nutrition)
- Preparation for use over several days
- Prepared in ISO Class 5
- Located in ISO Class 7 buffer area with ISO Class 8 ante area
- In the absence of a sterility test, the maximum BUDs are 30 hours room temperature, 9 days refrigerated, and 45 days frozen

High-Risk Level

- Non-sterile (bulk powders) ingredients
- Open system transfers
- Prepared in ISO Class 5
- Located in ISO Class 7 buffer area with separate ISO Class 8 ante area
- Examples include products prepared from bulk, non-sterile components, or final containers that are non-sterile and must be terminally sterilized
- In the absence of a sterility test, the maximum BUDs are 24 hours room temperature, 3 days refrigerated, and 45 days frozen

The majority of products considered for insourcing by hospital pharmacies will fall in the medium-risk category. But high-risk compounding should be considered as well, given the ongoing national drug shortages. Many critical products may only be prepared by using non-sterile ingredients and terminally sterilizing the final preparation, which constitutes high-risk compounding. Additionally, any pharmacy considering insourcing sterile compounding should also be aware of Drug Enforcement Agency (DEA) requirements if controlled substances such as patient-controlled analgesia

syringes are being considered as part of the compounding formulary.

Good Manufacturing Practice

With USP <797> as the minimum standard for a hospital-based sterile compounding program, hospital programs should also consider working toward an enhanced level of quality using Good Manufacturing Practice (GMP). GMP is a production and testing procedure that helps to ensure a quality product with no harm to patients.[8] GMP compliance is mandatory for commercial pharmaceutical manufacturing. The majority of hospital pharmacies in Europe follow GMP for their sterile compounding. Hospital pharmacies considering insourcing sterile compounding should also explore GMP to safeguard their patients and reduce risk associated with this process to the maximum extent possible and to avoid any future need for major reengineering.

GMP guidelines are not prescriptive instructions on how to manufacture products, but rather are the principles that must be observed when hospitals build their quality programs and manufacturing processes. There will be many ways GMP requirements can be met. Each hospital will need to determine the most effective and efficient processes a GMP program would include. These should incorporate, but not be limited to, the following areas:

- Clearly defined manufacturing processes with specified validation to ensure consistency and compliance with hospital formula specifications.
- A change control process for any manufacturing changes to ensure that there is no negative impact on the quality of the drug and that all modifications are properly validated.
- Complete documentation for all procedures written in clear and concise language.
- Training and certification programs for all personnel working in this operation.
- Creation of an appropriate record-keeping system to demonstrate that all the steps required by the defined procedures are in fact taken and that the quantity and quality of the drug is as expected.
- A process to investigate, document, and act on any deviations to the standard protocol.
- Creation of a record-keeping system for manufacture and product distribution that enables the hospital to trace the complete history of any batch created.
- Development of a distribution process that meets state board of pharmacy and DEA requirements to minimize any risk to the quality of the drug products prepared.
- A workable system for accurate recalling of any batch of drug prepared.

Some Economic Considerations

While quality, safety, and supply are the primary issues driving hospitals to consider insourcing sterile compounding operations, economics can also play a part in the decision making. Larger healthcare institutions that outsource significant amounts of compounding and repackaging may experience costs that exceed a million dollars annually. With impending cuts to government reimbursement under healthcare reform, hospitals and health systems are looking for any and all opportunities to reduce their expenses. Even though insourcing sterile compounding generally requires an initial investment in capital and personnel, if done correctly these programs can provide a positive return on investment. In the past, a major cost was the construction of a USP-compliant ante room and clean room configuration. A traditional "fixed wall" clean room setup could easily require a million dollar investment for a larger operation. Currently, modular clean room options provide a quick and easy option that offers a "self-contained" solution that can be dropped into a warehouse type of space with minimal HVAC work. These modular options can also be expanded, reconfigured, and moved as requirements dictate, presenting a more versatile and cost-effective option for hospitals considering insourcing.

SUMMARY

With increasing regulatory oversight for sterile compounding and a limited ability to assure the quality of compounded sterile products obtained from external compounding pharmacies, many hospital pharmacies are moving to insource these products. In making this decision, hospitals are gaining greater control of the quality, safety, and supply of these products. Done correctly, hospitals can also improve patient care options and institutional financial performance.

However, organizations embarking on this path should have a clearly defined plan to ensure compliance with all applicable regulations and standards to operate the safest possible program. Organizations moving in this direction must determine their internal level of expertise and consider outside assistance, if necessary. The most efficient physical and operational options must be clearly delineated to ensure that the best return on investment is realized.

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