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Special REPORT

Practical Considerations for A Health System–Based 503B Sterile Compounding Program

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In today's health care marketplace, directors of pharmacy and hospitals are challenged to improve operational efficiency, quality, and financial margins while reducing risk through consolidation and centralization of services. As a result, there is considerable interest in centralizing compounded sterile preparations (CSPs), among other pharmacy functions and operations. Centralizing a health system's sterile compounding program, however, is not simply an additive effort. The requirements for this type of program differ significantly from a typical pharmacy admixture service. It is critical that the director of pharmacy and the hospital or health system fully understand the legal, regulatory, facility design, operational, workflow, automation/technology, quality and risk management components, as well as the financial requirements and organizational risks and benefits, before pursuing a centralized sterile compounding program.

Historically, many hospital pharmacy departments performed sterile compounding in a centralized IV admixture room for either local use or distribution across the health system. The introduction of outsourced compounding vendors to the marketplace over the past 2 decades has facilitated the health system transfer of both patient-specific and batch compounding for selected CSPs to these companies. Recent evolution of federal agency and state board of pharmacy regulations and interpretations of compounding, along with ongoing significant cost containment marketplace pressures, have renewed interest in centralizing the production of aseptic preparations at the hospital or health system level. However, in 2013, the Drug Quality and Security Act (DQSA) created a new classification of 503B sterile compounding facilities, referred to as outsourcing facilities, in addition to the existing pharmacies defined within Section 503A.[1] As the regulations for 503A pharmacies and 503B outsourcing facilities are being developed for implementation, the FDA is utilizing a draft guidance and policy approach instead of a formal rulemaking process, while operationally implementing the draft guidance as final.

The purpose of this article is to guide hospitals and health systems through the grueling process of determining what is best for their operations by 1) analyzing how a hospital or health system may compound medications within the facility by meeting the requirements of the very limited office use exception while complying with all other provisions within Section 503A; 2) alternatively registering as a 503B outsourcing facility and complying with all requirements found within Section 503B; or 3) outsourcing compounded medications from a 503B outsourcing facility. This article will take an in-depth look at the requirements for each alternative and provides hospitals and health systems with a checklist that may guide their decision-making processes.

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FDA Draft Guidance

Office Use Compounding

Specifically, regarding 503A pharmacies, the FDA has published guidance that prohibits a 503A pharmacy from compounding for a physician, a hospital, or other health care system for administration to patients in their office or clinical setting (often referred to as "office use compounding"), even if state laws allow such practice.[2] While only guidance, the FDA is implementing a complete prohibition by issuing Warning Letters stating that due to the fact that the pharmacy is compounding for office use, the pharmacy is in violation of the Federal Food, Drug, and Cosmetic Act. In doing so, the FDA has drawn a distinction between "anticipatory compounding" (ie, compounding in advance of receiving a prescription and staying within the facility where compounded) and office use compounding. Compounding is deemed anticipatory—and thus allowed by the FDA in limited amounts—on the condition that the compounded medication does not leave the facility where compounded.[2] As such, the moment when a pharmacist sends the compounded medication to the physician or hospital without first receiving a patient-specific prescription, the FDA defines that compounded medication as office use and in violation of the Federal Food, Drug, and Cosmetic Act, even where state law allows such practice.

503A Hospital and Health System Guidance

In addition, the FDA released draft guidance directed at hospitals and health systems that distribute CSPs to facilities on the hospital campus or to other facilities within the health system, such as other hospitals, clinics, infusion centers, or long-term care facilities.[3] The FDA proposes within the draft guidance a very limited exemption from the office use prohibition defined within 503A.[3] It is important to note that this exemption is not a complete exemption to all provisions within 503A but, to the contrary, a very limited exemption to only the office use prohibition that the FDA is implementing. Under the draft guidance, hospitals and other health care systems are proposed to be exempt from Current Good Manufacturing Practices (cGMPs) under a 503A classification if they meet 3 criteria:

1. The drug products are distributed only to health care facilities owned and controlled by the same entity and located within a 1-mile radius of the compounding pharmacy;
2. The products are only administered within the health care facility to patients of that facility; and
3. The health care facility meets all other provisions within 503A.[3]

503B Outsourcing Facilities

If the hospital or health system cannot meet the criteria, then the hospital or health system must either obtain CSPs from a 503B facility or register with the FDA under 503B and comply with all requirements within 503B, including complying with cGMPs for all compounded preparations, prohibition of commingling, reporting requirements, positive and negative lists, commercially available drug restrictions, and labeling requirements, and be subject to FDA inspections of its facility, processes, and documentation requirements (Table).[3]

Table. 503B Facility Requirements

Compliance Requirement	Explanation
Registration	A 503B facility must register with the FDA.
Labeling	A 503B facility must meet specific labeling requirements mandated in the statute.
Inspections	A 503B facility is subject to FDA inspections of its facility, processes, and documentation.
Commingling prohibition	A 503B facility cannot "commingle" at the same street address, same building, or in close proximity to a 503A facility. Violations cannot be cured by segregating or subdividing compounding within the facility.
Reporting	A 503B facility must submit biannual detailed compounded product reports and serious, unexpected adverse events reports, as well as perform subsequent investigation, follow-up, and documentation processes.
Positive and negative lists	Under the DQSA, the FDA, with the assistance of the PCAC, is charged with developing and maintaining a list of drugs that are approved for sterile compounding (ie, positive list) and 2 lists of drugs that have been either withdrawn from the marketplace or demonstrated as difficult to compound (ie, negative lists).
Clinical difference	The FDA requires documentation of "clinical difference" to compound commercially available drugs, whether or not the product is prepared from API or sterile-to-sterile compounding.
Release testing	The FDA requires batch-level sterility, potency, and endotoxin testing.
Stability studies	The FDA requires initial validation and stability testing to establish beyond-use dating. In addition, stability studies are required for every specific combination of drug product, brand, strength, diluent, and end container closure system. Stability tests must be cGMP-level "stability indicating" studies with a full method validation, and not simple potency tests extended over time.

API, active pharmaceutical ingredient; **cGMP,** Current Good Manufacturing Practice; **DQSA,** Drug Quality and Security Act; **PCAC,** Pharmacy Compounding Advisory Committee

Based on references 3-11.

503B Facility Implementation Checklist

As noted in this article, an evaluation of whether or not to propose and implement a 503B outsourcing facility sterile compounding program for a hospital or health system should include multiple facility, operational, clinical, financial, risk, and personnel expertise considerations. A suggested checklist of these considerations is presented below:

- Do you have the necessary location and space to create a centralized IV compounding facility? If not, is there an appropriate location to lease, purchase, or build a facility?
- Do you have the necessary facility and workflow design expertise for this type of facility? As noted above, this is not simply a "supersized" hospital IV admixture room service.
- Are you willing to compete for capital and operational expenses? A 503B program request might be perceived as infrastructure instead of a core activity, and likely would compete against available patient-facing or physician support program resources and other pharmacy program priorities.
- Can your organization effectively manage the changing legal and regulatory requirements for a 503B program, which can routinely affect the capital for and operating needs of a pharmacy program?
- Can you effectively recruit the necessary operational, quality, and risk management expertise? The best outsourcing facility leader may be a nonpharmacist with a significant pharmaceutical manufacturing or engineering background.
- Do you have the logistics infrastructure for a separate facility operation? If not, how will you receive and transport products within the hospital and health system facility?
- Do you have or can you develop backup supply plans for planned and unplanned facility outages and active ingredient shortages? Where will these resources come from to monitor and achieve these needs?
- Do you have the requisite compliance, legal support, and expertise to support a 503B program as federal and state legislation, rules, and regulations are continually updated?
- Are you ready for an increased number of inspections from your state board of pharmacy or the FDA? Can your organization effectively manage the long-term ambiguity and uncertainty of implementing and maintaining a pharmacy 503B program?
- Are you willing to endure damage to your organizational, professional, and/or personal reputation resulting from the public disclosure of a Form 483, Warning Letter, or adverse incident in the context of alternative marketplace options?
- Is the potential financial gain worth the capital and operating dollar investments?
- Is insourcing, partnership, or outsourcing the right decision for your organization?

503B Current Good Manufacturing Practices

The most recent draft cGMP for 503B facilities was published in July 2014 and has specific and detailed requirements, including[4]:

- facility design and air quality;
- control systems;
- environmental and personnel monitoring;
- equipment, containers, and closures;
- production and process controls; and
- batch sterility, potency, and endotoxin testing

Additional 503B Requirements

Furthermore, the draft guidance indicates that a 503B facility cannot "commingle" at the same street address, same building, or in close proximity to a 503A facility. The guidance also makes clear that violations cannot be cured by "segregating or subdividing compounding" within the same facility.[5] In addition, a 503B facility must comply with registration[6] and reporting requirements, including the submission of detailed compounded product reports twice per year[7] and serious, unexpected adverse events reports,[8] as well as perform subsequent investigation, follow-up, and documentation processes.[8]

The Pharmacy Compounding Advisory Committee

In addition, under the DQSA, the FDA, with the assistance of the Pharmacy Compounding Advisory Committee (PCAC), is charged with developing and maintaining a list of drugs that are approved for sterile compounding (often referred to as the "positive list")[9] and 2 lists of drugs that have been either withdrawn from the marketplace or demonstrated as difficult to compound (often referred to as the "negative lists").[10] As such, a 503B facility must comply with these lists. In order to compound commercially available drugs, the FDA is also requiring documentation of "clinical difference," from the prescribing practitioner whether or not the compounded preparation is prepared from active pharmaceutical ingredient (API) or sterile-to-sterile compounding.[11] Furthermore, a 503B facility must meet specific labeling requirements mandated in the statute.[5]

Inspections

During the past several months, there has been a significant increase in the FDA oversight of sterile compounding facilities, including hospitals and health systems. These inspections have led to the issuance of Form 483s, Warning Letters, and onsite FDA inspections.[12] The most common findings have been insanitary conditions based on cGMPs and violations of the FDA office use compounding prohibition. Although the history of FDA inspections has been largely risk based, it is the agency's stated intent to inspect all sterile facilities within 18 months.[13]

503B Program Considerations

Given the current direction of the FDA, a hospital or health system should consider several important factors before centralizing (or recentralizing) a sterile compounding program. The decision likely would require consideration of 503B licensure; as current regulations and guidance are continually updated, significant due diligence should be performed before proceeding.

Initial and Ongoing Capital Investment

Identifying, leasing or purchasing, and constructing a separate facility for a sterile compounding program—and the supporting facility and operating systems—that meets cGMP requirements will likely require substantial amounts of capital expenditure. Routine inspections and ongoing guidance from the FDA and other oversight bodies may require periodic changes to the cleanroom infrastructure, which can be expensive, disruptive to production, and may be difficult for a health care organization focused on patient care.

Operational Leadership and Expertise

The knowledge and experience needed to operate effectively in this environment may not be present in many health systems. Positioning a high-achieving pharmacist manager of a hospital's IV admixture service to lead a 503B operation may not be the best option. There are many regulatory differences between US Pharmacopeial Convention (USP) Chapters <797> and <800> on one hand and FDA-mandated cGMP requirements on the other.[14] An in-depth knowledge of pharmaceutical manufacturing environments as well as production, automation, and quality assurance processes is essential for cGMP compliance, successful inspections, and thus a successful 503B program.

Compounded Product Selection

Efficient operation of a 503B facility requires a focus on compounded product needs with significant utilization to achieve cost-effective batch production. Furthermore, unlike sterile product preparation under USP Chapter <797> and 503A guidance, a product compounded in a 503B facility must first be validated per cGMP standards and undergo lengthy and expensive stability studies. Additionally, both the FDA guidance on compounding commercially available products and the negative lists, in effect, prohibit the compounding of certain products.[15]

Product Batch Labor, Testing, and Validation Expenses

Labor for technicians and pharmacists who prepare and document each product batch, as well as drug, diluent, container, and consumable supplies, all contribute to the compounded product cost. The preparation of the cleanroom, hoods, and compounding automation before and after each batch represents additional expenses. Other costs include conducting batch-level sterility, potency, and endotoxin testing, as well as initial validation and stability testing to establish beyond-use dating. Stability studies must be done for every specific combination of drug product, brand, strength, diluent, and end container closure system, underscoring the importance of standardizing compounded product utilization. Stability tests must be cGMP-level "stability indicating" studies with a full method validation—which can be extremely costly—and not simple potency tests extended over time.[4] In addition, FDA Form 483 observations indicate that batch-level release testing is a commonly overlooked requirement.[12]

Operational Overhead Costs

The financial feasibility analysis for a 503B program should include expenses for routine environmental monitoring, testing, and analysis; management and consultation expenses for regulatory/compliance interpretation of FDA rules and guidance; and general operating and maintenance costs.

Risk Management and Public Relations

The results of FDA 503B operation inspections and supporting documentation are made available for public review. Generally, the FDA uses standard language in these documents, but it can be perceived as alarming. Hospitals and health systems must be prepared for the possibility of reputational damage from public disclosure of FDA inspections, corrective actions, or adverse patient events resulting from their insourced compounding program, particularly if commercial marketplace options exist.

Multistate Operation Considerations

Hospitals and health systems must address the challenges of variation between state laws and/or conflict between state and federal laws, rules, and regulations regarding interstate shipping, the classification and inspection of centralized compounding facilities, and the definition and interpretation of CSPs for office use. A hospital or health system considering the operation of a 503B outsourcing facility must perform due diligence to ensure that the intended provision of sterile compounded products can be legally and cost-effectively accomplished within its marketplace and patient locations.

Conclusion

The implementation of an FDA 503B sterile compounding program entails significant investment as well as potential risks and benefits. Pharmacy directors and hospital or health system executives should conduct careful due diligence to determine how best to meet their current and future sterile compounding needs.

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