

## **Sterile product optimization during the SARS-CoV-2 pandemic at a large academic medical center pharmacy**

**Abstract**

**Purpose.** We describe the optimization of sterile compounding processes in the face of supply chain shortages from 503B vendors throughout the SARS-CoV-2 pandemic. We describe changes in inventory management and sterile compounding workflow to address frequently changing medication availability.

**Summary.** Inconsistent supply chain and increased sterile compounding regulations resulted in an increased reliance on 503B pharmacies to meet patient needs. The challenge with using 503B pharmacies to replace in-house sterile compounding is the increased cost associated with the service, their inability to always meet demand, long lead times, and occasional quality control issues. The arrival of the SARS-CoV-2 pandemic exacerbated many of these issues, which resulted in inconsistency with our intravenous medications. Our organization developed a team of supply chain, pharmacy operations, and pharmacy leadership personnel to develop a process to close the gap between sterile products purchased from 503B pharmacies and those compounded directly in our pharmacy IV room. The team developed a systematic approach for management of products purchased from 503B pharmacy while simultaneously working to standardize sterile products and improve sterile compounding operations. The various changes and results are described.

**Conclusion.** Implementation of a new 503B procurement and management process, combined with changes to sterile compounding operations, resulted in a significant improvement in inventory levels, fewer stock outs, and improved pharmacy satisfaction.

**Keywords:** sterile compounding, 503B, inventory management, pharmacy operations

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## **Introduction**

Dealing with drug shortages is nothing new for hospital pharmacies. Recent years have seen more than 100 drug shortages per year, peaking in 2011 with 267 national drug shortages recorded.<sup>1</sup> Therefore, it is not surprising that hospital pharmacies have looked to 503B pharmacies to help alleviate the supply chain woes caused by drug shortages. Between fiscal years 2015 and 2017, more than 77% of U.S. Community Hospitals used 503B pharmacies to bridge inventory gaps.<sup>2</sup>

Manufactured sterile preparations are preferred over compounded products due to safety concerns<sup>3</sup>, however, not all medications are commercially manufactured. This combined with an inconsistent supply chain and increased sterile compounding regulations and guidance, including United States Pharmacopeia General Chapter <797> and State Board of Pharmacy rules, among others, have led to increased reliance on 503B pharmacies to meet demand for sterile preparations. While 503B pharmacies provide a valuable service, cost, inability to meet demand, long lead times, and occasional quality control issues make their use a potential point of failure in the pharmacy supply chain. The arrival of COVID-19 amplified these issues as 503B pharmacies succumbed to many of the same problems experienced by other businesses during the height of pandemic, namely unexpected lockdowns, and in some instances, shortages in personnel.

## **Hospital demographics/Setting**

Community Medical Centers (CMC) is a Health System that consists of four facilities in the Central Valley of California consisting of over 1000 combined beds. Community Regional Medical Center (CRMC) is the largest of the four facilities with 685 licensed beds. The hospital, however, frequently exceeds a daily census of 750 patients, occasionally over 800, and greater than 850 during periods of the COVID-19 pandemic. CRMC functions as a level 1 trauma center and has the only dedicated burn unit in the Central Valley. The Emergency Department (ED) receives more than 110,000 visits yearly, making it one of the busiest EDs in the state.

CRMC Inpatient Pharmacy consists of more than 60 pharmacists and in excess of 80 pharmacy technicians. The department is comprised of one main pharmacy with a large IV room physically separated from the main pharmacy, and four satellite pharmacies: ED, NICU, PICU, and ICU. Of the satellites, only the NICU prepares sterile compounds outside of the main pharmacy IV room.

In February 2020, after a long construction project, CRMC Pharmacy went live with a new state-of-the-art IV room with integrated vertical laminar flow zones (IVLFZ, aka “open architecture”)<sup>4</sup>. The new IV room offered significantly more space, as well as dedicated hazardous and non-hazardous ante and buffer rooms. The space is a considerable improvement over the previous IV room which has led to several improvements in operational efficiency and productivity.

## **Background**

In early 2020, CRMC experienced an increase in the number of COVID-19 SARS-CoV-2 patients admitted to the hospital. Many of these patient’s developed respiratory failure requiring mechanical ventilation, neuromuscular blockage, and high-level sedation with analgesics and benzodiazepines. As has been described elsewhere<sup>5</sup>, COVID-19 ICU patients at CRMC required unprecedented opioid analgesics and benzodiazepine infusions to maintain sedation. This, in turn, lead to increased inventory turnover, resulting in drug shortages, stock outs, and increased sterile compounding for previously purchased products. In a brief period, these issues presented a significant problem for the health system.

A COVID Pharmacy Resource Group (COVID-PRG) consisting of supply chain, pharmacy operations personnel, and pharmacy leadership was pulled together to identify the problems, assess the existing processes, and determine next steps to realize solutions.<sup>6</sup> The group determined that there were two potential response options: 1) CRMC pharmacy would cease purchasing 503B products and compound the items in house, or 2) CRMC would work to improve 503B management and restructure pharmacy compounding services.

Usage of 503B products at CRMC, as shown in **Table 1**, were in the thousands of bags per month. At the time of writing, sterile pharmacy compounding services at CRMC were not capable of producing such volume in addition to day-to-day operations. As such, it was determined that CRMC pharmacy was ill-prepared to take on in-house sterile compounding to meet ongoing patient needs. Therefore, option 1 was summarily dismissed, leaving only the option for improving 503B product management and restructuring CRMC pharmacy sterile compounding services.

ITEM	Usage in bags per month						
	DATE	Jul 2020	Aug 2020	Dec 2020	Jan 2021	Aug 2021	Sept 2021
Fentanyl 10 mcg/mL – 100 mL		1552	1727	1928	2631	2230	1936
Fentanyl 20 mcg/mL – 100 mL		1428	1443	1360	1617	1682	2309
Midazolam 1 mg/mL – 100 mL		312	362	506	737	692	754
Midazolam 2 mg/mL – 125 mL		233	235	228	384	439	559

**Table 1 – Drug usage during representative months of high COVID-19 activity.<sup>a</sup>**

### Problems and Solutions

Focusing on 503B product management, along with corresponding improvements to sterile compounding services, the COVID-PRG identified several areas of concern (“problems”) and proposed solutions (**Table 2**).

**Table 2:**

Problem	Solution
1. Inconsistent Inventory Management	Enhanced Inventory Management Procedures
2. Mismatched Product Options	Standardization of Product Options
3. High Complexity Product Change Process	Low Complexity Product Change Process

From the problems identified, it was clear that a systematic approach was needed for procurement and inventory management processes to meet increasing medication dispensing demands and respond to new and ongoing drug shortages.

#### **Problem 1: Inconsistent Inventory Management**

Following review of the 503B procurement process, it became obvious that inventory levels and lead times had to be adjusted to match real-world experience rather than expectations.

<sup>a</sup> Data taken from Epic Systems Slicer Dicer database

Unfortunately, product availability from 503B pharmacies has proven inconsistent over time, resulting in inefficiencies in product procurement. Procurement inefficiencies were further challenged by increased customer demand from increases in COVID-19 hospitalizations contributing to variable lead times.

503B inventory must be treated differently than commercially available products. Inventory levels and lead times must be adjusted.

### **Solution 1: Enhanced 503B Procurement and Inventory Management**

Various strategies for tracking and managing 503B inventory were discussed. Initial consideration was given to the use of automation and technology. However, these options were quickly dismissed as existing automation and technology offered no obvious advantages over using a manual process.

A plan for managing 503B inventory was devised. Inventory was assessed and new trigger points, aka PAR levels, were developed for all sterile 503B products with consideration given to longer lead times. New PAR levels for 503B products were significantly larger than their commercial counterparts. Once determined, inventory was rapidly increased to the new PAR levels.

Daily and weekly monitoring sheets were created for tracking 503B product inventory and usage. Daily sheets were used to physically count 503B inventory each morning (**Image 1**). Daily monitoring sheets were reviewed by the IV room pharmacist to establish compounding activities. Items that reached PAR level were re-ordered from 503B providers (preferred) or, when 503B products were unavailable or delayed, compounded by the CRMC IV room. When compounding was required, a 3-day supply was compounded based on anticipated needs of current usage patterns. Day shift IV room personnel were responsible for priority items, while passing low priority items off to the night shift to compound as time permitted.

Weekly monitoring sheets were used to communicate 503B medication order status, current inventory, and projected “days on hand” based on usage patterns (**Image 2**). Information provided was analyzed by pharmacy leadership for trends in usage patterns to ensure accurate and timely decisions. As usage patterns changed, inventory levels were adjusted accordingly.

Daily and weekly monitoring strategies significantly improved inventory usage and decreased surprise shortages.

### **Problem 2: Mismatched Product Options Between 503B Products and Insourced Pharmacy Compounded Products**

The small size and outdated design of the previous CRMC Pharmacy IV room led to poor sterile compounding productivity, resulting in heavy reliance on 503B pharmacies for several commonly used medications. Historically, when 503B products were implemented, the in-sourced pharmacy compounded product formulations were not adjusted to match. Differences included, but were not limited to, product volume, concentration, and final diluent.

For example, CRMC’s standard fentanyl infusion pre-pandemic was compounded at 10 mcg/mL with a final volume of 125 mL (1250 mcg/125 mL) in 0.9% sodium chloride. The CRMC formula was designed purposefully to minimize waste and streamline the compounding process. The 503B fentanyl infusion product had the same 10 mcg/mL final concentration, but a different final volume, e.g., 100 mL (1000 mcg/100 mL) in 0.9% sodium chloride. While obviously interchangeable based on drug, concentration,

and diluent, the hospital's electronic health record (EHR - EPIC)<sup>b</sup> saw them as distinctly different products, resulting in product "mismatches". Similar issues were with CRMC's smart pump libraries<sup>c</sup>. These differences prevented direct substitution of products purchased from 503B pharmacies for sterile products compounded by the pharmacy.

### **Solution 2: Standardization of Product Options**

Formulations for 503B and compounded products must match, i.e., same volume, concentration, and final diluent.

Formulations for compounded sterile preparations were reformulated to match those purchased from 503B pharmacies. New formulations were added to the pharmacies electronic formulary (Epic) and made equivalent for bar-code scanning and administrative purposes. Other areas requiring adjustment we also addressed – order sets, smart pump library, automated dispensing cabinet formulary, and so on.

### **Problem 3: Highly Complex Product Change Process**

The difficulty in moving between 503B and products compounded in-house stemmed from differences between the two sterile products. Unfortunately, switching between products required several inefficient and time-consuming steps (**Image 3**). While not necessarily insurmountable for a single item, at the height of the COVID-19 pandemic, CRMC saw unprecedented usage of 503B products. This coupled with increased supply chain woes, resulted in inconsistent availability and more frequent shortages.

Over time, CRMC became efficient at moving between products. However, being efficient with a bad process does not make the process efficient. Each changeover highlighted shortcomings of the process, such as lost time, occasional downtime, increased waste, confusion among pharmacy and nursing staff, and potential compromised patient safety. It became clear that the existing model was unsustainable. The COVID-PRG determined that a more efficient process was needed.

### **Solution 3: Formulation Harmonization Leading to Process Simplification**

The process of moving between 503B products and compounded products must be simplified as much as possible.

CRMC Pharmacy worked to streamline the process for switching between products purchased from 503B pharmacies and products compounded in the pharmacy IV room. The process should be seamless to providers, nurses, and pharmacy staff. Products, whether 503B or compounded in-house, should be interchangeable for providers, nurses, and pharmacy staff.

A review of the process (**Image 3**) found that product changeover could be significantly improved by eliminating inconsistencies between 503B products and those compounded by the pharmacy. Redesigning CRMC formulations to match those from 503B pharmacies for final volume, concentration, and diluent resulted in a considerably more streamlined process for moving between 503B and pharmacy prepared products (**Image 4**).

The COVID-PRG compiled a list of all 503B products and matching pharmacy compounded sterile preparations. Products were separated into low and high-use categories. Should 503B sourced products

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<sup>b</sup> Epic Systems Corporation, Verona, WI

<sup>c</sup> BD Alaris Pump Module, BD, Franklin Lakes, NJ

become unavailable, items in the low-use category would be compounded on a patient-specific on demand basis. Items in the high-use category would be compounded in small anticipatory batches, e.g., 3-day supply based on usage data.

These simple adjustments created a seamless transition between products purchased from 503B vendors and items compounded by the pharmacy. The result was an improvement in operational efficiency, workload balance, and patient safety.

### **Conclusion**

In summary, supply chain woes exacerbated by the initial phase of the SARS-CoV-2 pandemic coupled with an inefficient sterile compounding process, required a comprehensive plan to mitigate the issue. Development of a standardized process that included frequent and thorough inventory counts, review of drug usage data, as well as changes to sterile compounding formulas and procedures was integral for the 503B product mitigation strategy.

### **Disclosures**

The authors have declared no potential conflicts of interest.

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503B Inventory Item	Earliest Exp. Date	PAR (6-week supply)	Quantity on Hand	Batch 3-day supply ONLY IF NEEDED
Fentanyl 1000mcg/100ml NS		1400	689	100
Fentanyl 2000mcg/100ml NS		3800	3755	180
Midazolam 250 mg/125 mL NS		250	348	20
Midazolam 100 mg/100 mL NS		750	1446	60
Fentanyl 2 mcg/mL - Bupivacaine 0.0625% in 250 mL NS		280	200	20
Diltiazem 125 mg/125 mL D5W		36	46	6
Norepinephrine 8 mg/250 mL NS		960	345	60
Vancomycin 1.25 g/250 mL NS		720	520	48
Vancomycin 1.5 g/500 mL NS		500	190	36
PAR represents a rolling 6-week average.				
Batch when QOH reaches 2-day supply and 503B product not available.				
Batch size = 3-day supply based on current usage. See supervisor for questions.				
Check with buyers for questions regarding expected arrival of 503B products.				

**Image 1 – Daily 503B Sterile Product Monitoring Sheet**

503B Inventory Item	QOH as of xx/xx/xxxx	503B Pharmacy #1	503B Pharmacy #2	503B Pharmacy #3	503B Pharmacy #4	Weeks Supply	Weekly Usage (average)
Fentanyl 1000mcg/100mL NS (DRUG ID #)	689	x	x	N/A	x	3.0	233
Fentanyl 2000mcg/100mL NS (DRUG ID #)	3755	xx/xx order - Qty #960 ETA xx/xx	Recurring order #650 bags weekly. Begins xx/xx.	x	x	5.9	633
Midazolam 100mg/100mL NS (DRUG ID #)	1446	x	x	x	x	11.6	125
Midazolam 250 mg/125mL NS (DRUG ID #)	348	N/A	N/A	N/A	N/A	on demand	42
Diltiazem 125mg/125ml D5W (DRUG ID #)	46	Qty #36 bags ETA xx/xx	x	x	x	7.7	6
Norepinephrine 8mg/250ml NS (DRUG ID #)	345	x	Recurring order - 80 bags weekly	Recurring order #100 bags weekly. Begins xx/xx	x	2.2	160
Vancomycin 1.25g/250ml NS (DRUG ID #)	520	x	Recurring Order - 100 bags weekly	x	x	4.3	120
Vancomycin 1.5g/500ml NS (DRUG ID #)	190	x	Recurring order #80 bags weekly Supplemental order #400 bags ETA xx/ss	x	x	2.3	83
***Fentanyl Recurring order setup complete. ETA start date xx/xx/xxxx							
NOTES							
NOTES							

Image 2 – Weekly 503B Sterile Product Monitoring Sheet

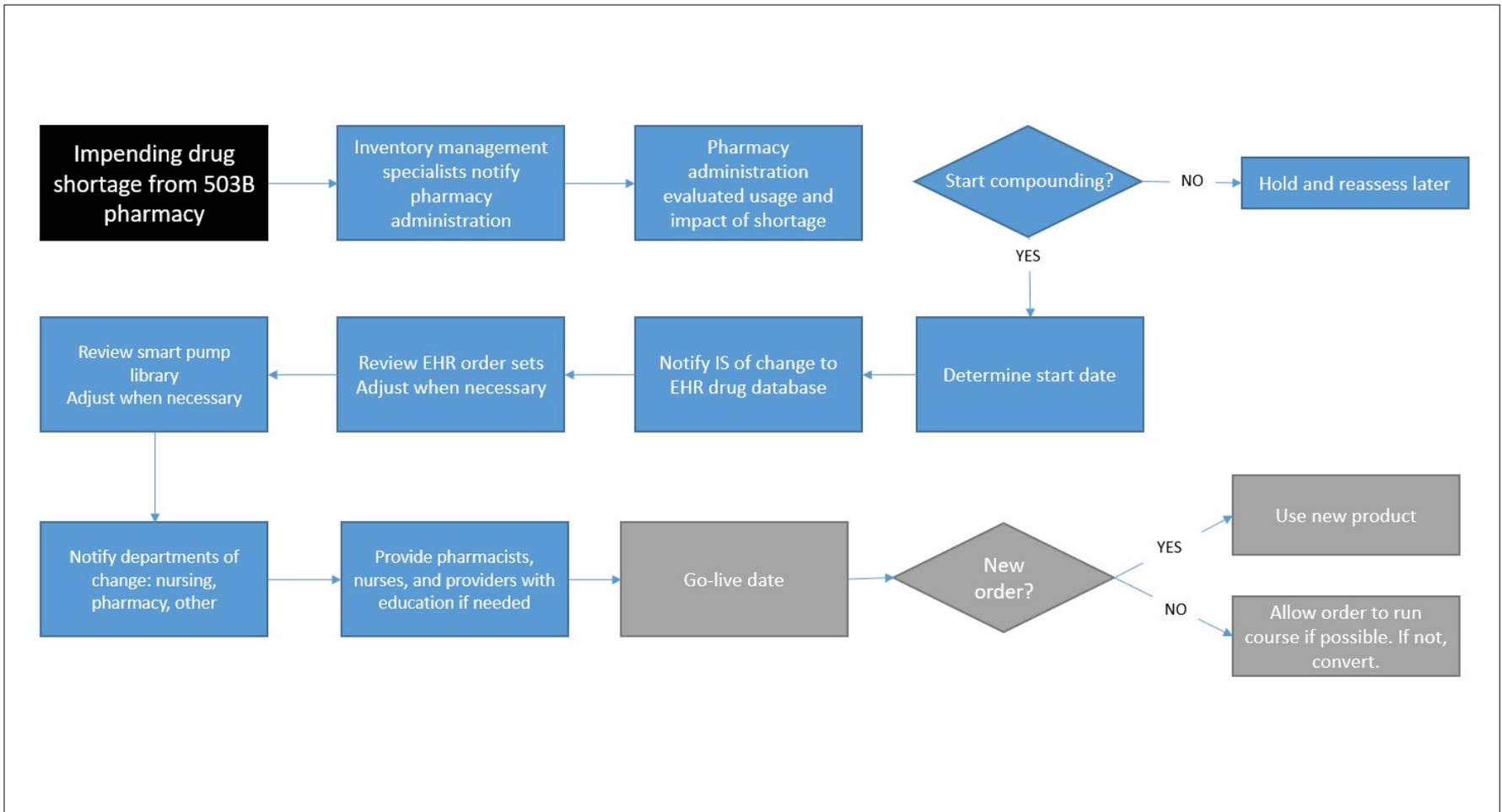


Image 3 – CRMC Pharmacy process for managing 503B pharmacy drug shortages before process changes.

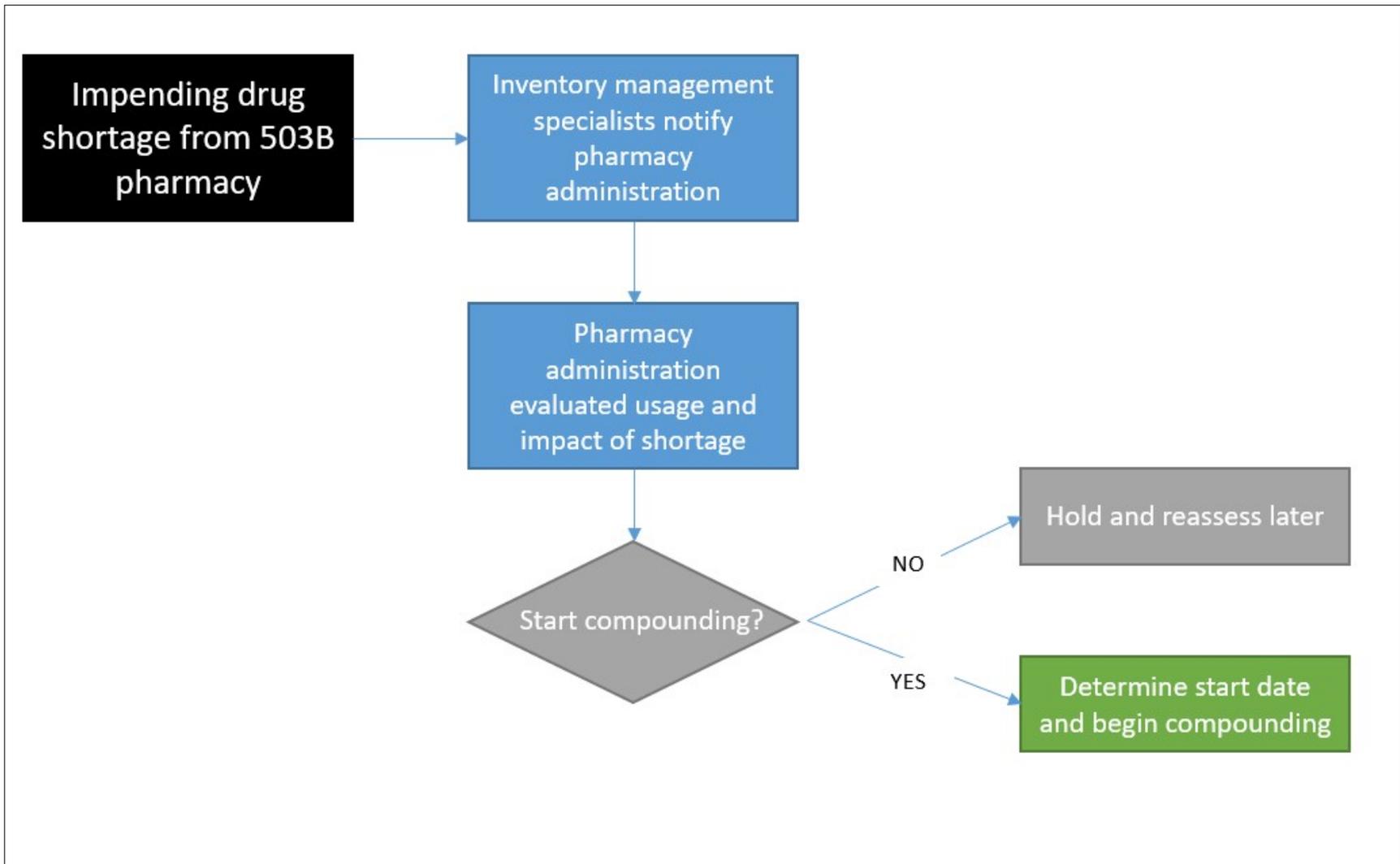


Image 4 – CRMC Pharmacy process for managing 503B pharmacy drug shortages after process changes.