



GUIDE:

503B Compounding - Regulatory Basis and Industry Good Practices for Outsourcing Facilities

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503B Compounding – Regulatory Basis and Industry Good Practices for Outsourcing Facilities

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Preface

As part of ISPE's commitment to our members, we monitor the regulatory environment and have noted the need for a dedicated focus on the pharmaceutical compounding community. This community, primarily 503B outsourcing facilities, has expressed the need for guidance that is more granular than what is currently available for aseptic facilities and that focuses on practices scaled to meet their needs. Although not typically viewed as traditional drug manufacturers, 503B compounders should operate similarly. Current Good Manufacturing Practices (CGMPs) for finished drug products are applicable to 503B outsourcing facilities and the FDA has cited 21 CFR 211 accordingly when outsourcing facilities do not comply.

To assist 503B outsourcing facilities, the FDA has issued numerous guidance documents on their current thinking regarding the regulations and laws. This ISPE Guide aims to help 503B facilities by combining information provided in the applicable regulations and guidances with good industry practices into one document. It covers basic CGMP concepts along with topics specific to 503B outsourcing facilities, such as default beyond-use dates and FDA's regulatory discretion. The references to original sources from the FDA and relevant organizations (such as ISO, PDA, and USP-NF) included in this ISPE Guide provide the reader with the rationale for implementing effective processes.

As of this ISPE Guide publication, the FDA's guidance document, Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act Guidance for Industry, is in draft form and subject to change.

The FDA states the following in their draft guidances:

"This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page."

It is recognized that the 503B regulatory environment is evolving, and this ISPE Guide reflects an understanding of it as of the publication date. The ISPE Pharmaceutical Compounding Community of Practice Steering Committee will continue to monitor the 503B regulatory environment and address changes as needed.

Acknowledgements

Recognizing the need for a dedicated focus on the pharmaceutical compounding community, ISPE engaged with multiple organizations with an interest in 503B outsourcing facilities resulting in this ISPE Guide.

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1 Introduction

The US FDA describes drug compounding as “the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient.” [1] Compounding may include the combining of two or more commercially available drugs already approved by the FDA. Compounded drugs, however, are not FDA-approved, which means the FDA does not verify the safety or effectiveness of compounded drugs through the traditional drug approval process via IND, ANDA, or NDA¹ submission.

1.1 Background

In 2012, the US Centers for Disease Control and Prevention (CDC), in collaboration with state and local health departments and the FDA, began investigating a multistate outbreak of fungal meningitis among patients that received contaminated preservative-free Methylprednisolone Acetate steroid injections from a compounding facility in Massachusetts. [2] These contaminated compounded injectable drug products were shipped across the country and, due to poor compounding practices, caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection, affecting patients in 20 states.

As a result of this crisis and the inspection findings, the need for federal oversight of compounding pharmacies was revealed. In 2013, the US Congress enacted Title I of the Drug Quality and Security Act (DQSA) [3], also known as the Compounding Quality Act, making important updates to the Federal Food, Drug, and Cosmetic Act (FD&C Act) [4] with respect to drug compounding. The DQSA added a new Section 503B [5] to the FD&C Act, establishing a new voluntary category of compounders called outsourcing facilities.

1.2 Current Situation

The Compounding Quality Act has had a positive impact on public health. Many compounders have implemented corrective actions to improve the quality of drugs produced. [6] A 2021 Pharmacy Times article concluded [7]: “503B compliance has raised the bar on quality and safety for patients and providers alike in the United States.... The benefit of the DQSA to the public is being realized.” However, more work is needed.

As noted in a May 2023 Pharmacy Times article [8]: “Pharmacies evaluating a 503B outsourcing service continue to face challenges. In 2023, supplier and supply chain issues emerged at...one of the country’s largest facilities, furloughing workers and facing possible closure after it received cGMP violations from the FDA. In addition, [another facility]...has shut down all operations.”

To assist outsourcing facilities with meeting the improved standards set forth in Section 503B [5], the FDA has clarified regulations by issuing several Guidance for Industry (GFI) documents specifically for 503B outsourcing facilities. The most notable GFI is the Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act Guidance for Industry² [9], which is in draft form at the time of this ISPE Guide’s publication.

Note: GFIs provide information on the agency’s current thinking on a topic. While not legally binding, GFIs play a critical role in helping firms understand the FDA’s expectations.

¹ IND = Investigational New Drugs, ANDA = Abbreviated New Drug Application, NDA = New Drug Application

² Referred to as draft GFI – CGMPs for 503B Facilities throughout this ISPE Guide.

There are also times when FDA issues guidances for a specific product or situation, such as a drug shortage, wherein CGMP requirements may be reduced to a certain extent to meet the public health demand. Examples of FDA guidances issued to assist compounding facilities in meeting the public health demand include:

- Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Issued April 2023) [10]
- Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency (Issued April 2020, Withdrawn March 2023) [11]
- Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (Issued March 2020, Withdrawn December 2021) [12]
- Temporary Policy Regarding Non-Standard PPE Practices for Sterile Compounding by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency (Issued April 2020, Withdrawn May 2023) [13]

503B outsourcing facilities are encouraged to monitor FDA activity, as the regulatory environment continues to evolve. For example, in May 2023 the FDA issued the GFI Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol [14]. This GFI was finalized for immediate implementation to *“alert pharmaceutical manufacturers, compounders...to the potential public health hazard of glycerin and other high-risk drug components contaminated with diethylene glycol (DEG) or ethylene glycol (EG).”* This guidance dictates additional testing requirements for products using the referenced excipients.

Another FDA initiative is the establishment of the Office of Compounding Quality and Compliance (OCQC) [15], whose aim is to protect patients from unsafe, ineffective, and poor-quality compounded drugs by evaluating incidents, compliance, regulatory and enforcement actions related to compounded drugs. The OCQC has developed and implemented the Compounding Quality Center of Excellence to assist outsourcing facilities and related stakeholders in their efforts to deliver high-quality drugs to patients by providing relevant and up-to-date information on:

- Laws and policies, oversight, and compliance actions
- Risk alerts
- Inspections, recalls, and other actions
- Compounding research
- Compounding information for states
- Registered outsourcing facilities
- 503B Bulks List [16]
- Trainings – both on-demand and live, instructor led
- Annual conferences
- Compounding Outsourcing Facilities Annual Study

1.3 Purpose

The purpose of this ISPE Guide is to provide detailed guidance on the regulatory considerations for 503B compounding outsourcing facilities and the current industry practices that should be followed. Discussions include the relevant portions of Section 503B [5] and CGMP regulations, focusing on the Quality System (QS) and its application throughout the process from incoming materials to facility and equipment, production controls, laboratory testing, and packaging and labeling operations. This ISPE Guide presents recommendations as described in the FDA's draft GFI – CGMPs for 503B Facilities [9]. This ISPE Guide also provides information on industry good practices and points readers to additional standards and guidances from other technical organizations such as the International Standard for Standardization (ISO) [17], Parenteral Drug Association (PDA) [18], United States Pharmacopeia or National Formulary (USP-NF) [19].

This ISPE Guide is intended for use by 503B compounding outsourcing facilities.

1.4 Scope

The scope of this ISPE Guide is 503B compounding outsourcing facilities. This Guide presents FDA policies and expectations as well as pharmaceutical industry standards to help 503B facilities compound and deliver safe, effective drug products. Pharmacy compounding under Section 503A of the FD&C Act [4] is out of scope.

Given the multitude of individual state regulations, the details on the rules of the State Board of Pharmacy (SBOP) and other equivalent state regulatory groups are out of scope.

While Drug Enforcement Administration (DEA) information on controlled substances is mentioned where relevant, not all DEA rules and regulations are discussed.

2 Regulatory Basis

2.1 Federal and State Oversight

Drugs compounded under Section 503B of the FD&C Act [5] are NOT exempt from following CGMPs, meaning 503B outsourcing facilities are subject to CGMP requirements in Title 21 of the Code of Federal Regulations (CFR) – Part 210 [20] and Part 211 [21]. Oversight and controls for the manufacture of drugs need to be established to ensure the quality of the compounded product as well as the protection of patients. The FDA recommends that 503B outsourcing facilities follow the guidance given in the draft GFI – CGMPs for 503B Facilities [9].

For 503B entities, the FDA is authorized to conduct inspections of the systems used by the facility and take appropriate regulatory actions (i.e., untitled letters, warning letters, recalls, or consent decree) when warranted.³ It is important to note that the FDA generally does not publish FDA-483 observations of drug manufacturers upon closure of inspections. However, for compounding pharmacies, particularly 503B facilities, FDA-483 observations may be posted on the FDA website after the inspection closes. Other regulatory actions such as consent decrees and risk alerts may also be posted [22].

Although 503B outsourcing facilities are primarily under FDA jurisdiction, the FDA's compounding program closely collaborates with state officials. 503B outsourcing facilities should also comply with the SBOP or other state regulatory governing group rules and regulations in the states where they manufacture and the states to which the finished drug product is shipped.

Most states have their own set of regulations and regulating groups for pharmacies and/or pharmaceutical manufacturing facilities. The National Association of Boards of Pharmacy (NABP) provides model language for state laws or board rules, known as The Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (Model Act) [23]. Each state passes laws or statutes that govern pharmacy practice, generally referred to as a state Pharmacy Practice Act (PPA). The PPA is the basis upon which the regulatory authority is established, usually known as the SBOP. The SBOP may elect to inspect 503B outsourcing facilities. However, each state has different laws/statutes, and the compounding pharmacy should be familiar with and follow the regulations of the SBOP for each state in which they manufacture and/or distribute the compounded drugs. See Section 2.4 for an overview of state pharmacy rules.

2.2 Establishment of Outsourcing Facilities

2.2.1 Definition

Section 503B(d)(4) [5] defines an outsourcing facility as:

“a facility at one geographic location or address that—

(i) is engaged in the compounding of sterile drugs;

(ii) has elected to register as an outsourcing facility; and

(iii) complies with all of the requirements of this section [Section 503B].”

³ FDA also has authority to inspect 503A pharmacies, especially in cases where there is suspicion that they are not functioning within the definition of a 503A pharmacy.

503B compounders are:

- Inspected by the FDA according to a risk-based schedule
- Required to report Adverse Drug Experiences (ADEs) that are categorized as both serious and unexpected per 21 CFR 310.305 [24] (see additional discussion in Section 3.10.2 of this ISPE Guide)
- Required to submit to the FDA twice yearly reports on the drugs compounded by the facility in the previous 6 months

Under Section 503B, compounding must be by or under the direct supervision of a licensed pharmacist. 503B outsourcing facilities are not required to be a licensed pharmacy. They are also not required to compound drugs only for an identified individual patient based on the receipt of a valid prescription. As such, they may distribute compounded drugs either based on a patient-specific prescription or in response to an order from a healthcare provider, such as a hospital. [5]

The FDA guidance, Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry⁴ [25], defines the conditions that a facility must meet in order to be considered as a 503B outsourcing facility. These conditions are outlined below to provide a clear definition of what would qualify a facility as a 503B outsourcing facility:

- The facility must be at one geographic location.
- The compounding must be done by or under the direct supervision of a licensed pharmacist.
- The facility must be engaged in the compounding of sterile drugs.
- The facility elects to register as an outsourcing facility.
- The organization cannot compound as a 503A pharmacy in the same facility.

The FDA has issued the following GFIs regarding the activities that an outsourcing facility may conduct:

- Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities [26]
- Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application [27]

2.2.2 Registration

Although registration as an outsourcing facility is voluntary, firms that make products without patient-specific prescriptions and compound sterile drug products may be inspected by the FDA, bringing them under the oversight of the agency. Some reasons a facility may choose to register as a 503B outsourcing facility are:

- Outsourcing facilities may want to compound approved drugs without obtaining ANDA or NDA approval for the compounded product (provided certain criteria are met, such as being on the Drug Shortage list [28] and meeting the requirements listed in Section 2.2.3).
- Outsourcing facilities may want to distribute compounded drugs to healthcare facilities and practitioners without first receiving a patient-specific prescription.

⁴ Referred to as GFI – 503B Facility Definition throughout this ISPE Guide.

- Healthcare facilities and practitioners often prefer to purchase compounded drugs from registered outsourcing facilities because the FD&C Act [4] subjects outsourcing facilities to CGMP requirements and federal oversight, including inspections on a risk-based schedule and specific adverse event reporting requirements.

The FDA issued two GFIs to help firms determine when registration is advised:

- Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act [29]
- Guidance for Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act [30]

2.2.3 Requirements

Section 503B [5] provides the set of conditions that 503B outsourcing facilities must meet in order to be exempt from the following:

- FD&C Act Section 502(f)(1) [4], which requires adequate directions for use in labeling.
- FD&C Act Section 505 [4], which states that no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection 505(b) (NDA) or 505(j) (ANDA) is effective with respect to such drug.
- Section 582 of the Drug Supply Chain Security Act [31], which outlines the requirements of the Enhanced Drug Distribution Security.

This means that outsourcing facilities not compliant with Section 503B conditions are subject to the requirements in these three sections. Thus, stating that an outsourcing facility is not required to file an ANDA or NDA is not exactly correct; however, if an outsourcing facility meets the conditions outlined in Section 503B to qualify as an outsourcing facility, the facility can be considered exempt from filing ANDAs and NDAs.

Section 503B [5] of the FD&C Act [4] states *“Sections 502(f)(1), 505, and 582 shall not apply to a drug compounded by or under the direct supervision of a licensed pharmacist in a facility that elects to register as an outsourcing facility if each of the following conditions is met:”*

1. Registration and reporting – The drug is compounded in a 503B facility that complies with the requirements outlined in the section “Registration of Outsourcing Facilities and Reporting of Drugs”.
2. Bulk drug substances/API⁵ – The drug is compounded from a bulk drug substance that appears on the 503B Bulks List [16] (designated for compounding in a 503B facility and published periodically in the Federal Register) or the drug product appears on the FDA Drug Shortages list [28] in effect under Section 506E at the time of compounding, distribution, and dispensing. In addition:
 - If an applicable monograph exists, the bulk drug substance must comply with the applicable monograph in the USP-NF [19] or another compendium or pharmacopeia recognized by the FDA.
 - The bulk drug substance must be manufactured by an establishment that is registered under Section 510 (including a foreign establishment that is registered under Section 510(i)).
 - The bulk drug substance must be accompanied by a valid Certificate of Analysis (COA).

⁵ Active Pharmaceutical Ingredient (API) and drug substance can be used interchangeably.

3. Ingredients (other than bulk drug substances) – If any ingredients (other than bulk drug substances) are used in compounding the drug, they should comply with the standards of the applicable USP or NF monograph, if such monograph exists, or of another compendia or pharmacopeia recognized by the FDA.
4. Drugs withdrawn or removed because they are unsafe or not effective – The drug cannot be compounded if it appears on the FDA-published list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness (21 CFR 216.24 [24]).
5. Essentially a copy of an approved drug – The drug cannot be compounded if it is essentially a copy of an approved drug.
6. Drugs presenting demonstrable difficulties for compounding – The drug does not meet the definition in Section 503B(a)(6)(A) and (B).
7. Elements to assure safe use – If the drug is compounded from a drug or bulk drug substance that is a component of a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use pursuant to Section 505-1, the 503B facility must follow the requirements in Section 503B(a)(7).
8. Prohibition on wholesaling – The drug will not be sold or transferred by an entity other than the outsourcing facility that compounded the drug, in accordance with Section 503B(a)(8).
9. Fees – The drug is compounded in an outsourcing facility that has paid all fees pursuant to Section 744K.
10. Labeling of drugs – The requirements for labeling compounded drugs and container, as outlined in Section 503B(10), are followed.
11. Outsourcing facility requirements – The drug is compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance with Section 503B.

Section 503B(d) [5] provides the following definitions:

- The term **compounding** includes *“the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug.”*
- The term **essentially a copy of an approved drug** is defined in Section 503B(d)(2) as:
 - A drug that is identical/nearly identical to an approved/ marketed drug not subject to Section 503(b) and not subject to approval in an application submitted under Section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under Section 506E at the time of compounding, distribution, and dispensing (Section 503B(d)(2)(A)); or
 - A commercially available drug product or a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to Section 503(b) and is not subject to approval in an application submitted under Section 505 that has a change needed for an individual patient, e.g., due to an allergy, difference in delivery (from solid dosage to liquid), or different dose (>10% difference from a commercially available dose).

Appendix A of the FDA GFI, Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act [32], can help in determining whether the compounded drug product fits the definition.

- The term **approved drug** means a drug that is approved under Section 505 and does not appear on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness (21 CFR 216.24 [24]).

- The term **sterile drug** means “a drug that is required to be sterile under federal or state law. a drug that is intended for parenteral administration, an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law.”

2.3 FDA Regulation of Outsourcing Facilities

2.3.1 Insanitary Conditions

Under Section 501(a)(2)(A) of the FD&C Act, a drug is deemed to have been adulterated “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.” [4] Insanitary conditions are a critical area of focus for the FDA, as this was a large contributor to the 2012 fungal meningitis outbreak discussed in Section 1.1 of this ISPE Guide. As such, the FDA issued the Guidance for Industry – Insanitary Conditions at Compounding Facilities⁶ [33], finalized in November 2020. The GFI – Insanitary Conditions gives specific examples of the insanitary conditions of concern from FDA for different areas of compounding, based on the types of products being compounded and the areas of the process or manufacturing. This topic is discussed in more detail in Section 5.4 of this ISPE Guide.

It is critical that compounding facilities are vigilant about insanitary conditions, as both “the facility and responsible individuals may be subject to several regulatory actions, including, but not limited to, a warning letter, seizure of product, or injunction. FDA may also recommend that the facility initiate a recall of some or all of its drugs and cease operations until the insanitary conditions have been adequately addressed.” (GFI – Insanitary Conditions [33])

2.3.2 Conforming to CGMPs

The draft GFI – CGMPs for 503B Facilities [9] provides the following background:

- Under Section 501(a)(2)(B) [4], a drug is deemed to be adulterated if “the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to ... [CGMPs] to assure that such drug meets the requirement of this [Act] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”
- Under Section 501 [4], the term CGMP “includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”

Note that even though 503B references CGMP requirements established in 21 CFR 211 [21], not all regulations under Part 211 are mentioned in the draft GFI – CGMPs for 503B Facilities [9]. Adherence to all CGMPs, even those not listed in the draft GFI, are required for 503B facilities; however, there are areas of enforcement discretion that may be granted if the facility follows the guidance.

A principle of CGMP that the draft GFI – CGMPs for 503B Facilities [9] states is that “quality is best assured by implementing appropriate controls throughout the manufacturing process, with end-product testing providing additional assurance.” End-product testing confirms product quality, but is not the only measure. This principle is known as building-in quality to the process/product, as opposed to testing quality into the product. In order to establish the appropriate level of controls, a risk-based quality approach may be utilized, with focus on the critical aspects of compounding, such as “control of raw materials, facility design and maintenance, production techniques and control, and personnel practices” and training. Evaluation of risk should also consider the compounding risk level/ compounded drug type as well as sterile/non-sterile compounded products.

⁶ Referred to as GFI – Insanitary Conditions throughout this ISPE Guide.

Expectations of CGMPs in any manufacturing or compounding facility include an oversight of quality, materials, facilities and equipment, production, packaging and labeling, and laboratory operations. These may not be specifically discussed in the draft GFI – CGMPs for 503B Facilities [9]; however, they should be followed as core concepts of CGMPs. They are further discussed throughout this ISPE Guide and include:

- Risk assessment procedures and processes, if a risk-based approach is used
- Defined/established responsibilities and procedures for quality oversight along with evidence of oversight (Chapter 3)
- Training requirements for all employees, consultants, and temporary employees of the 503B outsourcing facility (Section 3.3)
- Procedures related to manufacturing processes and controls, including batch production records, environmental monitoring records, cleaning, room clearance, aseptic processing/gowning/qualification process/training, compounding methods for sterile and non-sterile products, room access control, and room segregation (when applicable) (Chapters 3, 5, 6, and 7)
- Procedures related to Good Documentation Practices (GDP) (e.g., no sticky notes, no pencils, “if it is not written down, it didn’t happen”) (Section 3.4)
- Procedures related to training (Section 3.3)
- Procedures for, and evidence of, equipment cleaning, maintenance, and qualification (Section 5.3)
- Procedures for and records of programs for change management, complaint monitoring, and adverse events (Chapter 3)
- Established Quality Control (QC) program, including processes for assessment of Raw Materials (RMs), packaging, and labeling used for drug compounding (Chapter 8)
- Compliance with the defined QS as outlined in Chapter 3

2.3.3 Regulatory Discretion

The GFIs help compounders understand the applicable regulations for 503B facilities; however, they can also define instances where FDA will take regulatory discretion.

Appendix A of the draft GFI – CGMPs for 503B Facilities [9] outlines conditions under which FDA generally does not intend to take regulatory action regarding certain release testing requirements. Within this appendix, Table A outlines these conditions for non-sterile drug products.

For sterile products, the FDA generally does not intend to take regulatory action related to sterility testing *“if sterility testing is initiated before batch release (also see Table D in Appendix B for [Beyond-Use Dates] for products released without a completed sterility test).”*

The FDA also generally does not intend to take regulatory action for sterile products if the conditions described in Table B of Appendix A [9] apply. If multiple conditions apply, the least stringent option for each individual batch release test among the applicable conditions should be chosen from Appendix A.

Additionally, Appendix B of the draft GFI – CGMPs for 503B Facilities [9] describes conditions under which the FDA generally does not intend to take regulatory action regarding stability testing and expiration date requirements. See Chapter 9 of this ISPE Guide for additional information on stability and expiration date requirements.

2.4 State Pharmacy Rules Overview

According to federal law, 503B compounding facilities do not need to be a registered/licensed pharmacy even if they are receiving prescriptions for individual patients. However, depending on the state(s) where the 503B compounding facility manufactures and where they distribute product, there are additional state pharmacy rules and requirements that the facility should adhere to regarding registrations and/or licensing, which may include the need to register as a licensed pharmacy.

The NABP maintains a website [34] with links to SBOP websites that gives the most up-to-date information on the state laws with which facilities need to comply. However, as some states are regulated by a group other than a SBOP, 503B facilities should be familiar with the requirements of the regulating body in the states in which they manufacture and distribute. These websites typically provide information on the following topics, at minimum:

- How to obtain a registration/license and registration/license renewal
- Regulations to be followed depending on the role/company type – pharmacist/pharmacy, operator/compounding pharmacy, compounding facility, etc.
- General requirements including policies and procedures that should be put in place, inspections, appropriate storage, handling and security, notifications, etc.

The following should be posted in a prominent place at the facility:

- License details for the supervising licensed pharmacist(s)
- SBOP license(s) or similar, if required/applicable

Many state rules and regulations are linked to the federal (CGMP) regulations, although some may be associated with the following USP chapters [19]:

- USP <795> Pharmaceutical Compounding – Nonsterile Preparations
- USP <797> Pharmaceutical Compounding – Sterile Preparations
- USP <800> Hazardous Drugs – Handling in Healthcare Settings

Beyond the many regulations, there are three state requirements that apply to the majority of states that regulate 503B facilities:

- Facilities must be licensed/registered in the state in which they are located.
- Facilities must be licensed/registered in the states to which they distribute compounded medications.
- Compounding of preparations must be performed by, or directly supervised by, a licensed pharmacist.

3 Quality System

3.1 Introduction

Registered 503B outsourcing facilities are subject to CGMP inspections by the FDA. [5] CGMP regulations define the minimum requirements needed during the processing, testing, packaging, and distribution of drug products. In order to comply with CGMPs, 503B outsourcing facilities need to establish a QS. An important aspect of the QS is the establishment of the Quality Unit (QU) that is independent from other units within the outsourcing facility's organization. The QU's responsibilities include approving procedures, investigating deviations, and reviewing records. The QU is responsible for approving and releasing or rejecting incoming components, packaging materials, and final compounded products.

Another critical aspect of the QS in 503B facilities is the control and use of written procedures that provide clear, concise instructions for performing tasks. 503B facilities are required to have Standard Operating Procedures (SOPs) for compounding drug products as well as for executing activities performed as part of the QS. Procedures standardize the facility's processes and are a key tool in training personnel.

The draft GFI – CGMPs for 503B Facilities [9] uses a risk-based approach to CGMP requirements that focuses on control of RMs, facility design and maintenance, production techniques and controls, and personnel practices as the most critical aspects in ensuring quality for all drug products. Other CGMP requirements described in the appendices of the draft GFI are based on the FDA's regulatory discretion, i.e., their likelihood of taking regulatory action depends on the level of risk (high or low) of the compounding activities conducted at the 503B outsourcing facility. FDA regulatory discretion is discussed in Section 2.3.3 of this ISPE Guide.

This chapter provides information on key aspects of the QS with greater emphasis on the sections mentioned above as the focus of the FDA. While the QS can be scaled based on the organization's preferences and the type of drugs being compounded (such as high-risk or lower risk drugs), all aspects of the QS discussed in this chapter should be present in a 503B outsourcing facility.

3.2 Quality Responsibilities

3.2.1 Quality Unit

In CGMP manufacturing, the QU is frequently split into two sections: Quality Assurance (QA) and QC. The draft GFI – CGMPs for 503B Facilities [9] applies the phrase “quality control unit” to describe the responsibilities associated with the overall QU. As either approach is acceptable, this ISPE Guide uses the QA and QC naming convention and division of responsibilities, recognizing that 503B manufacturers may combine QA and QC functions under one QU to carry out quality assurance activities.

A QU needs to be established to provide independent, unbiased oversight of 503B compounding activities. QA activities are required to ensure compliance with the applicable 21 CFR 211 sections (§§ 211.22, 211.180, 211.192, 211.198) [21]. Quality oversight of production activities is necessary to ensure that the final compounded drugs are of the appropriate Strength, Quality, Identity, Purity, and Potency (SQIPP). Additionally, the QU is responsible for ensuring proper controls are in place during manufacturing of both sterile and non-sterile products so that the finished drug products are free from microbiological contamination.

The FDA requires the QU to maintain an organizational reporting structure independent of any functions outside of Quality. [35] Quality should not have a reporting structure, directly or indirectly, to production and should not take on any aspect of production activities for compounded drugs. The QU should be adequately staffed to ensure that sufficient Quality oversight can be provided to the facility and compounding activities. This may be accomplished through outsourcing activities, such as auditing, testing, etc., to qualified vendors/consultants.

The role of the QU is defined in 21 CFR 211 Subparts B, E, F, G, and H [21]. The required procedures describing the Quality framework for the outsourcing facility and QU responsibilities include:

- Establishment of written procedures for production and process controls that must be followed and documented at the time of performance. The procedures must be *“designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.”* (§ 211.100)
- Establishment of controls to prevent cross-contamination in the event that powder drugs are used in production. *“FDA recommends the physical segregation of areas in which powder drugs are exposed to the production environment.”* [9]
- Establishment and approval of drug product (§ 211.110), component (§ 211.84), and labeling (§ 211.122) specifications. This includes drug products compounded at the outsourcing facility and any drug product that is under contract by another company (§ 211.22).

Note: In the event that a drug product is manufactured, processed, packed, or held under contract by another company, the QU must provide oversight for these activities.

- Ensuring that adequate laboratory facilities are available for the testing and disposition of drug product, drug product containers, closures, in-process materials, packaging materials, and labeling. (§ 211.22)
- Establishment of sterility assurance activities for sterile products and of microbial quality for non-sterile products at the outsourcing facility as well as contract companies used for manufacturing any stage of the drug product (§ 211.113 and 211.167)
- Establishment of sampling procedures, including sampling tools, sampling process, and number of samples needed per lot (§ 211.160)
- Ensuring that each drug product batch, including drug product, drug product containers, closures, in-process materials, packaging materials, and labeling, is sampled, tested/examined, and reviewed against approved release specifications and approved/released prior to use in drug compounding [9]
- Establishment of warehousing and distribution procedures as outlined in 21 CFR 211 Subpart H
- Establishment of procedures for adding sterility results to compounding records in the event that sterile product is released with pending sterility testing results [9]
- Review of compounding operations, on an annual basis at a minimum, to determine if specifications or control procedures require revision. This review should include identifying trends and evaluating quality indicators for the following [9]:
 - Finished product testing results
 - Results of Environmental Monitoring (EM) and personnel monitoring
 - When water is used as a compounding component, results of water system testing for water that is purified/processed on-site or results of testing from the supplier/outsourcing facility for water purchased as an incoming component
 - Media fills/process simulations performed since the last review
 - Operations to determine if procedures are being followed and proper aseptic techniques are employed during drug compounding

- Complaints, nonconformances, failures (such as for system or equipment), and variation in yield
- Discrepancy and failure investigations along with identification and oversight of corrective actions, including changes implemented to prevent recurrence, with regard to any of the following as based on the draft GFI – CGMPs for 503B Facilities [9]:
 - Compounded drug evaluation testing, such as “sterility testing, endotoxin levels, content assay, impurity assay, particulate matter, reconstitution time, content uniformity, preservative content testing, microbial enumeration, tests for specified microorganisms, and weight, volume, or counts.”
 - Unexpected results or trends, such as Out of Trend (OOT)
 - Validation/revalidation failures (e.g., process validation, sterilization, depyrogenation)
 - Stability failures including drug product degradation and failures determined to be caused by factors other than degradation
 - EM and personnel monitoring results that exceed action or alert limits
 - Failures associated with aseptic techniques and procedures
 - Failures of drug product, RMs, components, or packaging/labeling
 - Process deviations or equipment malfunctions that involve critical equipment (e.g., sterilizers, homogenizers, mixer, lyophilizers)
 - Complaints that indicate possible compounded drug contamination or any complaint that identifies potential patient risk, such as particulate matter, precipitating particles, changes in drug appearance or color, etc.

3.2.2 Release Testing

The draft GFI – CGMPs for 503B Facilities states [9]: “[p]rocedures for release must be established to ensure that each batch of a drug product is not released until the following have been completed (see §§ 211.22, 211.165, 211.167, 211.192):

- *An appropriate laboratory determination has been conducted to ensure that each batch of a drug product conforms to specifications.*
- *A review of environmental and personnel monitoring data, if applicable, has been conducted to ensure that manufacturing conditions were acceptable during production of the batch.*
- *Associated laboratory data and documentation have been reviewed by the quality control unit, and they demonstrate that the drug product meets specifications.*
- *A designated qualified individual from the quality control unit has authorized final release.*

Under certain conditions described in Appendix A [of the GFI – CGMPs for 503B Facilities], FDA generally does not intend to take action against an outsourcing facility regarding [these] release testing requirements.”

3.2.3 Laboratory Controls

Contract laboratories must be qualified under the QU supplier/vendor qualification program. The draft GFI – CGMPs for 503B Facilities [9] states: *“When an outsourcing facility seeks the services of a contract facility to perform all or part of the testing of a drug, the outsourcing facility’s quality control unit is responsible for approving and rejecting drugs tested by the contractor.”* Refer also to the FDA GFI Contract Manufacturing Arrangements for Drugs: Quality Agreements [36].

Note: FDA recommends that contract facilities performing testing of a drug have ISO 17025 [37] accreditation.

3.3 Training

Per 21 CFR 211.25 [21], each person engaged in or supervising the manufacture, processing, packing, or holding of a drug product should be qualified to perform the assigned functions through any combination of education, training, and experience. Training should be provided in the area in which the employee works, and each employee should be trained according to CGMPs as outlined in 21 CFR 211. CGMP training *“shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.”*

The training record for a given individual should include a Curriculum Vitae (CV), when available, that provides information on their education (including training classes) and prior experience relevant to their role at the compounding facility. In addition, the training record should contain information on each training completed at the facility or externally, including the trainer name, course name/unique number, and the type of training, e.g., computer, in-person, job specific/On-the-Job Training (OJT).

Per 21 CFR 211.25, personnel training should be related to the operations that the employee will be conducting in their role. Likewise, each person supervising someone in operations must also be trained on any operations that they are responsible for supervising.

Per 21 CFR 211.34, consultants brought into a facility must also have the appropriate training or experience for the role they are performing. The outsourcing facility is required to maintain records of the name, address, and qualifications of the consultants, and what service they provided.

Training must be conducted by a qualified individual who possesses a combination of education, certification, or experience in the topic in which they provide training. The effectiveness of the training should be evaluated through assessment testing or via trainee demonstration of the skills, with documented evidence of the completed assessment. The skillset demonstration needs to be performed in the presence of a qualified trainer and should be properly documented. If performance issues indicate that the trainee did not appropriately learn the skillset, then retraining as well as evaluation of the individual’s appropriateness for the role should be conducted; the trainee shall not perform any function for which the training indicates that the trainee did not properly learn the skillset.

Training for personnel working in sterile processing should include an overview of the concepts of sterility, including the reasons a product is required to be sterile, aseptic gowning, and techniques required to ensure the sterility of the product. Job-specific aseptic training may employ demonstration of proper aseptic techniques followed by proficiency evaluations and written assessments. A gowning certification training program is recommended as well as additional OJT to ensure aseptic personnel are qualified to perform their job functions. An employee should not conduct aseptic processing prior to demonstrating proficiency in aseptic compounding activities per established aseptic training requirements, including satisfactory performance in a media fill. [9] Retraining on sterile aseptic techniques should be considered for inclusion in the annual training program.

3.4 Document Control

The policies, procedures, and instructions that define a manufacturer's QS requirements are subject to document control procedures per 21 CFR 211 Subpart J [21]. 503B compounded drugs manufacturers should have governing written procedures that describe the controls in place for issuing, approving, storing, and maintaining the CGMP documentation. Such controls include:

- Document lifecycle, including preparation, review, revision, approval, document obsolescence, and archival
 - Document development, review, revision, and approval to ensure that documents are accurate and meet the requirements of the QS
 - Periodic review of the documents to assess if changes/updates are needed to comply with current practices with respect to regulations, the firm, and the industry
 - Document obsolescence and archival to ensure that obsolete or superseded documents are retained per the record retention policy and managed to ensure that only the current and approved version is available for use
- Assignment of unique numbers as well as version numbers, effective dates, and change history
- Distribution and maintenance of documents to ensure that documents are made available for use to applicable personnel at the point of use

3.5 Change Management

The change management (change control) process for 503B compounded drug manufacturers should be consistent with the requirements presented in ICH Q10 [38] and the FDA guidance, Quality Systems Approach to Pharmaceutical CGMP Regulations [35]. Change management provides a system by which changes are evaluated prior to implementation to ensure that a change does not negatively affect the SQIPP, safety, and/or efficacy of the compounded drug product. The QU maintains primary responsibility for the direction and oversight of the change management process.

Within the governing procedure(s) for change management, the process should include documentation of the following:

- Reason for the change
- Type of change (permanent or temporary)
- Evaluation of the proposed change
- Impacted documents, products, processes, specifications, training needs, validation, etc. after change implementation
- Timing of the proposed change
- Personnel responsible for making, implementing, and approving the change, as well as other activities such as procedure, training, and specification updates and timelines for change activities and implementation

3.6 Deviations and Investigations

A deviation (sometimes referred to as a nonconformance) is an event in which the compounded product or any materials, components, labels, etc. depart from established procedures, processes, instructions (batch records), specifications, or established standards. Deviations can occur at any time during compounding including processing, filling, packaging, and testing/holding of a component, RM, intermediate, or drug product. Deviations may have an impact on the SQIPP or safety of a product and, therefore, each event is to be investigated and documented.

An investigation includes the documented review of the occurrence to determine if there is any impact to the safety and/or SQIPP of a product(s) due to the event. Once the need for an investigation is identified, it should be completed in a timely manner. It is recommended that an investigation team be assembled that, based on need, include appropriate members of technical, development/R&D, Quality, and operations/manufacturing (along with individuals involved in the event where possible) to ensure a complete investigation. Key parts of an investigation include:

- Clear, concise, and factual statements of the event, including date of occurrence, person that discovered the event, and product (RM/component/API/in-process/finished/equipment/batch record/SOP step) details; avoid opinion and conjecture
- Immediate actions taken to remediate the event/issue until the investigation is completed, when applicable
- Identification of all impacted products, lots, processes, equipment, etc.
- Review and analysis of the event in a logical manner, including a scientific evaluation of all laboratory data and testing related to the event, which must include a review in accordance with data integrity principles
- Evaluation of similar products/processes to determine if they need to be included in the investigation
- Historical review of related events to determine recurrence/trend
- Identification of a root cause and establishment of appropriate corrective action and preventive action to prevent recurrence
- Statement of regulatory review and notification, when required
- Documented Quality review and approval of the completed investigation report, with Quality as the last approver prior to closure

Written procedures must be in place to govern the deviation investigation and documentation processes. The deviation procedure designates responsibilities for the stages in the investigation with required reviewers and approvers. It is good practice for the procedure to include root cause analysis techniques such as generation of fishbone diagrams and application of 5 Whys. The deviation investigation should also document an assessment of impact to product currently on the market or that may have been recently dosed to a patient; this may involve application of risk assessment tools.

Laboratory investigations must be initiated when an Out of Specification (OOS) testing result is obtained. Each OOS must be investigated to determine its root cause; where some potential root causes may be ruled out, the investigation should document the sound scientific reasoning providing support for doing so. OOS results determined to not be associated with laboratory error must be further investigated to determine if anything in the manufacturing/compounding process contributed to or caused the event. Further information on investigating OOSs can be found in the FDA GFI Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production [39].

3.7 Corrective Action and Preventive Action

The Corrective Action and Preventive Action (CAPA) program is one of the most important and essential parts of the QS. The procedures governing the CAPA program prescribe the requirements for addressing the identified cause of a nonconformance and determining the actions to be taken in order to prevent recurrence. Additionally, CAPAs may be identified as the result of continual improvement, an audit, walkthrough, or other means. The identified preventive actions may help prevent further deviations by implementing/revising procedures, adding additional steps, clarifying batch records/procedures, identifying trends, etc. The CAPA program extends to all areas of the company, including production and process control, design, purchasing, laboratory, and audit findings.

Written procedures must be in place for the CAPA process. Once the need for a CAPA is identified through a nonconformance investigation or other means, the CAPA process should start in a timely manner. Key parts of the CAPA report include:

- Clearly defined problem statement
- Assessment of all potential impacts, including product, process, validation, equipment, documentation
- Assessment of previous CAPAs implemented for similar/like issues and effectiveness
- Assessment of the risks
- Action plan that details the required tasks to be completed to appropriately address the issue identified and prevent recurrence
- Defined effectiveness checks after implementation of the action plan to ensure that the CAPA addressed the issue and prevented recurrence

3.8 Batch Production Record and Batch Record Disposition

Batch production records are known by many names in the pharmaceutical industry, such as Master Batch Records (MBRs) and Batch Records (BRs)⁷. In 503B outsourcing facilities, they may be called Master Formulation Records (MFR). MBRs are required for each process created for a compounded drug and need to document all stages of the compounding process. MBRs may be one large document inclusive of the entire process or broken down by major processes (for example, dispensing, compounding, filling, labeling). Any of these terms and approaches are acceptable, as long as the site's written procedures are followed.

From a master production record, BRs are issued with a unique identifying number for each batch/lot⁸ of the compounded drug product to be manufactured. BRs are controlled/issued by the QU as needed for batch production and are required for each lot of compounded drug to document all stages of the compounding process. The BR should minimally include the following, in accordance with 21 CFR 211.188 [21]:

- An accurate reproduction of the approved master production or control record, issued and signed by the QU and assigned a BR number.
- Documentation of each significant step in the manufacture, processing, packing/packaging, or holding of the batch completed, including:
 - Date of manufacture

⁷ Within this Guide, MBR and BR are considered equivalent and used interchangeably.

⁸ Within this Guide, batch and lot are considered equivalent and used interchangeably.

- Identification of person performing or checking each significant step
- Defined parameters and specifications for each significant step, as established during validation/qualification activities
- Identification of major equipment and lines used
- Identification of each lot of component, containers/closures, or in-process materials used
- Weights/amounts of components used
- Defined limits for actual yield and theoretical yield at appropriate phases of compounding
- Inspection of the packaging and labeling area before use
- Complete labeling control records, including copies of all labeling used
- Sampling performed
- In-process and laboratory control results
- Any investigation that may have been initiated
- Results of inspections performed during compounding

All completed BRs are required to be reviewed and approved by the QU to ensure that the batch has been manufactured to all established specifications and procedures prior to release and distribution (21 CFR 211 Subpart J [21]). This review should include review of QC raw data, QC audit trails, and audit trails for any automated equipment used for compounding, where applicable. Any discrepancies or failures of the batch or component to meet specifications must be thoroughly investigated. Based on review of all this information, the QU determines the final disposition of the batch/lot.

3.9 Logbooks

Many outsourcing facilities record data/information in logbooks, which are maintained at the source of the work. Issuance, usage, and archival of logbooks should be governed by an SOP and referenced in the BR as appropriate. Completed logbook pages should be reviewed by the QU, preferably prior to batch release, to ensure that all entries have been properly documented and that the entries in the logbook, audit trail, and executed BP align with each other. Facilities often use logbooks for the following areas:

- Equipment logs: Used to record calibration activities (when required), usage dates and batch numbers, API, cleaning method and date, and who performed compounding and cleaning, at a minimum. For example, scales and balances may require daily verification, and these activities may be noted in a logbook or per other proceduralized method. Equipment logs are maintained in the designated area with the piece of equipment.
- Room logs: Used to record what batches numbers were processed in the room, including details such as processing dates, API usage, equipment used, cleaning method, date and who performed cleaning, who performed compounding, who entered/exited the room during compounding, at minimum. Room logs or a separate logbook should be used as a room sign-in during operations in cases where badge access is not required/traceable. Room logs are maintained in the designated area for the room.
- Laboratory notebooks: Issued and used per the procedure governing laboratory notebook control and usage.
- Other logs: Used to account for RM components, container/closures, etc.

3.10 Complaint Handling

A complaint is a notification by internal or external customers regarding the quality or purity of a product. It may be provided as either written or verbal communication, expressing dissatisfaction with the product. Written procedures for handling written or verbal customer complaints should be in place per 21 CFR 211.198 [21]. Key points for customer complaint evaluation include:

- Clear, concise written procedures and extensive training of personnel performing the complaint review/investigation to ensure proper, consistent complaint handling.
- 100% of all complaints received must be documented, including receipt of any returned sample or photographs depicting impacted sample/nature of the complaint. As much information as possible should be gathered at the intake call and if possible, the complainant's name and contact information should be obtained for follow-up if needed.
- All complaints need to be investigated to confirm if the complaint is valid. If the complaint is not verified due to lack of information, such as no sample provided, missing lot number, etc., then documentation should include the reason for not completing an investigation as well as the responsible person making the determination that the complaint does not require investigation.
- All complaint records are to be maintained for 1 year after the expiration date of the drug product or 1 year after the complaint was received, whichever timeframe is longer. The file should be maintained at the drug product manufacturing site or be readily available during an inspection.
- The QU should perform the final review and approval of all completed complaint write-ups, including those complaints that could not be investigated due to lack of information/samples. Per § 211.198, *"Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with §§ 310.305 and 514.80..."*
- There should be a process to determine the cause of the defect and evaluate the impact of the defect on other lots of products. In cases where a serious and unexpected ADE has occurred, it must be reported to FDA (see Section 3.10.2 of this ISPE Guide).
- A designated file/repository for compounded drug complaints should be maintained at the compounding, processing, or packaging facility.

Manufacturers typically focus first on assessing risk to the customer and on verifying whether a quality problem exists, the source of the problem, and the appropriate correction and/or corrective action. However, it is important to ensure that all information related to any specific product line is aggregated so that adequate investigation and data analysis may be performed to determine if any trends exist. This is the challenge that most manufacturers face: ensuring that all information representing a complaint is properly documented and handled, regardless of whether the information comes from customers external or internal to the manufacturer.

3.10.1 Complaint Investigation

During complaint investigation, it is important that an adequate complaint investigation is performed to determine if the complaint can be confirmed and verified, to discover the root cause of the complaint, and to identify the corrective action. If the complaint is not verifiable, the rationale for not performing an investigation needs to be documented. The extent of the investigation should be directly proportional to the magnitude and risk of the reported issue. These investigations may involve a review of records (i.e., BRs, risk management files, complaint files, or other QS records) to assess risk and determine if deviations occurred in the compounding process or if similar failures have occurred with the product in question or other related product lines. Failure investigations may also involve testing returned or retained samples, auditing suppliers, or other actions appropriate to identifying the root cause(s) for the complaint.

For customer complaint closure, the investigation package should include:

- Root cause summary
- Indication of whether the product was replaced and, if applicable, a reference to the order number
- Final complaint category
- Indication of whether a CAPA is required and, if applicable, a reference to the CAPA number
- Date that the investigation was approved or date of complaint closure
- Adverse event report if the complaint was determined to be a serious and unexpected adverse event (see Section 3.10.2 of this ISPE Guide)
- Summary of communication with the complainant including contacting the complainant to provide a follow-up summary of the investigation

Complaints should be trended annually. If a negative trend is observed (i.e., if the rate of complaints is increasing), an investigation must be opened to determine the root cause of the negative trend and a CAPA may be required. When the complaint is identified as a potential adverse event (see Section 3.10.2 of this ISPE Guide), the complaint should be investigated promptly to meet the 15-day FDA reporting requirement. (21 CFR 310.305 [24])

3.10.2 Adverse Events and Reporting

An adverse drug experience (ADE, also called an adverse event) is *“Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.”* [24] (21 CFR 310.305) ADE complaints should be documented and promptly addressed as they can result in serious impact to patient health and legal liability. The FDA requires manufacturers, packers, and distributors of compounded marketed prescription drug products to establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their drug per Section 503B(b)(5) of the FD&C Act [5] and 21 CFR 310.305. [24]

21 CFR 310.305 further defines the following ADE terminology:

“Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.”

“Serious adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.”

“Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity... ‘Unexpected,’ as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.”

Reporting ADEs alerts the FDA of potential quality problems that may be linked with a particular product or an issue with standard conditions or processes at the 503B facility. ADE reporting helps the FDA distinguish between quality issues limited to a particular facility or broader issues related to components or APIs used in compounding. Additionally, ADEs may be reported for issues unrelated to compounded drug quality, such as a patient's underlying medical condition.

Many companies employ a call center for intake of ADEs; however, anyone told about a serious or unexpected ADE is responsible for ensuring it is reported to the FDA. For example, if an employee is told by someone that they had an ADE that qualifies as a serious and/or unexpected ADE to one of the company's products, the employee should take down the information and report it to the group responsible for collecting this information for the facility. As much information as possible related to the ADE should be obtained by the drug compounder/intake call employee. ADE reporting requirements state that serious and/or unexpected ADEs must be reported as soon as possible, but no later than 15 calendar days from initial receipt of the information by the person whose name appears on the label. The information to be provided in the report are detailed in 21 CFR 310.305 [24], with key points as follows:

- Information related to the identifiable patient
 - Whenever possible, this should include patient code, contact information, age or age range, gender, and weight. Sometimes it is not possible to obtain all of this information, but significant effort should be made to obtain as much information as possible.
 - Patient identity must not be revealed when submitting reports to the FDA of an adverse event. In order to keep this information anonymous, the patient is assigned a unique identifying code in lieu of including information such as the patient's name or address. A cross-listing with the patient information should be maintained at the intake.
- Identifiable person that reported the serious and/or unexpected ADE, even if this person is the patient.
- Suspect drug information (all available information)
- Specifics of the serious and/or unexpected ADE
- A copy of the Drug Product Labeling in electronic format

In some cases, a medical event that does not result in the above outcomes could also be determined to be a serious ADE upon medical review per the GFI, these are called "important medical events."

"Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse" (21 CFR 310.305(b) [24]).

It is considered industry best practice that an appropriate medical professional evaluates ADEs to determine if the ADE reported is a serious and/or unexpected ADE.

All serious and/or unexpected ADEs associated with use of the compounded drug product must be reported by the outsourcing facility. When reporting the event, the facility must submit the report as a 15-day "Alert Report." A copy of the compounded drug product labeling (all labeling components) must accompany the ADE report. Information regarding the four data elements should be actively investigated by the outsourcing facility after receiving the information about the ADE:

1. An identifiable patient

2. An identifiable reporter
3. A suspect drug
4. A serious adverse event

In the case of a death, outsourcing facilities should also provide any available information on what led to the death, consult the FDA Guidance for Industry: Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act [40] for additional requirements.

The outsourcing facility should promptly investigate adverse events that are the subject of a 15-day “Alert Report.” It should *“exercise due diligence to obtain information about any of the remaining elements and should keep records of its efforts to obtain this and other relevant information (e.g., dates of discussions with the reporter to determine how many patients experienced a particular adverse event or dates of discussions with a health care facility to obtain contact information for an identifiable person who purports to have knowledge about the patient, adverse event, or drug involved).”* [40]

After the initial adverse event report is submitted, these reports should be promptly investigated (see Section 3.10.1). A follow-up report must be submitted to the FDA within 15 calendar days of receipt of any new information or as requested by FDA. Additionally, the outsourcing facility should report any new information concerning the initial report, as it is obtained, as the information could assist the FDA in investigating an adverse event. If additional information is not obtainable, the outsourcing facility should maintain records of the steps taken to seek the additional information. Reporting on adverse events should continue as long as the outsourcing facility continues to obtain new information regarding the suspect compounded drug product or the adverse event. [40]

Per 21 CFR 310.305 [24], records of adverse events reported to regulatory authorities, including raw data and any correspondence related to the adverse event, must be maintained for a minimum of 10 years and access to the records must be provided to the FDA for review, copying, and verification. The regulations acknowledge that the report does not mean an admission that the drug caused or contributed to any adverse event. [40]

3.10.3 Field Alert Reporting

According to the draft GFI – CGMPs for 503B Facilities [9], 503B outsourcing facility must have written procedures specifying the actions required if the drug product fails to meet a criterion for sterility:

- Immediate notification of the sterility failure to facilities that received the drug product, along with any appropriate information and recommendations to aid in the treatment of patients to which the compounded drug product was administered.
- The notification is documented.
- Written notification to the FDA within 5 working days of the discovery of the sterility failure via email to: OFAAlertReport@fda.hhs.gov.

In accordance with 21 CFR Part 211 [21], investigations initiated for deviations, complaints, or adverse events concluding that the product quality of a batch or batches was compromised should be evaluated as to whether a field alert/recall is warranted. See Section 3.11 for information on recalls.

3.11 Recalls

A product recall is a voluntary action that may be taken to remove potentially violative product distributed to the market that may present a risk or injury to public health based upon internal data (i.e., stability data, quality investigation) or external data (complaint). A product recall may be initiated on the company's own initiative, by FDA request, or, in the event that a firm's actions are not effective in recalling the product, FDA may consider taking other appropriate actions. In March 2022, FDA issued the Guidance for Industry and FDA Staff – Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C [41] to establish recall initiation procedures, ensure timely identification of and response to product problems that might lead to a recall, and to promptly issue recall communications and press releases or other public notices.

Companies should have recall policies and procedures for making a recall decision, documentation required for the recall, and a process to initiate a product recall or correction. The FDA provides a website of recall resources: www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/recall-resources.

The FDA reviews a firm's overall recall strategy including associated recall notifications and assigns a recall classification level. The recall classification is the numerical designation assigned based on the relative degree of health hazard presented by the product being recalled. The levels as stated in 21 CFR 7.3 are as follows [24]:

- *“Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.*
- *Class II is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.*
- *Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.”*

The company should initiate an investigation to determine the root cause of the product issue and determine the corrective actions to take to eliminate the issue. The firm should not delay the initiation of the voluntary recall pending investigation. The FDA should be updated on the progress and resolution of the investigation periodically (between 2 and 4 weeks, depending on the relative urgency of the recall) until the recall has been terminated. Recall status reports should include (21 CFR 7.53 [24]):

- Dates and method of customer notification
- Number of customers notified
- Number of customers that responded
- Quantity of recalled product returned or otherwise accounted for
- Number of customers that did not respond
- Estimated time frame for completion of the recall
- Details of the company's recall effectiveness checks

It is good practice to also include:

- Root cause of the problem that resulted in the recall
- A summary of the CAPA to prevent future occurrences of the problem, specifically focusing on:
 - Actions taken pertaining to the recall strategy
 - Investigation results
 - Underlying cause(s)
 - Actions taken to prevent recurrence

Termination of the recall can be requested when it is reasonable to assume that the recalled product has been removed and proper disposition or correction has been made. (21 CFR 7.55 [24]) A final status report and document of recalled product disposition should be provided to the FDA Division Recall Coordinator, after which the FDA will consider formal termination of the recall.

4 Supply Chain and Materials

4.1 Introduction

Section 503B [5] states that a compounder must use bulk APIs and components that comply with the standards of an applicable USP-NF monograph, if a monograph exists. In addition, as stated in Chapter 2, only bulk APIs listed on the current 503B Bulks List [16], which is updated periodically, can be used for compounding drug products, unless the drug product appears on the Drug Shortages List [28] in effect under Section 506E at the time of compounding, distribution, and dispensing. Per 21 CFR 210.3 Definitions [20], a component is *“any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.”*

21 CFR 211, Subpart E [21] sets requirements for the selection, purchase, receipt, handling, and use of APIs, drug products, materials (excipient and processing aides), and components (e.g., Container-Closure System (CCS)). These requirements apply to all compounded pharmaceutical products prepared by a 503B compounding facility.

4.2 Supplier/Vendor Qualification Program

Supplier/vendor selection should be made with preference given to drug products, components, and packaging and labeling materials manufactured at FDA-registered facilities that comply with the USP-NF monograph for the items to be purchased. API and drug products must be obtained from an FDA-registered facility or CGMP facility. It is preferable that the selected components have a USP-NF monograph.

Once a supplier/vendor is selected, the outsourcing facility should enter into a quality agreement with the supplier/vendor of each drug product, component, and packaging and labeling material that will be used in the final compounded product, as discussed in the FDA GFI Contract Manufacturing Arrangements for Drugs: Quality Agreements [36]. The quality agreement should minimally contain:

- Description of the testing performed prior to release for each lot and shipment
- Specific tests required on the COA to meet the compounding specifications for the material
- Defined responsibilities for incoming drug product/component sterility, when applicable
- Requirements for supplier/vendor notification to the compounding facility of changes to material testing specifications, test methods, manufacturing location, or manufacturing process
- Immediate notification of a quality issue of any item shipped or located at the outsourcing facility

The process for vendor qualification should be established by the outsourcing facility and documented to ensure that materials are purchased only from qualified suppliers/vendors. Approval by the QU of vendors and the signed quality agreements are the minimum requirements for supplier/vendor qualification. Additionally, a combination of the following is recommended:

- Supplier/vendor audits, where the frequency of audits is determined by the criticality of the vendor
 - For example, suppliers of sterile components should be audited more frequently than suppliers of packaging components
- Supplier/vendor material testing prior to supplier/vendor qualification

- Annual testing by the compounding facility of materials received from supplier/vendor
 - For service providers, an annual evaluation of services provided is used, where applicable (see Section 6.4 for more information on reduced testing for materials from qualified vendors).
- Periodic evaluation of deviations associated with the supplier/vendor or service provider

4.3 Critical Suppliers of Raw Materials, Components, or Services

4.3.1 Drug Products, Components, Packaging, and Labeling

RMs, processing aides (e.g., compressed gases), and components used in compounding should be obtained from an FDA-registered facility whenever possible. At a minimum, the bulk API must be manufactured in an FDA-registered facility. If components are not available from an FDA-registered facility, the 503B outsourcing facility should perform an evaluation (audit, etc.) to ensure that the components obtained are of high quality with appropriate identity and purity. Drug products and components cannot be used for compounding if they appear on the FDA-published list of drug products that have been withdrawn or removed from the market for safety or effectiveness reasons (21 CFR 216.24 [24]).

When selecting materials for use in compounding, the type of compounding (sterile versus non-sterile) should be considered. Appropriate controls should be exercised and documented for the purchasing, receipt, storage, material movement (quarantine, approval, rejection, release, return to manufacturer, destruction), and usage of drug products, components, and packaging and labeling in drug compounding.

Sterile drug products and components require additional written controls to ensure that sterility is maintained, where required, from receipt through compounding. Drug products and components should be labeled by the manufacturer with the drug product/component name, lot/batch number, and expiration date. When selecting drug products and components for the final compounded drug product, the impact of manipulation of the drug product/component relative to the intended use in compounding should be evaluated.

All RMs and components should have specifications established by the manufacturer that are scientifically based and comply with respective USP-NF monographs, if they exist. These specifications should address the critical quality attributes that ensure the quality of the finished drug product and that are appropriate for the route of administration of the compounded drug product. Specifications should minimally include those tests described in ICH Q6A Section 3.2, Universal Tests/Criteria [42].

APIs, drug products, RMs, and components received from all suppliers must be accompanied by a valid COA that must be reviewed for compliance to established internal specifications. Bulk containers must be labeled in accordance with Occupational Safety and Health Administration (OSHA) [43] procedures and associated Safety Data Sheets (SDS) must be available to personnel handling the material.

The selection of packaging materials and storage of materials are discussed in more detail in Chapter 7.

Upon receipt at the outsourcing facility, the following controls should be in place:

- Storage of all materials, APIs, and drug products in a manner that maintains the material according to the manufacturer-recommended storage conditions
- Written procedures detailing warehousing and specific storage areas/requirements
- Special storage conditions, such as temperature and humidity, specified by the supplier/vendor

- Segregation of materials as appropriate (see additional information in Chapter 7) while storing materials in a manner that prevents contamination, chemical reaction, or compromises material quality
- Storage of materials off the floor to allow for ease of cleaning storage areas
- Written warehousing procedures for management of inventory, including movement of final drug product to end user in order to trace compounded drugs in the event of a recall.
- Management of warehouse inventory should consider a First In, First Out (FIFO) method to ensure proper rotation of warehouse materials.

QC is responsible for approval/rejection of drug products, in-process materials, components, and labeling and packing materials. These QC responsibilities are discussed in more detail in Chapter 3 Quality System and reduced testing is discussed in Section 6.4.

4.3.2 Reserve Samples

An appropriately identified reserve sample representative of each lot or batch of drug product should be retained and stored in accordance with the compounded drug labeling. See Section M in the draft GFI – CGMPs for 503B Facilities [9] for additional information.

4.3.3 Services

Written procedures must be in place for managing the selection and qualification of providers of outsourced services, such as contract laboratories, consultants, uniform services, software vendors, etc. Each service vendor must meet the vendor qualification program requirements as well as enter into a quality agreement with the 503B outsourcing facility.

4.4 Shipping

Compounded drugs must be shipped from the 503B outsourcing facility in a manner that preserves the SQIPP and safety of the product. Packaging storage containers must be closed tightly, and the compounded drug must not interact physically or chemically with the packaging, as discussed in Section F of the draft GFI – CGMPs for 503B Facilities [9]. Procedures for shipping should be in place to ensure that temperature, humidity, and light requirements are maintained during shipment/delivery to the patient or healthcare provider. Shipping studies may be needed depending on the conditions for shipment/delivery of the compounded drug product.

Shipping requirements should also consider the Beyond-Use Date (BUD) of the compounded drug. (See Chapter 9.)

Where a manufacturer of 503B products cannot ensure that product will be shipped under the specified storage conditions, temperature studies and/or studies under accelerated conditions (e.g., stability studies) are recommended to determine the impact of temperature excursions on product quality. Shipping studies, representative of yearly temperatures during different seasons, may be considered to ensure that product storage requirements are maintained. Additionally, to determine the actual shipping conditions, using a temperature/humidity data logger or other monitoring device is recommended.