

# Quality Standards for Large Scale Sterile Compounding Facilities



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## Introduction

Legislation has established a new regulatory category for pharmaceutical compounders that supply healthcare providers with prepared non-patient specific medicines for use in hospitals, offices and clinics. These “outsourcing facilities” will be subject to more rigorous quality and safety standards modeled after the Current Good Manufacturing Practices (CGMPs)<sup>1</sup> that apply to pharmaceutical manufacturers. In light of the new law, this paper reviews the differences between traditional and outsourced compounding and describes the key CGMP provisions that are critical to ensuring drug quality and patient safety when compounding occurs at a larger scale. The scope and magnitude of sterile compounding has changed dramatically over the past three decades and includes many large scale commercial compounding operations providing compounded sterile preparations (CSPs) without the traditional benefit of a patient-specific prescription. This sector has outgrown existing traditional compounding standards of practice necessary to ensure product quality and sterility as well as added capacity. While outsourcing facilities will be subject to CGMPs, all large scale sterile compounding should meet more rigorous quality standards regardless of participation in the new regulatory category.

## The Emergence of the Outsourced Compounding Sector

Pharmacy compounding is the historical cornerstone of the pharmacy profession. According to a 1949 text, it is the “task in which all the scientific knowledge, professional skill and sense of responsibility . . . must find their expression and justification.”<sup>2</sup> Traditionally, compounding is the extemporaneous preparation and dispensing of medications in various dosage forms to meet the medical needs of patients pursuant to a prescription written by an authorized prescriber. The pharmacy profession, most notably hospital pharmacy, has redefined itself over time, and its focus has moved from production and distribution to clinical patient management.\* As

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\* This transformation was fostered by the 1985 Hilton Head invitational consensus-conference facilitated by the American Society of Health-System Pharmacists (formerly known as the American Society of Hospital Pharmacists) which shifted departmental pharmacy practice from the provision of discrete clinical services (e.g., aminoglycoside pharmacokinetic dosing services) to a comprehensive clinical enterprise where pharmacists take on a larger role in the safe and appropriate use of medications. Examples of the services currently provided by pharmacy

the institutional practice of pharmacy shifted away from compounding, commercial business enterprises found opportunities to fill this void.<sup>3</sup> Examples include manufacturers of automated medication dispensing cabinets and pharmacies specializing in extemporaneous compounding.

Drug manufacturers were some of the first to enter the outsourced compounding space specifically to service the hospital market. In July 1982, Baxter Healthcare began operations of the Travenol Regional Compounding Center (TRC) business,<sup>4</sup> first opening a center in Morton Grove, Illinois and later adding a second in Bridgeport, New Jersey. The TRC program was designed to operate on a large scale to transform commercially available drug powders and concentrates into dosage packages suitable for immediate administration to patients<sup>†</sup> without further aseptic manipulation at hospitals or other provider sites. Baxter and other companies that followed their approach argued that this service was an extension of the hospital's compounding operation.

Though a commercial success, the TRC program drew the attention of the FDA, which alleged that the TRC activities violated the Food, Drug and Cosmetic Act (FDCA). FDA believed the drug packages produced at the TRCs were new drugs, which must be separately tested for safety and efficacy,<sup>5</sup> and further that Baxter was creating new dosage forms of other pharmaceutical companies' proprietary medications. Subsequently, they intervened, issuing a consent decree that prohibited Baxter from providing these services without significant financial and punitive penalties.<sup>6</sup> As a result, Baxter closed these operations.

Hospitals, however, were still looking to outsource the compounding of certain products, such as parenteral nutrition. The preparation of parenteral nutrition is complex and requires specialized facilities that maintain optimal states of environmental control, trained personnel and costly equipment. In all but the biggest hospitals, the cost associated with compounding parenteral nutrition using these systems was prohibitive. In 1991, Central Admixture Pharmacy Services (CAPS), a division of B Braun Medical, started to provide hospitals with ready-to-use, patient-specific bags of parenteral nutrition.<sup>7</sup> This allowed hospitals that did not have the

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departments include anticoagulation dosing services, immunization tracking and administration and recently, new prescribing roles.

<sup>†</sup> Many drugs are not produced by drug manufacturers in the final form needed for patient administration. They are purchased in either lyophilized (freeze-dried) or liquid concentrate form. Hospitals have commonly responded to the need to prepare these drugs for administration to patients by operating their own centralized drug preparation programs for the reconstitution, dilution, and repackaging, of drugs.

resources to prepare this type of compounded sterile preparation (CSP) to purchase them on an as needed basis, freeing up both fiscal and human resources.

The CAPS locations providing this service were state licensed pharmacies. Since nutrition was one of Baxter's core products (they manufactured or distributed various parenteral nutrition components such as amino acids, dextrose, water and fat emulsions and offered a state of art automated compounding device that improved the safety profile of preparing these complex formulations), they wanted to re-enter the outsourced compounding business. Baxter sought and received FDA permission to provide compounding services but with the provisos that the Baxter facilities (then known as the COMPASS program which later became PharMEDium when divested by Baxter)<sup>8</sup> be registered with the FDA, employ pharmacists and pharmacy technicians, and meet a limited number of quality requirements from the CGMPs – the robust quality requirements for commercial pharmaceutical manufacturing – dictated by the FDA. Baxter was also required to provide these compounded solutions of parenteral nutrition in a patient-specific manner. (Personal Communication, John L. Quick-former Corporate VP of Quality and Regulatory Affairs, Baxter Healthcare, May 2, 2014). The FDA never formalized these expectations in a Compliance Policy Guide or any other written document.<sup>9</sup> At about the same time, the FDA required the CAPS program facilities to become registered establishments, so they operated as both licensed pharmacies and FDA registered establishments.

Over time, COMPASS and CAPS expanded their extemporaneous compounding services to include non-patient-specific cardioplegia, anesthesia syringes, antibiotics and narcotic dosage forms. The FDA exercised its enforcement discretion with these companies allowing them to provide these non-patient specific doses since they were under the purview of the Agency, however there was an expectation that these organizations had the ability to ultimately track the compounded medication to the patients for which they were used.<sup>10,11</sup>

In addition to outsourced compounding for hospitals, a second market began to emerge to serve physician office practices and ambulatory care clinics looking for certain medication doses to keep on site for use in those entities. In some cases these drugs were in short supply from the pharmaceutical companies, in other cases pharmacies identified commonly-prescribed compounded dosage forms and marketed their ability to supply them to prescribers regionally or nationally.

While COMPASS and CAPS had mainly prepared new dosage forms from packaged FDA-approved medicines, the new compounders entering this new market were

producing large quantities of non-patient-specific sterile injectable drugs from non-sterile bulk chemicals and they were not registered with the FDA. Compounding sterile preparations from non-sterile ingredients is a high risk activity that requires significantly more rigorous controls to ensure the quality and sterility of the final formulation versus those required by compounders using only commercially available FDA approved products as their starting materials.

Additional factors continued to drive demand for outsourced sterile preparation services. New standards for sterile compounding issued by the United States Pharmacopeial Convention (USP) – discussed below – presented compliance challenges for pharmacies, despite the fact that these standards were considered minimum practice for sterile compounding as early as 1995 in USP Chapter <1206>, Sterile Drugs for Home Use (which was replaced in 2004 by the new USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations).

Federal attention to the changing landscape of pharmaceutical compounding grew throughout this period. In the 1990s, the FDA became increasingly concerned with the expansion of this sector and grappled with how to appropriately regulate larger-scale compounding pharmacies that were operating like manufacturers. In 1992, the FDA published a non-binding Compliance Policy Guidance 460.200 that established nine criteria that the Agency used to determine when a pharmacy preparing large quantities of non-patient specific medications exceeded the traditional activities of a pharmacy and should be regulated under CGMPs. The compounding pharmacy industry, led by organizations like the Professional Compounding Centers of America (PCCA) and the International Academy of Compounding Pharmacists (IACP), battled with the FDA over their perceived right to compound medications to meet the growing demand for sterile injectable drugs, which included those kept in stock in physician office practices.<sup>12</sup>

In 1997 this regulatory gap prompted Congress to modify Section 503A of the FDCA to create a safe harbor for pharmacists who were compounding medications pursuant to physician's order. The Food and Drug Administration Modernization Act (FDAMA) section 127 amended the FDCA by adding section 503A (21 U.S.C. 353a), which governs the application of Federal law to pharmacy compounding. Under section 503A(a) of the act, a compounded drug product is a drug product made in response to, or in limited quantities in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounded drug products are exempt from three key provisions of the act:

1. *Adulteration* provision of section 501(a)(2)(21 U.S.C. 351(a)(2)(B)) (current good manufacturing practice [CGMP] requirements);
2. *Misbranding* provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (labeling of drugs with adequate directions for use);
3. New drug provision of section 505 (21 U.S.C. 355) (...use of drugs under Investigational New Drug Applications (INDs), New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)).<sup>13</sup>

This law was almost immediately challenged by various compounding pharmacists who argued that the inclusion of a prohibition on advertising and promotion was an unconstitutional violation of free speech. A decision in the United States Court of Appeals for the Ninth Circuit held that the restriction on advertising and promotion was unconstitutional and further that the unconstitutional provision was not severable from the rest of section 503A.<sup>14</sup> The Supreme Court reviewed the case and in 2002 affirmed the ruling of unconstitutionality, but did not review the question of severability.<sup>15</sup> Following this decision the FDA assumed that section 503A was not enforceable and issued a second Compliance Policy Guide on how it would use its underlying authority to control certain compounding activities.<sup>16</sup> In 2008, the United States Court of Appeals for the Fifth Circuit held that the restriction on advertising and promotion *was* severable and thus that the rest of section 503A was enforceable.<sup>17</sup> These conflicting rulings resulted in inconsistent legal status of the law in different parts of the country and affected the FDA's perception of its authority to regulate pharmacies that they believed were acting more like manufacturers.

## Compounding Quality Failures and Patient Harm

Alongside growth of the compounding sector and oversight challenges came high-profile incidents of contaminated drugs harming patients. The 1980s and 1990s saw a number of cases of contaminated sterile preparations involving eye drops,<sup>18</sup> parenteral nutrition solutions<sup>19</sup> and cardioplegia.<sup>20</sup> Because of these tragic and well-publicized sterile compounding failures, some FDA officials suggested banning certain types of pharmacy compounding under the FDA's discretionary authority to regulate

compounded preparations as unapproved new drugs under the adulteration and misbranding provisions of the FD&C Act. The following summarizes the FDA perspective at that time:

“Generally, FDA will defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. However, when the scope and nature of a pharmacy’s activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action.”<sup>21</sup>

One of the first major catastrophic compounding incidents occurred in 2001 when a generic sterile injectable drug went into short supply after the pharmaceutical company production line was shut down due to CGMP compliance deficiencies. The drug, betamethasone injectable suspension, was compounded by a community pharmacy and one lot of 60 vials was not terminally sterilized. The result was distribution of vials contaminated with a highly pathogenic gram negative microorganism.<sup>22</sup> Several patients were hospitalized and treated and three patients died as a result of the contamination.

The 2012 national fungal meningitis outbreak linked to contaminated medications prepared by the New England Compounding Center brought widespread attention to compounding quality. As of October 23, 2013, when the Centers for Disease Control and Prevention (CDC) last updated their data, the total adverse event case count was 751, with 64 deaths.<sup>23</sup> But while larger than other outbreaks, this was not an isolated event. Between January 2000 and 2012, eleven other outbreaks were identified, involving 207 infected patients and 17 deaths after exposure to other contaminated compounded drugs.<sup>24</sup> The past several years have also seen harm caused by other errors, such as super-potency. Three patients died in 2007 after receiving a dose of colchicine made by a compounding pharmacy that was eight-times stronger than the labeled concentration.<sup>25</sup>

In recent years the FDA has increased its inspections of compounding pharmacies and registered establishments that were known to have had quality issues or that in the Agency’s opinion posed a potential risk to patient safety. Since 2012, over 90 pharmacies have been inspected by the FDA and many were issued inspection reports known as “483s” which document and communicate observed conditions that may constitute violations of the FD&C Act.<sup>26</sup>



## Compounding Quality Standards

The incidences of injuries and deaths to patients during the late 1980s and early 1990s from pharmacy compounded injections, ophthalmic solutions and organ transplant baths became a call to action<sup>27,28</sup> prompting US-based professional and standards organizations to develop better quality guidelines.

In the early 1990s, both the American Society of Health-System Pharmacists<sup>‡</sup> (ASHP) and the USP issued voluntary standards for sterile compounding. ASHP published a Technical Assistance Bulletin (TAB) to help pharmacists and pharmacy technicians produce sterile preparations of higher quality.<sup>29</sup> Both the ASHP TAB and USP Chapter <1206>, Sterile Drug for Home Use, served as a foundation for USP General Chapter <797><sup>§</sup> issued in 2004 — the first U. S. national practice standard for sterile compounding that was enforceable by the U. S. Food and Drug Administration (FDA) and the State Boards of Pharmacy. Chapter <797> was developed by an expert General Committee, now called the Compounding Expert Committee (2010-2015), which updates the standard as needed.

The objective of Chapter <797> is to describe conditions and practices to prevent harm, including death, to patients that could result from:

- (1) microbial contamination (nonsterility),
- (2) excessive bacterial endotoxins,
- (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles\*\* (see “official” and “article” in the General Notices and Requirements) or 10% for nonofficial articles,
- (4) unintended chemical and physical contaminants and
- (5) ingredients of inappropriate quality in CSPs.

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<sup>‡</sup> Then called the American Society of Hospital Pharmacists

<sup>§</sup> USP sets standards in its drug and drug dosage form monographs, General Chapters numbered lower than 1000, and General Notices, which are legally enforceable under the 1938 FD&C Act by FDA, state regulatory boards, Joint Commission, etc., but USP per se lacks enforcement authority.

\*\* An article is a substance and an official article is an article that is recognized in USP or NF via monograph

Importantly, USP Chapter <797> describes *minimum* practice and quality standards for CSPs of drugs and nutrients based on current scientific information and best known sterile compounding practices.<sup>30</sup> The Chapter was never intended to describe the quality system requirements for large scale compounding practices described previously that are outside the traditional compounding role of pharmacists as defined Section 503A. Chapter <797> was last revised in June 2008. Its next revision – expected in the coming year or two – should reflect advances of science and industry understanding of best practices learned over the past several years, as well as lessons learned from the national fungal meningitis contamination event. These standards have historically been intended for traditional pharmacy compounding practices only. The quality system described in USP General Chapter <797> was not created to ensure drug quality and patient safety at the scales of large compounding facilities.

## USP Chapter <797> - Good But Not Sufficient for Large Scale Compounding

USP General Chapter <797> has advanced compounding practice and describes a standardized compounding quality system as well as the expectations for personnel who compound and the processes needed to engender a quality CSP. But the Chapter leaves room for pharmacists and pharmacy technicians to exercise professional discretion. Unfortunately this discretion has at times resulted in a lack of compliance with standards of practice.<sup>31</sup> Additionally, lack of critical oversight by state boards of pharmacy, failure of accreditation organizations to establish an expectation of compliance and inadequate knowledge and expertise explain the profession's slow pace of adoption of effective compounding quality systems. In 2007, one study showed that only one in six pharmacists was prepared for sterile compounding work.<sup>32</sup> The results of a 2013 national survey of compliance with USP General Chapter <797> has showed little to no significant improvement in the overall scores of participating organizations over time despite the extensive and protracted educational efforts of professional and private organizations since 2004.<sup>33</sup>

The misapplication of professional discretion relative to sterile compounding practice has at times yielded inconsistent quality. This presents a much greater public threat when compounders operate on a large scale and their products can reach hundreds of patients across the country. Preparing medicines in large volumes necessitates much more robust quality assurance practices, such as those described under CGMPs. For

example, one element central to the CGMP approach is the focus upon building quality into the overall process and the prevention of problems. Quality is consistently producing products or services that the customer wants while simultaneously decreasing errors. Though quality can represent a measurement at a defined instance, it is better explained as a dynamic process leading to continual improvement of the output to customers over time. Systematic evaluation and elimination of variability within a manufacturing process is a cornerstone of predictable quality outcomes. The practice of large scale sterile compounding is no different and the absence of these concepts in large scale compounding was starkly illustrated by the national fungal meningitis outbreak and other such events.<sup>34</sup>

The current Chapter <797> does not adequately address large scale sterile compounding, whether it is done at an outsourcing facility without prescriptions, or at a large compounding pharmacy that aggregates many prescriptions and produces high volumes of sterile drugs. While the later example of compounding may be considered patient-specific – a criteria commonly used to differentiate traditional from non-traditional compounding – the sheer volume of drugs made by these prescription aggregator pharmacy operations most certainly exceed the *traditional* patient-specific compounding practices that Chapter <797> was intended to cover. Despite this, many large scale pharmacies that dispense patient-specific formulations will continue to operate under state board of pharmacy oversight, and therefore will still only be required to meet USP Chapter <797> or other similar standards set by the state.

USP Chapter <797> is currently under revision. The USP Compounding Expert Committee should add a more robust set of quality requirements to Chapter <797> to address high volume compounding pharmacy practices. Though it may be challenging to develop metrics based on volume and scale of production, they are nonetheless needed – the risk of patient exposure to potentially unidentified safety problems at high volume compounding pharmacies demands it. More robust sterile compounding quality systems must be adopted for all outsourcing facilities as well as for large scale compounding pharmacies that remain under state oversight.

## Current Good Manufacturing Practices

Compounding pharmacies that meet federal requirements under 503A are not required to establish drug efficacy and safety, obtain FDA approval, or comply with manufacturing and labeling standards. This assumes that compounded drugs are

prepared as result of (or in limited quantities in anticipation of) the receipt of a valid prescription for an identified patient.

In contrast, drug manufacturers prepare large amounts of identical medicines for wide distribution. The pharmaceutical industry, unlike pharmacies that compound medication, is subject to rigorous regulations – CGMPs<sup>††</sup> – that are enforced by the FDA and define and safeguard critical aspects employed in the manufacture of all drugs. CGMPs are minimum guidelines for practice in the manufacture, processing, packing or holding of drug products to be administered to humans or animals. Their purpose is to ensure that all pharmaceutical products are produced in such a manner as to ensure consistent quality and integrity. CGMPs establish the “what to do” not the specific elements of “how to do.” In addition to the CGMPs, the FDA has published a Guidance for Industry document titled “Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice.” That document reflects the Agency’s current thinking about the specific application of CGMPs to sterile production.

Exhibit 1 compares traditional pharmacy compounding, large scale compounding, and manufacturing based on certain central attributes. Large scale outsourced compounding shares elements of both categories. But as the scale of production grows, so does the public health risk when quality errors occur, underscoring the need for robust quality system requirements.

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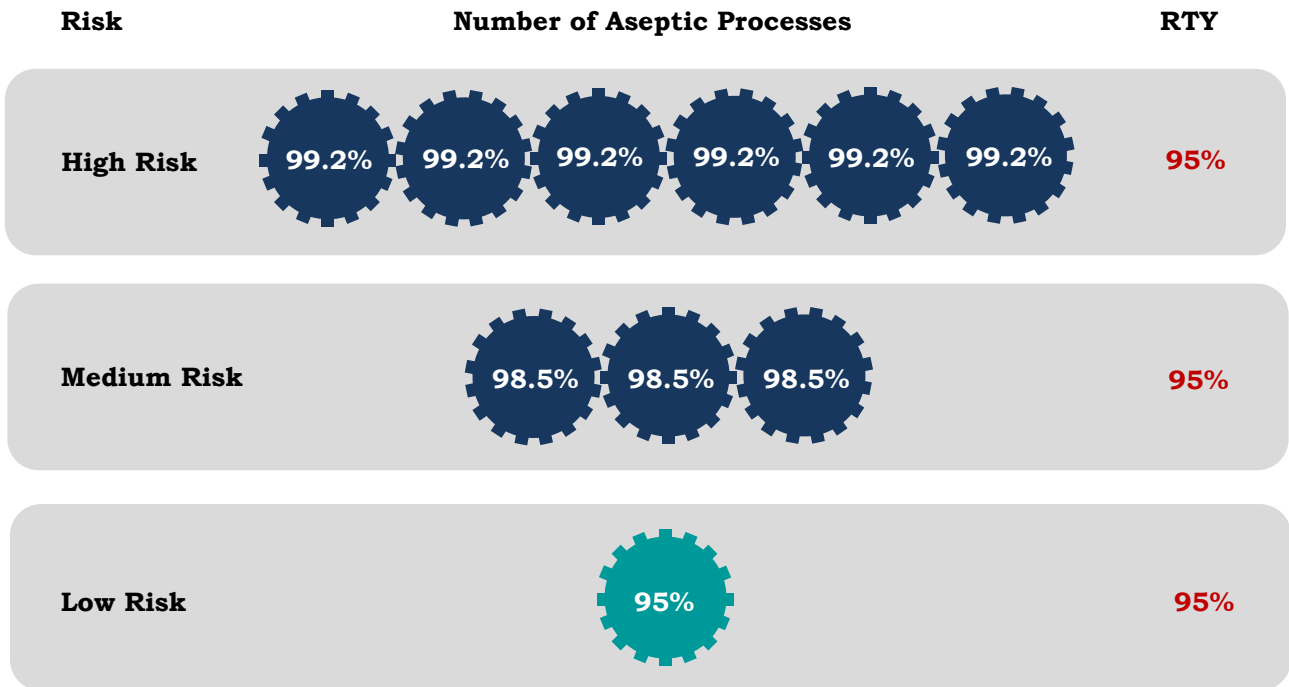
<sup>††</sup> 21 Code of Federal Regulations (CFRs) Part 210 and 211

Exhibit 1: Comparison of Traditional and Large Scale Compounding with Drug Manufacturing<sup>35</sup>

Attribute	Traditional Compounding	Large Scale Outsourced Compounding	Drug Manufacturing
<b>Who is the Customer?</b>	The patient upon receipt of a valid prescription from an authorized prescriber.	Hospitals, home infusion entities and prescribers.	Pharmacies, wholesalers and prescribers upon receipt of an order.
<b>Therapeutic Paradigm</b>	Matches drug to patient at the time of receipt of valid prescription.	Matches drug to customer requirement. Customers match drug to patient at the time of receipt of a valid prescription.	Matches patient to drug based on FDA approved indications.
<b>Public Health Risk from Deviations in Quality System (Contamination or Ingredient Error)</b>	Can be limited or significant: Typically only one patient is exposed when drug is prepared in response to a specific patient prescription. But large scale batch compounding, even when in anticipation of a prescription, increases the risk of exposure when errors occur.	Significant: Drug is produced in larger volumes than a traditional pharmacy but less than traditional manufacturing.	Significant: Drug is mass produced in response to market demand.
<b>Main Regulatory Oversight</b>	State Board of Pharmacy Rules and Regulations.	US Food and Drug Administration.	US Food and Drug Administration.
<b>Published Quality System</b>	USP General Chapter <797> Pharmaceutical Compounding-Sterile Preparations.	21 Code of Federal Regulations Parts 210 and 211 (CGMPs) and anticipated guidance.	21 Code of Federal Regulations Parts 210 and 211 (CGMPs).
<b>Degree of Enforcement</b>	Low to moderate: 21 states require compliance with the published quality system.	High: FDA is inspecting all establishments registering as outsourcing facilities.	High: All registered establishments can expect to be periodically inspected.

Strong quality systems are important for high-volume compounding, but also for higher risk compounding activities such as compounding sterile drugs from non-sterile bulk ingredients. The concept of Rolled Throughput Yield (RTY) is a helpful way to understand this. RTY is the probability that a single unit can pass through a series of process steps free of defects. The fewer the number of steps, the lower the potential for defects or points of failure. As the number of units in a batch increases or the number of steps in a process increases, the greater the chance of error, thus the precision of the process must improve. Exhibit 2 below represents three different processes and their relative risk based on the complexity of the relative compounding or manufacturing processes.

Exhibit 2: Rolled Throughput Yield (RTY). As a process becomes more complex, the accuracy and precision of each process step needs to improve



In low and medium-risk level compounding as defined by USP Chapter <797>, compounders use FDA approved, commercially available, sterile release materials (e.g., medications and diluents), sterile components (e.g., tubing, syringes and needles) and packaging (e.g., empty IV bags, cassettes and elastomeric devices) as starting materials. During the aseptic processing of low and medium-risk level CSPs, the sterility of the materials, components and packaging is maintained by using proper aseptic technique — highly technical work that requires meticulous attention to detail.

In high-risk compounding as described in Chapter <797>, *nonsterile* materials, components or packaging and the final product are required to undergo some form of individual sterilization (filtration, steam, dry-heat or irradiation) prior to being compounded and subsequently released for use by patients. However, USP Chapter <797> only requires sterility testing according to USP Chapter <71> for batches of 25 or more or when the default beyond-use dates (BUDs) set based on risk-level in USP Chapter <797>, are exceeded. Otherwise compounders rely solely on careful aseptic processing to ensure sterility when manipulating commercially available, FDA approved sterile drugs and solutions. According to the FDA’s guidance on drugs produced by aseptic processing:

“Any manual or mechanical manipulation of the sterilized drug, components, containers or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the potential for error.”<sup>## 36</sup>

CGMP contains rigorous requirements for terminal sterilization, as discussed below. High-risk compounding involves numerous steps, each with a higher degree of complexity and therefore the precision, accuracy and effectiveness of each step must be more robust in order to ensure a predictable and acceptable outcome. Each individual process requires validation and control, as each can introduce error that could result in a contaminated medicine.

Exhibit 3 provides a comparison of selected quality system requirement attributes of CGMPs and USP General Chapter <797> that illustrates key differences between these standards.

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<sup>##</sup> According to the FDA, nearly all drugs recalled due to nonsterility or lack of sterility assurance in the period spanning 1980-2000 were produced via aseptic processing

Exhibit 3: Comparison of Selected Quality System Requirement Attributes of CGMPs and USP General Chapter <797>

Quality System Requirement	CGMP	USP General Chapter <797>
Engineering Control Smoke Studies To Assess Proper Air Flow	Yes <sup>§§</sup>	Yes
Inbound Component ID Test	Yes	No <sup>***</sup>
Stability Testing of Formulation via Stability Indicating Method to Assign Expiration / Beyond-Use Date	Yes	No <sup>†††</sup>
Sterility Testing as Release Test (USP General Chapter <71>)	Yes	Limited <sup>†††</sup>
Cleaning Validation	Yes	No
Continuous Particle Count	Yes	No
Use of Sterile Disinfectants	Yes	Only Isopropyl Alcohol
Environmental Monitoring During Production	Yes (Air, surface, personnel)	No
Frequency of Environmental Monitoring	Daily (Air, surface, personnel)	Air-twice yearly Surface-routinely Personnel-initially and 1-2 /year
Sterile Garb	Yes	Only sterile gloves
Reserve Samples	Yes	No

<sup>§§</sup> Critical to demonstrate that unidirectional first-air is delivered from the HEPA filter through the critical site and out of the device without refluxing or rollout into the critical site.

<sup>\*\*\*</sup> There is no requirement for direct testing of bulk non-sterile active pharmaceutical ingredients (API). Certificate of Analysis from FDA registered supplier is acceptable if component is part of a FDA approved drug.

<sup>†††</sup> Peer-reviewed literature acceptable

<sup>†††</sup> Only w/extended dating & High-Risk batches > 25



## Drug Quality and Security Act

In 2013, Congress passed the Drug Quality and Security Act, which was signed into law by President Obama on November 27. Title I of the Act addresses compounding and eliminates the unconstitutional provisions of Section 503A of the FDCA, effectively reinstating Section 503A as a safe harbor for traditional compounding practices. Though it exempts traditional compounders from complying with CGMPs, it does require compliance with general chapters on compounding (specifically Chapters <795> and <797> as well as other applicable USP chapters).<sup>37</sup>

The law also creates a new section of the FD&C Act - Section 503B - that recognizes pharmacies that engage in the manufacture and shipment of larger quantities of compounded drugs without prescriptions. These organizations, called outsourcing facilities, may receive exemptions from the drug approvals and labeling requirements of the FDCA if they voluntarily register with the Agency. Under the law such facilities are subject to the CGMPs, risk-based inspections and other standards to be defined by the agency with guidance from the FDA Pharmacy Compounding Advisory Committee.

As of this writing, over forty establishments have voluntarily registered with the FDA as Section 503B facilities. The FDA has yet to issue specific CGMP guidance for 503B facilities, but has indicated they will do so.<sup>38</sup> Lack of guidance creates a compliance challenge for 503B registrants.

In addition to the application of the CGMPs, additional guidance should be offered by the Agency similar to that in the FDA Aseptic Processing Guidance Document.

The section below describes key CGMP concepts that should be applied by 503B facilities, given their larger scale and non-patient specific operations, to ensure drug quality and patient safety. In addition, the appendix to this paper contains a crosswalk between the CGMPs and USP General Chapter <797> Pharmaceutical Compounding - Sterile Preparations, highlighting the detailed differences between these two quality standards.

## Key CGMP Concepts for 503B Outsourcing Facilities

The central tenet articulated in the CGMP regulations and in robust modern-day quality systems is that quality must be built into the product and that testing alone cannot be relied upon to ensure quality. This Quality by Design<sup>39</sup> concept has been missing from the compounding regulatory schema that were intended for traditional pharmacy activities, not large scale compounding.

Through the lifecycle of a compounded sterile medication from receipt of raw materials to the point of administration, there are several key areas where the CGMPs provide a more robust way to ensure product quality and patient safety compared to USP General Chapter <797>, especially when large quantities of sterile products are made.

They are:

### 1. CGMP Mindset

CGMPs are a set of requirements from the U.S. FDA that serve as the cornerstone for assuring quality. This regulation is considered the premier quality model and has been adopted globally in the pharmaceutical industry. The “CGMP Mindset” is a term used to describe a desired attitude and vigilant adherence to detail that is harmonized with a set of actions and behaviors in the manufacturing process. This mindset must be fostered by organizational culture that embraces CGMP compliance, provides clear, understandable, consistent direction to all employees and decreases production errors and costs.

Another driver of the CGMP mindset is the dynamic tension that the FDA creates through their inspection process. The Agency holds organizational leadership accountable for complying with the CGMPs. A healthy respect for oversight has been absent in pharmacy compounding but is beginning to gain traction in state-based inspection models conducted by some State Boards of Pharmacy.

### 2. An Autonomous Quality Unit (QU)

The Quality Unit (QU) within a drug manufacturing operation is responsible for ensuring that the various operations associated with all systems are appropriately

planned, approved, conducted and monitored. The QU must review production records to ensure that no errors have occurred and has the authority to reject any product. In properly managed CGMP programs, manufacturing error and deviation rates are low. When mistakes are made or deviations occur, a robust quality system facilitates effective error tracing. Quality Units typically have no production responsibilities thereby insulating quality decision-makers from either financial or production pressures. Their decisions to accept or reject products are based instead upon a comprehensive set of predetermined specifications. This type of organizational check and balance is not an absolute expectation of USP General Chapter <797>. The Chapter states “when time and personnel availability so permit, compounding manipulations and procedures are separated from post compounding quality inspection and review before CSPs are dispensed.”

### 3. Receipt and Release of Non-Sterile Ingredients, Materials, Supplies and Packaging

Confirming the identity and quality of starting materials is fundamental to building quality into the manufacturing process. Allowing ingredients, supplies and packaging that may not meet predefined specifications into production potentially introduces variability that may affect drug quality and patient safety. 503B entities need to establish a process to receive, evaluate and release non-sterile ingredients, materials, supplies and package components against predetermined acceptance specifications. This includes identity testing and assessing the degree of bioburden – the type and amount of microbial contamination present before sterilization. The microbiological quality of active pharmaceutical ingredients (APIs) and other components will have an impact on the effectiveness of sterilization methods.

USP General Chapter <797> does not identify specific requirements to determine this quality parameter stating “nonsterile active ingredients and added substances or excipients for CSPs should preferably be official General or NF articles. When nonofficial ingredients are used, they shall be accompanied by certificates of analysis from their suppliers to aid compounding personnel in judging the identity, quality and purity in relation to the intended use in a particular CSP.”

Relying on a certificate of analysis for bulk APIs used in a larger-scale production process is not sufficient as API repackagers are not required to perform any qualitative assessment of these substances. USP General Chapters on compounding do not adequately address this regulatory gap. Analysis of bulk substances must be

performed to verify their identity and quality. Materials that fail to meet all pre-defined specifications must be rejected. Vendors of bulk APIs, other ingredients and components need to be qualified by the 503B entity and appropriately registered with the FDA. In addition, a system must be developed and maintained to track the lot numbers of non-sterile ingredients, materials, supplies and packaging components based on the date received ensuring they are used on a first in/first out basis.

#### 4. Receipt and Release of Sterile Ingredients, Materials, Supplies and Packaging

Some 503B entities use only FDA approved, commercially available, sterile ingredients, materials, supplies and packaging in their operation, which have already undergone the necessary release testing by the original manufacturer. Despite the known quality of these items, 503B entities of this type must ensure the pedigree of their ingredients, materials, supplies and packaging. Mechanisms must be established to obtain certificates of analysis from the original manufacturers to confirm ingredient identity and the sterility. Predetermined specifications for all sterile ingredients, packaging and components must be developed and used to release these items. Should any of the material fail to meet these predetermined specifications, they must be rejected.

#### 5. Buildings and Facilities and Environmental Monitoring

Any quality manufactured medication must be produced in a suitable environment that controls the risk of contamination and error. The CGMPs describe the critical elements of a suitable environment; but the specific criteria required are dependent on the organization's processes and must focus on the anticipated exposure of the materials, components and packaging to the immediate environment during each processing step. The buildings and facilities should be of suitable size for the activities performed and constructed of suitable materials and in a manner to facilitate cleaning, maintenance and proper operations. A well-designed, one-way flow of traffic for personnel, materials and equipment will reduce the risk of processing errors. All areas of a sterile production must be maintained in a strict and sanitary manner to prevent infestation, cross-contamination or damage to incoming / in-process materials and finished products.

Each of the defined areas of operation in an aseptic processing facility must be controlled for suitable air quality depending on the nature of the operation, equipment

and products. This involves ensuring microbiological and particle contaminants do not exceed set minimum levels, such as those in ISO<sup>§§§</sup> classifications for air cleanliness. Air quality should be measured during initial qualification studies performed under as-built, static conditions, but ongoing sampling must also occur during routine aseptic operations to ensure an environmental state of control. Frequent sampling under dynamic operating conditions facilitates the early identification of drift from a state of control and permits timely investigation and remedial action before product quality is compromised.

The environmental sampling program described in the current USP General Chapter <797> is considered inadequate for traditional pharmacy sterile compounding practices and is grossly inadequate for large scale compounding outsourced operations. The limited data collection required is insufficient to establish a microbial state of control, and it is certainly not able to detect any drift from that state of control in a timely fashion.

The quality of the environment and the interaction of human operators with the product during aseptic filling operations can affect the microbial quality of product being manufactured. The elements of comprehensive environmental monitoring program must include air sampling, surface sampling and personnel sampling (e.g., sterile gloves and other sterile garb) during each compounding session. 503B facilities must monitor both viable and non-viable particle counts during any aseptic processing procedures, which is the expectation under CGMPs. Environmental monitoring data also must be considered in conjunction of other quality data for product release.

Organizations must respond to data indicating an unfavorable trend away from the state of control. The FDA 4803 observations from the inspection of New England Compounding Center (NECC) showed that NECC was conducting more frequent environmental monitoring than what was required in Chapter <797>, but they failed to act upon that troubling data to eliminate the presence of unacceptable levels of microbial bioburden.<sup>40</sup>

## 6. Standard Operating Procedures (SOPs)

In order to ensure process uniformity within an organization and maintain it consistently, standard operating procedures are critical. Properly designed SOPs

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<sup>§§§</sup> ISO (International Organization for Standardization) is a large developer of widely-used voluntary international standards.

clearly articulate the steps to ensure product consistency and quality. To develop effective SOPs that meet an organization's requirements, consensus must be achieved between production and quality control units and there must be an understanding of the activities necessary to consistently bring about the desired outcome. Though SOPs are required by Chapter <797>, compliance has been imperfect. The detailed process understanding needed to write SOPs is often lacking in organizations that function out of verbal tradition rather than from a well-defined and disciplined quality system. Unfortunately this paradigm is all too common within pharmacy compounding operations and it represents a failure of leadership. For example, only 48% of pharmacies surveyed in 2013 responded that they had a detailed written policy and procedure on all aspects of surface and viable air sampling which includes preparation of plates, labeling of plates according to the Environmental Sampling Plan, reading plates; documentation of result as well as procedure for sending them to contracted lab (in the event that is applicable).<sup>41</sup>

Subsequent to the development of detailed SOPs, is training of staff in the SOPs. Compounding staff must also be involved in the ongoing development and revision of SOPs. SOPs can and should be living documents that are refined continually as potential points of failure are identified. In a true quality system, the staff is encouraged to identify instances of "close calls" where mistakes were almost made. As issues and variances are identified, solutions are found and tested. When solutions are successful, the changes to the SOP are made permanent and the personnel are again retrained. This type of process and these expectations are self-evident in organizations that comply with CGMPs.

## 7. Personnel Training, Qualification and Monitoring

The personnel working in an aseptic processing area are the greatest source of both microbial and particulate contamination. Traditional pharmacy compounding is almost exclusively a manual process involving a significant human presence. This presence creates an increased risk in large scale compounding operations, as a greater number of products may be affected by contamination introduced by humans.

USP General Chapter <797> requires that "Compounding personnel are adequately skilled, educated, instructed and trained to correctly perform and document the following activities in their sterile compounding duties:

- a. perform antiseptic hand cleansing and disinfection of non-sterile compounding surfaces;

- b. select and appropriately don protective garb;
- c. maintain or achieve sterility of CSPs in ISO Class 5 (see Table 1) PEC devices and protect personnel and compounding environments from contamination by radioactive, cytotoxic and chemotoxic drugs
- d. identify, weigh and measure ingredients; and
- e. manipulate sterile products aseptically, sterilize high-risk level CSPs and label and quality inspect CSPs.”

These requirements for traditional compounding practices lack the qualitative and quantitative specificity and rigor needed for large scale compounding operations. For example, proper sterile garbing is critical to preventing microbial contamination, especially for entities that produce large scale batched products. USP General Chapter <797> describes the minimum garbing requirements but does not provide any qualitative guidance on this topic. In CGMP facilities, operators working in the aseptic processing area may not have any exposed skin and personnel in critical processing areas (e.g., ISO 5) must be vigilant about how they move and work within the critical filling zones.

Ideally, any aseptic processing procedures must minimize the presence of humans and maximize the use of automated equipment that has been validated to not add bioburden to the process. CGMP manufacturing operations have worked diligently to automate aseptic processing as much as possible, greatly reducing the risk of contamination. These commercial scale manufacturers employ automated sterilization / decontamination cycles to eliminate contamination from inbound ingredients, materials, supplies and packaging. USP General Chapter <797> relies on a manual decontamination and there is no requirement to validate the effectiveness of that decontamination.

Chapter <797> lacks a clear and comprehensive list of personnel training core elements. By contrast, the FDA Aseptic Processing Guidance used in the CGMP context states “Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. Fundamental training topics should include aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards posed by a non-sterile drug product and the specific written procedures covering aseptic manufacturing area operations. After initial training, personnel should participate regularly in an ongoing training program. Supervisory personnel should routinely evaluate each operator’s conformance to

written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and aseptic technique during manufacturing operations.”

## 8. Stability Program and Expiration Dating

CGMPs require a program to determine the stability characteristics and shelf-life for each product. Chapter <797>, however, does not provide sufficient guidance for 503B facilities on robust methodology for establishing compounded drug stability and beyond-use dates (i.e. expiration dates). In fact, the Chapter permits individuals to use their professional judgment to assign this critical date. Chapter <797> states:

“To ensure consistent practices in determining and assigning beyond-use dating (BUDs), the compounding facility should have written policies and procedures governing the determination of the BUDs for all compounded products. When attempting to predict a theoretical BUD, a compounded or an admixed preparation should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components.”

“Compounding personnel who assign BUDs to CSPs when lacking direct chemical assay results must critically interpret and evaluate the most appropriate available information sources to determine a conservative and safe BUD.”

503B facilities must have a more robust stability program that uses appropriate and validated methods and procedures to determine the stability characteristics of the manufactured product and to establish appropriate storage conditions and expiration dates. Stability is specific to the ingredients, materials and containers used in the manufacturing process and must be demonstrated through objective qualitative and quantitative data derived by validated scientific tests.

Some compounders use contract testing laboratories to conduct stability studies, but the methods and procedures used by contract testing laboratories have recently come under scrutiny. Several contract testing laboratories were issued 483s by the FDA calling into the question the veracity of the systems needed to support compounding practices when drug strength, sterility and endotoxin testing is required.<sup>42</sup>



Under a CGMP model, an organization's stability program is fully articulated within the organization's standard operating procedures. SOPs will describe the sample size, test intervals, storage conditions and test methods to determine stability, as well as the number of batches to evaluate each the formulations manufactured.

## 9. Cleaning and Disinfecting; Equipment Use Logs

Under CGMP regulations, facilities and equipment must be qualified, calibrated, cleaned and maintained to prevent contamination and mix-ups. Properly maintaining facilities and equipment is critical to ensure suitability and fitness of use. USP General Chapter <797> states the importance of cleaning and disinfecting, but it lacks specificity. Additional detail is necessary to describe proper cleaning and disinfection activities as well as how to inspect for adequacy.

As required under CGMP, only sterile chemical agents should be used to clean and disinfect facilities where sterile products are manufactured and these agents must be validated against the microbial bioburden of the facility to determine their effectiveness. USP General Chapter <797> does not require validated cleaning methods, but relies on limited environmental sampling alone to demonstrate that microbial bioburden is being appropriately controlled.

As a subset of cleaning and disinfecting procedures, all equipment (e.g., primary engineering controls, autoclaves, pumps, scales and other items that influence the quality of the product) must have operating SOP, maintenance, cleaning and use logs. Equipment must also be properly identified for tracking purposes – each product batch record must document the equipment used.

## 10. Process Validation

The effectiveness of any procedure used to sterilize or assure the quality / stability of a manufactured product must be established through process validation. Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities that take place over the lifecycle of the product and process.<sup>43</sup> Although Chapter <797> requires that “sterilization methods achieve sterility of CSPs while maintaining the labeled strength of active ingredients and the physical integrity of packaging,” it lacks specific guidance in how to determine that this standard has been met.

Each 503B entity must establish validated methods to ensure quality and sterility within their processes and not merely rely on documentation provided by companies that sell bulk chemicals and other services to the compounding industry. Quality cannot be adequately assured merely by in-process and finished-product checks, which is the present-day model used under Chapter <797>.

## 11. Equipment Calibration, Validation and Preventative Maintenance System

A robust process validation system requires a clear understanding of how equipment will be used to achieve the quality, integrity, strength and sterility of each batch. Each piece of processing equipment used in batch manufacturing must be shown to be operating within its predetermined specifications.

A fundamental failure discovered in many compounding contamination events is the ineffective and improper use of equipment and procedures to terminally sterilize the CSPs. These critical quality assurance procedures were not validated and the sterility of the final product was not assured.

SOPs must define a calibration program that identifies the necessary steps to ensure the precision and accuracy of equipment. This includes all production and laboratory equipment that perform quantitative measurements, such as balances, thermometers, pipettes and temperature sensing devices in autoclaves or dry-heat ovens. Each piece of equipment or group of equipment requires a calibration log that specifies the frequency of calibration, points where calibration is checked and its acceptable operating range. Calibrated equipment should be tagged or labeled to show who performed the calibration, the date of the calibration and the scheduled date of the next calibration.

## 12. Area Clearance and Label Accountability System

This quality system element prevents product mix-ups and mislabeling. Area clearance applies to procurement, control and segregation of supplies and components and documentation throughout the manufacturing process. To reduce the risk of error, the manufacturing of a specific formulation occurs in a segregated area with assigned personnel working on only one formulation at a time. Strict control of all product labels must be in place to prevent errors in product labeling. This concept is not described in USP General Chapter <797>.

Area clearance and a label accountability program is a required element of the organization's SOPs. Whenever product is labeled, it must be performed in a cleared area free from label materials or documentation from other batches. An individual different from the person preparing the formulation should examine the labels to assure that the correct label is affixed to its corresponding product and that it properly identifies the product. This individual must also reconcile the quantity of labels issued vs. the quantity of labels used. Any discrepancies in the label reconciliation process must be fully investigated before the batch released. Any excess batch labels should be destroyed to prevent mislabeling.

Labels need to be stored in a manner to prevent mix-up and within a labeling area or room where labels are inspected prior to performing the labeling operation. An area clearance should be conducted to assure that all labels from the previous labeling operation are removed before bringing in the next batch to be labeled.

### 13. Change Control

Change control is another well-known CGMP concept that focuses on managing change to prevent unintended consequences. The system must manage the end-to-end change control process including initiating, reviewing, approving, distributing and storing the history of changes in procedures, processes, testing, formulations and other critical tasks that can impact product quality or regulatory filings. It captures the relevant information about the objective, nature and scope of change. A well-managed change control program can provide evidence of CGMP compliance to the FDA. A 503B entity would require a robust change control policy to ensure drug quality and patient safety. The CGMP regulations provide for change control primarily through the assigned responsibilities of the quality unit. Effective change control activities (e.g., quality planning and control of revisions to specifications, process parameters, procedures) are key components of any quality system.

### 14. Finished Product Release System

Required under CGMPs, a finished product release system assures that each batch of product conforms to predetermined specifications. Written procedures for the release of finished products must include an established sampling plan for testing the completed batch of finished product. Products failing to meet established specifications must be rejected. Products that can be reprocessed must again be sampled, tested and meet the established specifications before release. All products

need to be quarantined according to written procedures until released by the quality unit.

USP General Chapter <797> does not require a formal finished product release system. The standard does require sterility testing, but only when the default beyond-use dating of compounded medications made from sterile ingredients is exceeded; and for high-risk CSPs, such as those made from non-sterile bulk ingredients, and only for batches of larger than 25.

## 15. Operational Variances and Complaint System/Corrective and Preventive Action (CAPA)

A compliance system that tracks and trends feedback to improve the manufacturing process is a cornerstone of CGMP quality systems. A Corrective and Preventive Action (CAPA) system focuses on the systematic investigation of discrepancies (failures and/or deviations) in an attempt to prevent their reoccurrence (corrective action) as well as eliminate the cause of potential nonconforming product and other quality problems (preventive action).

To ensure that corrective and preventive actions are effective, failures must be systematically investigated and corrective actions must be standardized and integrated into the SOPs.

Performance feedback may be manufacturing process data on operational variances, or may come from customer complaints. A robust CAPA system must include a written SOP about how complaints are handled as well as a written record of each complaint. If the complaint requires an investigation, the investigation must be documented and made readily available in the CAPA record.

## Summary

The uninterrupted availability of sterile formulations is an important part of delivering comprehensive pharmaceutical care to patients. The passage of the Drug Quality and Security Act provides the FDA, USP, State Boards of Pharmacy and various stakeholders with the opportunity to rethink the resources, standards and requirements necessary to ensure availability of manufactured/compounded drug

with suitable quality for patient safety. USP General Chapter <797> provides minimum practice and quality standards for traditional pharmacy sterile compounding activities. It does not describe nor was it intended to describe an appropriate quality system for large scale compounding activities. Producing large scale sterile batches requires a higher degree of discipline consistent with the approach described in the Current Good Manufacturing Practices. As Chapter <797> is revised, it should also address large scale sterile compounding activities and identify higher quality standards where necessary, even for compounders that ultimately link drugs to individual patient prescriptions. The description of key GMP concepts for large scale compounding listed in this paper may be useful in that effort. Regardless of the standard applied, a robust, detailed timely quality oversight process is required to drive meaningful compliance. The state boards of pharmacy are working to ensure that their inspectors are adequately skilled, educated and trained to enforce the requirements of Chapter <797>.<sup>44</sup> Large scale operations working within the provisions of Section 503B of the Drug Quality and Security Act must be regulated and inspected by the U.S. Food and Drug Administration. The FDA and State Boards of Pharmacy must work together to identify non-traditional compounding facilities that have not registered with the FDA as a 503B entity in order to ensure that they receive appropriate regulatory oversight. Only when all compounding facilities are held fully accountable to appropriate quality systems can drug quality and patient safety be assured.

## Authors

Eric S. Kastango, MBA, RPh, FASHP  
President/CEO, Clinical IQ, LLC and CriticalPoint, LLC

Katherine H. Douglass, MS, RN, APN,C, CRNI  
Vice President, CriticalPoint, LLC

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This paper was peer-reviewed by

James Agalloco, BE Chem Eng., MS, MBA  
President, Agalloco & Associates  
Belle Mead, NJ

Patricia C. Kienle, RPh, MPA, FASHP  
Director, Accreditation and Medication Safety  
Cardinal Health Innovative Delivery Solutions

David W. Newton, B.S. Pharm., Ph.D., FAPhA,  
Professor  
Department of Biopharmaceutical Sciences  
Bernard J. Dunn School of Pharmacy  
Shenandoah University

John L. Quick, BS, MBA  
President, Quick & Associates  
Genoa City, WI

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