THE IMPORTANCE OF CGMP TO THE SAFETY OF COMPOUNDED DRUGS

How Current Good Manufacturing Practices (CGMP) Offer a Reliable Remedy to Poorly Compounded Drugs

THE FDA GROUP LLC

TABLE OF CONTENTS

MEET THE AUTHOR

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As a USP in-house expert on the FDA Process Analytical Technology and Quality by Design Initiative, he was responsible for over thirty Pharmacopeial chapter revisions that incorporated and reflected the revisions by the FDA on the 21st Century CGMP Initiatives. He also led collaborations on several FDA, USP and industry projects that resulted in several Pharmacopeial standards. Gary has more than twenty-five peer reviewed papers and book chapter contributions; four issued patents, numerous industry journal articles and has been invited to give many conference and symposia presentations worldwide.

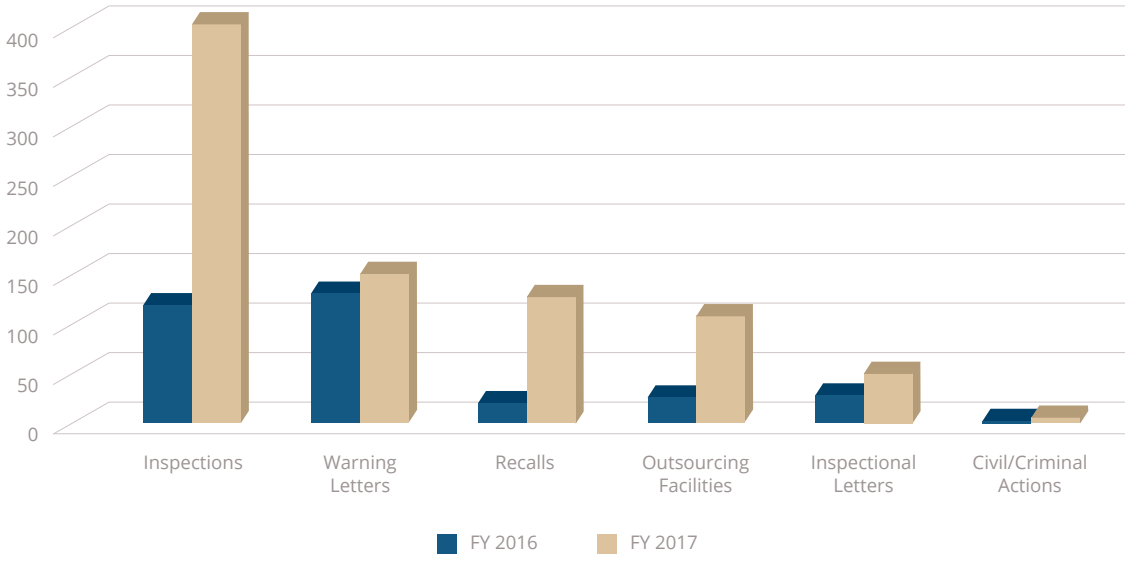
INTRODUCTION

In the minds of many pharmacists, current good manufacturing practices (CGMP) have unduly raised the bar of compliance under the jurisdiction and authority of state boards of pharmacies (SBOP).

But compared to the potential financial and safety-related consequences of noncompliance, properly implemented CGMP should not be seen as a regulatory burden, but a reliable safeguard against potentially disastrous outcomes—a point made clear in 2012 when improper compounding at the New England Compounding Pharmacy sparked an **outbreak** of fungal meningitis which resulted in 64 deaths, 751 injuries, and 25 counts of second-degree murder.

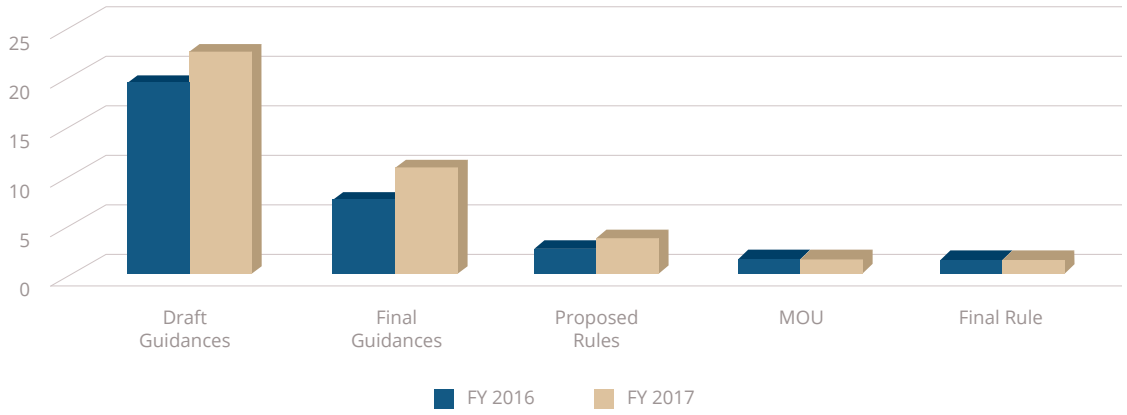
As of November 2017, no studies have been published that provide financial data on the impact to drug compounding pharmacies' compliance to CGMP or its significance to protecting the health of the public. But as we approach the four-year anniversary of the Drug Quality and Security Act (**DQSA, 2013**), U.S. Food and Drug Administration (FDA) 2016-2017 inspection and regulatory data (shown in the graphs below) and State Board of Pharmacy (SBOP) data provided in the most recent **annual Government Accounting Office (GAO) report** provides compelling evidence that, for the most part, compounding pharmacies are not realizing the importance CGMPs have on sustaining compounded medicines as a viable resource to patients.

FDA Compounding Inspection Activity
(As of 6/2017)



Acknowledgment: Data from FDA (2017)

FDA Regulatory Activity
(As of 6/2017)



Acknowledgment: Data from FDA (2017)

> *This is a critical time to elevate the necessity of CGMP compliance as a means of motivating compounding pharmacies to take steps toward implementing the practices FDA requires of them to meet both the health and economic needs of an already burdened healthcare system."*

Gary E. Ritchie

While much work still needs to be done to eliminate the risk of exposing the public to poorly compounded drugs, education offers the best mechanism for beginning to change risky behavior among compounding pharmacists. With the right knowledge about what the FDA and the public require from quality compounded drug products, the FDA's mission can be realized in such a way that works to everyone's benefit.

Along these lines, compounding pharmacists should consider the following three questions in order to understand the risks of failing to adopt GCMPs throughout their organization:

1. How does CGMP apply to compounding?

2. How does a compounding pharmacy comply with CGMP?

3. How does the FDA assess the state of CGMP compliance once implemented?

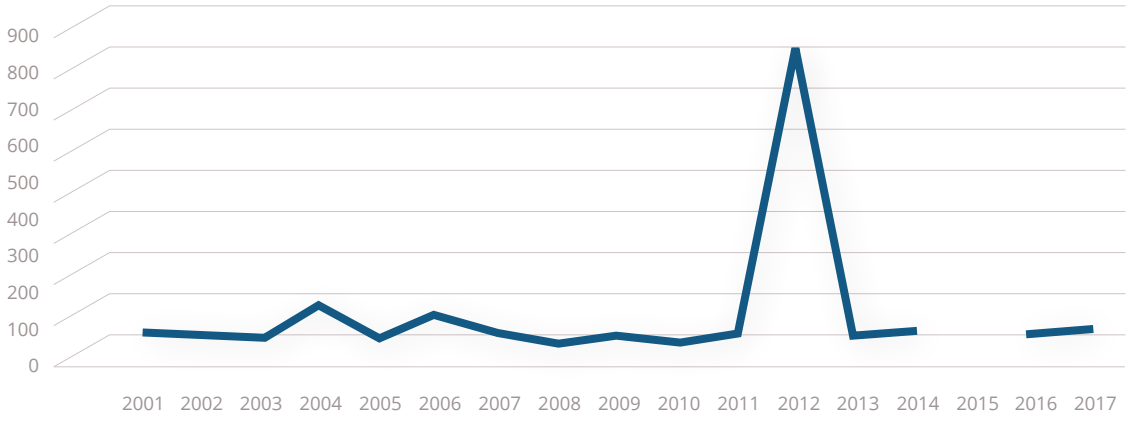
Rather than contending whether or not regulators are misapplying the rules, and if the FDA, in the words of congress is "overstepping" their regulatory authority, educating and implementing appropriate strategies that enhance patient safety while making economic sense best serves the compounding pharmacies in the long run.

THE LAW AND COMPOUNDING PHARMACIES

While the public's attention has fixated on the debate taking place between the president and the incumbents in congress regarding repealing and replacing the Affordable Care Act (ACA), another debate has been brewing quietly in the background—this one between compounding pharmacists and the FDA.

Following the New England Compounding Center (NECC) tragedy of 2012 (see data below), congress acted quickly to promulgate new rules codified in DQSA, giving the FDA regulatory oversight of drug compounding activity in the United States and its territories.

Adverse Events Reported



Acknowledgment: Pew Charitable Trust

Since then, some statutory practices that have evolved over the last twenty-five years following another significant event in the evolution of the modern US drug regulatory law are being questioned when applied to drug compounding. These concerns have been further accelerated by an FDA now more proactive in its initiative to bring its operations into the twenty-first century.

Today, CGMP regulations are the cornerstone of the Food, Drug and Cosmetic Act (FD&C) ("The Act"). CGMP provides a mechanism for drug manufacturers to produce pure, safe, and effective drug products and for the FDA to inspect; issue observations, warnings, injunctions, and consent decrees to drug manufacturers who fail to comply with the CGMP rules found in Title 21 of the United States Code of Federal Regulations (CFR) Part 210, 211, and other applicable sections.

Since DQSA was passed, The Act has now been extended to drugs for human and veterinary compounding. Through legal mechanisms that have evolved between the FDA and Department of Justice (DOJ) since the FD&C Act was passed in 1938, the FDA can and will continue, in the words of the Commissioner, "to actively oversee drug compounders and, when appropriate, initiate regulatory action as it fulfills the FDA public health mission on behalf of patients."

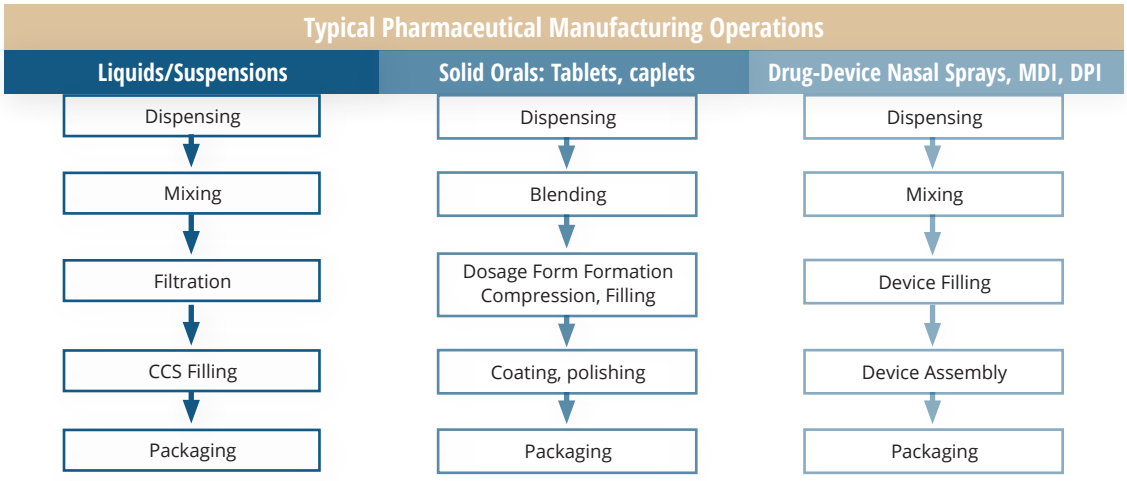
FDA's list of recent inspections, recalls, and other enforcement actions clearly shows that regulators not only intend to make good on this initiative, but are actively doing so right now.

With roughly ninety percent of pharmacies not yet registered as an outsourcing facility, it is certain that the FDA will continue to leverage their enforcement of CGMP on compounding pharmacies to protect the public from poorly compounded drugs.

THE PROCESS

To assess the applicability and necessity of CGMP to drug compounding, several definitions provided in section 210.3 Definitions of the FD&C law must be mentioned:

- Drug manufacturing is defined as the "manufacture, processing, packing, or holding of a drug product [that] includes packaging and labeling operations, testing, and quality control of drug products." The diagram below illustrates the necessary steps required to manufacture several different forms of drug products and a device.



Acknowledgment: Food and Drug Administration, Vibhakar Shah, Ph.D., Consumer Safety Officer Office of Policy for Pharmaceutical Quality, OPQ, CDER, Vinayak Pawar, Ph.D., Senior Review, Microbiologist Office of Process and Facility Assessment, OPQ, CDER

- A **drug product** "means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients." The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

21 CFR section 3.2(e) and (f) define drug as it is applied in combination with a device.

- A **combination product** includes two key components:
  - A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity
  - Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products
- A **device** is defined in section 201(h) of the act as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Given these definitions as they apply to drug manufacturing, it's necessary to ask the core question: **How does CGMP apply to pharmacy compounding?**

The ensuing steps for dispensing, mixing or blending, filtration, compression or filling, container closure system (CCS) filling, coating, polishing, device filling, and packaging of a drug product must occur under a strict CGMP systems of controls:

(1) in a registered and suitable facility on qualified and calibrated equipment,

(2) by a validated production system,

(3) using authorized and recognized materials,

(4) that are processed and tested by trained operators and qualified laboratory analysts and

(5) packaged and labeled,

(6) under a quality management system.

Similarly, the drug compounding steps (shown in the table below) begin with a prescription for traditional pharmacies or anticipatory compounding (preparing compounded medications before the actual receipt of a prescription for outsourcing and hospital pharmacies), followed by gathering together the drug(s) and excipient material(s) being prescribed, weighed, compounded, mixed, sterilized in the case of compounded sterile preparations (CSP and CP for non-sterile compounds), filled and packaged.

Typical Pharmacy Compounding Operations	
Compounded Sterile Preparation	**Compounded Non-Sterile Preparation**
Prescription	Prescription
Drug(s) and Excipient(s) Material	Drug(s) and Excipient(s) Material
Weigh	Weigh
Compound	Compound
Mix	Mix
Sterilize	Fill
Fill	Package
Package	...

The requirements spelled out in the CGMP rules and FDA guidances for drug products are now being enforced for the production of CSP/CP and must also be implemented as directed in the DQSA, 2013 except where exemptions apply, which will not be discussed here. See section 503 of the Compounding Quality Act for a detailed explanation.

Compounding practices have become de facto as originally promulgated by the United States Pharmacopeia (USP) (Section 501(b) of the FD&C), to be recognized by congress as the official drug compendium of the United States and its Territories.

The drug compendium creates standards for such characteristics as potency, sterility, endotoxicity, stability, dissolution, weight variation, content uniformity

and other product properties that, when taken together, result in a specification for drugs published in a drug substance (DS) or drug product (DP) monograph. A monograph includes the test, method, and acceptance criteria that are the DS and DP specification.

Manufactured Drugs (DS/DP) vs. Compounded Preparations (CSP/CP)

It's important to note several differences between manufactured drugs (DS/DP) and compounded preparations (CSP/CP):

1. The USP monograph is by definition a public specification for approved drug substances and products. These monographs are mostly intended to be used by pharmaceutical companies that manufacture what are commonly referred to as "generic" DP using an approved DS.
2. The FDA approves specifications for DS and DP that are private specifications between a branded manufacturer/sponsor of the substance or product. Both generic and branded specifications come under the authority of the FDA and CGMP is strictly enforced when a DS and DP are manufactured.
3. These approved DS and DP have been approved by a scientific methodical approach that studies the toxicology (safety) and efficacy in animals and humans respectively in designed clinical trials.
4. Since a compounded preparation is not an approved product (they have not been studied for toxicity or efficacy in animal studies or clinical trials), congress created caveats in DQSA and the FDA has written CGMP guidelines that effectively place safeguards on the extent to which pharmacists can compound a drug.
    - A compounded drug cannot be a copy of an approved drug product.
    - A compound must consist of only drug substances approved and included in the USP and published by the FDA on approved drug lists. Conversely, compounds cannot consist of drugs that appear on do not use lists published by the FDA.
    - DQSA mandates that all compounded preparations meet the minimum standards of CGMP for their identity, strength, purity and quality.

A violation of any of these caveats by a pharmacy results in an adulterated product under the FD&C Act.

The answer to our core question—how CGMP applies to drug compounding—should now be obvious for the same reason it applies to drug manufacturing:

> *To prevent an adulterated product from being prescribed to a patient, CGMP creates a state of control for the compounding, processing, packing, or holding of a drug including packaging and labeling operations, testing, and quality control of drug products throughout the life cycle of the drug substance and drug product."*

Gary E. Ritchie

Now that we've connected the CGMP link between drug manufacturing and compounding and described how it applies to the drug compounding process, the next question is, how does a compounding pharmacy comply with CGMP?

THE PRODUCT: COMPLYING WITH CGMPS

In answering our first question, which asked how CGMPs apply to drug compounding, it's shown that a system to regulate the manufacturing of drug products can be equally valid for drug compounders. If CGMPs are the link between drug manufacturing and compounding, can the resulting quality attributes of drug product (DP) and compounded sterile preparation (CSP) or non-sterile compounded preparation (CP) also shown to be linked?

Just as drug manufacturers produce drug products using a systems approach that acts as a set of controls to meet a previously described product specification, compounding pharmacies have been required to demonstrate that CSP/CP are produced using the same systems since the passage of DQSA in 2013.

DQSA dictates that without toxicology or clinical studies to demonstrate safety and efficacy, the only recourse the public has is to rely on a number of indicators of proof of purity, safety, and efficacy, such as:

- Compounding pharmacists' ability to demonstrate that they have used approved drug substances to make their product;
- that they don't make copies of already approved drug products;
- that they adopt and adhere to CGMP rules that dictate that they don't make their product in insanitary conditions;
- that they use validated processes;
- that they use qualified and calibrated equipment;
- that they are trained operators and analysts;
- that they test their product by an FDA registered laboratory [that also operates under CGMP] before it is prescribed, compounded, and dispensed to a patient.

A pharmacist may comply with this system of controls by first instituting a key component of CGMP that allows a compounding pharmacy to be run and ably managed such that all of the requirements under CGMP are effectively met, by first adopting and then committing to a quality management system (QMS).

At its most basic level, a QMS ensures that four main criteria of a DP and CSP/CP that directly impact patient safety are met: quality, identity, strength and purity (free of contaminants such as bacteria and endotoxins). The QMS is designed to ensure these criteria are met by dividing its process into eight elements:

1. Document Management System
2. Investigation/ Out-of-Specification (OOS) Management System
3. Corrective Action Preventive Action (CAPA) Management System
4. Deviation/Incident Management System
5. Change Control Management System
6. Complaints Management System
7. Audit Management System
8. Training Management System

Every QMS element is designed to ensure compliance to CGMP.

THE INSPECTION

Since CSP/CP are not approved by the FDA, CGMP provides a mechanism to ensure that only approved drugs recognized in the official drug compendium are compounded. Furthermore, the QMS provides a system for compounding pharmacies to adopt in order to meet the requirements of DQSA while also allowing the SBOP to maintain a shared responsibility and oversight with the FDA to ensure that poorly compounded drugs do not make their way to unsuspecting patients.

The FDA expects that SBOP inspectors will also be able to verify compliance to DQSA by subscribing to and accessing the same documents and records that FDA inspectors check.

The QMS acts as a set of standards by which the FDA, compounding pharmacy and SBOP can communicate with a common set of data in order to verify that a state of control is or is not in effect at the time of an inspection."

Gary E. Ritchie

GMP inspections follow a classic blueprint commonly known as the "level 5" Inspection. It asks:

1. **Is the CGMP system in place?**
2. **Do standard operating procedures (SOPs) exist for the required system?**
3. **Are the SOPs being followed?**
4. **Do reports, databases, records, and other activities exist as a result of following the SOPs?**
5. **Are the SOPs effective in maintaining a state of control of the compounding process?**

The document management system should be a complete and secure record of the QMS and the drug compounds prepared under it, including original data that must be shown upon inspection to be attributable, legible, contemporaneous, original, and accurate (ALCOA). Good document practice (GDP) and data integrity are at the core of both compounding pharmacies compliance to CGMP and the SBOP and FDA ability to verify that compounding pharmacies are compliant with the CGMP regulations.

- The investigation (Out-of-Specification (OOS) Management System) should define roles and responsibilities of laboratory personnel, production personnel, and management. It should direct how to investigate suspect or OOS test results in the laboratory and operations phase of the investigation. It must enumerate what, if any, additional testing that may be needed and the final evaluation of all test results.
- The corrective action preventive action (CAPA) management system should address requirements of the quality system regulation that define and present documented evidence that CAPA measures have been undertaken. The CAPA should identify sources of product and quality problems. Confirmation of non conforming data from these sources are analyzed to identify existing product and quality problems (root cause analysis) that may require corrective action.
- The analysis should pinpoint trends and confirm that data from these patterns are analyzed to identify potential product and quality problems that may require preventive action.
- The CAPA system should be based on sound statistical methods that detect the frequency of quality problems.
- Compounded batches before, concurrent, and after should be included in the analyses to determine the extent of product and quality problems.
- Risk assessments should be incorporated into all SOPs that are critical to process steps, testing methods and investigation protocols.
- With all investigations and CAPAs, the level of effort should be commensurate with the level of risk of conformity and nonconformity of the product. Additionally, there must be some evaluation of the effectiveness of the Corrective or preventive action.
- Each CAPA task should be evaluated over time to ensure that it was directed at the root cause of the issue and not just a symptom leaving the circumstances in a position to occur again.

Deviation/Incident reports should be timely. The report should contain the following:

- A summary clearly describing the event that triggered the investigation
- A description of the deviation / Incident
- The materials/lots impacted
- A root-cause investigation
- Impact assessment to materials/lots
- Trend analysis
- CAPA follow-up
- Outcomes and recommendations

The change control management system should be used to document when material, process, methods etc., change outside of the SOP.

- The changes should be frequently evaluated.
- The documentation should have levels of approval with them commensurate with the impact of the change. Changes should be periodically reviewed to ensure that changes have been effective.
- A complaints management system should include electronic or written procedures that state how information was reported, collected, and evaluated.
- Trend analysis should accompany complaint reports.
- The audit management system is similar to the investigation system discussed previously. Internal audits are conducted on a routine basis to evaluate the internal controls from a fresh perspective. These types of audits are generally performed in a team approach utilizing a variety of backgrounds to ensure that SOP instructions are clear for example.
- Finally, a training management system should incorporate onboarding, CGMP reviews, and proficiency training in their operational functions (i.e. aseptic techniques, laboratory measurements). Management should undergo annual quality systems training that address the policies, processes, procedures, and written instructions.

It is not a valid argument that these systems of controls are too costly and impose a burden to the practice of a compounding pharmacy.

To adopt or not adopt CGMP is no longer a business case argument. That was effectively removed with the advent of DQSA. CGMP is not a "want have" to make or market a compounding pharmacy's business model. It is mandatory. It is the law."

Gary E. Ritchie

Also, and this must not go without being explicitly stated, there is no such thing as a compounding pharmacy or testing facility that is only partly CGMP. In all the years spent working in the pharmaceutical industry, we are not aware of any CGMP operation in the US or its territories that is only partially CGMP if it manufactures or compounds drugs for human or veterinary use. Not one. CGMP is an all or nothing proposition.

OUTSTANDING PROBLEMS FACING COMPOUNDING PHARMACIES

The previous review of the current state of DQSA—now approaching four years from its passage—needs to be concretely positioned as current data indicates that compounding pharmacies have been slow to grasp the importance of CGMP regulations.

A comparison of the regulations as they're applied to both pharmaceutical and compounding activities reveal that as a result of the DP and CSP/CP having similar qualities of identity, strength, purity, sterility, and endotoxin contamination where applicable, as well as identical CCS and labeling requirements, there is no reason to conclude that the FDA is overreaching its regulatory mandate to protect the public from the possibility of adulterated CSP/CP where a lack of compliance may be found as the root cause.

Simply stated, a drug that is manufactured or compounded for human or veterinary use, that is, processed, packaged, labeled and held and further, distributed, are subject (with exemptions) to the minimum CGMP standards of the United States.

Several outstanding issues remain at the heart of the pharmacists complaints:

Misconceptions around CGMP enforcement

Contrary to what is indicated by congress, the FDA will continue to vigorously enforce CGMP requirements until compliant compounding pharmacies become the standard bearers of CGMP.

If history is any indication, the new focus of the FDA to become a scientific, risk-based organization that values prevention rather than correction will ensure that catastrophic events like those of the past will not be the reason for congress to enact new regulations to enforce compliance. Instead, the FDA intends and would prefer that an educated, well-trained, and compliant workforce that will evolve into a culture of CGMP will be the reason that these catastrophes don't ever occur again.

The current challenge to the safety of compounded medicines is not trivial. It is the current focus of bodies representing compounding pharmacy associations as they make a business case against complying with CGMP. For instance, consider the ongoing practice of potency over time testing (POT) for determining beyond use dating (BUD) as a surrogate for stability testing of compounded preparations. POT is not an accepted methodology according to CGMP because it does not answer two key questions that stability studies, as defined by CGMP regulations seek answers to:

1. Has the active drug substance or other components of a compounded preparation degraded at its recommended labeled storage condition?
2. Are the byproducts of these degradants present at levels that could pose a health risk to the patient?

CSP/CP shelf life determinations

At issue is the contention by pharmacists that a CSP/CP shelf life can be determined by the length of time that a formulation maintains its potency (strength, or the amount of the active drug substance) within its acceptance criteria (typically 90.0 – 110%) of its nominal dosage amount.

Drug manufacturers of approved drugs must demonstrate shelf life by determining the amount of degradation that a product undergoes by rigorous analytical testing methodology that is specific and sensitive to the presence of degradants in the compound. The active drug, components and degradants are tracked by a designed study interval of time to ensure that the product remains stable over its calculated and derived shelf life (also referred to as expiry dating).

To ensure there is recourse to test the product while it is on the market, a representative sample (or retain container of each and every lot released) is maintained at the labeled storage conditions so in the case of an adverse event or other activity requiring the re-assay of the marketed product, the retain sample is tested and compared against the complaint sample if it exists, and the resulting test result is assessed for both identity, potency/strength, and the presence of any new degradants that may have formed in the retain sample stored under controlled label storage conditions.

This cannot be done with CSP/CP because no degradants are ever measured at the time of the POT test point, only the potency/strength is determined on the active ingredient.

It has been argued that where a stability-indicating assay method is used in some cases for POT determination, this in effect a stability study. But this is in fact not true. Degradants are not identified or quantified against a known reference standard, so the true "mass balance" of the actual assay value is never truly known if degraded material is present.

This presents a serious problem to the FDA since, as stated previously, CSP/CP are not approved products. Furthermore, their safety in human and animal trials has not been demonstrated. The pharmacists and the SBOP are at an impasse on this issue, but the FDA is not. The number of inspectional observations for lack of stability data in support of a marketed product is steadily increasing.

The FDA guidance for stability (December 2008) states, "there can be only one set of standards. Samples of products (from production lots) on stability should be representative of those in the marketplace. Expiration dating is based on the ability of the product to be measured over a certain period of time against the established specifications or standards."

Transference of POT/BUD shelf life data across products

A more serious issue occurring in the compounding market is the suggestion that POT/BUD shelf life data can be transferred across products from different manufacturers if the formulations are identical. Based on the FDA guidance cited above as well as current and longstanding customary practice for drug product submissions for NDA and ANDA, this activity should be addressed and ended. This theory is tantamount to manufacturing data where none exists and is putting patients in serious jeopardy.

For instance, stability data from a lot manufactured by compounder "A" based on their standards (i.e. their raw materials, formulation and process development, process and method validation, packaging, and batch record protocols used for lot release) cannot be used for compounder B lot release, because it is highly probable that compounder A and compounder B used different standards during development, validation, and batch release. Therefore, the data cannot be representative to both lots.

Currently, very few if any stability test methods for compounded preparations (CSP/CP) use actual reference standards for known degradants. Even if the formulas are in fact chemically and physically identical, other parameters of the standard applied for stability testing are most certainly not (i.e. the reference standard material used in the stability studies, the facilities and the SOPs are all different, to name a few obvious and key ones).

Simply stated, data from stability studies generated from a compounder are not transferable per CFR 211.137, 211.166 and FDA guidance. That being said, it is clearly prohibitive to transfer the data from one compounder's formulation to any other compounder's release lot since there is no reciprocity of samples among multiple compounders that can achieve the status of a representative sample. Although the chemistry may be identical, representation is physically impossible. This is exactly what is meant to be prohibited by the FDA guidance.

Lack of good documentation practices

Lastly, the continued lack of good documentation practices will be a deciding factor of whether the compounding industry can keep pace with other requirements evolving in the drug manufacturing industry. Supply chain and data integrity is undergoing significant evolution with emerging Blockchain technology.

This technology has been introduced as an IT solution for creating and maintaining a secure and permanent supply chain, process, and quality record of every step taken for every batch manufactured. As the drug industry evolves from batch manufacturing to continuous manufacturing modes, technological solutions will be required to meet the exponentially growing volume of data—the so-called "big data" explosion.

What does this mean for compounding? The current requirement in DQSA for a robust QMS that includes a reliable and sustainable documentation management system is a relatively simple requirement compared to the emerging Blockchain technology.

When regulatory bodies are faced with changing practices emerging from the field, they can no longer afford to be reactive, as stated previously. New approaches to managing big data from the drug industry is also having a residual if not larger effect on the management of quality practices in the compounding industry.

The impact on both the drug manufacturing and compounding industry is, to be sure, a game changer. While Industrial Manufacturing 4.0 is being adopted by Big Pharma, it is not a far stretch of the imagination to see both of these activities begin to divide the compounding pharmacy industry. If that happens, it may actually have the outcome that the FDA intended.

> *Traditional and smaller outsourcing pharmacies would, and should, adapt quickly to the minimum CGMP requirements mandated in DQSA just to keep pace with the larger outsourcing conglomerates and large hospital health centers as they migrate towards the emerging Blockchain and industrial manufacturing 4.0 systems just as their like minded drug manufacturers have begun to do."*

Gary E. Ritchie

If this sounds too futuristic to be true, keep in mind that the advancements we are seeing now are no longer being realized in ten to twenty years, but often five or less.

If the compounding pharmacies want to be a viable healthcare solution provider now and in the future, they must play by the rules. The FDA will not let them continue to give poorly compounded drugs to patients. Technology may enhance the performance of a business, but it cannot ensure the safety of patients. Only compliance to CGMP can provide assurance to pharmacists, regulatory bodies and the public that compounded sterile/non-sterile preparations are on an equal footing with drug products, based on the best data and current state of regulatory science can provide.

503A VS. 503B COMPOUNDING PHARMACY REQUIREMENTS

Given the relatively recent 503A and 503B sector distinctions FDA has applied to compounding pharmacies in an effort to separate "traditional" compounding pharmacies from outsourcing facilities producing products for use in healthcare facilities, we've provided a summarized breakdown of the key similarities and differences between the regulatory requirements for each.

One of the most significant differences between 503A and 503B facilities (which also happens to be a major component of CGMP), is the requirement for all processes to be validated in a 503B facility.

Multiple batches must be made and submitted for testing and stability studies before any new product can be brought to market. This may result in longer lead times for getting new products to customers, however, from FDA's perspective, it ensures that every batch made during normal production is consistent in quality and meets high standards. Not only must products be validated, but testing methods must also be validated to ensure accuracy and precision, in accordance to USP standards. All vendors that supply raw materials must be thoroughly vetted, and on-site inspections are performed by the Quality Assurance team for all critical suppliers.

503A REQUIREMENTS	503B REQUIREMENTS
• Human sterile medications must be dispensed as patient specific • Must comply with USP <795> and <797> • Must comply with state boards of pharmacy regulations • Must perform environmental monitoring every 6 months • Patient information, medication information, company information, and adequate directions for use of medication required for labeling	• Must comply with USP <795> and <797> • Must comply with 21 CFR Part 210 and 211 (CGMP) • Must comply with state boards of pharmacy regulations • Human sterile medications may or may not be dispensed as patient specific • Must have a robust environmental monitoring program developed and performed per production shift in the ISO 5 primary compounding areas and weekly in the secondary compounding areas

- Pharmacists may review their own work and investigate any potential anomalies
- Beyond Use Dating (BUD) may be assigned based on internal or external scientific literature showing stability
- May compound from Category 1 bulk drug substances under the 503A
- May compound from bulk drug substances that have a USP or NF monograph
- May compound with drug substances that are components of drugs approved by the Secretary
- Required to register with each state board of pharmacy and DEA

- Must adhere to labeling requirements per the Drug Quality and Security Act (DQSA)
- Must have a quality department in place independent of operations and sales departments with complete autonomy for investigations and releasing product
- Must have a robust stability program to scientifically confirm the stability of a medication when subjected to degradation variables
- May compound from Category 1 bulk drug substances
- Must register with each state board of pharmacy, DEA and FDA
- Must to report product list to FDA biannually

CONCLUSIONS AND RECOMMENDATIONS

This critical analysis presents an overview of CGMP as it applies to both drug manufacturing and drug compounding and argues for the necessity of traditional, outsourcing and hospital pharmacies to adopt and follow CGMP in the compounding of human and veterinary drugs.

Evidence is presented that argues for the authority and jurisdiction of CGMP based upon scientific data. The SBOP and the FDA are working together to protect patients receiving compounded preparations to ensure that compounded drugs have the identity, strength, purity, quality and are sterile and free from endotoxins.

A discussion about the QMS six system of controls followed that presents elements that if implemented by compounding pharmacies correctly, will ensure a state of control and provide state and federal inspectors with a common standard from which an assessment of the state of compliance can be made.

Several recommendations are made relating to what pharmacists should focus on in adopting CGMP quality management system practices and analytical stability testing as opposed to potency over time (especially with respect to the lack of appropriate stability testing of CSP/CP and the improper transfer of POT/BUD data across multiple compounders possessing the same formulation) and emerging IT developments to enhance data integrity and overall quality records that are being made.

Finally, a forward-looking discussion is had on an emerging IT technology that is impacting the development of drug manufacturing, that if adopted by large compounding conglomerates and large hospital health centers, could have the intended outcome that the FDA is seeking from compounding pharmacies in the first place.

This analysis suggests that it is no longer in the compounding pharmacist's and certainly the patient's best interest to continue to ask why they must comply with CGMP, but begin to ask how they must comply.

Are you in need of quality and compliance assistance at your compounding pharmacy? Our staff of former FDA and industry experts can help you stay ahead of mounting requirements and regulatory expectations while ensuring your systems and processes are safe and effective.

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