
The Importance of cGMP (503B) Compounded Drugs



8000 Commerce Parkway, Suite 600
Mount Laurel, NJ 08054

503A

Traditional compounding pharmacies (503A) compound according to prescriptions specific to patients and are required by state boards of pharmacy to comply with USP and other state-mandated guidelines.

Generally, this type of compounding can be very customized, but also very risky depending upon the pharmacy's investment into cGMP-like practices. While the consumer or in some cases offices receiving these compounded drugs feel they benefit from getting "exactly" what they want and seemingly good expiration dates, the reality can be very different.

This type of compounding does not require adherence to cGMP. This means that drugs compounded under 503A do not have to adhere to standards that ensure the stated ingredients meet their label claims. Examples include batch record controls, environmental monitoring, potency testing, stability testing, sterility testing, endotoxin testing, and equipment validation.

While 503A compounding pharmacies can voluntarily invest in some of these quality attributes, it is both rare and cost prohibitive. Generally speaking, 503A drugs are compounded upon theoretical outcomes that have not been validated or tested. Further, documentation is not required to be cGMP compliant, which leaves records openly available to alterations and modifications. Whether innocent or intentional, the integrity of data is always in question and may not truly represent what actually occurred.

503B

The FDA has designated 503B compounding pharmacies as outsourcing facilities that may manufacture large batches with or without prescriptions to be sold to healthcare facilities for office use.

These facilities are required to maintain full compliance with current good manufacturing practices (CGMP). 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.

The importance of drugs compounded under 503B is important to both health care professionals and patients alike. This class of compounded drugs was manufactured following strict

procedures and processes that have been both proven through validation and continuously measured to ensure the expected outcome is achieved. This means that the integrity of the compounded drug should not be a variable in patient care. Health care professionals often may not have an easy way to measure the effectiveness of a compounded drug which can obfuscate the observed patient outcome.

Because 503B compounded drugs are measured throughout the process, and again required to be verified through potency, stability, and sterility as applicable, healthcare providers can treat their patients with a high level of assurance that the drugs meet their label claims. Often, these drugs will include or have readily accessible certificates of analysis and in-process testing as required.

The documentation system is a complete and secure record of the quality management system and the 503B 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 503B compounding pharmacies compliance to cGMP. This assures the FDA's ability to verify that compounding pharmacies are compliant with the cGMP regulations.

The perceived drawback is that 503B pharmacies may not have such a robust offering of a particular drug, only offering a single or few strengths. This is in contrast to 503A pharmacies offering "customized" strengths often at whatever the health care professional wants. While "customized" is often seen as ideal patient care, the risks are not warranted. While the healthcare professional can offer their patient a 5.13 mg dosage as calculated, these strengths are often created ad hoc via a theoretical formula with a theoretical expiration date. Further, there are no testing requirements adding significant uncertainty to the 5.13 mg dose.

It would seem then that the 503B drug produced following cGMP with a validated process complete testing protocol at only 5 mg and maybe 10 mg will ultimately be the better patient care choice since there is high assurance of the label claims. You can be assured that every batch was instrumentally verified as required by cGMP to meet label claims before it was provided to the healthcare professional.

There are many varieties of “tests” for compounded drugs. While it may be true that 503A compounded drugs can be tested or pharmacists produce testing documents, they often are not cGMP compliant and only test one aspect of a complex compounding process. Every unique dosage may require significant investment to achieve this required level of assurance and can easily cost \$100,000 or more. For this very reason you will often see limited offerings in 503B drugs.

Below is a general comparison of drugs compounded via 503A versus 503B

Attribute	503A	503B
Document Management System	No specific requirement	Part of QMS cGMP system
CAPA Management System	Some SBOP requirements	Part of QMS cGMP system
Deviation/Incident Management System	Some SBOP requirements	Part of QMS cGMP system
Change Control Management System	No Specific Requirement	Part of QMS cGMP system
Complaints Management System	Some BOP requirements	Part of QMS cGMP system
Audit Management System	No Specific Requirement	Part of QMS cGMP system
Training Management System	No Specific Requirement, Training is required for most SBOP	Part of QMS cGMP system
Environmental Monitoring	Every 6 months	Per production batch, multiple sites, generally daily-weekly other sites
BUD – Beyond use dating	Theoretical based on literature or actual testing	ICH stability Program, validated methods, with degradation variables with min 3 batches
Regulations	USP <795>, <797>, <800>, SBOP	FDA 21 CFR Part 210 and 211 (cGMP)
Release Testing; Potency	Not Required	Every Batch
Release Testing; Sterility	Following USP <71> if sufficient material	Every Batch of purported to be sterile
Release Testing; Endotoxin	Following USP <85> if sufficient material	Every Batch of purported to be sterile
Stability Testing	No Specific Requirement most SBOP, theoretical allowed	Full ICH Stability program with validated methods
Container Closure Systems	Not Required	Fully Validated
Equipment Validation	Minor Calibrations	Full Calibrations, Fully Validated per method
Registration	SBOP(S)	FDA