

# **CAPS<sup>®</sup> 503B Pharmacy cGMP Compliance**

**June 2016**



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## Introduction

With the implementation of the Drug Quality and Security Act of 2013, the pharmacy compounding industry has had to reinvent itself to meet new regulatory standards. Specifically, the law amends the Federal Food Drug and Cosmetic Act (FFDCA) to provide for a new category of compounding pharmacy, under its section 503B called “Outsourcing Facilities.” While 503B pharmacies are exempt from certain provisions of the FFDCA, such as those pertaining to new drug applications, they are nonetheless required to follow current Good Manufacturing Practices (cGMPs). These cGMPs, while familiar to the pharma drug industry, are not as well known and were not previously mandated for compounding pharmacies. Pharmacy practitioners responsible for evaluating outsourced sterile injectable preparations can be unfamiliar with cGMP compliance rules.

The Food and Drug Administration (FDA) has issued a draft guidance on 503B cGMP compliance. In addition, FDA has been inspecting pharmacies for cGMP compliance even though the guidance has not been finalized. Thus, despite a lack of clarity on several interpretive issues, Outsourcing Facilities registered with the FDA are required to be compliant with cGMPs. The purpose of this paper is to describe the procedures of Central Admixture Pharmacy Services, Inc. (CAPS<sup>®</sup>) regarding compliance with cGMPs as of June 8, 2016.

## Executive Summary

CAPS has been registered with and inspected by the FDA since 1994 and has developed and implemented policies and procedures based on cGMP principles for many years. In 2014, CAPS reorganized its network of 25 pharmacies into 22 regional 503A Patient-Specific pharmacies and two 503B Outsourcing Facilities registered with the FDA. This white paper describes the procedures and controls utilized in the CAPS 503B Outsourcing Facilities as of June 8, 2016.

CAPS cGMP compliance is independently managed by the Quality team. This includes receipt and release of both non-sterile and sterile ingredients, materials, supplies and packaging in CAPS buildings and facilities. Important highlights include CAPS industry-leading Compounded Sterile Preparation (CSP) release program that will incorporate Test, Hold and Release steps following compounding. This release test program is referred to as THR whereby every CSP batch is quarantined prior to release, pending the outcome of tests for sterility, endotoxin, and potency (drug strength).

The following includes some of the cGMP requirements for which CAPS Quality Unit maintains oversight:

- Environmental Monitoring (EM)
- Standard operating procedures
- Personnel training
- Validations – System, Process, Equipment, Facility, Cleaning
- Beyond use Dating (BUD) validations
- Aseptic process (media-fill) validations
- Internal Audit Program
- Preventive Maintenance Program
- Batch and area clearance
- Label accountability and verification
- CSP batch level “THR” release program
- Change control system
- Product complaint/incident system
- Corrective and Preventative Action (CAPA)
- Proactive quality data trending
- Key performance and quality indicator monitoring

## The CAPS Quality Program

The CAPS Quality team functions as an autonomous unit within the CAPS Organization. This Quality Unit has a Director of Quality Assurance who reports directly to the President of CAPS. Each CAPS 503B Outsourcing Facility has an experienced Quality staff, including a microbiologist and chemist. The Quality staff reports directly to an onsite Quality Assurance (QA) Manager. The local Quality Units are supported by a centralized team of Quality Systems, Validation, Investigation & Analysis, and Quality Compliance Specialists.

Each member of the local Quality Unit has the following responsibilities:

- Approve or reject raw material components such as drug CSP containers, closures, in-process ingredients, packaging ingredients, labels, labeling and drug CSPs.
- Review compounding records to determine whether errors have occurred.
- Fully investigate any potential compounding deviations.
- Approve and/or reject procedures and specifications impacting the identity, strength, quality and purity of the CSP.
- Review and approve sampling plans.
- Review and approve test procedures or other laboratory controls.
- Review and approve CSP compounding and control records, including those for compounding and labeling.
- Determine compliance with established and approved procedures before a batch is released and distributed.
- Review and release CSPs for distribution.

The Quality Unit has no direct compounding responsibilities. However, they have the authority to discontinue compounding production based on a quality issue. The Quality Unit is responsible for notifying Senior Management regarding the monitoring and enforcement of quality related policies and procedures. This can include, but is not limited to the following:

- Distribution of a compounded preparation that may require further investigation
- Out of specification results secondary to notification by a manufacturer
- Out of specification results for CSPs
- Validation failures
- Customer complaints (e.g. potency or sterility)
- Adverse Drug Events
- Unfavorable quality trends
- Tampering

- Diversion
- Counterfeiting
- Regulatory inspections
- Issuance of regulatory observations

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

CAPS' policy is to use FDA approved commercially available, sterile drugs as ingredients when available. In cases where FDA approved sterile drug ingredients are not available, vendor qualifications must be completed for any Active Pharmaceutical Ingredients (API) used in non-sterile to sterile compounding. The vendor qualification process provides CAPS with data on the acceptability of use of these API for routine compounding.

In addition to vendor qualification, CAPS maintains controls for the receipt and release of API:

1. Deliveries of non-sterile ingredients are immediately placed into a Quarantine Test Area.
2. Upon receipt of API into the Quarantine Test Area, available information must be compiled on a Non-Sterile Component Inventory (NSCI) Log, as applicable.
3. Non-sterile raw materials must pass acceptance or identity tests in accordance with an appropriate Material Specification Sheet or CAPS Tested Item Specification procedure (per CAPS SOP- which includes Non-sterile Component Identification and Acceptance Tests, and Certificate of Analysis Verification) before the material can be used for compounding.
4. USP identity or manufacturer identity tests for each component must be performed with acceptable results and documented on the NSCI Log before the component may be moved to the Non-sterile Component Release Area.
5. In the event the API fails an identity test, the supplier is notified and the component is returned to the supplier. Only API that meets test requirements is used in the compounding process.
6. The NSCI Log must accompany each lot and shipment of non-sterile components at all times.
7. Reconciliation of all non-sterile components is completed as each lot/shipment is depleted.
8. A copy of the manufacturer's Certificate of Analysis must be attached to the NSCI Log.

## **Equipment, Containers and Closures**

Equipment, containers, and closures that come into contact with the CSPs are evaluated to establish their adequacy for the intended use. This includes all holding areas and containers and storage conditions in order to establish sterility and cleanliness at the time of use. When CAPS does not use pre-sterilized and/or depyrogenated single-use equipment (e.g., filters, transfer tubing, temporary storage containers) and containers and closures (e.g., vials, syringes), the equipment, containers, and closures are sterilized and depyrogenated before first use, through a sterilization and depyrogenation process that has been validated.

Each lot of equipment, containers, and closures are examined to verify identity and to establish conformity with appropriate specifications before use. CAPS does not perform identity testing of each lot of single-use equipment, containers, and closures when a finished CSP is intended to be sterile provided that, (1) the supplier certifies and labels the material as ready-to-use, sterile, non-pyrogenic; (2) the supplier's packaging integrity is verified upon receipt before use; and (3) the Certificate of Analysis (COA) provided by the supplier is reviewed to verify that the CSP is represented to meet the required specifications including sterility and depyrogenation.

Any single-use equipment, container, or closure not meeting acceptance requirements is rejected and will not be used in the compounding process.

CAPS also employs the following additional critical controls:

1. Equipment is qualified as capable of performing its intended functions or operations before first use.
2. Procedures for routine calibration and maintenance are established and followed.
3. Appropriate criteria for containers and closures are pre-established so that they are suitable for each particular CSP for which they will be used.
4. Appropriate procedures are pre-established for testing the containers and closures at the time they are selected to determine whether they meet the criteria for use and the tests and results are documented.
5. Integrity testing of the CSP container closure system is performed to verify its ability to maintain the quality of the CSP and sterility over the expiry period (See Stability Program and Beyond Use Dating).

CAPS establishes the identification of sterile drug components, without direct testing, by comparing them to acceptance criteria for CSPs that are approved finished human drug CSPs. These sterile drug components are purchased directly from a manufacturer who is registered and listed with the FDA under section 510 of the FDCA, or are purchased from a distributor that certifies that the component has not been subject to repacking or other alteration since initial manufacture. In addition, the label of each lot of the component has been examined to verify that the component meets required specifications before use and the shipment's package integrity has been verified upon receipt before use. Components not meeting these acceptance requirements are rejected and will not be used in the compounding process.

## **Buildings and Facilities**

CAPS utilizes an environmentally controlled area constructed and operated to minimize the introduction and generation of particles within the area. A cleanroom must be classified as one of the following: Level 1, 2, 3 or 4. There are written procedures for the operation, maintenance, and cleaning of these facilities and their support systems. Limits are established detailing the actions to be taken when controlled parameters fail to meet established specifications.

The following lists the classifications and functions for CAPS Outsourcing Facility compounding rooms:

**Level 1** - Cleanroom where Class 100 (ISO Class 5) Particles/ft<sup>3</sup> conditions are met. Third Party Certification is required.

**Level 2** - Cleanroom where Class 10,000 (ISO Class 7) Particles/ft<sup>3</sup> conditions are met. Third Party Certification is required.

**Level 3** - Cleanroom where Class 100,000 (ISO Class 8) Particles/ft<sup>3</sup> conditions (or per state requirements, whichever is better) are met. Third Party Certification is required.

**Level 4** - An environmentally controlled room constructed and operated for transferring materials into and out of the cleanroom that it serves.

The cleanroom HVAC system is designed to provide the air flow and air quality required to comply with the air filtration, air exchange, air velocity, temperature, and humidity requirements. Conditioned supply air enters the cleanroom space through HEPA filters mounted in the ceiling and leaves through return air ducts mounted low in the walls around the perimeter of the cleanroom.

Instruments for monitoring and indicating pressure differentials are installed in a conveniently accessible area near the entrance to the cleanroom space being monitored. These instruments are included in the Daily Environmental Monitoring (EM) Program.

The ISO Class 5 zone or critical area (Level 1) is qualified to include, but is not limited to the following:

- In-situ smoke, airflow studies conducted under dynamic conditions to initially qualify the HVAC/HEPA unit and when any changes are made to the HVAC/HEPA unit or the critical area that might affect airflow. Indications of sub-optimal air control (e.g., non-laminar, turbulent) are corrected before use.
- HEPA periodic testing/recertification is performed at least twice a year to maintain appropriate air flow and quality. These tests include integrity testing of the HEPA filters, particle counts, and air velocity checks.
- Velocities of unidirectional air should be measured six inches from the HEPA filter face and at a defined distance close to the work surface in the ISO Class 5 area (Level 1).
- If any portable ISO Class 5 (Level 1) units are moved from one location to another, re-qualification is performed before resuming sterile compounding in the unit.

The clean areas in which components, CSPs, in-process materials, equipment, and container/closures are prepared, held, or transferred are designed to minimize the level of particle contaminants in the final CSP.

The cleanroom suite (Class 5, 7, and 8 areas) are continuously monitored for pressure, humidity, and temperature through an automated monitoring and alarm system that is capable of detecting excursions. Monitoring for pressure differentials, humidity, and temperature occur during CSP production, and prompt action is taken to correct deviations to expected conditions. If a problem cannot be immediately corrected, CSP production is stopped until corrected. Drug storage areas, incubators, and refrigerators are monitored for temperature and humidity through a similar automated monitoring and alarm system.

## Environmental Monitoring (EM)

The CAPS EM program is designed to facilitate the preparation of safe and effective CSPs through the establishment of acceptable air particulate levels and microbiological bioburden levels of air and surfaces in the CAPS pharmacy cleanrooms.

The program demonstrates that compounding areas are designated with the following:

- Level 1 (ISO Class 5) have laser particle counts not exceeding 100 particles larger than or equal to 0.5 µm per cubic foot.
- Level 2 (ISO Class 7) have laser particle counts not exceeding 10,000 particles larger than or equal to 0.5 µm per cubic foot.
- Level 3 (ISO Class 8) have laser particle counts not exceeding 100,000 particles larger than or equal to 0.5 µm per cubic foot.

CAPS EM program establishes monitoring procedures for air, surface, gloved fingertips, cleanroom components, and gown bioburden as well as a microbiological identification base line in the CAPS Pharmacy cleanrooms. A base line microbiological identification study has been performed. The study includes microbial identification information on all bioburden samples showing growth, whether or not the number of Colony Forming Units (CFU's) grown reaches alert or action limits.

CAPS utilizes the VITEK® 2 Compact System along with the API Manual Microbial Identification System for microbial identification. The innovative VITEK® 2 is a fast and accurate identification system with an expanded identification database capable of performing Gram-Negative, Gram-Positive, Yeast Identification, and Susceptibility Tests. The rapid response time means results can be provided more quickly than with manual microbial identification techniques. After primary isolation, handling is minimized in a simple inoculum preparation, standardization and dilution step which is then placed into the appropriate BioMérieux VITEK® 2 identification card. These cards contain 64 microwells where each well contains identification substrates or antimicrobials which are identified and analyzed once the cards are placed into the VITEK® 2 Compact System.

The CAPS compounding cleanrooms and compounding ISO Class 5 laminar airflow hoods, work stations, and zones are monitored daily under dynamic conditions for particulate matter air counts, bioburden air counts, and surface bioburden counts. CAPS compounding personnel are monitored under worst case conditions for gloved fingertip and gown bioburden counts. CAPS Irvine QA Microbiology Lab conducts growth promotion and sterility testing per USP <71> for each media lot that is used for environmental testing. Each media lot must pass sterility and growth promotion tests prior to its release for use in CAPS Pharmacies. In addition, a Negative Control test is conducted at CAPS Pharmacies on each day that media is used. Routine environmental testing (surface bioburden, air bioburden, particle counts, cleanroom components, and personnel bioburden) is conducted during dynamic conditions on a daily basis. Every day that high risk compounding occurs, EM testing (surface bioburden, air bioburden, particle counts, cleanroom components, and personnel bioburden) is conducted in each room and ISO Class 5 workstation where high risk compounding is performed.

Environmental testing is performed in controlled cleanroom areas. Equipment & packaged media that are used for EM are sanitized with Spor-Klenz, 2% bleach, or equivalent, and immediately followed by sterile 70% Isopropyl alcohol (IPA), prior to their introduction to the controlled cleanroom areas.

EM growth from ISO Class 5 areas undergo microbial identification testing to the species level by CAPS QA Microbiology Lab or a qualified third-party microbial laboratory. For all other ISO Class areas, the EM counts that reach or exceed confirmed alert and action limits undergo microbial identification testing. In addition, random samples are sent at least once per quarter from one air bioburden, one fingertip touch plate, surface contact plate (e.g., door, LAFW), and one sterile sleeve cover surface contact plate, containing growth. These samples are sent to CAPS QA Microbiology Lab or a qualified third-party microbiological laboratory for microbial identification to the genus and species level. Identified organisms are reviewed by a CAPS QA Microbiologist to determine if further action is required. The QA Microbiologist informs the Director of Pharmacy (DOP), QA Manager, and staff in the Pharmacy when an atypical organism is identified for an investigation, corrective, and preventive action(s), as necessary. Annually, microbial isolates recovered from EM data are trended. A documented assessment is completed to determine whether there is a need to include any new isolate or atypical isolate in sterility Bacteriostasis & Fungistasis (B&F) validations or disinfectant efficacy testing (see Compounding Sterile Preparation Release System).

Microbiological identification test results are trended and evaluated as part of the monthly quality system analysis and presented at management review board meetings. EM logs are reviewed on a monthly basis by the DOP (or designee) for compliance with all applicable Standard Operating Procedures. The Quality Unit trends monthly EM data. The DOP and QA Manager review and approve environmental trend data for the monthly Key Performance Indicator (KPI) report. If an adverse trend is identified, the CAPS Corrective and Preventive Action (CAPA) system is utilized in order to investigate the root cause and implement corrective and preventive actions to resolve the discrepancy and minimize recurrence.

Each ISO class 5 hood or workstation is monitored within 6 inches of the critical exposure or aseptic manipulation site. The pharmacy maintains site-specific cleanroom diagrams that show sampling locations in compliance with ISO 14644-1:1999 standard (for sampling site determination) and the CAPS EM program. Sample locations are chosen by calculating the minimum number of sampling point locations from the equation  $NL = \sqrt{A}$  so that the sample locations are evenly distributed throughout the cleanroom area and positioned at the height of the work activity. [Where  $NL$  = the minimum number of sampling sites and  $\sqrt{A}$  = square root of the area of the cleanroom in square meter ( $m^2$ )]. The sampling diagram is approved by the DOP and the QA Manager prior to implementation. Copies of the approved diagrams are maintained in the EM notebook.

Seven days of consecutive EM under static conditions and three days of consecutive EM under dynamic operating conditions are conducted upon new facility start-up. In the event that there is a deviation in compliance with the EM program or in the event that microbial counts reach or exceed confirmed alert or action limits, an appropriate deviation investigation, CSP impact assessment, corrective action, and preventative action is performed and documented.

New CAPS staff that will be participating in CSP compounding must complete and pass the compounding sterile gownned sleeve forearm bioburden count test and gloved fingertips bioburden monitoring test three times before participating in cleanroom activities in a CAPS pharmacy. Each sterile sleeve forearm test and gloved fingertips bioburden monitoring test are conducted after each run of their three run aseptic qualification tests. Compounding employees must complete two sterile sleeve bioburden count tests (using one touch plate per test) and two gloved fingertips bioburden count tests (using one touch plate for each gloved hand), for each day that they participate in parenteral compounding.

Employees who fail a sterile sleeve forearm bioburden count test or gloved fingertips bioburden monitoring test must immediately be retrained and tested in gownning requirements with specific emphasis on hand washing, glove and sterile sleeve cover donning technique, and cleanroom hand sanitization. Surface agar touch plates and Reuter Centrifugal Sampler RCS strips are incubated at 30 - 35 degrees

Centigrade for a minimum of 48 hours, then at 20 – 25 °C for 5 - 7 additional days to capture all slow-growing microorganisms that may have been recovered from the environment.

## **Standard Operating Procedures (SOPs)**

CAPS has Standard Operating Procedures (SOPs) for all aspects of Quality Systems, including, Compounding and Operations, Information Technology, and Human Resources. CAPS SOPs are created and maintained in an electronic document management system known as the “B.Docs/Live Link Document Processing System” (B.Docs). Procedures are written in a standard format for ease of understanding and to aid in compliance with applicable Federal, State and Local laws and regulations, and CAPS policies. Controlled Forms are used when data records are generated for process and/or testing. A standard SOP, “LiveLink CAPS Document and Collaboration System B.Docs” describes creating, modifying, and maintaining controlled documents in the Electronic Document Management System (EDMS). This includes SOP numbering, editing, approving, issuing, retiring, and history file maintenance. CAPS personnel who have Author, Content Management or Business Administrator privileges are subject to the instructions in this document. The EDMS automatically inserts the document number, name and applicable document status and dates.

Documents created and maintained in B.Docs are categorized as various document types including Corporate Operating Procedures (COPs), and SOPs which may reference one or more subtypes such as Prescription Admixture Master (PAM) and Compounding Admixture Master (CAM), Compounding Admixture Record (CAR) and Specifications (SPEC) which may reference one of the following document sub-types: Materials Sampling Specification (MSS) and Test Article Specification (TAS) – Additional documents include Test Procedure (TP) Forms (FRM), and Training Module (TM, See Personnel Training, Qualification, and Monitoring).

CAPS SOPs follow a uniform format for clarity and ease of application. Document Authors are responsible for updating existing documents to adhere to the required format.

## **Personnel Training, Qualification and Monitoring**

The CAPS SOPs are written to encompass the fundamentals of current GMP standards. The CAPS training philosophy is to maintain standard training modules, corresponding proficiency tests, and performance evaluations centrally with input from each 503B pharmacy, as appropriate. The Quality Control Coordinator (QCC), Technical Training Coordinator or designee schedules and coordinates training. A “train the trainer” approach is used with designated pharmacy staff assuming responsibility as the principle Subject Matter Expert (SME) for various functions. SME’s are those that have demonstrated acceptable levels of performance and have been qualified through the completion of the procedure training, proficiency tests, and evaluations. The CAPS Training program is completed in a modular format, addressing the needs of the trainee as outlined below.

Orientation training is provided to all CAPS employees including introduction to CAPS scope of business, confidentiality, HIPAA and other topics. General training is provided in areas such as purchasing and inventory systems, software programs, LANCE computer system training, cleanrooms and gowning procedures, stocking of materials and supplies, etc. This training is provided to staff members based on the requirements for their job duties.

Regulatory training that is aligned with the regulations applicable to each CAPS business unit is provided to CAPS employees. ASHP’s Basics of Aseptic Compounding Technique training is provided annually.

CAPS has partnered with UL Quality, Compliance and Learning (UL) to bring educational material that enhances employees' professional knowledge, enhances compliance with US standards and regulations, and assists in providing the highest levels of CSP quality through the supply chain. This educational material is the same proven solutions used by the FDA to train federal, state and local inspectors. UL serves as the AdvaMed exclusive online compliance partner.

Pharmacy skills include training on aseptic technique, handling of cytotoxic drugs, quarantine/release procedures, compounding procedures, disposal of preparation materials and proper insulin handling. Successful completion of training proficiency tests and initial evaluations are required prior to performing these functions independently.

**Process Training** – CAPS dispensing methods training is provided to all personnel directly involved in each aspect of the process. This training includes proper documentation, process controls and strict adherence to process standards. Successful completion of required proficiency tests, on the job training sessions and evaluations are required prior to performing these functions independently.

**Certification Program** – Documentation of personnel licensure and certification is the responsibility of the DOP at each site. Certification requirements are determined according to applicable state laws. Pharmacy Technicians are required to pass the Pharmacy Technician Certification Board (PTCB) Exam and maintain their certification throughout their employment with CAPS.

**Retesting and Re-evaluation** – Retesting on proficiency tests and re-evaluation may be required at any time based on observation and/or process deviation. Re-evaluation is mandatory on an annual basis for Pharmacy Skills and Process Training topics.

**Training Documentation** – The training curriculum is maintained in an electronic Learning Management system. This system is linked to the Document Management System through which the training requirements are automatically updated as documents are revised. Personnel are notified through a missing requirement report for revision training. Hard copy training records are maintained at each facility.

The training process consists of 4 primary elements:

- Didactic training on procedures with required proficiency testing.
- Practical, on the job training that is Trainer guided.
- Practice, on the job training that is Trainee guided.
- On the job evaluation and annual re-evaluation on all compounding processes.

The CAPS Training Manager oversees the training program and makes changes appropriately based on Regulatory requirements/guidelines.

## **Stability Program and Beyond Use Dating (BUD)**

CAPS' beyond use dating is based on stability extension studies performed by CAPS.

CAPS follows a strict methodology for establishing BUD and storage guidelines for non-patient specific CSPs. Stability information is maintained in the CAPS BUD Database. To request a BUD for a new non-patient specific CSP, the DOP or designee must complete New Preparation Review, Approval, and BUD Form (NRAB), and forward the NRAB to the CAPS Central Data Exchange (CDEX) work team. CDEX

compiles client information and forwards the NRAB to the New Formulation Work Team (NFWT). The NFWT reviews the NRAB request and determines if the new compounded preparation request should be forwarded to the BUD Committee for review.

BUD and storage information for all CSPs admixed within CAPS 503B Outsourcing Facilities is based on FDA approved manufacturers' guidelines and stability studies performed by CAPS. All BUD recommendations for CAPS 503B Outsourcing Facilities are approved by the BUD Committee, which includes a member of the Quality Unit. The BUD Committee evaluates all submitted NRAB's to determine if BUD can be assigned. Beyond use dating and storage requirements are determined by the BUD Committee. BUD is established based upon maximum validated time and storage conditions (i.e. light and temperature). BUD studies must include stability indicating chemistry, sterility, endotoxin, particulate matter, and container closure integrity testing, USP Monograph analysis, and potency or drug strength evaluation. BUD studies are container-type and container-size specific. Container type/size equivalency is allowed provided there is a technical assessment justifying the equivalency claim.

In addition, BUD studies must be fill-volume, drug concentration and API specific. Bracketing studies using minimum and maximum fill-volumes and concentrations may be employed. CSPs should maintain their labeled strength within USP Monograph Limits. If no USP monograph limit exists, then CSPs should maintain their labeled strengths within  $\pm 10\%$  from time zero established within the study protocol. Worst case fill-volume and container-size bracketing is appropriate provided that there is a technical assessment and concomitant calculation of the highest allowable surface to volume ratio justifying the worst case claim. Packaging selected for CSPs must be appropriate to preserve both the sterility and strength of the CSP until the beyond use date.

The DOP is responsible for ensuring that all compounded sterile preparations dispensed by the 503B Outsourcing Facility have BUD that has been approved by the CAPS BUD Committee. The New Formulation Work Team is responsible for determining if new formulation requests made by DOP's will be forwarded to the BUD Committee. The BUD Committee is responsible for assigning BUD to CAPS CSPs, management of all CAPS BUD studies, and maintaining the CAPS BUD Database.

## **Cleaning and Disinfecting**

CAPS cleaning processes specifically address but are not limited to ISO Class 5 hoods or workstations, compounding rooms, gowning rooms, CSP introduction rooms, ante-rooms CSP release rooms, refrigerators, incubators, warehouse space, change rooms, and reusable totes in a CAPS pharmacy.

Daily cleaning is documented and independently verified by CAPS employees on a daily cleaning log. Weekly and monthly cleaning is documented and independently verified by CAPS employees on the Weekly/Monthly Cleaning Log. A total cleandown of the cleanroom suite is performed once per week. ISO Class 5 Laminar Air Flow (LAF) Hoods, ISO Class 5 Zone Workbenches and compounding equipment is cleaned daily at the beginning of the day before use and on an as needed basis throughout the day. ISO Class 5 LAF Hoods, ISO Class 5 Zone Workbenches, compounding equipment, and cleanroom suite floors are cleaned daily at the end of the day. Two sporicidal cleaning agents, bleach and Spor-Klenz, are used interchangeably. With either cleaning agent, a minimum of 15-minutes contact time on the cleaned surface is used to provide adequate sporicidal effectiveness.

Two tacky mats are placed in succession at the entrance of the material transfer room to reduce entry of cart wheel particulates into the material transfer room. Carts are sprayed with Bleach or Spor-Klenz before entering the material transfer room. Sterile Water for Irrigation (SWFI) may be used as part of any cleaning process to remove excessive stains, dirt, or residue as long as Sterile Filtered 70% Isopropyl

Alcohol (70% IPA) is used after SWFI cleaning. Cleanroom suite shelving, storage bins, and their contents are cleaned weekly. ISO Class 5 Hood HEPA filter diffuser grills are visually inspected daily and cleaned and sanitized as needed. This includes a visual inspection of the diffuser and the inner circumferences of the circular perforations for cleanliness.

In the event that solution splashes on a HEPA diffuser, compounding activity is temporarily discontinued while the HEPA filter diffuser is cleaned with a sterile lint-free disposable cleanroom wipe moistened with sterile water. Cleanroom rated microfiber mitts or pads may also be used. A particle count sample is taken in the ISO CLASS 5 workspace that was cleaned so that the HEPA filter is not compromised. If the particle sample meets ISO CLASS 5 specifications, compounding may resume. This type of event is documented according to the procedure in CAPS deviation SOP.

Cleaning supplies are introduced into the cleanroom suite in compliance with a strict procedure, "Cleanroom Compounding Area – CSP Intro / Removal." Mop handles, buckets and other cleaning tools are cleaned daily after use and stored in an area of low traffic outside the cleanroom. Mop head covers are discarded after each cleaning session.

Open containers of sterile wipes are stored within the ISO Class 5 workspace until used or discarded. 70% IPA spray containers are cleaned and refilled as outlined in CAPS SOP.

Non-CAPS personnel (e.g., contractor performing maintenance) are only allowed to enter cleanroom areas where no compounding is actively being conducted. Upon completion of work the entire cleanroom suite is cleaned per CAPS SOP.

CAPS conducts a cleaning validation where bioburden of cleanroom surfaces are measured before and after cleaning and sanitization, as a supplement study in demonstrating the effectiveness of CAPS' cleaning and sanitization process. CAPS' cleanroom sanitization contact time and effectiveness is based on the overall lethality, or D-value results, of each challenge organism in each cleanroom material surface from the disinfectant validation study. The disinfectant validation study demonstrates that Spor-Klenz reduces the population of non-spore forming bacteria, conidiospore-forming mold, and yeast to 6 logs within 5 minutes of exposure, and spore-forming bacteria from 2 – 6 logs within 15 minutes of exposure. The 400 ppm bleach reduces the population of non-spore forming bacteria and yeast to 6 logs within 15 minutes of exposure. The 70% IPA disinfectant reduces the population of yeast, non-spore forming bacteria and conidiospore-forming mold to 6 logs within 15 minutes of exposure.

## **Process Validation**

CAPS media fill process validations demonstrate that the compounding staff, processes, and equipment used at CAPS are capable of maintaining the appropriate level of sterility assurance during the preparation of CSP's. CAPS media fill process validations simulate all CAPS compounding processes and are tailored to variables such as number of drugs, risk level of compounding process, and type of equipment used. Compounding personnel must complete media fills for all sterile to sterile processes they are assigned to annually. Additionally, compounding personnel must complete media fills for all non-sterile to sterile processes they are assigned to every 6 months. Simulations are performed at worst case or representative dynamic conditions in cleanrooms and ISO Class 5 LAF work stations or benches such as maximum or number of compounding personnel, aseptic interventions and manipulations.

## **Equipment Calibration, Validation and Preventative Maintenance System**

CAPS maintains and documents the maintenance and certification of compounding and laboratory equipment used in compounding and testing finished prescriptions or in process components. Laminar flow hoods are certified initially, and then recertified semi-annually. Biological safety cabinets are certified in accordance with the National Metrology Management System (MMS) 1 Sanitation Foundation Standard 49 Class II Biohazard Cabinetry. CAPS utilizes two different automated compounders. Volumetric checks are performed on a set frequency as recommended by their respective manufacturers. Cleanrooms are certified initially and then recertified every 6 months or when renovations occur in accordance with CAPS SOP specifications, or per State and local requirements, whichever is stricter. Cleanroom pre-filters are changed every three months. Power failure emergency backup generators are inspected and maintained every six months. Calibration/maintenance records and reports are maintained at the CAPS pharmacy. Each record or report is reviewed, approved and signed by both the CAPS DOP (or designee) and by the Quality Unit within 30 days. Issues noted on the certification report(s) must be addressed and documented on CAPS "Investigation/Corrective Action Report". Calibration and certification is performed by qualified personnel, or an approved vendor.

## **Area Clearance and Label Accountability System**

CAPS maintains a line clearance policy describing label accountability and reconciliation processes whereby material (raw material, components, and documentation) from the previous CSP order is removed prior to start-up of a new compounding session and whereby labels are accounted and reconciled to prevent CSP mix-ups and mislabeling.

Each specific formulation or batch is compounded in a separate ISO Class 5 hood or workbench. This separation in compounding occurs in a manner that keeps materials and supplies dedicated to each type or distinct compounding session together. Between batch or distinct compounding sessions, a total line clearance and ISO Class 5 area cleaning and sanitization is conducted and verified.

CSP label contents are verified by a Pharmacist for correctness, and compliance with State and Federal rules and regulations. The Quality Unit conducts accountability of any labels that are printed, used, damaged, and destroyed. Label accountability is documented on batch records for each distinct batch. Label(s) printed but not used are secured, accounted for, made unusable, and destroyed. Reprints are approved by the Quality Unit. Batches where there are any discrepancies on label accountability are segregated and investigated prior to batch disposition.

## **Change Control**

CAPS has a robust change control program that provides detailed instructions for initiation, review and approval of additions or changes to CAPS validated systems. CAPS change control program is a key responsibility of the CAPS Quality Unit. The change control program provides a classification scheme whereby proposed changes are approved prior to implementation following evaluation for potential impact on CSP quality and validation requirements of critical systems. CAPS defines critical systems as those physical facilities, utilities, raw materials, suppliers, test methods, and support systems that are directly involved in the CSP production or maintenance of the quality characteristics of safety, identity, strength, purity, functionality, and sterility of CSPs.

## Compounding Sterile Preparation (CSP) Release System

CAPS has extensive policies and procedures for release testing for both non-sterile to sterile compounding and sterile to sterile compounding of CSPs. The CAPS test-hold-release (THR) testing process, is distinct and unique to CAPS.

For non-sterile to sterile compounding CSPs, the following quality assurance tests are completed for each batch of solution compounded:

- Mixing vessel/liner integrity testing
- Filter integrity testing (Bubble Point Test)
- Yield verification
- Label ID verification
- Visual appearance
- LAL ( Endotoxin testing per USP/NF)
- USP <71> sterility testing using membrane filtration method or Rapid Sterility Method using an FDA Approved BacT/Alert<sup>®</sup> System
- Particulate matter test (per current USP/NF HIAC)
- Chemical identification
- pH, and concentration per USP

Each CSP batch is reviewed by a registered pharmacist and by the on-site independent Quality Unit. No CSP lot may be released for patient use, unless test results are within specifications and the on-site independent Quality Unit has authorized the batch for release.

For sterile to sterile compounding, CAPS pharmacy employs numerous microbial reduction/control steps. CAPS maintains engineering controls and has aseptic gowning procedures in place inside the ISO Class 8 ante area prior to entering into the compounding cleanroom. CSP compounding occurs under ISO Class 5 laminar flow benches located within ISO Class 7 clean rooms by highly trained CAPS pharmacists and IV technicians. CAPS performs extensive daily EM of its personnel, equipment, and cleanroom facilities. The effectiveness of the cleaning and sanitizing processes and maintenance of the ISO classified cleanroom environment is assured and continuously verified through routine, periodic viable and non-viable environmental testing, which includes sampling of surfaces and personnel. CAPS comprehensive media fill validations routinely demonstrates that the compounding personnel, equipment, and environment are capable of producing sterile compounded preparations free of microbial contamination. To further assure that the compounded sterile preparations are sterile and have the proper identity, purity, and potency or drug strength, CAPS conducts sterility testing, endotoxin testing, concentration and potency assay testing\*\* as well as a visual check for particulate matter, labels, and other critical container defects for each batch of CSPs compounded using sampling that represents the entire batch. Each batch must pass all these quality tests and checks prior to release for distribution.

CAPS utilizes a BacT/Alert<sup>®</sup> 3D Instrument, a FDA approved rapid technology for CSP sterility testing. The BacT/Alert<sup>®</sup> 3D Instrument utilizes a colorimetric sensor and reflected light to determine the amount of Carbon Dioxide (CO<sub>2</sub>) that is produced as the organisms metabolize the substrates in the culture

medium. The user injects a volume of testing solution to the BacT/Alert® culture bottle, scans the bottle bar code, and inserts it into the incubator. The BacT/Alert® incubator system incubates, agitates, and with solid-state reflectometers, continuously monitors the status of each culture bottle for microbial growth by using a Light Emitting Diode (LED) to scan the bottle sensor every ten minutes. Samples are monitored individually. The system will immediately alert if a positive culture is detected with visual and audible signals. The system will identify the location of the positive sample through the control module. CSP sterility method or B&F validation is conducted for each CSP prior to its implementation for routine sterility testing. For Cardioplegia solutions admixed utilizing a compounding device, composite sterility testing samples are obtained at three intervals (beginning, middle, and end) of an admixing session. These composite samples are sterility tested in lieu of randomly selected samples of finished CSPs intended for customers. In the event that a sterility positive is observed from these composite samples, all CSPs within this grouping will be implicated. Sterility testing is one of the critical parameters for CSP disposition or release in CAPS. The entire batch is quarantined until sterility testing is completed.

For CSP bacterial endotoxin testing, CAPS utilizes the Endoscan-V Kinetic Turbidimetric System to detect and quantify endotoxins in CSPs. The Kinetic Turbidimetric method is one of the methods used to perform bacterial endotoxin testing where the early onset of turbidity, which precedes gelation, can be detected and precisely measured. The Endoscan-V Kinetic Turbidimetric System consists of microplate readers, computer and software system using Kinetic Turbidimetric Limulus Amebocyte Lysate and Control Standard Endotoxin for the creation of a known value standard curve. The time for onset of turbidity is inversely related to the amount of endotoxin in the sample, so endotoxin levels in unknown samples are determined by comparison to a standard curve. The microplate reader analyzes a kinetic turbidimetric assay by using temperature control to provide stability for temperature sensitive assays and high quality optics with a range 340 nm – 900 nm wavelength to accurately detect the early onset of turbidity. The Endoscan-V endotoxin measuring software is then used to perform required calculations to generate endotoxin values for all test samples and provide secure data reports for all test data. CSP bacterial endotoxin method or Inhibition & Enhancement validation is conducted for each CSP prior to its implementation for routine sterility testing. For routine CSP bacterial endotoxin testing, samples from the beginning and end of each batch are tested. Bacterial endotoxin testing is one of the critical parameters for CSP disposition or release in CAPS. CSPs are quarantined until this test is completed.

CAPS utilizes high-precision ACQUITY Ultra Performance Liquid Chromatography (UPLC) new generation, H-Class System technology for CSP potency or concentration testing. The ACQUITY UPLC H-Class system provides separation and quantitative analysis of organic compounds in order to separate impurities and measure the concentrations of drug CSPs. The UPLC can be used to measure multiple drugs within a single dose and is capable of indicating the stability of CSPs. The UPLC is composed of a sample manager, column heater, quarternary solvent manager, tunable UV detector, and Empower software. After a sample is prepared, the sample manager injects a volume of sample into a gradient managed by the quarternary solvent manager. The sample interacts with the column particles which results in the separation of mixtures and impurities for accurate quantitative analysis of the compound of interest. The compound is detected through a tunable UV detector which identifies the absorption of light at the wavelengths specified. This data is relayed to the Empower software which manages sample information, processes raw data, and reports results relevant to the test. CSP method validation, including forced degradation, is conducted for each CAPS CSP prior to its implementation for routine potency or concentration testing. For routine CSP potency or concentration testing, samples from the beginning and end of each batch are tested. Potency or concentration testing is one of the critical parameters for CSP disposition or release in CAPS. CSPs are quarantined until this test is completed.

For electrolytes testing, CAPS utilizes Inductively Coupled Plasma for Optical Emission Spectrometry (ICP-OES). When combined with the SPS 4 auto-sampler and the ICP Expert data management software,

this new technology is a fully automated analytical technique that is capable of detecting elemental concentrations at trace levels with its vertical plasma torch. Liquid samples to be analyzed are turned into a fine mist in a nebulizer and sprayed into the argon torch at 10,000°C, a temperature where molecules break down to their constituent atoms, providing the detector with a signal proportional to the concentration of each analyte. The instrument is designed to operate with dual view functionality to produce higher sensitivity, accuracy, and sample throughput when quantifying concentrations of electrolytes at low levels.

CAPS also conducts visual inspection of CSPs for turbidity, particulate matter, color change and leaks, along with label and batch record verification of accuracy, correctness, and completion, as part of routine CSP testing and release disposition for each batch. Visual inspection is conducted using a 0.01 Acceptable Quality Limit (AQL) sampling plan across the batch with 95% confidence level and acceptance criteria of 0/1 (accept / reject).

The testing and CSP release verification, which are independently conducted by the Quality Unit, are designed to establish that each batch of CSP conforms to predetermined specifications.

## **Operational Variances, Complaint System, and Corrective and Preventive Action (CAPA)**

CAPS has a systematic CAPA program to identify, eliminate the causes, and prevent recurrences of actual or potential non-conformities relating to CSP processes and the quality system. CAPS' CAPA procedure establishes requirements for CAPA inputs, criteria for initiation, tracking corrective and preventive actions, implementation, closure, documentation, and verification. CAPAs are initiated based on identification of adverse trends from CSP testing, complaint system, EM, microbiological investigations, Out of Specification (OOS) investigations, Supplier Corrective Action Notices (SCAN), audit observations, and from any CSP recall. The Quality Unit is responsible for monitoring the corrective and preventive actions, reviewing their implementation, verifying their effectiveness, assuring all changes are documented, and verifying that appropriate personnel are trained in corresponding procedures, if applicable. CAPS CAPA program includes an effectiveness evaluation, which verifies the root cause(s) identified during the investigation have been corrected thereby eliminating or significantly reducing non-conformity. The effectiveness evaluation includes evidence to confirm successful implementation of the change or corrective and preventive actions while ensuring such actions have not adversely affected the finished CSP. The documentation evidence includes, but is not limited to, process validation, change control, design verification, non-conformance or deviation report trends, customer complaint trends, Statistical Process Control (SPC) charts, and process or system audit.

## **Recall Procedure**

CAPS maintains a SOP for Drug/Device Recall so that any drug or device that is recalled by a manufacturer or FDA will be removed from the CAPS pharmacy. This SOP also defines the process and responsibilities for the initiation, implementation, and administration of a CAPS initiated product recall.

Supplier or FDA initiated recalls must be promptly communicated to the CAPS DOP. In the event that the DOP determines that other CAPS pharmacies may be affected by the recall, Quality Assurance should be notified. The CAPS DOP or designee will review supplier recall notices for products used in CAPS pharmacies. If the product is not stocked in the CAPS pharmacy, the notice will be disregarded. After

notification from manufacturer or FDA of a stocked item, the CAPS DOP or designee will thoroughly search the Pharmacy to recover the specific lot number of drug involved and/or determine if the product has been used within the pharmacy.

If the specific drug/product identified in the recall is found on the premises, it must be logged into the Recalled Drug/Device Inspection Record. The letter or notice of recall from the manufacturer or supplier will be kept on file by the DOP or designee, along with the Recalled Drug/Device Inspection Record documenting action taken for the items recalled. If the drug/device is located at the CAPS pharmacy, all units will be quarantined until such time they are returned to the manufacturer or are destroyed as advised in the recall. Returned shipping or destruction documentation is kept on file along with the Recalled Drug/Device Inspection Record. If a controlled substance is involved, the drug/device will be destroyed as advised by the Drug Enforcement Administration with proper documentation and confirming signatures or witnesses. If a specific recalled drug/device lot number has been used to prepare CSPs, an Investigation/Corrective Action Report will be completed for product impact assessment

Customers confirmed to have received the drug/device will, as applicable, be notified via phone and/or mail. The manufacturer will be notified of distribution of such drug/device. CAPS will utilize their Customer Inquiry Form and Product Complaint File to document recall/advisory actions. In the event a Medical Device Report (MDR) is deemed appropriate, a MDR will be completed and submitted.

Upon investigation, the CAPS pharmacy will obtain a complete list of all affected catalog/prescription numbers (if appropriate), lot numbers and the original release/dispensed quantity. Packing lists will be pulled to determine shipments of affected lots. A mailing list of customers will be prepared from the packing list documentation. Mailing labels will be created for each customer that will be contacted with a recall letter or advisory notice.

If CAPS has internally identified the need for a recall after reviewing internal complaint reports and/or internal investigations, CAPS will make appropriate notifications to the U.S. Food and Drug Administration. If deemed appropriate, a recall Letter or advisory notice will be prepared and signed by the Regional Director of Operations including the statement "URGENT – COMPOUNDED STERILE PREPARATION RECALL" prominently displayed in the document header. Customer specific recall letters will be prepared as appropriate.

A Recall Information form will be prepared to accompany the letter containing the following information: list of affected catalog numbers; list of affected lot numbers; preparation description; preparation disposition information; return information or destruction information as necessary; spaces for the customer signature/title/date; adequate space for the customer to document their inventory of the affected lots; return addressed envelope for the Recall Information form. The outer envelope will be stamped with a statement such as "URGENT – COMPOUNDED STERILE PREPARATION RECALL."

Return of the Recall Information forms will be monitored and a follow-up letter with another Recall Information form will be sent to all non-respondents. Recalled products which are returned to CAPS will be quarantined until disposition is determined. Copies of all information regarding the recall are maintained in a recall file. The recall will be closed after preparation disposition, tracking and documentation has been completed according to CAPS recall procedures.

Inquiries will follow CAPS investigation procedures. This includes any patient specific or facility specific inquiries.

## Technology Developments and Continuous Quality Improvement

As part of continuous quality improvement efforts, CAPS recently acquired a highly advanced steam sterilizer and validated a robust terminal sterilization cycle for equipment used in cleanrooms. This sterilizer (autoclave) is equipped with a fully automatic THEMA4 controller system with capability to terminally sterilize CSPs, material or equipment. The chamber shell of the system is designed for a maximum allowable working positive/negative pressure. The autoclave is controlled and monitored by the THEMA4 Touch Panel Controller which is a stand-alone computer based system. The controller manages communication with the operator through interface devices according to 21 CFR part 11 standards. The controller also commands all the ancillary control devices and provides proportional control of both pressures and temperatures by means of interpretation of analog inputs/outputs and programmed set points. CAPS is in the process of developing terminal sterilization cycles for CSPs.

CAPS is also evaluating Vapor Hydrogen Peroxide (VHP) bio-decontamination technology. This is being evaluated to minimize human handling, to standardize, and further increase the effectiveness of CAPS' commercial products/equipment sanitization process prior to their entry into the cleanroom. This technology uses vaporized liquid hydrogen peroxide in its carrier air stream system, which is re-circulated through the chamber for a controlled time until surface decontamination is achieved. This technology also has the capability of breaking down the residual hydrogen peroxide gas into components of water and oxygen in its chamber as a safety mechanism for the user, products, equipment, and environment.

### Acronyms

API	Active Pharmaceutical Ingredients
AQL	Acceptable Quality Limit
B&F	Bacteriostasis & Fungistasis
B.Docs	B.Docs/Live Link Document Processing System
BUD	Beyond Use Dating
CAM	Compounding Admixture Master
CAPA	Corrective and Preventive Action
CAPS	Central Admixture Pharmacy Services
CAR	Compounding Admixture Record
CDEx	Central Data Exchange
CFU's	Colony Forming Units
cGMPs	Good Manufacturing Practices
CO2	Carbon Dioxide

COA	Certificate of Analysis
COPs	Corporate Operating Procedures
CSP	Compounding Sterile Preparation
DOP	Director of Pharmacy
EDMS	Electronic Document Management System
EM	Environmental Monitoring
FDA	Food and Drug Administration
FFDCA	Federal Food Drug and Cosmetic Act
FRM	Forms
IPA	Isopropyl alcohol
KPI	Key Performance Indicator
LAF	Laminar Air Flow
LAFW	Laminar Air Flow Workbench
LED	Light Emitting Diode
M&TE	Measuring and Testing Equipment
MDR	Medical Device Report
MMS	Metrology Management System
MSS	Materials Sampling Specification
NCR	No Calibration Required
NFWT	New Formulation Work Team
NRAB	New Preparation Review, Approval and BUD Form
NSCI	Non-Sterile Component Inventory
OOS	Out of Specification
PAM	Prescription Admixture Master
PTCB	Pharmacy Technician Certification Board
QA	Quality Assurance
QC	Quality Control

QCC	Quality Control Coordinator
SCAN	Supplier Corrective Action Notices
SME	Subject Matter Expert
SOPs	Standard Operating Procedures
SPC	Statistical Process Control
SPEC	Specifications
SWFI	Sterile Water for Irrigation
TAS	Test Article Specification
THR	Test, Hold and Release
TM	Training Module
TP	Test Procedure
UL	UL Quality, Compliance and Learning
UPLC	Ultra Performance Liquid Chromatography

## References

Quality Standard for Large Scale Sterile Compounders

[http://www.clinicaliq.com/images/stories/clinicaliq\\_compounding%20quality%20standards.pdf](http://www.clinicaliq.com/images/stories/clinicaliq_compounding%20quality%20standards.pdf)

The Drug Quality and Security Act

<https://www.congress.gov/113/plaws/publ54/PLAW-113publ54.pdf>

Guidance for Industry Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf>