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STERILE COMPOUNDING: A REGULATORY OVERVIEW

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HOUSEKEEPING

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Questions

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Pharmacist UAN	0864-9999-18-079-L07-P	0864-9999-18-079-L07-T
Credits	1 CPE Hours = 0.1 CEUs	1 CPE Hours = 0.1 CEUs
Release Date	October 27th 2018	October 27th 2018
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ACCREDITATION

HOW TO OBTAIN CREDITS

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4. Submit a completed **Evaluation** (within 14 days) online for **each Workshop**.
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- Graduated from the Faculty of Pharmacy at the University of Manitoba in 2002.
- Past experience owning and managing community pharmacies.
- Currently owns and manages a large scale sterile and non-sterile pharmacy compounding practice.
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***Disclosure**: Surveyor, Accreditation Commission for Health Care (ACHC); Consultant, Gates Healthcare Associates; Consultant, MEDISCA Inc., Consultant, CPM.*

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LEARNING OBJECTIVES

PHARMACISTS

1. Describe the sterile compounding regulatory environment.

2. Discuss what's new in USP <797> and NAPRA aseptic compounding guidelines and standards of practice.

3. Evaluate the feasibility of integrating Good Manufacturing Practices (GMPs) into your compounding practice.

LEARNING OBJECTIVES

PHARMACY TECHNICIANS

1. Recognize key features of the sterile compounding regulatory environment.

2. Analyze what's new in USP <797> and NAPRA aseptic compounding guidelines and standards of practice.

3. Evaluate ways in which you can optimize your compounding technique through the implementation of Good Manufacturing Practice (GMP) elements.

OUTLINE

Sterile Preparations

- Risks
- Adverse Events

The Response

- DQSA
- NAPRA
- USP

The Path to Improvement

- Infrastructure and Operations
- Environment
- Preparation / Product

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LET'S BEGIN

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STERILE PREPARATIONS

Sterile preparations are at most risk for errors and failures in quality

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STERILE PREPARATIONS

Risks in compounding include:

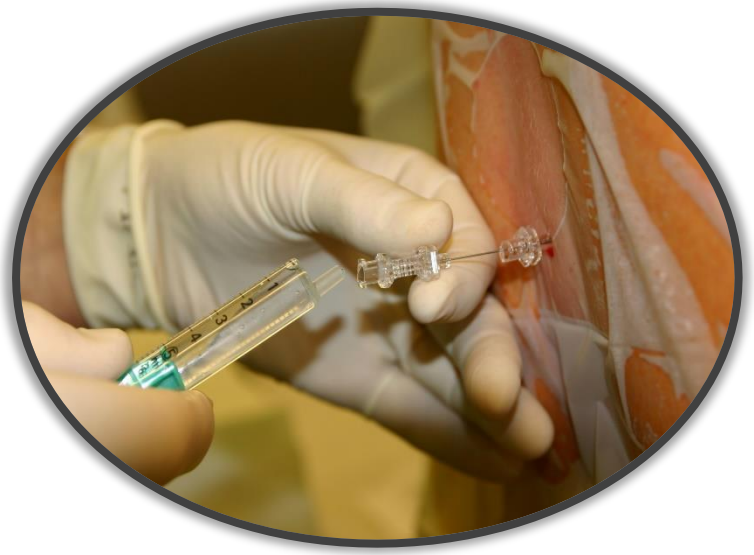
- Using incorrect formulae and calculations
- Selecting incorrect ingredients
- Using incorrect quantities
- Producing unstable products
- Improper storage and/or labeling of products
- Not applying proper aseptic technique

THE 1990s

- 1990, Nebraska: Four patients die due to a contaminated solution
- 1990, Pennsylvania: Two patients lose vision due to contaminated eye drops
- 1998, California: Ten children test positive for *Enterobacter cloacae*, from contaminated saline syringes

THE 2000s

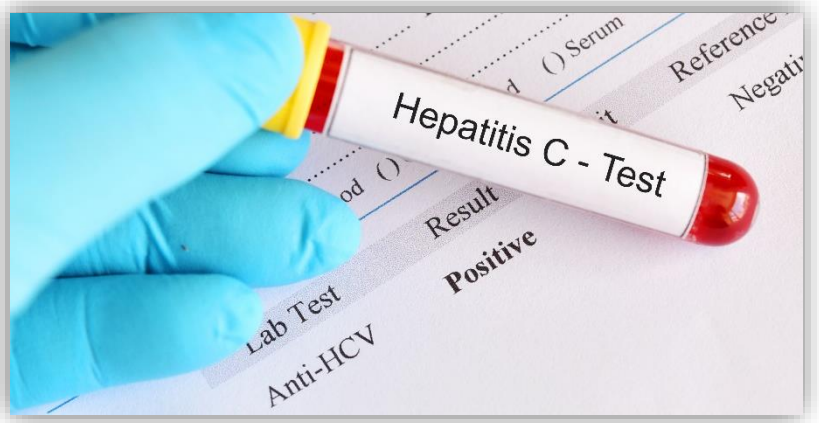
- 2001, California: Three deaths and 13 hospitalizations from contaminated spinal injections.
- 2001, Missouri: Four pediatric patients develop an infection after receiving IV ranitidine.
- 2002, South Carolina: Five patients receive contaminated steroids, resulting in one death.



THE 2000s (cont'd)

- 2004, Maryland: Sixteen patients contract hepatitis C infections after exposure to contaminated radioisotope equipment.

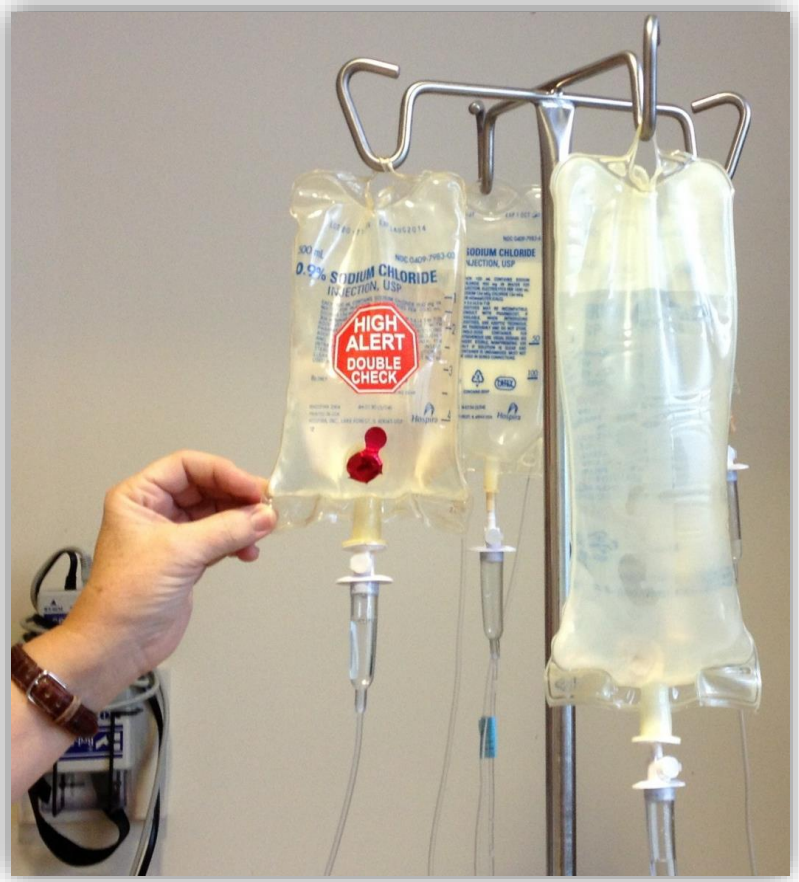
- 2007: Study reveals lack of prepare pharmaceutical graduates – only 13% of deans claimed students were adequately trained in sterile compound before graduation.



THE 2010s

- 2010: Pediatric patient dies due to improperly compounded sodium chloride concentrate.
- 2011, California, Florida and Tennessee: Multiple patients blinded after receiving contaminated Bevacizumab.
- 2012: Fungal meningitis outbreak linked to contaminated methylprednisolone injections. According to the CDC, 751 people were affected, with 64 deaths (as of 2017) directly associated.

THE 2010s (cont'd)



- 2013, Canada: Approximately 1200 people receive lower than intended doses of chemotherapy agents.
- 2013, Connecticut: Hospital identifies magnesium sulfate contaminated with mold.
- 2013, Georgia: Pharmacy recalls 79 lots of compounded retinal injections for risk of eye infection.
- 2013, Texas: 15 patients infected, 2 death – due to a contaminated batch of compounded IV calcium gluconate

THE 2010s (cont'd)

- 2014, Oregon: Patient dies after receiving the wrong drug.
- 2015: In March, a large pharmaceutical company begins a recall due to mold contamination in its compounded drugs.
- 2015: In September, the FDA announced that a large outsourcing facility had issued a voluntary recall of all its sterile compounded products.
- 2015: Voluntary recalls continue across the U.S. (7 recalls impacting compounded drugs).

THE 2010s (cont'd)

- 2015: The National Institutes of Health (NIH) suspend 46 clinical drugs trials after the U.S. Food and Drug Administration found several defects in drug manufacturing.

- 2017, Canada: A patient dies after receiving a 1000-fold incorrect dose of Selenium. The pharmacy incorrectly prepared the solution in milligrams, NOT micrograms.

- 2018, Canada: Again, over 1200 patients receive lower than intended doses of chemotherapy agents.

WHAT DOES THE DATA POINT TO?

- The Institute for Safe Medication Practices (ISMP)
  - Collecting data on compounding events since the 1990s
  - Data based on self-reporting; true extent unknown
  - Many events do not go public due to legal proceedings

- Many variables affect sterile compounding risk profiles
  - Need more inspections and data collection to identify issues

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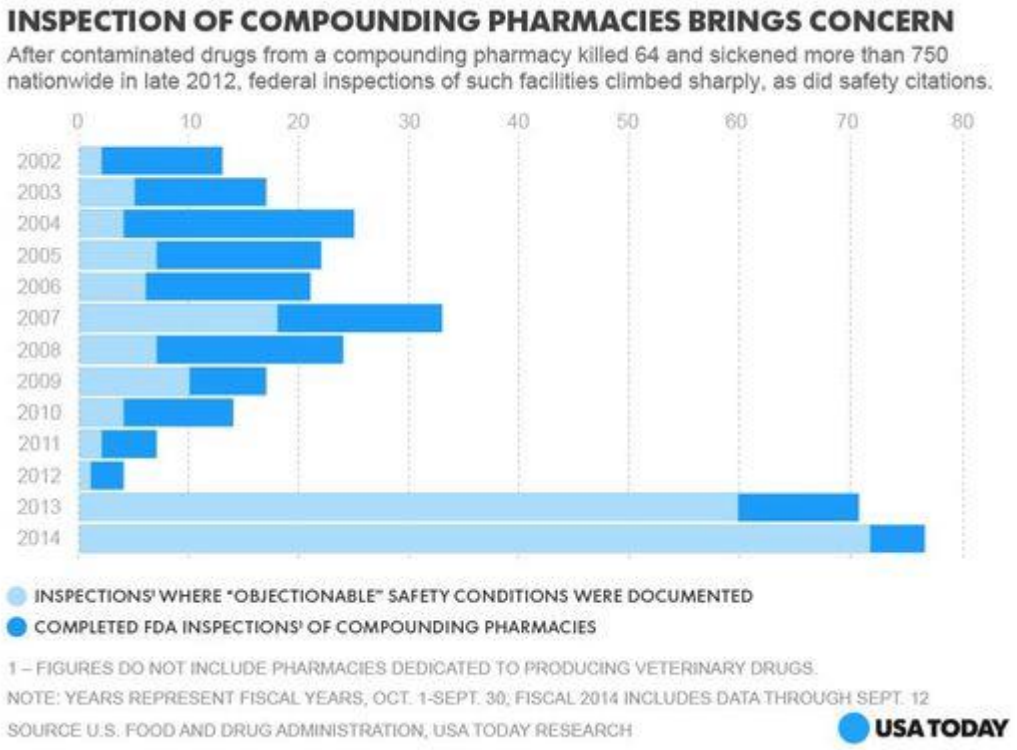
THE RESPONSE

- The highly publicized events of 2012 and 2013 prompted the review and overhaul of sterile compounding practices currently underway
- Resulted in significant increase of:
  - Reporting/public knowledge of occurrences
  - Inspections and enforcement of regulations:
    - 2012 – 4 Federal inspections
    - 2013 – 71 Federal inspections
- In Canada, the first inspectors tasked exclusively with reviewing sterile compounding standards were hired in 2013



NEXT STEPS

- Introduction of the Drug Quality and Security Act (DQSA)
  - Signed into law in 2013

- The National Association of Pharmacy Regulatory Authorities (NAPRA) in Canada published updated Model Standards:
  - 2014: Compounding of Non-Hazardous Sterile Preparations
  - 2015: Compounding of Hazardous Sterile Preparations
  - Up until that point, Canadian regulatory authorities were referencing standards from the 1990s

- The United States Pharmacopeia (USP) released proposed revisions to General Chapter <797>
  - Posted for public commentary on July 27th, 2018
  - Expected official implementation date of December 1st, 2019.

DRUG QUALITY AND SECURITY ACT

Signed into law in 2013, the **Drug Quality and Security Act** was prompted by the multistate outbreak of fungal meningitis in 2012 that affected more than 750 people and led to 64 deaths, drawing national attention to the dangers of inappropriate, large scale compounding

- Distinguishes between 2 types of compounding pharmacies:
  - **503A** (Traditional Compounders)
  - **503B** (Outsourcing Facilities)

DRUG QUALITY AND SECURITY ACT

503A: Traditional Pharmacies

- Patient-specific prescription
- Primarily regulated by State Boards of Pharmacy
- Follow USP standards of practice

503B: Outsourcing facilities

- Large volume pharmacy or facility
- Typically involved in sterile compounding
- Does not require patient-specific prescription
- Primarily regulated by the FDA
- Follow cGMP standards of practice

Access the entire DQSA text at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376732.htm

DRUG QUALITY AND SECURITY ACT

503A PHARMACY

- Require compliance with the United States Pharmacopeia chapters on pharmacy compounding.
  - ➢ FDA interprets as <795>, <797> and related standards compliance
- Compounded product is not “essentially” a copy of a commercially available drug product

DRUG QUALITY AND SECURITY ACT

503B FACILITIES

- Voluntary registration
  - *If you want to drive, you have to volunteer to get a driver's license*
- Requires compliance with Good Manufacturing Practices (cGMP)
- Do not have to be licensed as pharmacies, but must be supervised by a Pharmacist
- Patient-specific prescription is not necessary
- Difficult to combine 503A & B operations in same building

DRUG QUALITY AND SECURITY ACT

503B FACILITIES

- Compounded product is not "essentially" a copy of a commercially available drug product.
  - Unless the drug appears on FDA's drug shortage list
- Cannot produce medications for resale.
  - Selling to hospitals/physicians for office use is not resale

NAPRA MODEL STANDARDS

- 2014 - Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations
- 2015 - Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations
- Implementation dates vary across the Provinces and Territories
- Phased in Approach

NAPRA ANORP

National Association of Pharmacy Regulatory Authorities ®
Association nationale des organismes de réglementation de la pharmacie

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PROPOSED USP <797> REVISIONS

Major proposed changes:

- 3 microbial risk categories (e.g. low-, medium-, and high-risk) collapsed into 2 categories
- Maximum BUD changes
- Introduction of “in-use-time”
- Major changes to environment for CAIs/CACIs
- Requires use of sterile cleaning supplies
- Cross-references to <800> for hazardous drugs
- Public comment period closes November 30th, 2018
- Planned effective implementation date: December 1st, 2019

BOTTOM LINE

- More often than not, these adverse events are preventable
- Typically result from failures in quality assurance
- Regulations exist to protect the public, but when they are not adhered to, the consequences can be fatal

THE PATH TO IMPROVEMENT

- Regulations represent a *minimum* requirement
- Set a higher standard of quality and apply best practices
- These efforts will clearly differentiate you and set you apart from the crowd

TIME FOR THE HANDOFF!

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COMPOUNDING VS MANUFACTURING

- **Compounding:**
  - Patient specific
  - Performed by a licensed pharmacist or physician
  - Must adhere to appropriate guidelines and regulations (State boards, USP, DQSA, FDA, and other regulatory bodies)

- **Manufacturing:**
  - Large-scale mass production
  - Follows Current Good Manufacturing Practice (cGMP)
  - Regulations enforced by the FDA
  - Assures the identity, strength, quality, and purity of drug products

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https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm
https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm

PRACTICES AND PRINCIPLES OF MANUFACTURING

- Manufacturing operations must be controlled by:
  - Establishing strong quality management systems
  - Obtaining appropriate quality raw materials
  - Establishing robust operating procedures
  - Detecting and investigating product quality deviations
  - Maintaining reliable testing laboratories

https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm

IMPROVING THE QUALITY OF PREPARATIONS

- Develop a cGMP mindset!
- Manufactured products go through a rigorous quality process
- Incorporate certain cGMP concepts into your practice

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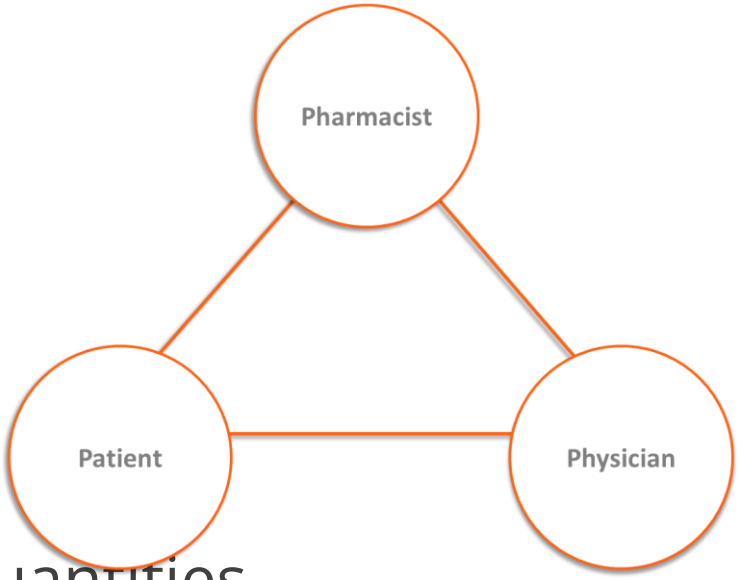
SCOPE OF PRACTICE – TAC (TRADITIONAL ASEPTIC COMPOUNDER)

- **Formulates for one patient**



- Compound for:
  - Patient-specific prescription
  - Office-use or hospital
    - Note: This is unacceptable from a federal perspective
  - Anticipatory compounding (batching) in limited quantities

SCOPE OF PRACTICE – cGMP

Manufactures for many patients

- Prepare medications before, with or without receipt of a prescription for an individual patient
- Distribute for:
  - Office-use and hospitals
    - No patient-specific prescription required
- Distribute or sell:
  - For interstate commerce with no maximum
  - To healthcare facilities that provide medical services directly to patients or a network of licensed providers

PERSONNEL MINDSET - cGMP

- Develop a cGMP mindset!

> **Fundamental cGMP Concept – Can you apply it to TAC?**
> Construct an ideology, an **attitude** and **vigilant adherence** to detail that is harmonized with a set of **actions and behaviors** in the formulation production process.

HOW DO YOU DEVELOP A cGMP MINDSET?

- Look for opportunities to take **cGMP** concepts and bring them into your **TAC (Traditional Aseptic Compounder)** practice.

- You can become **"TAC / A+"** (A+ performer of Good Compounding Practices - GCP)

INFRASTRUCTURE AND OPERATIONS

PERSONNEL MANAGEMENT – TAC (TRADITIONAL ASEPTIC COMPOUNDER)

- Standards Require Personnel must undergo:
  - Training
  - Qualification
  - Annual refresher training and requalification
- Format:
  - Written
  - Documented outcome measures

- United States Pharmacopeia. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations (published for public comment in Pharmacopeial Forum (PF) 41(6) [Nov.–Dec. 2015] on November 2, 2015).

PERSONNEL MANAGEMENT – cGMP

- Personnel must maintain constant and consistent:
  - Training
  - Qualification
  - Monitoring

> **Fundamental cGMP Concept – Can you apply it to TAC?**
> The **qualitative and quantitative specificity and rigor** of personnel working in non-aseptic and aseptic manufacturing environment is essential to ensuring quality.

PERSONNEL MANAGEMENT – TAC / A+ CONSIDERATIONS

- Conduct Observational Checklists beyond USP requirements
  - Packaging
  - Weighing
  - Calibrating
  - Change to a Pro-Active Approach
    - Emergency Preparedness **Drills**
    - Recall **Drills**
    - HD Spill **Drills**
  - **Constant training (not yearly/biannually)**

QUALITY MANDATE – TAC (TRADITIONAL ASEPTIC COMPOUNDER)

- Standards Require:
  - Quality assurance (QA) and quality control (QC) program
- Responsible for:
  - Written processes that, at a minimum, verifies, monitors, and reviews the adequacy of the compounding process (QA)
  - Observation of techniques and activities that demonstrate requirements are met (QC)

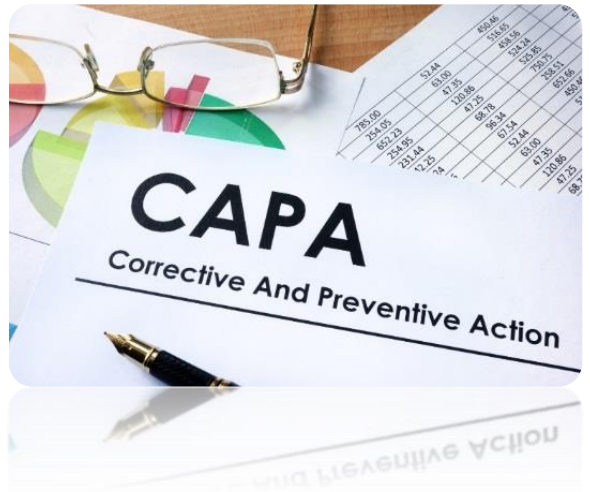
- United States Pharmacopeia. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations (published for public comment in Pharmacopeial Forum (PF) 41(6) [Nov.–Dec. 2015] on November 2, 2015).

QUALITY MANDATE – cGMP

- cGMP Requires:
  - Construction of an autonomous quality team
- Responsible for decisions to accept or reject formulations:
  - Based upon a comprehensive set of predetermined specifications
  - Independent of either financial or distribution pressures

CORRECTIVE ACTION AND PREVENTIVE ACTION (CAPA) – cGMP

- cGMP Requires:
  - Construction of **compliance system**
    - To identify operational variances
    - To operate a complaint system/CAPA plan
    - To **track and trend** feedback to improve the formulation / manufacturing process
  - CAPA system focuses on:
    - Systematic investigation of discrepancies (failures and/or deviations)
    - Attempts to **prevent their reoccurrence (corrective action)**
    - **Eliminates the cause of potential nonconforming product and other quality problems (preventive action)**



QUALITY MANDATE – TAC / A+ CONSIDERATIONS

- Construct a Quality Team
- **Add CAPA management processes (Correction processes required)**
  - **Prevention needs to occur**
- Acquire Compliance Software System
  - **Reminders**
    - **Competency events**
      - **Media fills**
      - **Garbing/Gowning**
  - Licensure
  - **Environmental Certifications**
  - **Maintenance Events**
  - Computerized LUMACs (Logs of Use Maintenance and Cleaning)
- Quality indicators
  - Formal system for input, tracking, and trending

STANDARD OPERATING PROCEDURES

- Construct and operationalize standard operating procedures
- **SOP – TAC**
  - Requires SOPs that address USP general chapters:
    - <795>, <797>, and <800>
- **SOP – cGMP**
  - Requires process validation driven SOPs

Fundamental cGMP Concept – Can you apply it to TAC?

In order to ensure process uniformity within an organization, and maintain it consistently, detailed and specific standard operating procedures must drive all critical processes.

TAC / A+ – Change Control SOP – LUMAC – Vendor Validation

INFRASTRUCTURE AND OPERATIONS

FROM RECEIPT TO RELEASE – TAC (TRADITIONAL ASEPTIC COMPOUNDER)

- Standards require: a minor process centered around **trust** but not a verification

- As per the USP General Chapter <795>:
  - If a manufactured drug product is the source of an active pharmaceutical ingredient, then the drug product shall be manufactured in an FDA-registered facility

FROM RECEIPT TO RELEASE – cGMP

- A vendor validation process drives the process in manufacturing
- The process is from the receipt to the release of:
  - Materials
  - Supplies
  - Packaging
  - Non-sterile ingredients

> **Fundamental cGMP Concept – Can you apply it to TAC?**
> Confirming the identity and quality of starting materials is fundamental to building quality into the manufacturing process.

FROM RECEIPT TO RELEASE – TAC / A+ CONSIDERATIONS

- Chemical Purchasing
  - Determine appropriate amount and **container size of chemical** to order.
  - **Review the need for special chemical storage** conditions including but not limited to:
    - Space.
    - Temperature and humidity.
    - Hazardous Nature/Ventilation.
    - Lighting.
    - Segregation.
  - **Ensure that vendor qualification procedures have been satisfied** prior to placing a purchase order.
  - Insure vendor is FDA registered and licensed in good standing.
  - Review vendor sampling methods and quality control procedures, whenever possible.
  - Consolidate orders such that all items needed from the same vendor are placed on the same order.
  - Verify and document method of payment for all orders.

EQUIPMENT MANAGEMENT - TAC

- USP General Chapter <797> requires that:
  - "The equipment used for compounding compounded sterile preparations (CSPs) **must be of appropriate design and adequate size".**[1]

1. United States Pharmacopeia. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations (published for public comment in Pharmacopeial Forum (PF) 41(6) [Nov.–Dec. 2015] on November 2, 2015).

EQUIPMENT MANAGEMENT - cGMP

- cGMP Requires:
  - An equipment calibration, validation, and preventative maintenance system
  - A **robust process validation system**, i.e.,
    - Understand how equipment will be used to achieve the quality, integrity, strength, and sterility of each batch
  - **Initial and regular validation of each piece of equipment** or group of equipment
  - A calibration log that specifies:
    - Frequency of calibration
    - Points where calibration is checked
    - Acceptable operating range

EQUIPMENT MANAGEMENT – TAC / A+ CONSIDERATIONS

- Thermal mapping of temperature-related equipment
  - Refrigerators
  - Autoclave
  - Dry heat oven
  - Lower cost modified mappings can be constructed
- Use NIST-certified devices (National Institute of Standards and Technology)
- Create LUMACs (Logs of Use Maintenance and Cleaning) for critical equipment
- Barcode equipment to track usage and maintenance

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FACILITY MANAGEMENT - TAC AND cGMP

- Any quality compounded/manufactured medication must be produced in a suitable environment that controls the risk of contamination and error

> **Fundamental cGMP Concept – Can you apply it to TAC?**
> Operate and maintain all buildings/facilities with extreme vigilance with an emphasis on environmental monitoring.

ENVIRONMENTAL MANAGEMENT

- Standards Require:
  - Comprehensive cleaning and disinfecting procedures and processes
  - Facilities and equipment to be qualified, calibrated, cleaned, and maintained
    - Prevent contamination and errors
    - Critical to ensure suitability and appropriateness of use
  - Equipment use logs
- Must Recognize the human factor in environmental management
  - **10 Million Particles / Cu Ft.**

TAC / A+ Considerations

- Sterile Containment Suits
- Sterile Gowns/Sleeves
- Sterile Cleaning Utensils/Solutions, Autoclave
- Garb Management at Facility

ENVIRONMENT

CERTIFICATION - TAC

- Standards Require: "Sterile compounding facilities must be qualified initially using environmental air and surface sampling to establish a baseline level of environmental quality."[1]

- Do We "Trust" but Verify?

1. United States Pharmacopeia. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations (published for public comment in Pharmacopeial Forum (PF) 41(6) [Nov.–Dec. 2015] on November 2, 2015).

CERTIFICATION - cGMP

- Perform **triple clean 3** consecutive times (validation)
  - sterile bactericidal agent
  - sterile sporicidal agent
  - sterile isopropyl alcohol (SIPA)
- Time **interval between cleanings** (e.g., 1 week for full cleans)
- Sampling, incubation, and interpretation of results
- Failure implies excursions to action levels
  - Reassess procedure for effectiveness
    - Improve, if required
  - Repeat 3 consecutive runs
  - Results must meet acceptance criteria

CERTIFICATION – TAC / A+ CONSIDERATIONS

- Examine certifier competency (CETA)
- Construct a Vendor Validation of Certifier
- Control and monitor certifier behaviors (SOPs)
- PEC and SEC smoke visualization
- Triple clean monthly

1. United States Pharmacopeia. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations (published for public comment in Pharmacopeial Forum (PF) 41(6) [Nov.–Dec. 2015] on November 2, 2015).

CLEANING AND SANITIZING FREQUENCY – TAC / A+ CONSIDERATIONS

- Internal smoke visualization
- Triple clean monthly
- Documentation
- Peer validation (sign)
- GoPro camera
- Sterile solutions/utensils
- State of control documentation

- Construct MFR and CR for cleaning process including dilution preparation
- Record lot number of cleaning solutions
- Checklist for cleaning process
- Observational checklist for operator validation
- Separate mop handles per room
- Include non-pathogenic biological indicators in cleaning validation

NONVIABLE AIRBORNE PARTICLE SAMPLING – TAC / A+ CONSIDERATIONS

- Acquire Particle Counter or..
- Increase Frequency
- Utilize During Compounding Processes
  - Batching (anticipatory compounding)
  - Trend particulate levels per site over time
  - Personnel behaviors (unwrap, wipe down, type of materials)

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PREPARATION MANAGEMENT – TAC / A+ CONSIDERATIONS

- Purchase chemicals in smaller containers to reduce exposure and cross contamination
- Utilize nitrogen gas to be bubbled into aqueous CSPs to reduce oxidative load
- Destruct all non-used chemicals once removed from the original container
- Conduct viable air sampling during Media fills
- Conduct non-viable sampling during batch activities
- Validate formulas
- Incorporate process validation principles
- Barcode & validate all Ingredients
- Convert all liquids into density
- Peer review of all ingredients, volumes and masses
- Video recording of compounding process
- Employ compounding validation software

STERILIZATION PROCESSES – TAC / A+ CONSIDERATIONS

- Evaluate physiochemical stability of APIs/excipients and container/closures
- Terminally sterilize as much as possible
- Increase the quantity of BIs
- Map the position of the BIs
- Locate BIs within vials to simulate CSPs
- Include and enhance chemical integrators
- Sample retention
- Incorporate bioburden reduction for formulation process

RELEASE TESTING/SYSTEM – TAC / A+ CONSIDERATIONS

- Barcoding all substances in the formulation process
- Barcoding all equipment used in the formulation process
- Convert all liquids into a mass (density) for accuracy
- Photograph finished preparations
- Develop a formulary system
- Increases opportunity to validate formulas
- Test all aliquots for potency prior to use (1 for many)
- Test all batches for potency
- Acquire color sampling for accuracy
- Conduct container closure evaluations on susceptible and high volume preparations

SUMMARY

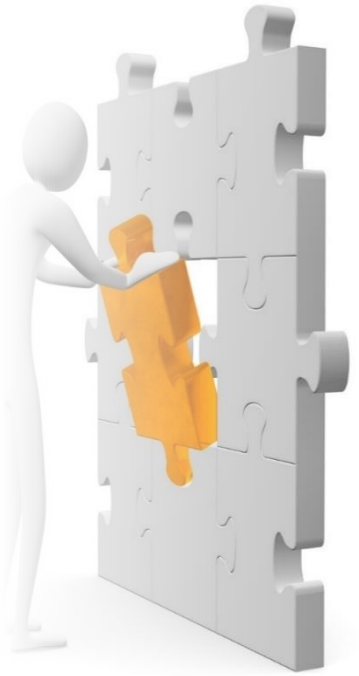
12 Tenets to cGMP

1. GMP Mindset
2. Autonomous Quality Team
3. Process for Release/Receipt
4. Facility Vigilance
5. Process Validated of SOPs
6. Constant/Consistent Training
7. Maintain Final Prep/product check
8. Facility/ Equipment Cleaning
9. Process Validation Critical Steps
10. Facility/ Equipment Maintenance
11. Activate CAPA
12. Maintain Prep/Product Release

WHERE DO YOU BEGIN?

IT DEPENDS?

- Changing Directions…from a TAC to cGMP practice
- Integrating concepts of cGMP into a TAC
  - TAC + cGMP (concepts) = TAC / A+
- Current regulatory status
- Potential market



PRIORITIZE HIGH RISK, HIGH VOLUME AND PROBLEM PRONE AREAS

- Change Culture to a Quality Culture
- Evolve from fire fighting to fire prevention
- Trend Past Data and QREs to determine areas of need/risk. Don't let history repeat itself.
- Learn from GMP – advance knowledge
- Review revise formulations based on HR/HV/PP

TRACKING CODE

WCC2018STERILE

THANK YOU FOR LISTENING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