A cGMP Culture: What 503As Can Learn from 503Bs

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Agenda

- The unique challenge of 503A compounding
- Implementation of advanced technologies
- Operational strategies to improve efficiency, safety, & compliance
- Quality culture
  - Regulatory strategy
  - Robust quality assurance program

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The Unique Challenge of 503A Compounding

It's hard to ensure reproducibility and reliability when N = 1

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Manufacturing vs. Compounding

Manufacturing	Compounding
FDA approved drugs	Compounds
Large commercial scale batch sizes (>5000 units)	Small scale batches (1-250)
Use of automated filling machines	Manual processing
Reduced need for operator intervention or manipulation	Extensive human manipulation - interventions made from start to finish
Increased separation of operator from critical site	Operator in close contact with the critical site

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The Challenge is Personalized

- Compounds are patient-specific
- Small scale not commercial scale
- Several types of compounds are requested
- Several types of container/closures are used
- Machines do not match manual processing flexibility or cost to entry
- Manual methods are considered the riskiest of all aseptic processes

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FDA Warning Letter

Your firm **failed to sanitize tubing between production of different sterile drug products**. The tubing connected to the stock solutions of (b)(4) in IV bags located in the ISO 5 Laminar Flow Hood was not sanitized between the production of different sterile drug products. The investigator observed the operator touching the tubing several times during drug product production. Not sanitizing the tubing between the production of different sterile drug products could contribute to cross contamination of drug products.

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FDA Warning Letter

- **Poor aseptic technique was used** by personnel engaged in aseptic processing. This includes blocking first air to containers during aseptic processing, moving quickly within the ISO 5 classified IV room and placing sterile gloved hands on gowning during aseptic processing.
- Materials and supplies were not adequately disinfected prior to entering the aseptic processing area.

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FDA Warning Letter

During the production of Phenylephrine Hydrochloride, the investigator observed your technician leaning into the ISO-5 hood with her elbows and forearms touching the working surface inside the ISO-5 area.

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Implement Advanced Technologies

To improve efficiency, safety, & compliance

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Advanced Technologies

- Single-use mixing systems
- Single-use transfer tubing & IV bags
- Sterilization capsule filters
- Single-use connectors
- Advanced closed systems
- Sterile bulk containers & closures
- Tools
- Tabletop filling
- Pharmaceutical isolators
- CVEs & downflow booths
- Flexible nonsterile filling equipment & 3D printing
- QMS software

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Single-Use Mixing

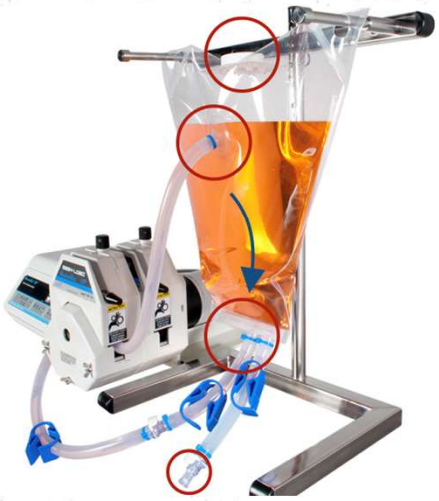

Image Credit: Meissner Filtration Products

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Single-Use Tubing, Bags, & Sterilization Filters

Image Credit: MilliporeSigma

Image Courtesy of PALL Corporation

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Single-Use Connectors

Image Credits: PALL Corporation, Meissner Filtration Products, Qosina Corp, Thomas Scientific, & Baxter

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Advanced Closed Systems

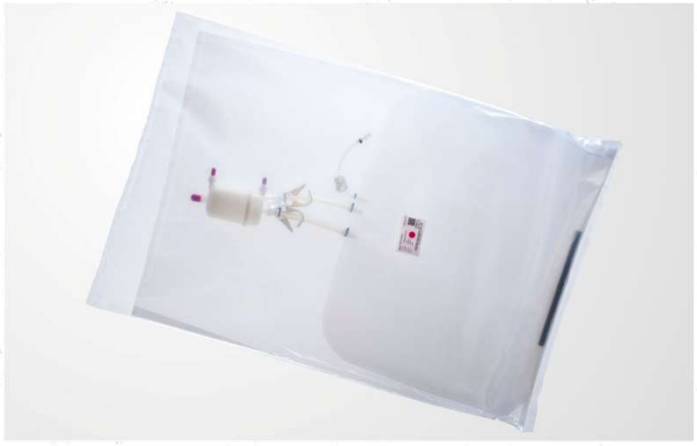

Image Courtesy of MDI Membrane Technologies

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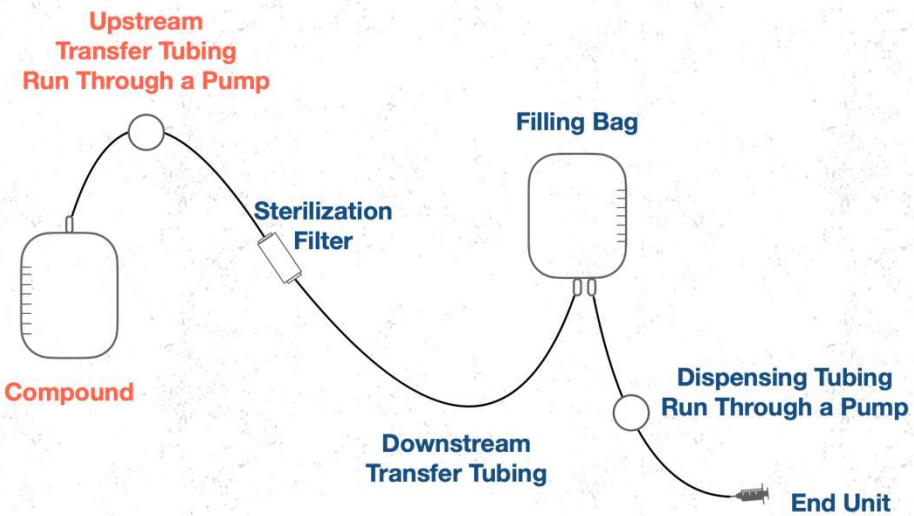
Advanced Closed Systems



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Sterile Bulk Containers

Image Courtesy of Prince Sterilization Services

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Sterile Bulk Containers

Image Courtesy of Prince Sterilization Services

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Single-Use Tools

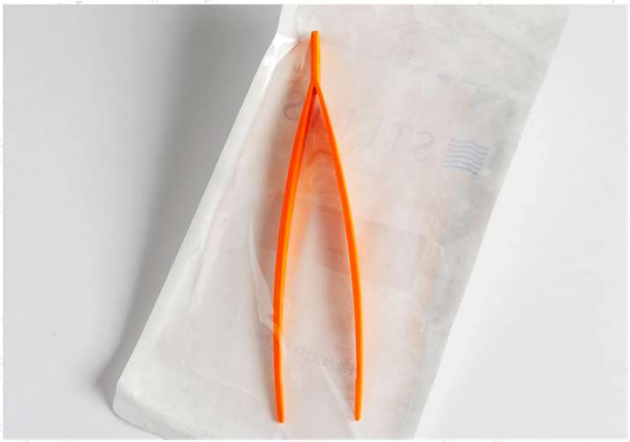

Image Credit: Steris Life Sciences

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Closed Container/Closure

Image Credits: Aseptitech

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Vial/Syringe Tabletop Filling

Image Courtesy of AST-Inc.

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Bag Tabletop Filling

Image Courtesy of Filamatic

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Pharmaceutical Isolator

Image Courtesy of Ecolab

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Powder Containment

Image Courtesy of Howworth

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Downflow Booth

Image Courtesy of Howworth

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Tabletop Filling

Image Courtesy of ATG Pharma

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3D Printing

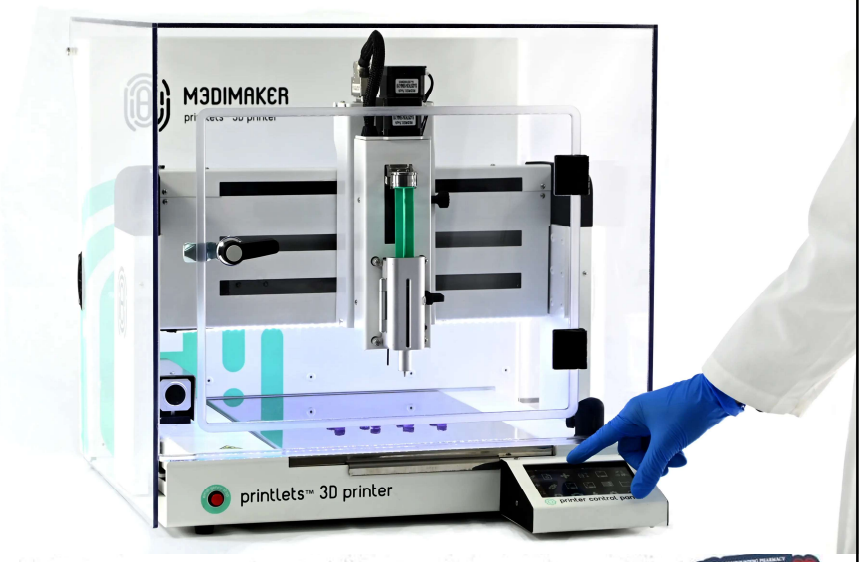

Image Courtesy of Fabrx

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QMS Software

- Dot Compliance
- Pestle
- Qualio
- Veeva
- Many more (some free)

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Operational Strategies

To improve efficiency, safety, & compliance

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Who am I and Why am I Here?

- Know your capabilities: What can you make?
- Know your capacities: How much can you make?
- Operate in a purpose-built facility
- Operate with equipment that's fit for purpose
- Use materials with appropriate quality attributes
- Stay within the confines of the 503A regulatory framework

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Key Elements to Success

- Detail the complete sterile compounding process design
- Minimize direct human interventions when possible
- Minimize interaction of operator with the environment
- Use advanced single use supplies that maintain a closed system
- Consider the type of PEC used
- Operators must exhibit good aseptic technique

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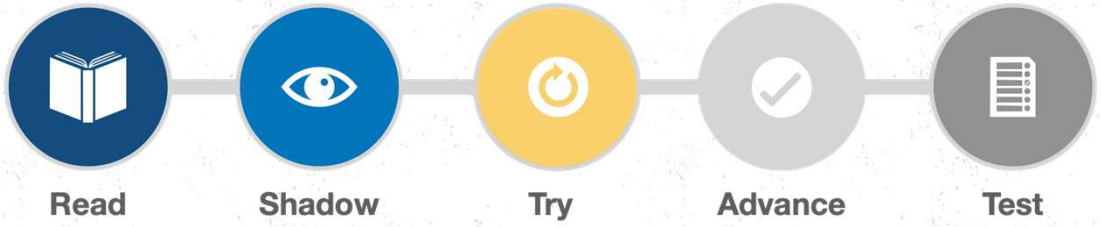
Provide Robust Training



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Have a Quality Unit

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Quality Culture

A cGMP culture is a quality culture

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Quality Culture as a Regulatory Strategy

- Why do you do what you do?
  - Patient safety
  - Less complaints, ADE, recalls & regulatory issues
  - Increased efficiency & revenue
- How do you get buy in?
  - Leadership
  - Training
  - Do what you say you do
  - Stay current
  - Give rewards

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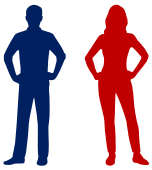
Cost of Quality



People

Technology

Time

Quality is not a revenue generating department
but it provides protection to the patient and therefore to the business.

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What does that look like?

People — Head of quality, personnel, auditor feedback

Tech — Track and report training, document control, equipment/facility maintenance/calibration, investigations/CAPA, incidents, etc.

Time — Training, spent away from operations

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Expected From Day 1

- Quality is non-negotiable
- Start with new employees - job description
- Built into the org chart, vision, values, meetings, SOPs
- Everywhere

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Challenges

- Lack of leadership involvement
- Lack of accountability
- Time to implement or improve changes
- Create systems and assurances

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References

- 21 CFR 211: Current good manufacturing practice for finished pharmaceuticals.
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- Compounding: Inspections, Recalls, and other Actions. www.fda.gov//drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions.
- Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act Guidance for Industry.

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