Current Good Manufacturing Practices

Cleveland American Institute of Chemical Engineers 24OCT2019 Meeting

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Session in Summary

- United States Food and Drug Administration
- What are CGMPs?
- FDA Observations
- Need for Public Protection
- cGMPs in Finished Pharmaceutical Manufacturing
- Risk Management
- Implications for Performance and Compliance
- cGMP Seminar Series in Summary with Cleveland State University

United States Food and Drug Administration

- **Food and Drug Administration**
  - FDA is an agency within the U.S. Department of Health and Human Services
  - FDA is responsible for protecting public health
    - Ensuring **foods** are safe and properly labeled
    - Ensuring that **human and veterinary drugs, vaccines, and other biological products and medical devices** intended for human use are safe and effective
    - Ensures that **cosmetics and dietary supplements** are safe and properly labeled
    - Advancing public health by **helping to speed up innovations that make medicines effective, safe, and affordable**
    - **Helping the public get accurate, science-based information** on medicines and foods to maintain and improve their health
    - Regulating the manufacturing, marketing, and distribution of **tobacco products**
    - Ensuring the **security of the food supply**, and **development of medical products** for protection from public health threats

What are cGMPs?

- CGMP refers to the **C**urrent **G**ood **M**anufacturing **P**ractice regulations enforced by the FDA.
- Provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
- Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. Including:
  - Strong quality management systems
  - Obtaining appropriate quality raw materials
  - Establishing robust operating procedures
  - Detecting and investigating product quality deviations
  - Maintaining reliable testing laboratories

What are cGMPs?

- The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.
- It is important to note that CGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

What are cGMPs?

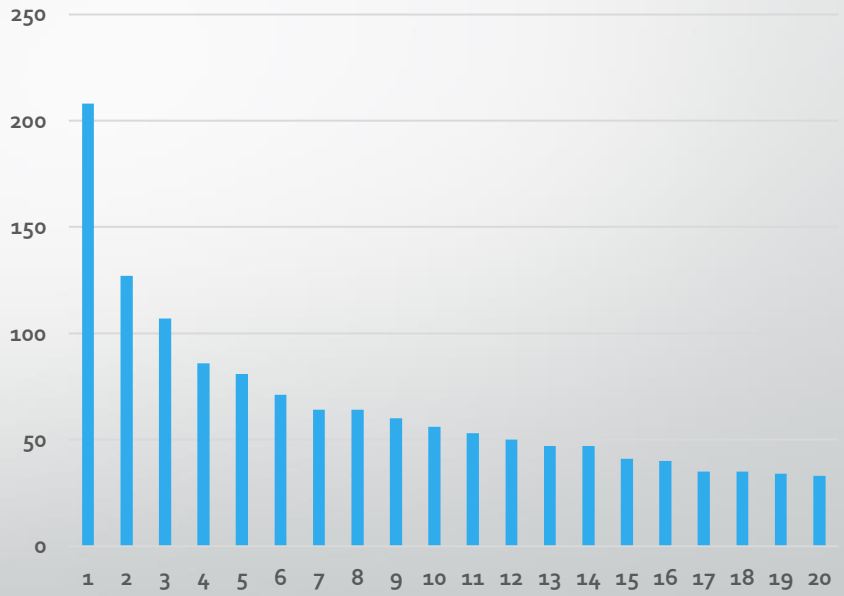
- **cGMPs are not just "best practice" they are law.**
- **Regulatory requirements of current Good Manufacturing Practices**
  - After an FDA audit inspection of a facility, the **FDA may issue a "Form 483" of observations** that require a response
  - If the manufacturer does not respond or remediate the Form 483 observation the **FDA may issue a warning letter**
  - If the **manufacturer does not respond or remediate the observations** in the FDA warning letter, then the FDA may have **a judge issue a court injunction** that will impose a consent decree that stops manufacturing
- **If a company is not complying with CGMP regulations, any drug it makes is considered "adulterated" under the law.**
- **While FDA cannot force a company to recall a drug, companies usually will recall voluntarily or at FDA's request. If a company refuses to recall a drug, FDA can warn the public and can seize the drug.**

What are cGMPs?

- **Objectives need to comply with regulations while retaining a highly competitive position**
  - Design, delivery, and maintenance of manufacturing support facilities, utilities, process equipment, and automation control so that they **perform as intended to meet business objectives, such as capacity, yield, operational efficiency, and reliability**
  - Development of a **production process** that can repeatedly produce a quality product
  - Creation of a **quality system** necessary to meet regulatory as well as business requirements
    - **Criteria: SISPQ**: Strength, Identity, Safety, Purity, Quality
    - **Project and process deliveries** are targeted to be within budgets and schedules and meet or exceed quality attributes.

Top 20 FDA Observations from 2018

Series	Code	Observation	Frequency
1	21 CFR 211.22(d)	Procedures not in writing, fully followed	208
2	21 CFR 211.160(b)	Scientifically sound laboratory controls	127
3	21 CFR 211.192	Investigations of discrepancies, failures	107
4	21 CFR 211.100(a)	Absence of Written Procedures	86
5	21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	81
6	21 CFR 211.68(b)	Computer control of master formula records	71
7	21 CFR 211.67(b)	Written procedures not established/followed	64
8	21 CFR 211.110(a)	Control procedures to monitor and validate performance	64
9	21 CFR 211.68(a)	Calibration/Inspection/Checking not done	60
10	21 CFR 211.165(a)	Testing and release for distribution	56
11	21 CFR 211.63	Equipment Design, Size and Location	53
12	21 CFR 211.113(b)	Procedures for sterile drug products	50
13	21 CFR 211.25(a)	Training , Education , Experience overall	47
14	21 CFR 211.166(a)	Lack of written stability program	47
15	21 CFR 211.25(a)	Training--operations, GMPs, written procedures	41
16	21 CFR 211.192	Written record of investigation incomplete	40
17	21 CFR 211.42(c)(10)(iv)	Environmental Monitoring System	35
18	21 CFR 211.22(a)	Lack of quality control unit	35
19	21 CFR 211.100(b)	SOPs not followed / documented	34
20	21 CFR 211.165(e)	Test methods	33



Need for Public Protection

Murder Trial Set to Begin Over Meningitis Outbreak

By Peter Loftus

Two pharmacists face second-degree murder charges in coming trials in connection with the sale of a contaminated pain medication that caused a deadly U.S. outbreak of fungal meningitis in 2012.

Jury selection is expected to begin in federal court in Boston on Wednesday for the trial of Barry J. Cadden, who co-owned the now-closed New England Compounding Center in Framingham, Mass. The trial of another pharmacist who worked there, Glenn Chin, is set to begin immediately after Mr. Cadden's ends.

They have pleaded not guilty to all charges. They face a maximum sentence of life in prison if convicted.

The New England Compounding Center made three contaminated lots of an injected steroid pain medication that caused 750 cases of fungal meningitis in 20 states, including 64 deaths, according to the U.S. Centers for Disease Control and Prevention. Shortly after the outbreak, U.S. Food and Drug Administration inspectors found contaminated drug batches and unsanitary conditions at New England Compounding Center, according to an FDA report.

The trials are expected to shed new light on an opaque corner of U.S. health care: thousands of compounding pharmacies that make drugs but aren't subject to the same federal quality standards as pharmaceutical companies. Compounding pharmacies create alternate formulations of medications that are supposed to be tailored to the needs of individual patients.

The 2012 meningitis outbreak prompted Congress to pass legislation in 2013 giving the FDA more authority to regulate product quality at certain compounding facilities, but not all of them.

The trials against Messrs. Cadden and Chin could reveal important details about what led to the quality lapses at New England Compounding Center, said Kevin Outterson, a Boston University law professor who served on a Massachusetts state commission formed to investigate compound pharmacies after the outbreak.

In 2014, a federal grand jury convened by the U.S. attorney's office in Boston indicted Messrs. Cadden and Chin on charges of violating the federal Racketeer Influenced and Corrupt Organizations Act, including by committing second-degree murder in the deaths of 25 people who took the drug in seven states.

The U.S. attorney's office said in 2014 it brought charges for deaths that occurred in states with criminal laws that don't require prosecutors to prove Messrs. Cadden and Chin had "specific intent to kill" the patients to prove second-degree murder, but rather that they acted with "extreme indifference to human life."

The indictment says Mr. Chin, a supervising pharmacist, failed to properly sterilize batches of the drug before they were shipped to pain clinics and surgery centers in several states, and that he acted under the direction of Mr. Cadden.

Prosecutors also charged the men with mail fraud and introducing misbranded drugs into interstate commerce with the intent to defraud and mislead.

Stephen Weymouth, an attorney for Mr. Chin, said in an interview that his client was at most negligent in his actions at the New England Compounding Center but "did not murder anybody."

Attorneys for Mr. Cadden didn't respond to requests for comment. In a court filing in December, his lawyers said there wasn't sufficient evidence to show that his actions caused the 25 deaths, or that he believed the drugs would kill patients.

A spokeswoman for the U.S. attorney's office said prosecutors weren't available for comment because the trials are pending.

Above, federal agents at the New England Compounding Center in 2012. Below, Glenn Chin, left, and Barry J. Cadden, right, in 2014.

Wall Street Journal, January 04, 2017 Article

Two pharmacists face second degree murder charges from contaminated injectable steroid pain medication causing an outbreak of fungal meningitis in 2012.

This caused 750 cases of the disease in consumers in 20 states, and resulted in the deaths of 64 people.

The New England Compounding Center in Farmington, MA made three contaminated lots for distribution. These compounding pharmacies made drugs, but were not subject to the same federal quality standards as pharmaceutical companies.

This caused congress to pass legislation in 2013 to give the FDA more authority to regulate product quality at some compounding facilities but not all.

cGMPs in Finished Pharmaceutical Manufacturing

- **21 CFR Parts 210 & 211 are applicable to pharmaceutical manufacturing**

- **21 CFR Part 210: CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL**
  - 210.1 Status of current good manufacturing practice regulations.
    - (a) The regulations set forth in this part and in parts 211 (Current Good Manufacturing Practice For Finished Pharmaceuticals), 225 (Current Good Manufacturing Practice For Medicated Feeds), and 226 (Current Good Manufacturing Practice For Type A Medicated Articles) of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.
  - 210.2 Applicability of current good manufacturing practice regulations.
  - 210.3 Definitions.

cGMPs in Pharmaceutical Manufacturing

- **21 CFR Parts 210 & 211 are applicable to pharmaceutical manufacturing**
- **21 CFR Part 211: CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS**
  - **Subpart A – General Provisions**: For prescription drugs, biologics, and OTC drugs
  - **Subpart B – Organization and Personnel**: Quality control unit, personnel responsibilities
  - **Subpart C – Buildings and Facilities:** Design & construction, lighting, HVAC, plumbing
  - **Subpart D – Equipment:** Design & construction, cleaning, maintenance, automation
  - **Subpart E – Control of Components and Drug Product Containers and Closures** –Receipt and storage of components, component testing, use and rejection
  - **Subpart F – Production and Process Controls**: Written procedures, deviations, Eq. ID's
  - **Subpart G – Packaging and Labeling Control:** Examination, labeling, inspection, dating
  - **Subpart H – Holding and Distribution:** Warehouse and distribution procedures
  - **Subpart I – Laboratory Controls:** Test and release for distribution, stability, contamination
  - **Subpart J – Records and Reports:** Equipment cleaning log, production records, complaints
  - **Subpart K – Returned and Salvaged Drug Products**: Returned drug products, salvaging

cGMPs in Pharmaceutical Manufacturing

- **21 CFR Parts 210 & 211 are applicable to pharmaceutical manufacturing**
- **21 CFR Part 211: CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS**

  - **Subpart C – Buildings and Facilities:** Design & construction, lighting, HVAC, plumbing
  - **Subpart D – Equipment:** Design & construction, cleaning, maintenance, automation

21 CFR Part 211 Subpart C: Buildings and Facilities

- **§211.42 Design and construction features.**
  - (a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

21 CFR Part 211 Subpart C: Buildings and Facilities

- **§211.44 Lighting.**
  - Adequate lighting shall be provided in all areas.
- **§211.42 Design and construction features.**
  - i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
  - (ii) Temperature and humidity controls;
  - (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
  - (iv) A system for monitoring environmental conditions;
  - (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
  - (vi) A system for maintaining any equipment used to control the aseptic conditions.

21 CFR Part 211 Subpart C: Buildings and Facilities

- **§211.46 Ventilation, air filtration, air heating and cooling.**
  - (b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
  - (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
- **§211.58 Maintenance.**
  - Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

21 CFR Part 211 Subpart C: Buildings and Facilities

- **§211.42 Design and construction features.**
  - **(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:**
    - (1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;
    - (2) Holding rejected components, drug product containers, closures, and labeling before disposition;
    - (3) Storage of released components, drug product containers, closures, and labeling;
    - (4) Storage of in-process materials;
    - (5) Manufacturing and processing operations;
    - (6) Packaging and labeling operations;
    - (7) Quarantine storage before release of drug products;
    - (8) Storage of drug products after release;
    - (9) Control and laboratory operations;
    - (10) Aseptic processing

21 CFR Part 211 Subpart C: Buildings and Facilities

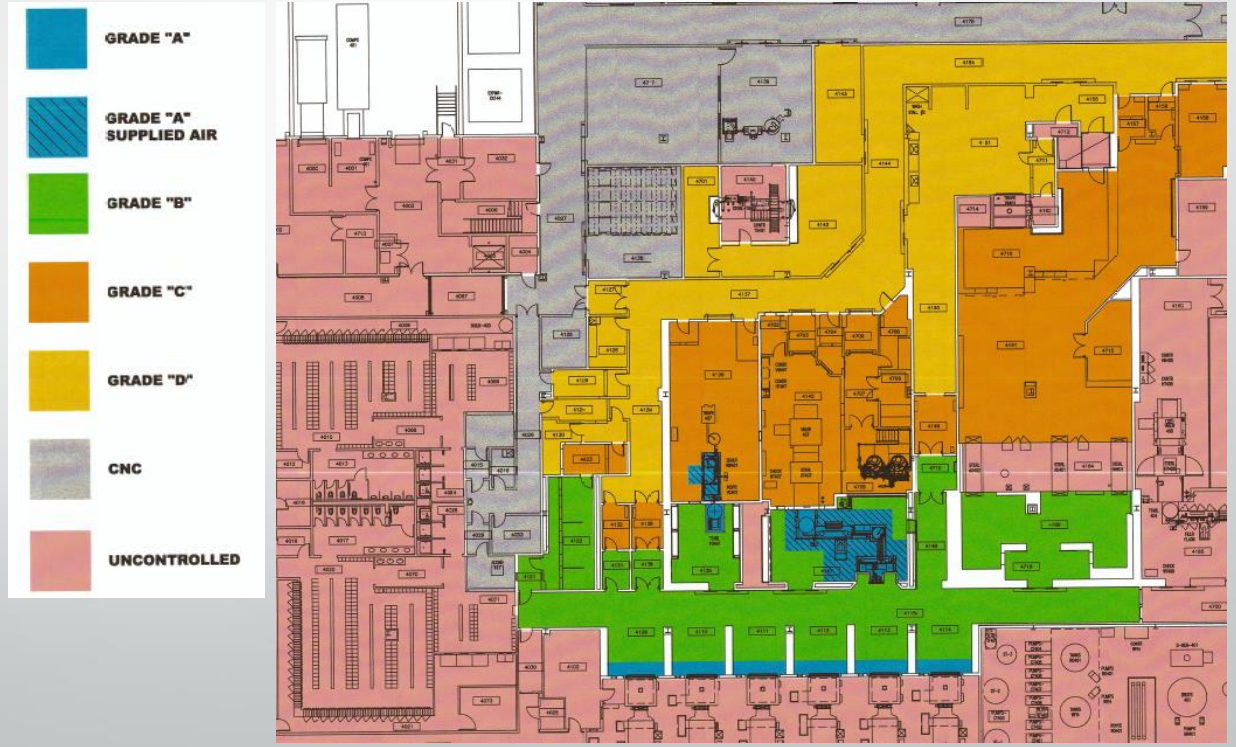
- **§211.42 Design and construction features.**
  - (c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups.
  - (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

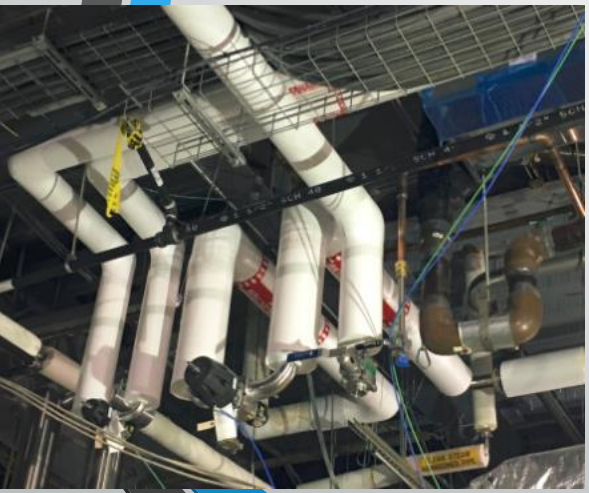
Grade	Examples of operations for aseptic preparations.
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered.
D	Handling of components after washing.

Eudralex, Vol4, Annex 1



21 CFR Part 211 Subpart D: Equipment

- **§211.63 Equipment design, size, and location.**
  - Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.



21 CFR Part 211 Subpart D: Equipment

- **§211.65 Equipment construction.**
  - (a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive.
  - (b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products.
- **§211.67 Equipment cleaning and maintenance.**
  - (a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the drug product beyond the official or other established requirements.

21 CFR Part 211 Subpart D: Equipment

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21 CFR Part 211 Subpart D: Equipment

- **§211.72 Filters.**
- Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products.
- Fiber-releasing filters may be used when it is not possible to manufacture such products without the use of these filters. If use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product.
- The use of an asbestos-containing filter is prohibited.

Risk Management

- **The requirements can be satisfied using various methods so designers must be thoroughly knowledgeable of industry practices and systems related to pharmaceutical design**
- **Risk Management**
  - Risks that equipment and systems present to product and process helps to ensure the development of adequate design, mitigation, and control plans that ultimately **increase product quality**
  - **Product development, process development, and technology** focus the information needed by the engineering design team
  - All **project risks** need to be continuously assessed and controlled, including **business risk, contractor performance risk, safety risk, environmental risk, and risk to the patient.**
  - **Design and manufacturing practice regulations** are the basis for controlling these risks
  - **A pharmaceutical engineer focuses on** analyzing, controlling, and managing the risks to the patient that may be present in the design of the manufacturing process, equipment, utilities, facilities, and automation

Compliance References

- **International Society for Pharmaceutical Engineers**
  - Baseline Guides (created in partnership with FDA)
    - Volume 1: Active Pharmaceutical Ingredients
    - Volume 2: Oral Solid Dosage Forms
    - Volume 3: Sterile Products Manufacturing Facilities
    - Volume 4: Water & Steam Systems
    - Volume 5: Commissioning and Qualification
    - Volume 6: Biopharmaceutical Manufacturing Facilities
    - Volume 7: Risk Based Manufacturing of Pharmaceutical Products
  - Good Practice Guides (best industry practices and solutions)
    - Good Engineering Practice
    - Project Management in Pharmaceutical Industry
    - Management of Engineering Standards
    - Operations Management
    - Maintenance
    - Heating, Ventilating, and Air Conditioning (HVAC)
    - Process Gasses
    - Commissioning & Qualification of Pharmaceutical Water and Steam Systems

Compliance References

- **American Society of Mechanical Engineers (ASME)**
  - BioProcessing Equipment Standards (BPE)
    - **General Requirements**: Inspection and Manufacturers Quality Assurance Program
    - **Design for Sterility and Cleanability**: Piping, Tubing, Vessels, and Equipment
    - **Dimensions and Tolerances for Stainless Steel Automatic Welding**: Swagelok Equipment
    - **Materials Joining**: Orbital Welding, Piping, Tubing, Vessels, Passivation
    - **Surface Finish of Stainless Steels**: Inspection, Electropolishing, Passivation, Rouge
    - **Equipment seals, gaskets, and diaphragms**: Extractables and Leachables after cleaning
    - **Polymer-Based Materials**: Polymeric piping, tubing, fittings, valve bodies, and components
    - **Certification**: ASME BPE Certification Stamp on Equipment
    - **Metallic Materials of Construction**: Alloy designation, fabrication, and corrosion resistance

Compliance References

- **US FDA**
  - Guidance Documents
    - Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry
    - Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
    - Current Good Manufacturing Practice for Medical Gases
  - Inspection Guides
    - High Purity Water Systems (7/93)
    - Lyophilization of Parenterals (7/93)
    - Microbiological Pharmaceutical Quality Control Labs (7/93)
    - Pharmaceutical Quality Control Labs (7/93)
    - Validation of Cleaning Processes (7/93)
    - Dosage Form Drug Manufacturers cGMPs (10/93)
    - Oral Solid Dosage Forms Pre/Post Approval Issues (1/94)
    - Sterile Drug Substance Manufacturers (7/94)
    - Topical Drug Products (7/94)
    - Oral Solutions and Suspensions (8/94)

FDA Design & Construction Features

- **Process Qualification**
  - Determine if it is capable of reproducible commercial manufacture
    - Design of the facility and qualification of the equipment and utilities
    - Process performance qualification
      - cGMP compliant procedures must be followed
      - Successful completion of process qualification is necessary before commercial distribution
      - Products manufactured during this stage, is acceptable, can be released for distribution

FDA Design & Construction Features

- **Design of a Facility and Qualification of Utilities and Equipment**
  - **Proper design of a manufacturing facility** is required under part 211, Subpart C, of the cGMP regulations on buildings and facilities
  - Activities performed to **ensure proper facility design and commissioning** precede process performance qualification
    - Selecting appropriate utilities and equipment construction materials, operating principles, and performance characteristics
    - Verifying that utility systems and equipment **are built and installed** in compliance with the design specifications
    - Verifying that utility systems and equipment **operate in accordance** with the process requirements in all anticipated operating ranges. Also challenging the equipment or system functions at startup, shutdown, maximum or minimum runs
  - **Qualification of utilities and equipment** can be under individual plans or as part of an overall project plan
    - Plan identifies: Tests to use, assessment criteria, timing of activities, responsibilities, approval procedures

FDA Design & Construction Features

- **The quality control unit must review and approve the qualification plan and report**
  - The project plan should include the firm's requirements for the evaluation of changes
  - Qualification activities should be documented and summarized on a report with conclusions that address criteria in the plan
  - The quality control unit must review and approve the qualification plan and report (21CFR211.22)
  - The quality system model four factors: Management responsibilities, Resources, Manufacturing Operations, and Evaluation activities
- **Under a quality system the technical experts (engineers & development scientists) are responsible for defining specific facility and equipment requirements**
  - Under cGMP regulations the quality unit must review and approve all initial design criteria and procedures for facilities and equipment (21CFR211.22c)
  - Under cGMP regulations equipment must be qualified, calibrated, cleaned, and maintained to prevent contamination and mix-up (21CFR211.63, 211.67, 211.68)
  - The full text of 21CFR210 and 211with Quality Systems Approach to Pharmaceutical cGMP Regulations guidance can be obtained from http://www.FDA.gov

Implications for Performance and Compliance

- **Implications for Performance and Compliance**
  - The scope and overall approach for the development of the regulatory and quality strategy throughout the project life cycle is dictated by the project scope and objectives. Integrating this strategy into the project management effort provides key input for the design approach and for overall project success.
- **Requirements and Design; Phase 1**
  - Engineering team develops the design from concept through construction
  - Project team defines cGMP aspects of project life cycle and documents them in validation plan
  - The validation plan is developed in parallel with the basis of design for the facility
  - Goals and objectives of the manufacturing unit depend on corporate philosophy, operating principles, and regulatory requirements
  - Capital investments must meet criteria for Return on Investment (ROI) before funds are committed
  - cGMP regulations provide requirements for the design of the facility
  - User Requirement Specifications (URS) define expectations of end user of equipment and systems
  - Process flow diagrams are used to show basic steps of manufacturing process to help with analysis
  - Engineering and Validation teams have approved Validation Master Plan before construction

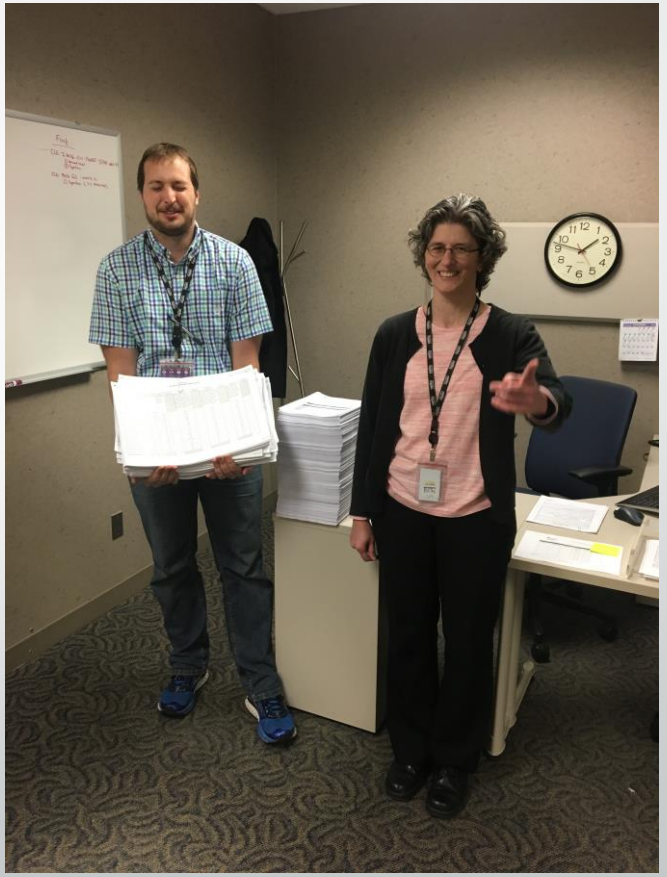
Implications for Performance and Compliance

- **Construction of Equipment, Systems, and Facilities and Testing; Phase 2**
  - Equipment fabricators, service providers, and trade contractors receive the URS and generate a Functional Requirement Specification (FRS) that details how they will provide what the URS calls for and a Design Specification (DS) detailing how the equipment or system will be built to comply with the cGMPs
  - After FDS has owner approval the suppliers will generate P&IDs, mechanical, piping, electrical, structural, automation, and architectural drawings for construction
  - After construction the following testing will occur, and those items that affect product quality and patient safety will receive the most attention by Subject Matter Experts (SMEs)
    - Factory Acceptance Test (**FAT**) the equipment at the fabricator's factory before shipment
    - Site Acceptance Test (**SAT**) the equipment at the pharmaceutical site after shipment
    - Installation Qualification (**IQ**) will test the equipment for the detailed Design Specifications (**DS**)
    - Operational Qualification (**OQ**) will test the equipment for the Functional Requirement Specifications (**FRS**)
    - Performance Qualification (**PQ**) will test the equipment for the User Requirement Specifications (**URS**)
  - Project Change Management system to track changes during project for budget and schedule control

Implications for Performance and Compliance

- **Turnover Phase 3**
  - Formal execution of all testing work
  - Process equipment and systems test protocols are approved for intended manufacturing operations
  - Process equipment and systems test protocols will be reviewed by a Subject Matter Expert, engineering, maintenance, manufacturing, validation and quality if the equipment/system is critical
  - Project size will have impact on staging commissioning, qualification, and validation (CQV) of non-critical systems needed for critical systems (air & water & steam for WFI)
  - Project complexity will have impact on long lead times for specialty equipment needing construction, transportation, and programming
  - Existing facility upgrades, retrofit projects, and expansion projects have challenges to keep the existing process in operation and profitable while constructing a new process around it
  - Unknown product and process requirements are not scaled up to production from pilot plant scale to define the utility loads and reactor geometry for mixing/heat transfer/mass transfer parameters

Implications for Performance and Compliance



Project LIFE Compounding Vessel Skid Installation Qualifications and Operational Qualification Protocol Tests

Global Regulatory Environment

- **Global Regulatory Environment**
  - Global regulations in a harmonized approach for a **better understanding** by various national authorities to **align approaches to regulatory compliance**:
    - The International Conference on Harmonization (ICH); www.ich.org
    - The International Organization for Standardization (ISO); Part of ICH
    - The American Society for Testing and Materials (ASTM) International; www.astm.org
    - The World Health Organization (WHO); www.who.int/en
    - **Food and Drug Administration** (FDA); www.fda.gov
    - **European Medicines Agency** (EMA); www.ema.europa.eu/ema
  - Regulator Expectations
    - **Design, operating, and quality decisions are based on scientific knowledge of product and process**. Attributes of the product necessary to deliver the desired effect to the patient are known
    - **Risks to the patient should be understood and managed.** This understanding will drive the design, operation, and quality system of the manufacturing operation
    - **A comprehensive quality system for designing, verifying, and maintaining process, equipment, and systems is in place**.

cGMP Seminar Series in Summary

1. Pharmaceutical Industry Profile
2. Current Good Manufacturing Practices
3. Process Engineering
4. Containment Technology (Isolators & RABS)
5. High Purity Water Systems
6. QA / QC Laboratories and Related Support Spaces
7. Facility Utility Systems
8. Legacy Facility Master Planning
9. Architectural Design & Midterm Exam
10. Sterile Manufacturing Facilities
11. Biotechnology Facilities
12. Codes and Standards
13. Commissioning, Qualification, and Validation
14. Occupational Health and Safety
15. Sustainability (LEEDs)
16. Process Automation
17. Packaging and Warehousing
18. Final Exam
19. Awards Ceremony

Washkewicz College of Engineering

xellia PHARMACEUTICALS

Session in Summary

- United States Food and Drug Administration
- What are CGMPs?
- FDA Observations
- Need for Public Protection
- cGMPs in Finished Pharmaceutical Manufacturing
- Risk Management
- Implications for Performance and Compliance
- cGMP Seminar Series in Summary with Cleveland State University

Questions?