503B Regulatory Compliance and Quality Systems

Regulation, Guidance and Inspection Overview

About the Presenter

Donald Prentiss has over 16 years in healthcare experience.

Served as a USAF Medical Laboratory generalist with a specialization in Microbiology. Was one of the first certified operators of the portable DOD real-time PCR system (RAPIDS) designed to identify biological agents in the field, and served as key personnel on the local, state and federal domestic joint biological response team.

After the military, went on to serve in Quality and Operations Management roles in the medical device, clinical reference laboratory and esoteric laboratory (pharmacogenetics and toxicology) fields. Designed and implemented lab automation, quality systems and inspection preparedness programs.

Transitioned to 503A compounding pharmacy and 503B outsourcing facility operations management, and leveraged knowledge in quality systems, operational efficiency and regulatory compliance. Designed ISO 7 cleanrooms, implemented primary engineering controls and sterility assurance programs for both hazardous and non-hazardous sterile drug compounds.

Currently serves as President of Operations for Carie Boyd's, a multistate licensed and FDA registered 503B outsourcing facility.

Agenda

- Regulatory Oversight
- USP Guidance
- CGMP Regulation
- Quality Systems Guidance
- Inspection Overview

Regulatory Oversight

- Onsite Inspections
  - State
    - Board of Pharmacy (BOP)
      - Texas BOP – Bi-annual renewal and inspection
      - California BOP – Annual renewal and inspection
      - Florida BOP – Bi-annual renewal and inspection (FDA inspection report accepted if within 2 years)
    - Department of Health
      - Texas Department of State Health Services – Bi-annual renewal and inspection
  - Federal
    - Food and Drug Administration (FDA) – annual renewal, risk-based inspection schedule, semi-annual reporting
    - Drug Enforcement Agency (DEA) – Annual renewal, variable inspection schedule, bi-annual inventory
- Information Sharing
  - State
    - Inspections
      - Renewals – non-resident states request copies of most recent resident state and/or FDA inspection
    - Disciplinary
      - Action taken must be reported to other states where required, and within specified time frame
      - Renewals – application requirement to report action taken during previous period

USP Guidance

- United States Pharmacopeia (USP)
  - USP is a scientific nonprofit organization that sets public standards for identity, strength, quality and purity of medicines. USP standards are recognized in various provisions of the federal Food, Drug and Cosmetic Act (FDCA) and in laws, regulations and policies promulgated by states. These standards are enforced by the U.S. Food and Drug Administration (FDA), states and other oversight organizations.[1]
  - USP provides both general chapters and monographs for compounded preparations.[2]
- General Chapters referenced by State and/or FDA (guidance documents etc.) examples:
  - USP General Chapter <795> Pharmaceutical Compounding — Nonsterile Preparations
  - USP General Chapter <797> Pharmaceutical Compounding— Sterile Preparations
  - USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings
  - USP General Chapter <71> Sterility Tests
  - USP General Chapter <85> Bacterial Endotoxins Test
  - USP General Chapter <51> Antimicrobial Effectiveness Testing

CGMP Regulations

- CGMP
  - FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.[3]
- Title 21 CFR and FDA Guidance
  - 21 CFR part 210 - current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general
  - 21 CFR part 211 - current good manufacturing practice for finished pharmaceuticals
  - 21 CFR part 11 - electronic records; electronic signatures
  - Periodic Guidance Document examples:
    - Guidance for Industry - Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act[4]
    - Guidance for Industry - Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act[5]
    - Guidance for Industry (Draft) - Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act[6]

Quality Systems Guidance

- Guidance for Industry - Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations[7]
  - This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211).[7]
- 21 CFR part 820 – Quality System Regulation[8]
- Guidance for Industry – ICH Q10 Pharmaceutical Quality System[9]

Quality Systems Guidance - continued

- Quality
  - Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.[7]
  - The quality system provides the foundation for the manufacturing systems that are linked and function within it.[7]
- Major sections of the quality systems model include the following[7]:
  - Management Responsibilities
  - Resources
  - Manufacturing Operations
  - Evaluation Activities

Quality Systems Guidance - continued

Quality System Element	21 CFR CGMP Regulations Related to	Regulatory Citations
Leadership	Management Responsibilities	—
Structure	Management Responsibilities	Establish quality function: § 211.22 (a) (see definition § 210.3(b)(15))
		Notification: § 211.180(f)
Build QS	Management Responsibilities	QU procedures: § 211.22(d)
		QU procedures, specifications: § 211.22(c), with reinforcement in: §§ 211.100(a), 211.160(a)
		QU control steps: § 211.22(a), with reinforcement in §§ 211.42(c), 211.84(a), 211.87, 211.101(c)(1), 211.110(c), 211.115(b), 211.142, 211.165(d), 211.192
		QU quality assurance; review/investigate: §§ 211.22(a), 211.100(a-b) 211.180(f), 211.192, 211.198(a)
		Record control: §§ 211.180(a-d), 211.180(c), 211.180(d), 211.180(e), 211.186, 211.192, 211.194, 211.198(b)
Establish Policies, Objectives and Plans	Management Responsibilities	Procedures: §§ 211.22(c-d), 211.100(a)
System Review	Management Responsibilities	Record review: §§ 211.100, 211.180(e), 211.192, 211.198(b)(2)
General Arrangements	Resources	—
Develop Personnel	Resources	Qualifications: § 211.25(a)
		Staff number: § 211.25(c)
		Staff training: § 211.25(a-b)
Facilities and Equipment	Resources	Buildings and facilities: §§ 211.22(b), 211.28(c), 211.42 – 211.58, 211.173
		Equipment: §§ 211.63 – 211.72, 211.105, 211.160(b)(4), 211.182
		Lab facilities: § 211.22(b)
Control Outsourced Operations	Resources	Consultants: § 211.34
		Outsourcing: § 211.22(a)

21 CFR CGMP Regulations Related to Quality System Model Major Factors[7]

Quality Systems Guidance - continued

Quality System Element	21 CFR CGMP Regulations Related to	Regulatory Citations
Design and Develop Product and Processes	Manufacturing Operations	Production: § 211.100(a)
Examine Inputs	Manufacturing Operations	Materials: §§ 210.3(b), 211.80 211.122, 211.125 – 211.94, 211.101, 211.122, 211.125
Perform and Monitor Operations	Manufacturing Operations	Production: §§ 211.100, 211.103, 211.113 211.110, 211.111, 211.113
		QC criteria: §§ 211.22(a-c), 211.115(b), 211.160(a), 211.165(d), 211.188
		QC checkpoints: §§ 211.110(c) 211.22 (a), 211.84(a), 211.87, 211.110(c)
Address Nonconformities	Manufacturing Operations	Discrepancy investigation: §§ 211.22(a), 211.100, 211.115, 211.192, 211.198 Recalls: 21 CFR Part 7
Analyze Data for Trends	Evaluation Activities	Annual Review: § 211.180(e)
Conduct Internal Audits	Evaluation Activities	--
Risk Assessment	Evaluation Activities	
Corrective Action	Evaluation Activities	Discrepancy investigation: §§ 211.22(a), 211.192
Preventive Action	Evaluation Activities	—
Promote Improvement	Evaluation Activities	§ 211.110

21 CFR CGMP Regulations Related to Quality System Model Major Factors[7]

Inspection Overview

- Generally no limit on the length of inspection or number of inspections in any given year.
- There are different inspection types, examples:
  - Initial
  - Routine
  - For cause
  - Compliance follow-up
  - Complaint follow-up
  - Industry trends
- All aspects of the manufacturing operation and ancillary activities are under review. General underlying approach as requirements are inspected:
  - Is there a procedure that meets the intent of the regulation?
  - Is the procedure being followed?
  - Is the process documented?

Inspection Overview - continued

- Common Inspection Flow Overview
  - Introduction
  - Facility tour
  - Document request
  - Process inspection
  - Personnel inspection
  - Document inspection
  - Quality systems inspection
  - Close out
  - Inspection response
  - Additional correspondence

References

1. United States Pharmacopeia, *Recognition of USP Compounding Standards.* Retrieved from https://www.usp.org/compounding/legal-considerations
2. United States Pharmacopeia, *Legal Recognition – Standards Categories.* Retrieved from https://www.usp.org/about/legal-recognition/standard-categories
3. U.S. Department of Health and Human Services, Food and Drug Administration, *Current Good Manufacturing Practice (CGMP) Regulations.* Retrieved from https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations
4. U.S. Department of Health and Human Services, Food and Drug Administration (2016), *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act. Guidance for Industry.* Retrieved from https://www.fda.gov/media/90173/download
5. U.S. Department of Health and Human Services, Food and Drug Administration (2015), Center for Drug Evaluation and Research. *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act. Guidance for Industry.* Retrieved from https://www.fda.gov/media/90997/download
6. U.S. Department of Health and Human Services, Food and Drug Administration (2018), Center for Drug Evaluation and Research. *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act. Guidance for Industry. DRAFT GUIDANCE.* Retrieved from https://www.fda.gov/media/88905/download
7. U.S. Department of Health and Human Services, Food and Drug Administration (2006), Center for Drug Evaluation and Research. *Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations.* Retrieved from https://www.fda.gov/media/71023/download

Thank You

- Questions?