

CGMPS AND COMPLIANCE IN THE DRUG INDUSTRY

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ESTABLISHED IN 1982

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Robert Schiff, PhD, RAC, CQA, FRAPS is founder and CEO of Schiff & Company, a Regulatory Affairs, Compliance and Clinical Research Organization, established in 1982. Prior to founding Schiff & Company, Dr. Schiff served with a number of companies including: the Warner Lambert Company as Group Vice President, Diagnostics Research and Development; Hoffmann-La Roche, Inc. as Director, Department of Diagnostic Research and Product Development; the J. T. Baker Chemical Company (Richardson-Vicks) as Director of Research & Development, Diagnostics Division; the Hyland Division Travenol Laboratories (Baxter) as Manager, Serology Research; and as an Assistant Professor in the Department of Anatomy at Tufts University Schools of Medicine and Dental Medicine. Dr. Schiff has authored over 50 publications and holds several patents on medical products. He received his BS from the City College of New York, MS from Iowa State University, and PhD from the University of California at Davis. He was a member of the Graduate Business faculty at Farleigh Dickinson University, and also lectures on International Business and Compliance with FDA rules and regulations. He serves on the Boards of several companies, is a member of the Editorial Board of the Regulatory Affairs Professional Society, is a Fellow of the Regulatory Affairs Professional Society and is listed in Marquis' Who's Who in America, Who's Who in the World, Who's Who in the East, Who's Who in Science & Engineering, and American Men of Science. Dr. Schiff is board certified in Regulatory Affairs and is a Certified Quality Auditor.

REGULATIONS

- 21 CFR Part 210
- 21 CFR Part 211
- 21 CFR Part 600

THE FDA INSPECTION

- Preapproval (PAI)
 - Prior notice given
 - Staff having direct contact with inspector should be trained
 - Have all materials available, i.e., validations, batch records, design history files, etc.
 - Keep in mind that the inspector is an enforcement officer
 - The PAI consists of two parts:
 - Verifying information in a submission
 - CGMP of the company

THE FDA INSPECTION CONT.

- General
 - Announced or unannounced
 - Follow same suggestions as a PAI
 - Have staff available for questions
 - A **For Cause** inspection can be adversarial
 - Focused audit because of a major violation

THE CLOSEOUT

- Discuss all findings
- Listen to explanations
- Establish follow-up and curing of observations
- Be pleasant

PROBLEMS DURING FACILITY INSPECTIONS

- Is the company in a state of control?
- Failure to document (Violation 1)
- Failure to perform corrective and/preventive action (Violation 2)
- Failure to perform root cause analysis (Violation 3)
- Failure to investigate (Violation 4)
 - Out of specification results
 - Non-conformances
 - Deviations

PROBLEMS DURING FACILITY INSPECTIONS CONT.

- Not conducting an appropriate CAPA analysis (Violation 5)
- Failure to validate process (Violation 6)
- Releasing product out of specification (Violation 7)
- Failure to follow company's own SOPs and directions (Violation 8)
- Failure to report product failure or adverse event (Violation 9)

PROBLEMS DURING FACILITY INSPECTIONS CONT.

- Marketing an adulterated, misbranded, or unapproved product (Violation 10)
- Failure to follow a sampling plan for product release (Violation 11)
- Inadequate complaint handling (Violation 12)
- Failure to maintain adequate design control (Violation 13)

THE AUDIT

- Note requirement differences
 - Drug substance
 - Drug product
 - Device
 - Biologic
 - Domestic versus international

THE AUDIT FACILITIES

- RECEIVING
- WAREHOUSE
 - QUARANTINE
- STAGING
- PRODUCTION
- FILLING
- PACKAGING
- SHIPPING
- QUALITY CONTROL

BUILDINGS AND FACILITIES CONTINUED

- Warehouse
 - Arrangement
 - Labeling of items for status
 - Red, yellow, green
 - Segregation of goods
 - Separate raw, in process and finished
 - Separate regulated from non-regulated
 - Neatness counts
 - Eliminate possibility for error

BUILDINGS AND FACILITIES CONTINUED

- Manufacturing area
 - Staging
 - In-process storage
 - Line clearance
 - Blending
 - Filling
 - Packaging

BUILDINGS AND FACILITIES CONTINUED

- SHIPPING AREA
 - HOLDING AREA PRIOR TO RELEASE
 - STORAGE OF RELEASED GOODS
 - RECORD KEEPING
 - SECURITY

BUILDINGS AND FACILITIES CONTINUED

- UTILITIES
 - WATER SYSTEM
 - TESTING ROUTINELY
 - LIGHTING
 - MAINTENANCE
- PEST CONTROL
 - RECORD KEEPING
 - VERIFICATION

EQUIPMENT, CONTAINERS AND PRODUCTION DOCUMENTS

- EQUIPMENT
 - DESIGN
 - FOR WHICH IT WAS INTENDED
 - LOCATION
 - CROSS DRAFT
 - OPEN DOORS
 - MATERIALS
 - EXTRACTABLES
 - LUBRICANTS AND COOLANTS
 - JACKETED EQUIPMENT

EQUIPMENT, CONTAINERS AND PRODUCTION DOCUMENTS CONTINUED

- Equipment maintenance
 - Mechanical equipment
 - Precision equipment
 - Automatic equipment
 - Electronic and computers
 - Calibration
 - Cleaning
 - Log books and records

PRODUCTION AND PROCESS CONTROLS

- Products must meet predetermined specifications
- Validation
- Qualification
- Monitoring
- Process control

THE INTERNAL AUDIT DOCUMENTATION

- The quality manual and quality systems
- Standard operating procedures
- Master records
- Batch records
- Non-conformances
- Deviations
- Validations and qualifications
- Complaint handling

DOCUMENT CONTROL

- Supports a company's quality system by ensuring that information is
 - Current
 - Available to users
 - Approved by proper authority
 - Changed in a controlled manner
 - Monitored for
 - Access
 - Distribution
 - Revisions
 - Control of obsolete documents

CORRECTIVE AND PREVENTIVE ACTIONS

- Out of specification results
- Non-conformances
- Deviations
- Complaints

OUT OF SPECIFICATION

- Quality control tests
- Result is a failure
- Document
- Investigation
 - **Assignable cause**
 - Operator
 - Reagents
 - Equipment
 - Retest or resample
 - Consistent algorithm

THE TRUE NON-CONFORMANCE

- Investigation
- Root cause analysis
 - It may not be obvious
 - Retraining is not always the solution
- Corrective action
- Preventive action
- Document

DEVIATIONS

- Generally found in production
- Occasionally found in quality control
- Requires an immediate response
- Must be reviewed
- Investigated
- Documented

MIX-UPS AND ERRORS

- Wrong item used
- Expired goods
- Test numbers not correct
- Improper storage
- Failure to follow instructions
- “Tweaking”

CONTAMINATION

- Failure to properly clean
- Not validating cleaning method
- Follow standard operating procedure (sop)
- Regulations clearly state that mixing anything not called for in the batch record is a contaminant

PARTICULATE CONTAMINATION

- Unclean clothes
- Dandruff
- Hair skin
- Pocket items
- Microbial
- Viral

VALIDATION AND QUALIFICATION INTERPRETING REGULATORY REQUIREMENTS

- What are the differences between validation and qualification
- Equipment is qualified
- Methods and processes are validated
- Before a method can be validated the associated equipment must be qualified

STABILITY, EXPIRATION DATING AND VALIDATION

- How is stability established
- Stability testing is validation
- Validation of expiration
 - Poolability of slopes
 - Poolability of intercepts
 - Confidence intervals

ROOT CAUSE ANALYSIS

- Not that a mistake was made but why did the error occur
- Poor training
 - Whose fault is it?
- Failure to trend
- Distraction

CORRECTIVE ACTION

- Rework
- Repair
- Reject and scrap
- Recalibrate
- Accept as is
 - Justify scientifically
 - Document
 - No supposition please

PREVENTIVE ACTIONS

- Retrain employee and/or supervisor
- Change systems
- Additional reviews
- Statistical controls
 - Proper sampling
- Trend analysis

CASE STUDIES

- Baxter Biosciences
 - Failure investigations
 - Process controls
- Centrix Pharmaceuticals
 - Unapproved drugs
- Sumitomo Chemical Company
 - Validation
 - Sterility
- Bayer Healthcare-Bayer Schering Pharma AG
 - Laboratory controls
 - OOS

THANK YOU