



Inspection Topics

Focus on Aseptic Processing

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Quick Bio

Former FDA reviewer/inspector 2012-2019

CBER/OCBQ/DMPQ

5+ years consulting experience for FDA regulated industry

Validation Manager in industry 2004-2012

Experienced in protein purification, cell culture, and fermentation

Areas of expertise:

Facility and CMC requirements for review of BLAs and supplements, Drug Master Files, and INDs of biologic products including Vaccines and Cell/Gene Therapy.

Performance and leading of pre-licensing and pre-approval inspections, preparation of reports, and review of observations and responses.



Fundamental Principles

To properly prepare for any health authority inspection, you should

- Understand the law governing your operations
- Understand the law governing how the agency inspects your facility
- Read and understand the inspection references used by the inspecting agency
- Prepare your inspection SOP based on the above
- Set up inspection management policies and logistics
- Train your personnel thoroughly
- Rehearse what you have planned

Note: mastery in understanding your product, operations, and records is a given

Approach: Laws, Regulations, and Guidance

- The primary laws enforced by FDA are the Federal Food, Drug and Cosmetic Act and the Public Health Service Act. Key principles include:
 - A product is adulterated if it is not manufactured in accordance with Good Manufacturing Practices
 - A product may be refused entry into the U.S. if it appears adulterated

LAW

- The primary regulation for pharmaceutical manufacturing enforced by FDA is Title 21, CFR, Part 211 (also 21 CFR 600 for biologics), with sections including:
 - Buildings and Facilities
 - Production and Process Controls
 - Laboratory Controls

REGULATIONS

- There are many relevant guidance documents established that explain FDA's "current thinking" in a certain area. For example:
 - OOS
 - Process Validation
 - Aseptic Processing
 - ICH Documents (ICH Q7 is a standard for API production and, practically, is treated more like a regulation)

GUIDANCE

Key Assessments of a Pre-License Inspection

Three main priorities of Inspection Team

- Readiness for Commercial Manufacturing
- Conformance to Application
- Data Integrity

Note: PLIs and PAIs are Routinely Preannounced (with one simple question: Are you doing what you say you're doing?)

Readiness for Commercial Manufacturing

- Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and manufacturing operations.
- Manufacturing and laboratory changes, deviations, and trends relating to the development of new drug substance and product manufacturing have been adequately evaluated.
- A sound and appropriate program for sampling, testing, and evaluation of components, in-process materials, finished products, containers and closures for the purpose of releasing materials or products has been established, including a robust supplier qualification program.
- The establishment has sufficient facility and equipment controls in place to prevent contamination of, and by the application product (or API).
- Adequate procedures exist for batch release, change control, investigating failures, deviations, complaints, and adverse events; and for reporting this information to FDA, such as field alert reporting.

Data Integrity Audit



- Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, batch data) were submitted in the CMC section such that CDER product reviewers can rely on the submitted data as complete and accurate.

Inspection Outcomes

- Site inspected found to have an effective quality system and operating in a state of control
- No adverse findings
- In a pre-approval context, firm also found capable of producing the drug product at scale and accurate/complete data verified with marketing application

***NO ACTION
INDICATED (NAI)***

- Site inspected found to have an effective quality system
- Some adverse findings; corrective action expected
- In a pre-approval context, firm also found capable of producing the drug product at scale and accurate/complete data verified with marketing application

***VOLUNTARY ACTION
INDICATED (VAI)***

- Site inspected found not operating in a state of control
- Significant or systemic adverse findings
- In a pre-approval context, firm may not be capable of producing the drug product at scale and/or accurate/complete data not verified

***OFFICIAL ACTION
INDICATED (OAI)***

Form 483 and Establishment Inspection Report

Form FDA 483

- List of observations made by the FDA investigator during inspection
- Observations do not represent final Agency determination regarding compliance



An issued Form 483 is not the end of the world

EIR

- Content
- Summary of Findings
- Individual Responsibility
- Findings
 - Conformance to Application
 - Integrity of Data in Application
 - Readiness for Commercial Production
 - Conformance to GMP
- Discussion with Management

Inspector Preparation for a PAI

- PLI/PAI inspections are usually a team approach with at least one investigator and one analyst. Districts assign investigators and analysts to perform PAIs (CDER). Inspection teams from CBER usually consist of the DMPQ reviewer and Product Office reviewer assigned to the file. Investigators and analysts conducting these inspections will be qualified by appropriate training and experience.
- Develop an inspection strategy specific to the establishment and product being inspected that is consistent with this program's objectives and inspection/audit techniques.
- Review the history of the firm and FDA-483 observations from previous inspections.
- Contact the chemistry and microbiology reviewer assigned to the application and discuss his/her findings. Determine if the reviewer(s) recommends special areas for data audit coverage during the inspection. For certain applications, a Knowledge Transfer Memorandum (KTM) will be prepared and will include specific areas of coverage (CDER)
- Review the CMC section of application and any related DMFs for the establishment to be inspected. CBER reviewers and inspectors will most likely have a draft review memo created prior to the inspection

The Application itself -- particularly the CMC section which includes analytical test methods for the drug product, specifications of the drug product and drug components, and a general description of the product's manufacturing and control procedures -- becomes another "standard" against which to assess operations for conformance.

Full CGMP inspection

System approach to inspection

- Quality system
- Production system
- Facilities and equipment
- Material system
- Package and labeling system
- Laboratory control system
- Donor eligibility (human cell, tissues and cellular and tissue-based products)

Three critical elements for each system

- Standard operating procedures
- Documentation
- Training



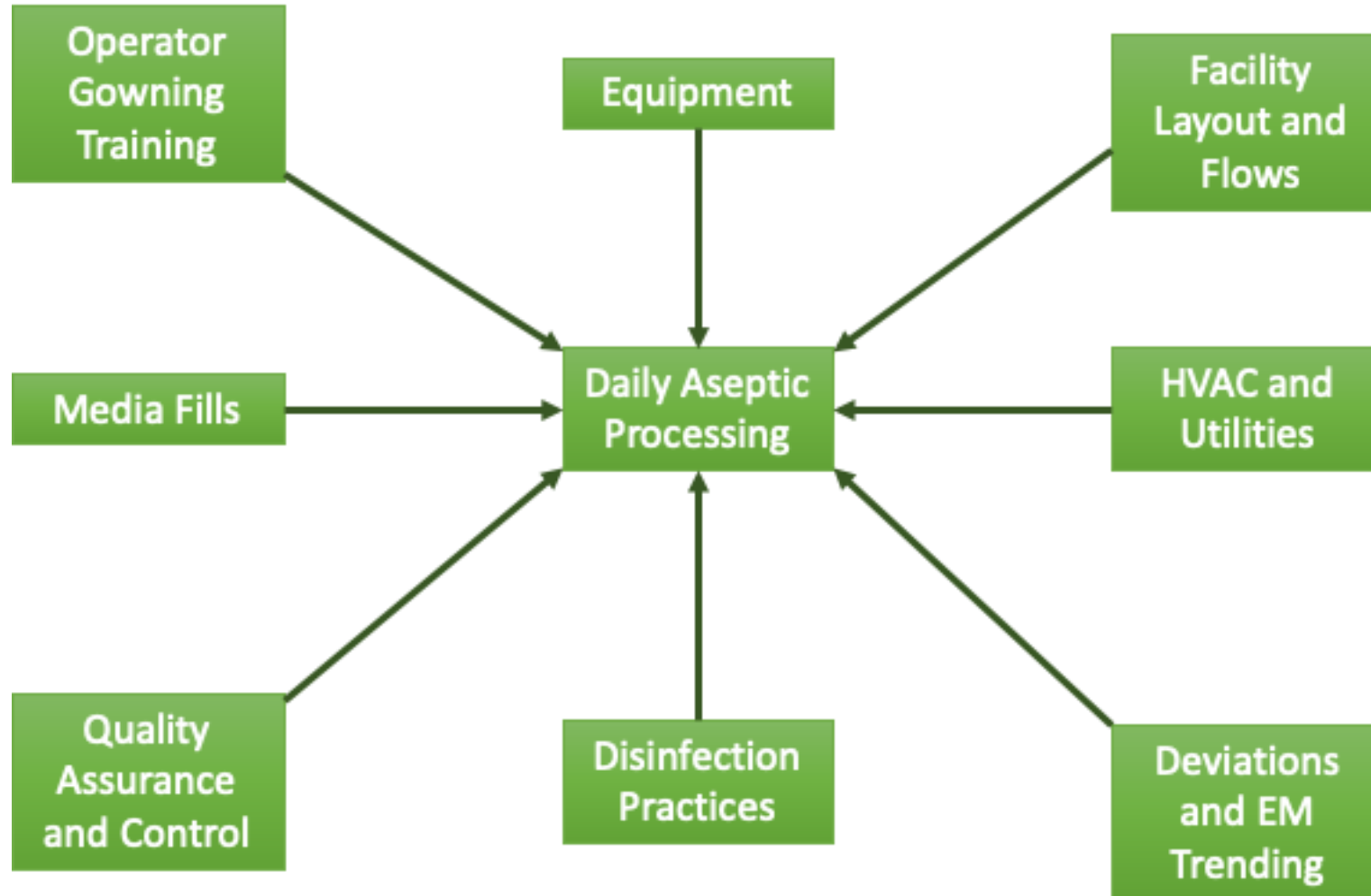
Compliance Program Guidance Manual Chapter – 45 Biological Drug Products Inspection of Biological Drug Products (CBER) 7345.848

Compliance Program Guidance Manual Chapter – 56 Sterile Drug Process Inspections (CDER) 7356.002A

Inspection Topics

Assessment of Aseptic Processing Elements

Elements of Aseptic Processing



Quality System Elements for Aseptic Processing

- Training Program
- Procedure and Batch Record Control
- Review of Executed Batch Records
- Media Fill (Aseptic Processing) Procedures
 - Videotaping media fills
- Line Clearance



Manufacturing Records

All records required under CGMP are subject to FDA inspection. You must allow authorized inspection, review, and copying of records, which includes copying of electronic data (§§ 211.180(c) and 212.110(a) and (b)).

- Batch Records
- Deviation Reports
- Corrective and Preventive Actions
- Out of Specification
- Change Control
- Stability Record
- Adverse Events
- Complaints
- SOPs
- Complaints/Pharmacovigilance Reports

Production System Elements for Aseptic Processing

- Autoclave and Depyrogenation Validation Studies
 - Validated loads match production loads
- Sterile Filter Validation
- Environmental Monitoring
 - EMPQ
 - Routine EM and PM
 - EM Trending
- Cleaning and Disinfectant Efficacy
- Gowning Qualification
- Executed Media Fills
 - Number and types of interventions
 - Hold times
 - Capacity of 'manufacturing system'
- Observation of Aseptic Manufacturing



Facilities and Equipment System Elements for Aseptic Processing



- Facility and Equipment Boundaries
 - Viral Boundary
- Equipment Calibration and Qualification
 - CIP/SIP
 - Hold Times/Closed System
- Maintenance Program
- Utilities/HVAC Qualification
 - HEPA Certification
 - TAB Report
 - Smoke Studies
 - DP Cascade
- Building Monitoring System

Material System Element for Aseptic Processing

- Receipt, Quarantine, and Release of Media



Package and Labeling System Element for Aseptic Processing

- Screening process for media fills
- Container Closure Integrity Testing



Laboratory Controls Elements for Aseptic Processing

- Sterility Testing
- Endotoxin Testing
- Growth Promotion Testing
- EM Sample Logistics
- Review of executed records



Donor Eligibility Element for Aseptic Processing

- Collection Qualification



Examples of Form 483 Observations

- Inconsistent labeling system to maintain chain of identity of product
- No tracking system in place for samples and testing status
- Lack of detailed process description in batch records
- Media simulations do not simulate all critical aseptic processes
- Inadequate qualification of sterilization and depyrogenation processes
- Smoke studies performed do not depict normal operating conditions

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	
DISTRICT OFFICE ADDRESS AND PHONE NUMBER 6000 Metro Drive, Suite 101 Baltimore, MD 21215 (410)779-5455 Fax:(410)779-5707 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	FEI NUMBER
FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED Producer of sterile and non-sterile drug products
<small>THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.</small>	
<small>DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:</small>	

References for Aseptic Processing

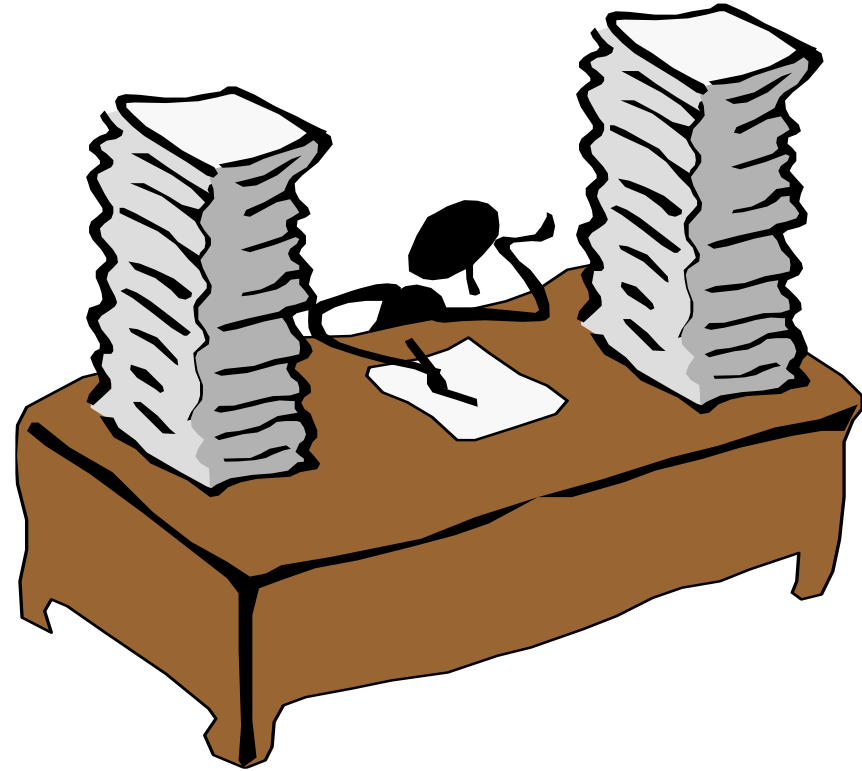
- ISO 13408-7, Aseptic processing of healthcare products – Part 7: Alternative processes for medical devices and combination products, 2012-08-01
- ISO 13408-1, Aseptic processing of healthcare products – Part 1: General Requirements
- Guide to Inspections of Quality Systems – Quality System Inspection Technique (QSIT)
- Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004
- Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, November 1994
- Aseptic Processing Recognized Consensus Standards
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm?start_search=1&productcode=&category=&type=&title=aseptic%20processing&organization=&referencenumber=®ulationnumber=&effectivedatefrom=&effectivedateto=&PAGENUM=25

Inspection Management and Logistics

Have a plan to control the event

Inspection Management

- Personnel Roles
 - Escorts
 - Scribes
 - Runners
 - Coaches
 - Ready room support
- Logistics
 - Log requests
 - Track status
 - Track when completed



Escorts

Duties

- Accompany FDA personnel at all times
- Ensure that personnel, documents, etc. are delivered as requested
- Provide support to interviewees during discussions with FDA

Caution: Do not direct anyone's answers, just help as needed – judgment is called for here

Scribes

Duties

Take company notes for the record of the inspection

– Include:

- Names of FDA and company personnel who take part in interviews
- Capture main points of what is said by whom
- Note areas of concern expressed by FDA
- Other key issues that arise during the inspection

Concentrate just on taking notes – do not become involved in discussions or be distracted by other activities

Runners

Duties

- Respond to requests from FDA for documents or people to interview
- Make sure the correct document is delivered
- If time permits, have document reviewed by a subject matter expert prior to delivery to FDA, but do not allow anyone to alter the record
- Carry messages back and forth to “Back Room”

Coaches and Back Room Support

Also sometimes called the 'War Room' personnel

- Coaches
 - Meet with interviewees to help them organize thoughts, go over discussion points
 - Remind people to stay focused, help them to relax
 - Rehearse anticipated problem areas if time permits
- Back Room Staff
 - Locate and copy documents
 - Track status of document requests, interview requests
 - Compile exact duplicate copies of all documents provided to FDA – usually on colored paper and identified with request number
 - Preparation of memory stick for each inspector

Inspection Logistics

What to prepare for and expect

- Inspection Opening
 - Receipt / Credential Check of Inspectors
 - Housekeeping matters / Safety / Company Procedures
 - Company Background Presentation that includes:
 - History
 - Products manufactured at site
 - Any other topics requested by Agency during planning meetings
- Daily Close Out
 - Issues from the day
 - Outstanding requests
 - Plans for next day
- Internal Daily Close Out
 - Meeting with participants from the day's topics
 - Daily report of organized scribe notes distributed to team
 - Discussion of events/issues from the day
 - Begin corrective action process for any findings noted by inspection team

Create a procedure that outlines practices utilized to host an inspection. This can include preparation of a general slide deck that can be the basis of an opening presentation.