International GMP Inspections

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The countries visited by CKL as an inspector and/or trainer since 1987

<table>
<thead>
<tr>
<th>Argentina</th>
<th>China</th>
<th>Iran</th>
<th>Myanmar</th>
<th>Thailand</th>
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<tbody>
<tr>
<td>Australia</td>
<td>Colombia</td>
<td>Japan</td>
<td>Philippines</td>
<td>USA</td>
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<tr>
<td>Brazil</td>
<td>Cuba</td>
<td>Korea</td>
<td>Russia</td>
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<td>Bulgaria</td>
<td>Denmark</td>
<td>Mexico</td>
<td>Singapore</td>
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<td>Chile</td>
<td>Indonesia</td>
<td>Mongolia</td>
<td>Taiwan</td>
<td>Vietnam</td>
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# Comparison of Air Cleanliness Classifications

<table>
<thead>
<tr>
<th></th>
<th>Descriptive</th>
<th>Class 100</th>
<th>Class 10,000</th>
<th>Class 100,000</th>
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<tr>
<td><strong>FDA</strong></td>
<td>In Operation</td>
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<tr>
<td></td>
<td>≥ 0.5 μm /ft³</td>
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<td>10,000</td>
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<td>Action Level</td>
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<td>ND</td>
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<td>CFU/m³</td>
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<td><strong>EU, WHO, PIC/S</strong></td>
<td>At Rest</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
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<td>≥ 0.5 μm/m³</td>
<td>3,520</td>
<td>3,520</td>
<td>352,000</td>
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<tr>
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<td>≥ 5 μm/m³</td>
<td>20</td>
<td>29</td>
<td>2,900</td>
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<td><strong>ISPE</strong></td>
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<td>Grade 5</td>
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<td>ISO. 5</td>
<td>ISO. 7</td>
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<td><strong>ISO</strong></td>
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<td>20</td>
<td>2,930</td>
<td>29,300</td>
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<td>≥ 5 μm/m³</td>
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A. Inspection Process & Preparation
Type of Inspections

- Comprehensive Inspection
- Abbreviated Inspection
- Directed Inspection
Critical Areas to be Inspected

- Buildings, facilities and equipment
- Personnel training, qualifications and experience
- Components
- Manufacturing operations
- Laboratory controls
- Packaging and labeling operations
- Records and reports
- Validation
Preparation for Inspection

- Development of SOPs governing the handling of inspections
- Selection & training of inspection coordinators
- Organization chart
- Brief biographical data on manager, QA/QC/Production manager & other key personnel
- A simple line drawing of the manufacturing process
- A simple layout of building
- Flow diagrams of personnel, materials, equipment, products, waste, air
Preparation for Inspection

• A simple diagram of WFI system
• A simple diagram of air system
• Samples of current labels, quarantine & release tags, etc.
• Pest-control status
• Product-retrieval procedures
• Records of past inspections
Inspection Dos

• Examine the credentials of the inspector and ask the purpose of the inspection
• Receptionist shall call both principal and alternate inspection coordinators when an FDA inspector appears
• Inform the manager and other key managers of the purpose of the inspection

• Brief presentation of organization, products, manufacturing process, building layout
• Review pertinent company policies
• Work out a rough schedule for the visit
Inspection Dos

• Take immediate corrective action when appropriate and ask to have such action in the establishment inspection report
• Take complete notes
• Obtain duplicate copies of any documents taken
• Obtain duplicates of any sample taken and get a receipt for all such samples

• Make a complete write-up of the inspection
• Follow up to see that all comments have been resolved
Inspection Don’ts

- Do not get uptight
- Do not leave the inspector(s) unescorted
- Do not lie
- Do not volunteer information
- Do not respond to questions outside your area of expertise or authority
- Do not guess
- Do not threaten to contact the investigator’s boss
Exit Interview

• Exit interview involves the company manager, the inspector, the coordinator and other key management personnel
• The investigator reviews the results of the inspection
• A request to note the corrective action on “483”
• Any misunderstandings about the facts of an observation must be cleared up at this point
After the Inspector Leaves, the Inspection Coordinator Should Prepare a Detailed Report Including:

- The date, times and purpose of the inspection
- Attached copies of:
  - FDA 482 Form (notice of inspection)
  - FDA 483 Form (inspectional observations) if any
  - FDA 484 Form (receipt for samples)
- The area toured and the individuals contacted
- The questions asked by the inspector and the responses given
- The documents viewed
- Attach duplicates of items copied
- The inspector’s spoken comments
- All actions taken as a result of the inspection
The Inspection Should be Discussed with Appropriate Staff Groups

- Production
- Quality control / Quality assurance
- Maintenance / Engineering
- Management
Formal Response Should be Made to the FDA District Office on All 483’s

- Commitment to comply with applicable regulations
- Address each item on the 483
- Quote each citation & reply
- Avoid long discussion of background information
- Well thought-out action plan
- Proof-read the response for editorial errors
Make Sure Actions are Carried Out as Promised
Enforcement

- Administrative Sanctions
  - Government wide QA program (GWQAP)
  - Withhold approvals
  - Warning letter (Notice of adverse findings letter & regulatory letter)
Enforcement

• Legal sanctions:
  – Seizure: a civil action taken against articles, not against companies or their responsible individuals
  – Injunction: a civil action taken against a company and its responsible individuals
  – Prosecution: a criminal action taken against a company and its responsible individuals
B. FDA’s System-based CGMP Inspection
Quality System

- Quality Control Unit to fulfill
  - to review & approve all procedures for production/QC/QA
  - to assure the procedures are adequate for their intended use
  - to maintain record keeping systems
  - to link quality problems to other systems
- Written & Approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Annual product review & trends
Quality System

- Written & Approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Complaint reviews: corrective action where appropriate
  - Discrepancy & failure investigations: manufacturing & testing
  - Change control
  - Product improvement projects
  - Reprocess / Rework: review, approval, impact on validation & stability
Quality System

- Written & Approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Returns/Salvages: assessment, investigation, disposition
  - Rejects: investigation, corrective action where appropriate
  - Stability failures: investigation, need for field alerts evaluated, disposition
  - Quarantine products
  - Validation: status of required validation/revalidation
  - Training/Qualification of Quality Control Unit personnel
Quality System

• Significant deficiencies
  - Pattern of failure
    • To review/approve procedures
    • To document execution of operations as required
    • To review documentation
    • To conduct investigations & resolve discrepancies/failures/deviations/complaints
    • To assess other systems to assure compliance with GMP & SOPs
Facilities & Equipment System

• Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.

• Facilities
  - Cleaning & maintenance
  - Facility layout & air handling systems for prevention of cross-contamination (e.g. penicillin, beta-lactams, steroids, hormones, cytotoxics, etc.)
  - Specifically designed areas to prevent contamination or mix-ups
  - Control system for implementing changes in the building
  - Lighting, potable water, washing & toilet facilities, sewage & refuse disposal
  - Sanitation of the building, use of rodenticides, fungicides, insecticides, cleaning & sanitizing agents.
Facilities & Equipment System

- Equipment
  - IQ & OQ
  - Adequacy of design, size & location
  - Equipment surfaces should not be reactive, additive, or absorptive.
  - Lubricant, coolants, refrigerants, etc. contacting products/containers
  - Cleaning procedures/validation
  - Controls to prevent contamination: pesticides, toxic materials, other drug, etc.
  - Qualification, calibration & maintenance of storage equipment
Facilities & Equipment System

• Equipment
  - Equipment qualification, calibration & maintenance
  - Control system for implementing changes in the equipment
  - Equipment identification practices
  - Documented investigation into any unexpected discrepancy
Facilities & Equipment System

• Significant deficiencies
  - Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination with demonstrated avenues of contamination, such as airborne or through unclean equipment
  - Pattern of failure to validate cleaning procedures for non-dedicated equipment. Lack of demonstration of effectiveness of cleaning for dedicated equipment.
  - Pattern of failure to document investigation of discrepancies
  - Pattern of failure to establish/follow a control system for implementing changes in the equipment.
  - Pattern of failure to qualify equipment, including computers
Materials System

• Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Training / qualification of personnel
  - Identification & inventory of components, containers, closures
  - Storage conditions
  - Quarantine area
  - Sampling plan
  - At least one specific identity test on each lot of each component
  - Visual identification for each lot of containers & closures
Materials System

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Testing or validation of supplier’s test results for components, containers & closures
  - Rejection of any component, container, closure not meeting acceptance requirements
  - Investigate fully the firm’s procedures for verification of the source of components.
  - Retesting/reexamination of components, containers, closures
  - FIFO principle
  - Quarantine of rejected materials
Materials System

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Water & process gas supply, design, maintenance, validation & operation
  - Containers & closures should not be additive, reactive, or absorptive to the drug product.
  - Control system for implementing changes in the materials handling operations
  - Qualification/validation and security of computerized or automated processes
  - Finished product distribution records by lot
  - Documented investigation into any unexpected discrepancy
Materials System

- Significant deficiencies
  - Release of materials for use or distribution that do not conform to established specifications
  - Pattern of failure to conduct one specific identity test for components
  - Pattern of failure to document investigation of discrepancies
  - Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations
  - Lack of validation of water systems as required depending upon the intended use of the water
  - Lack of validation of computerized processes
Production system

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Training/qualification of personnel
  - Control system for implementing changes in processes
  - Adequate procedures & practice for charge-in of components
  - Formulation/Manufacturing at not less than 100%
  - Identification of equipment with contents and/or phase of manufacturing
  - Validation and verification of cleaning/sterilization/depyrogenation of containers & closures
  - Calculation & documentation of actual yields & percentage of theoretical yields
Production system

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Contemporaneous & complete batch production documentation
  - Established time limits for completion of phases of production
  - Implementation & documentation of in-process controls, tests & examinations: e.g. PH, adequacy of mix, weight variation, clarity
  - Justification & consistency of in-process specifications & drug product final specifications
  - Prevention of objectionable microorganisms in non-sterile drug products.
Production system

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Adherence to preprocessing procedures: set-up, line clearance
  - Equipment cleaning & use logs
  - Master production & control records
  - Batch production & control records
  - Process validation
  - Change control: need for revalidation evaluated
  - Documented investigation into any unexpected discrepancy
Production System

• Significant deficiencies
  - Pattern of failure to establish/follow a control system for implementing changes in the production system operations
  - Pattern of failure to document investigation of discrepancies
  - Lack of process validation
  - Lack of validation of computerized processes
  - Pattern of incomplete or missing batch production records
  - Pattern of nonconformance to established in process controls, tests, and/or specifications
Packaging & Labeling system

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
- Training/qualification of personnel
- Acceptance operations for packaging & labeling materials
- Control system for implementing changes in packaging & labeling operations
- Adequate storage for labels & labeling, both approved & returned after issued.
- Control of labels which are similar in size, shape and color for different products
Packaging & Labeling system

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - 100 percent electronic or visual verification system or the use of dedicated lines for cut labels which are similar in appearance
  - Gang printing of labels is not done, unless they are differentiated by size, shape or color
  - Control of filled unlabeled containers that are later labeled under multiple private labels
  - Adequate packaging records that will include specimens of all labels used
  - Control of issuance of labeling, examination of issued labels and reconciliation of used labels.
Packaging & Labeling system

• Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Examination of the labeled finished product
  - Adequate inspection(proofing) of incoming labeling
  - Use of lot numbers, destruction of excess labeling bearing lot/control numbers
  - Physical/spatial separation between different labeling & packaging lines
  - Monitoring of printing devices associated with manufacturing lines
Packaging & Labeling system

• Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Line clearance, inspection & documentation
  - Adequate expiration dates on the label
  - Conformance to tamper-evident packaging (TEP) requirements (21CFR211.132)
  - Validation of packaging & labeling operations including validation & security of computerized processes
  - Documented investigation into any unexpected discrepancy
Packaging & Labeling system

- Significant deficiencies
  - Pattern of failure to establish/follow a control system for implementing changes in the packaging and/or labeling operations
  - Pattern of failure to document investigation of discrepancies
  - Lack of validation of computerized processes
  - Lack of control of packaging & labeling operations that may introduce a potential for mislabeling
  - Lack of packaging validation
Laboratory Control System

- Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
- Training/qualification of personnel
- Adequacy of staffing for laboratory operations
- Adequacy of equipment & facility for intended use
- Calibration & maintenance programs for analytical instruments & equipment
- Validation of computerized or automated processes
- Reference standards : source, equivalency to current official reference standards
- System suitability checks on chromatographic system (e.g., GC or HPLC)
Laboratory Control System

• Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
- Specifications, standards & representative sampling plans
- Adherence to the written methods of analysis
- Validation/verification of analytical methods
- Control system for implementing changes in lab. operations
- Required testing is performed on the correct samples
- Documented investigation into any unexpected discrepancy
- Complete analytical records from all tests and summaries of results
Laboratory Control System

• Written & approved procedures, documentation resulting therefrom & the firm’s adherence to written procedures should be verified.
  - Quality & retention of raw data (e.g., chromatograms & spectra)
  - Correlation of result summaries to raw data: presence of unused data
  - Adherence to an adequate OOS procedures including timely completion of the investigation
  - Adequate reserve samples: documentation of reserve sample examination
  - Stability testing program including stability indicating profile
Laboratory Control System

• Significant deficiencies
  - Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations
  - Pattern of failure to document investigation of discrepancies
  - Lack of validation of computerized and/or automated processes
  - Pattern of inadequate sampling practices
  - Lack of validated analytical methods
  - Pattern of failure to follow approved analytical procedures
  - Pattern of failure to follow an adequate OOS procedure
  - Pattern of failure to follow raw data
  - Lack of stability indicating methods
  - Pattern of failure to follow stability programs
Thank You