International GMP Inspections

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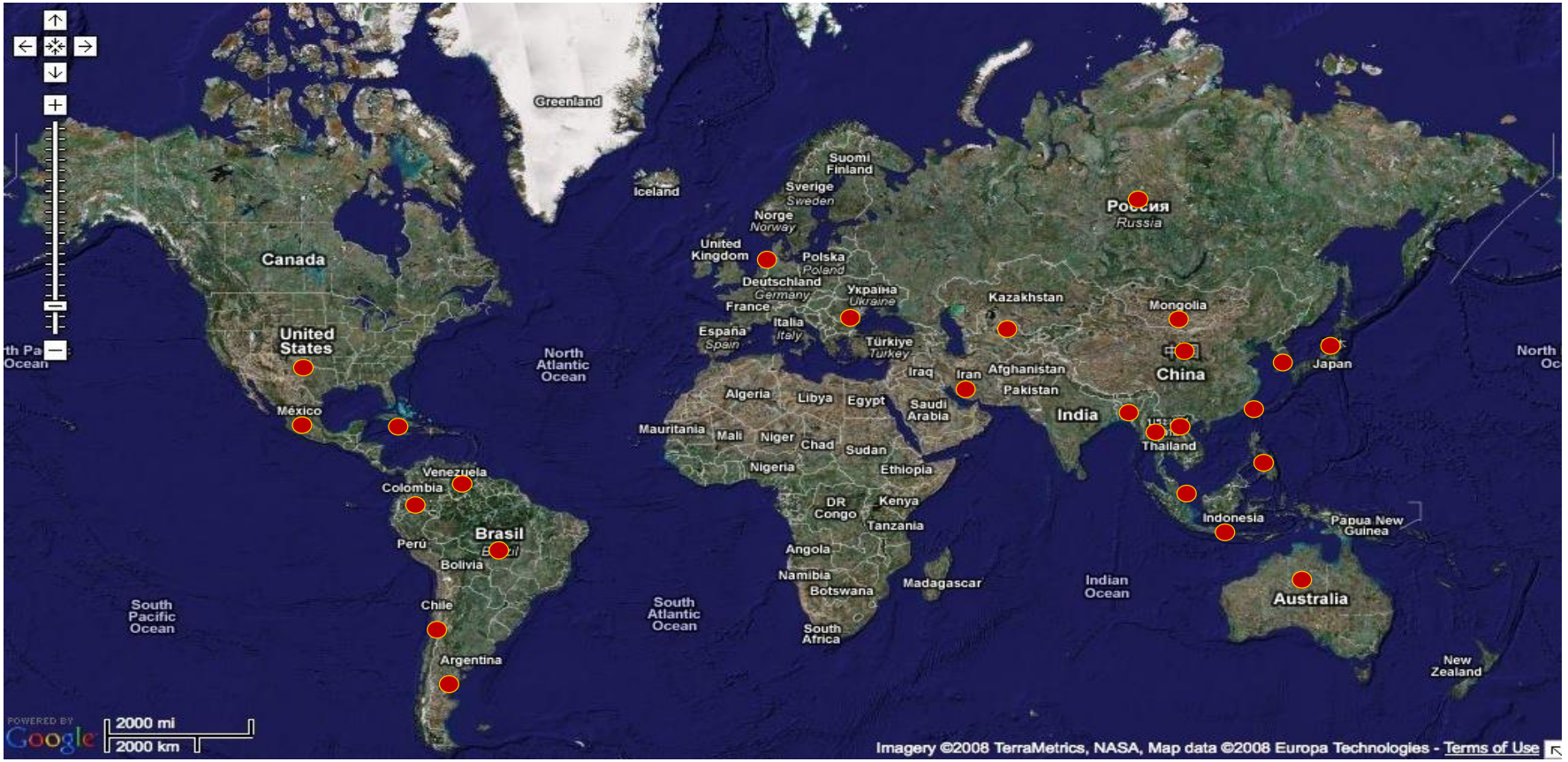
The countries visited by CKL as an inspector and/or trainer since 1987



Argentina	**China**	**Iran**	**Myanmar**	**Thailand**
Australia	**Colombia**	**Japan**	**Philippines**	**USA**
Brazil	**Cuba**	**Korea**	**Russia**	**Uzbekistan**
Bulgaria	**Denmark**	**Mexico**	**Singapore**	**Venezuela**
Chile	**Indonesia**	**Mongolia**	**Taiwan**	**Vietnam**

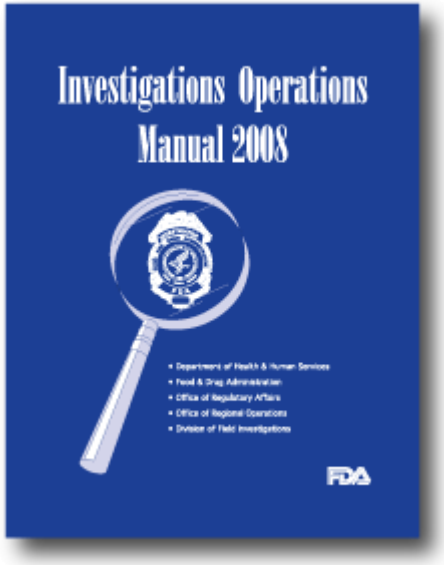
Comparison of Air Cleanliness Classifications

FDA	Descriptive		Class 100	Class 10,000	Class 100,000	ND	
	In Operation	≥ 0.5μm /ft^3	100	10,000	100,000	ND	
		Action Level CFU/m^3	1	10	100	ND	
EU, WHO, PIC/S	Descriptive		A	B	C	D	ND
	At Rest	≥ 0.5μm /m^3	3,520	3,520	352,000	3,520,000	
		≥ 5μm /m^3	20	29	2,900	29,000	
	In Operation	≥ 0.5μm /m^3	3,520	352,000	3,520,000	ND	
		≥ 5μm /m^3	20	2,900	29,000	ND	
		CFU/m^3	< 1	< 10	< 100	< 200	
ISPE	Descriptive		Grade 5	Grade 7	Grade 8	CNC+	CNC
ISO	Descriptive		ISO. 5	ISO. 7	ISO. 8	ISO. 9	
	In Operation	≥ 0.5μm /m^3	3,520	352,000	3,520,000	35,200,000	
		≥ 5μm /m^3	20	2,930	29,300	293,000	

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 impementing 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