US FDA Inspection at Celltrion

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CELLTRION

주의사항

- 본 자료는 ㈜셀트리온 내부절차 및 규정, 문서 등의 기밀 정보를 포함하고 있으며 식약청 주관 “GMP 해외실사 대응 전략 세미나”의 교육자료로 작성되었습니다.

- 본 자료는 최근 **US FDA**의 ㈜셀트리온에 대한 **PAI**의 준비, 실제 수행과정, 결과의 이해를 돕기 위한 교육자료로 작성 되었으며, 다른 목적의 사용시 법적 책임을 질 수 있음을 명시 합니다.

Subjects

I.	US FDA Inspection Policy & Program
	Inspection Experience of Celltrion with System Based Inspection
II.	Quality Systems
III.	Production Systems
IV.	Facilities and Equipment Systems
V.	Materials Systems
VI.	Packaging and Labeling Systems
VII.	Laboratory Control Systems

I. US FDA Inspection Policy & Program

US FDA Inspection Policy

- **FDA's Vision**
  - All medical products are safe and effective.

- **FDA's Mission**
  - Protecting consumers and enhances public health by maximizing compliance of FDA-regulated products and minimizing risk associated with those products.

US FDA Inspection Policy

❖ Type of Inspection

- Pre-Approval Inspection
  - ✓ Quality System + minimum 3 systems
- Regular Inspection
  - ✓ Quality System + minimum 2 systems
- For Cause Inspection
  - ✓ Quality System + the area
- Follow Up Inspection
  - ✓ Quality System + the area

US FDA Inspection Policy

- **Potential Legal Action after Inspection**
  - 483
  - Warning letter
  - Consent decree
  - License revocation
  - Recall
  - Civil money penalty

US FDA Inspection Policy

- **Investigations Operations Manual (IOM)**
  - Primary source regarding FDA's policy and procedure for investigators and inspectors.
    - ✓ **IOM, Chapter 5 Establishment Inspections**

FDA's Inspection (IOM)

❖ 5.1 Inspection Information

FDA inspectors must fulfill the following requirements for inspection approach.

- Authority to enter and inspect
  - ✓ FDA inspector's responsibility, written notice & request, etc.
- Inspectional approach
  - ✓ Depth of inspection, inspection walk through, inspection team leader & member's responsibilities, etc.
- Inspection of foreign firms
- Inspectional precautions
  - ✓ Clothing, sanitary practices, etc.
- General procedures & techniques
  - ✓ Label review, field exams, etc.

FDA's Inspection (IOM)

❖ 5.2 Inspection Procedures

FDA inspectors must perform the following activities during inspection, when applicable.

- Pre-inspectional activities
- Notice of inspection
- Reports of observations
- Receipt – factory samples
- Inspection refusal
- Inspection warrant
- Discussions with management
- Consumer complaints
- Interviewing confidential informants
- Routine biosecurity procedures for visits to facilities housing or transporting domestic or wild animals

FDA's Inspection (IOM)

❖ 5.5 Drugs

FDA inspectors must inspect the following issues deeply during drug inspection.

- Drugs inspections
- Drug registration & listing
- Promotion and advertising
- Guarantees and labeling agreements
- Other inspectional issues
- CDER bio-research monitoring
- Adverse event reporting / risk evaluation and mitigation strategies (REMS)
- Drug inspection report

FDA's Inspection (IOM)

❖ 5.10 Reporting

FDA inspectors must report the result of inspection as following information.

- Establishment inspection report (EIR)
- Endorsement
- Facts establishment inspection record (EI record)
- Narrative report
  - ✓ Non-violative establishments
  - ✓ Violative establishments
  - ✓ Individual narrative headings
    - Summary, history, persons interviewed, training, MFG design, operation, complaints, recall procedure, samples collected, signatures, and etc.
- Exhibits
- Addendum to EIR

FDA's Inspection Program

- **International Operation Branch (IOB), Division of Field Investigations (DFI) within ORA**
  - Responsibilities
    - ✓ Day-to-day activities related to international inspection
    - ✓ Global harmonization and related activities
    - ✓ Consisted of CSOs (Chief Safety Officers) and Program specialists
  - Inspection Team
    - ✓ Cadre of most experienced investigators who are dedicated to drug inspections

FDA's Inspection Program

- **Inspection Requests: from the Centers as a result of:**
  - (S)NDA, (S)BLA, ANDA or PMA submission as a supplier or an alternate of materials, products, or services
    [*Note: (S) stands for supplement*]
  - Surveillance inspections of firms which have been identified using a tiered approach based on factors such as risk, volume of products, complexity of processes, etc.
  - Firms that have problems related to MDRs, adverse reactions, or were involved in recalls.
- **BIMO inspection is also conducted.**

FDA's Inspection Program

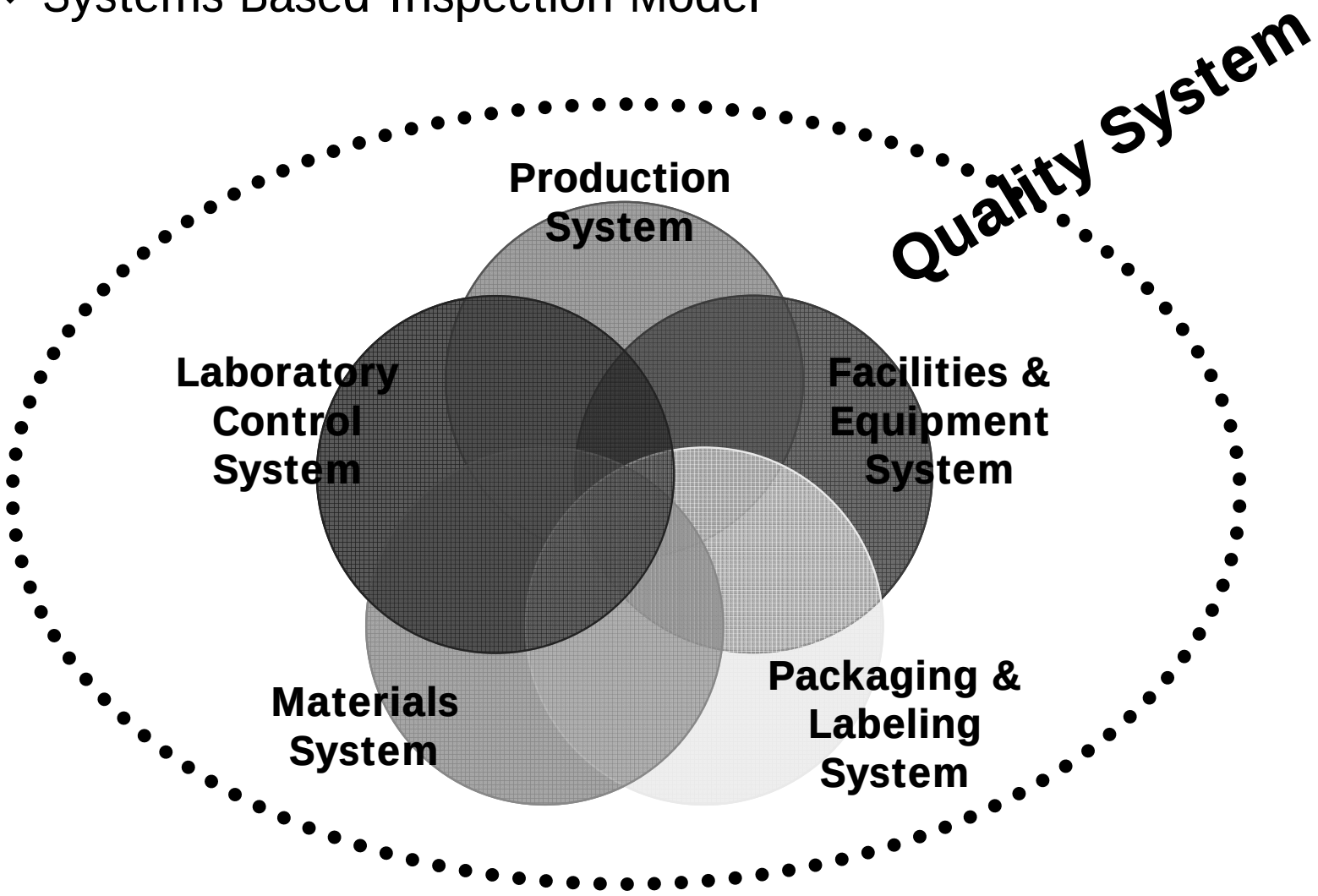
- **Inspection Duration**
  - Duration of each inspection varies – one trip (about three weeks) covers several firms that manufacture one type of product.
- **Type of Inspections**
  - Pre-Approval inspection (PAI) and Pre-License inspection (PLI)
  - Routine Inspection
  - "For Cause" Inspection
- **All inspections cover CGMP/Quality System**
  - May involve more than one assignment

What Drives the Inspections

- **FDA's 21 Century Initiatives** announced in 8/2002 and objectives include:
  - Encourage adoption of new technologies.
  - Promote industry use of modern quality system approaches.
  - Encourage risk-based approaches which focus on critical elements.
  - Ensure FDA review, compliance and inspection policies based on state-of-art pharmaceutical science.

What Drives the Inspections

- Systems Based Inspection Model



What Drives the Inspections

- Risk-Based Approach to Manufacturing and Regulation
- Pharmaceutical Inspectorate
- PAT Guidance document/ PAT Team
- Quality Systems Guidance document
- Process Validation (Compliance Policy Guide revised; Guidance being revised)
- 21 CFR Part 11 Electronic Records Guidance (risk-based; geared toward GMP documents)

Focus of Inspections

- **State of Control**
  - Detailed inspection of a system so that the findings reflect the state of control in that system for every product (profile) class.
  - If one of the six systems is out of control, the firm is considered out of control.
  - A system is considered out of control based on GMP deficiencies which suggest lack of assurance of quality.

US FDA Top 4 483 Categories

- **Failure Investigations**
  - Inadequate risk assessment
  - Failure to look at all potentially impacted products
  - No trending of problem data

- **Equipment / Facilities**
  - Poor Qualification of equipment and instrumentation
  - Poor maintenance practices, documentation
  - Lack of calibration of critical equipment

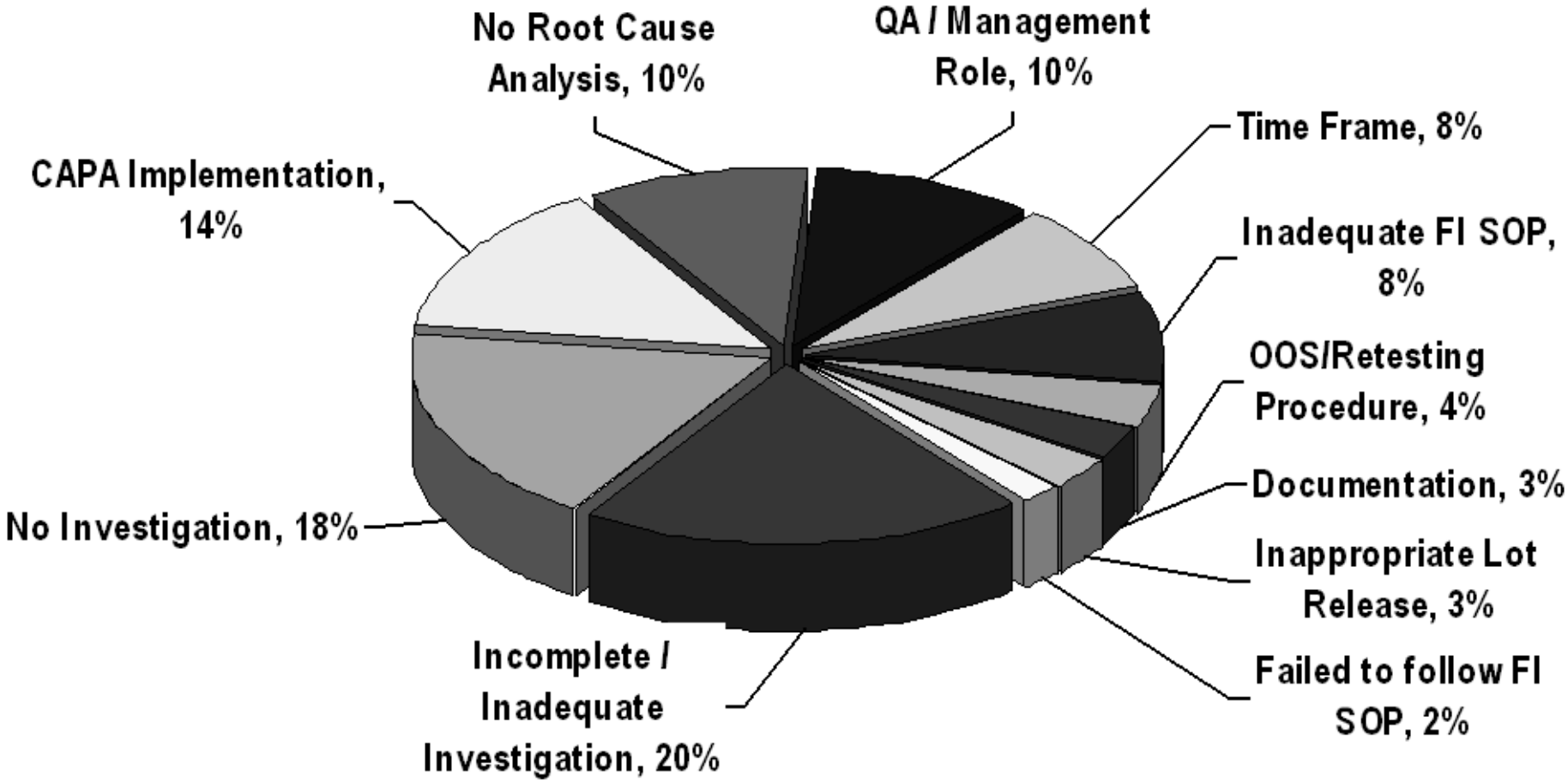
US FDA Top 4 483 Categories

- **Validation**
  - Column resin cleaning
  - Aseptic room cleaning
  - Disinfectant testing
  - Using insensitive test methods for supporting studies

- **Record Keeping**
  - Insufficient information
  - Inadequate SOP
  - Document Control

US FDA Top 4 483 Categories

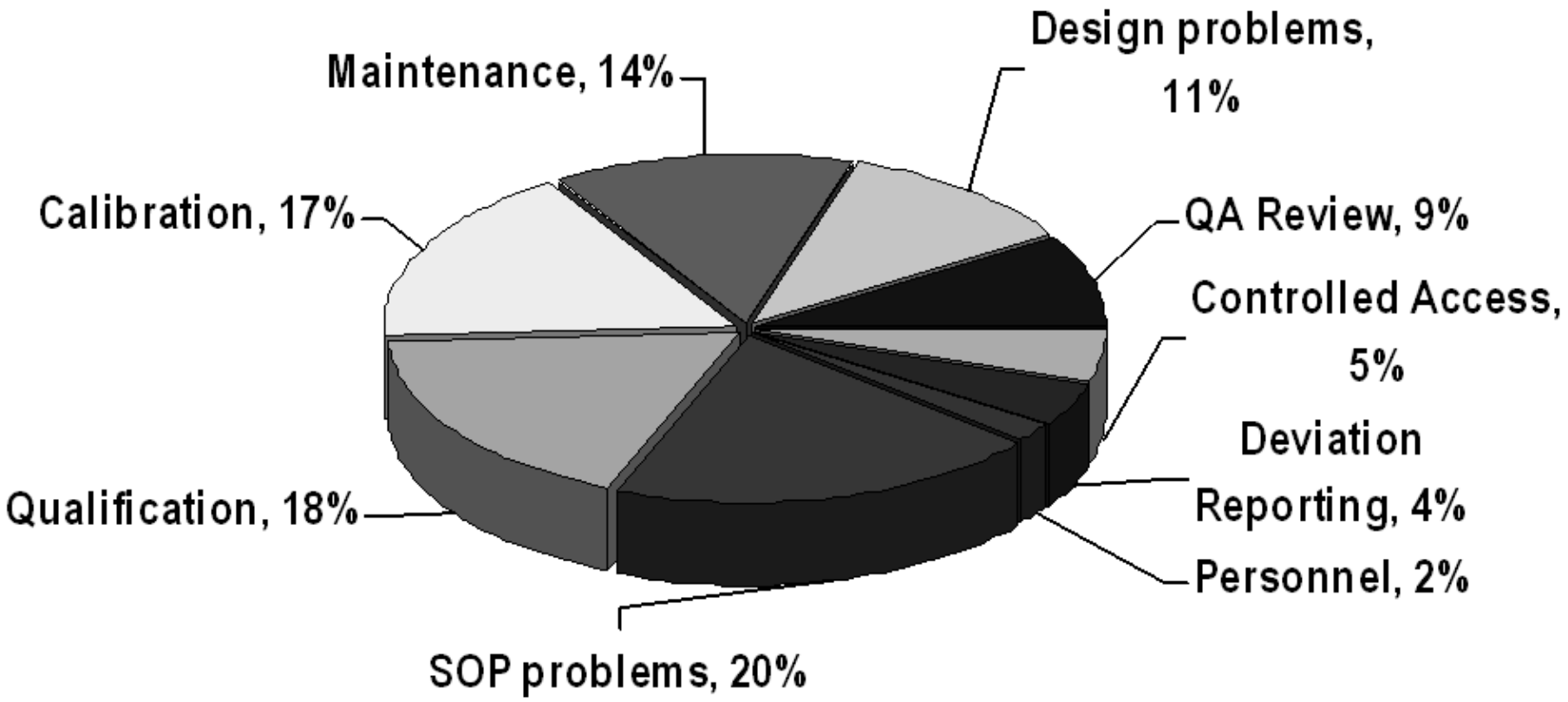
- **Failure Investigations**



2008 yr 483 summaries, BioQuality, January 2009

US FDA Top 4 483 Categories

- **Equipment / Facilities**



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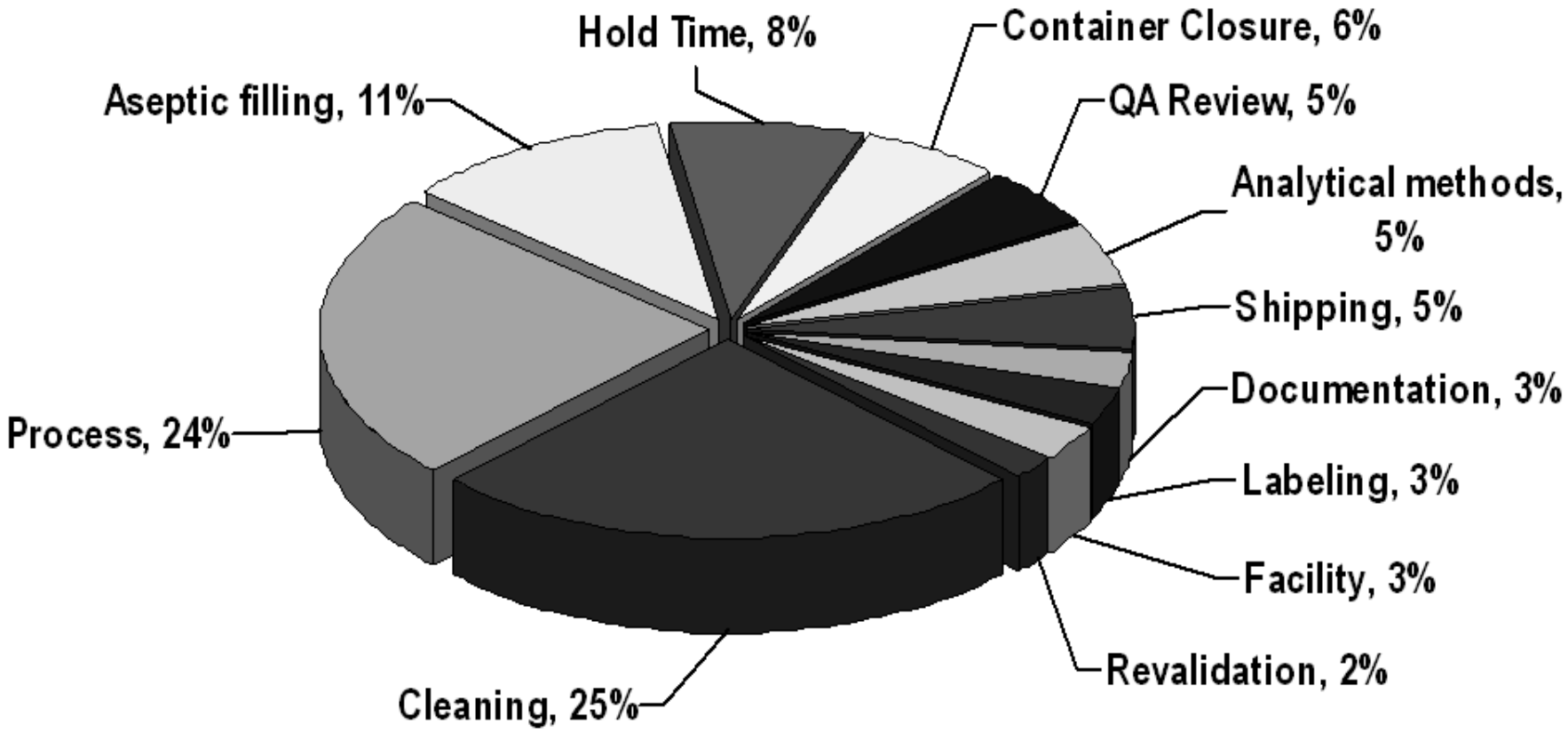
US FDA Top 4 483 Categories

- **Validation**



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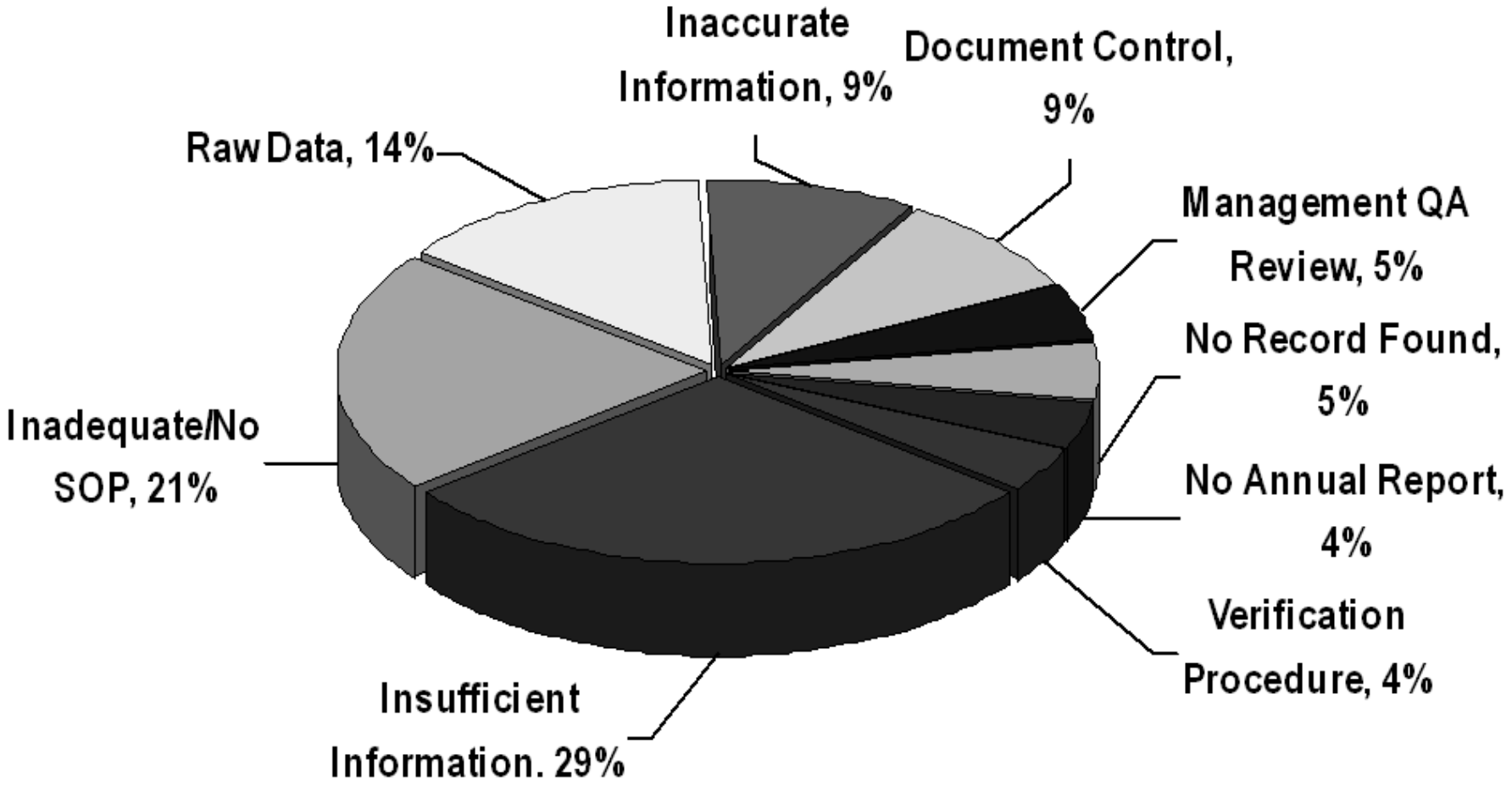
US FDA Top 4 483 Categories

- **Record Keeping**



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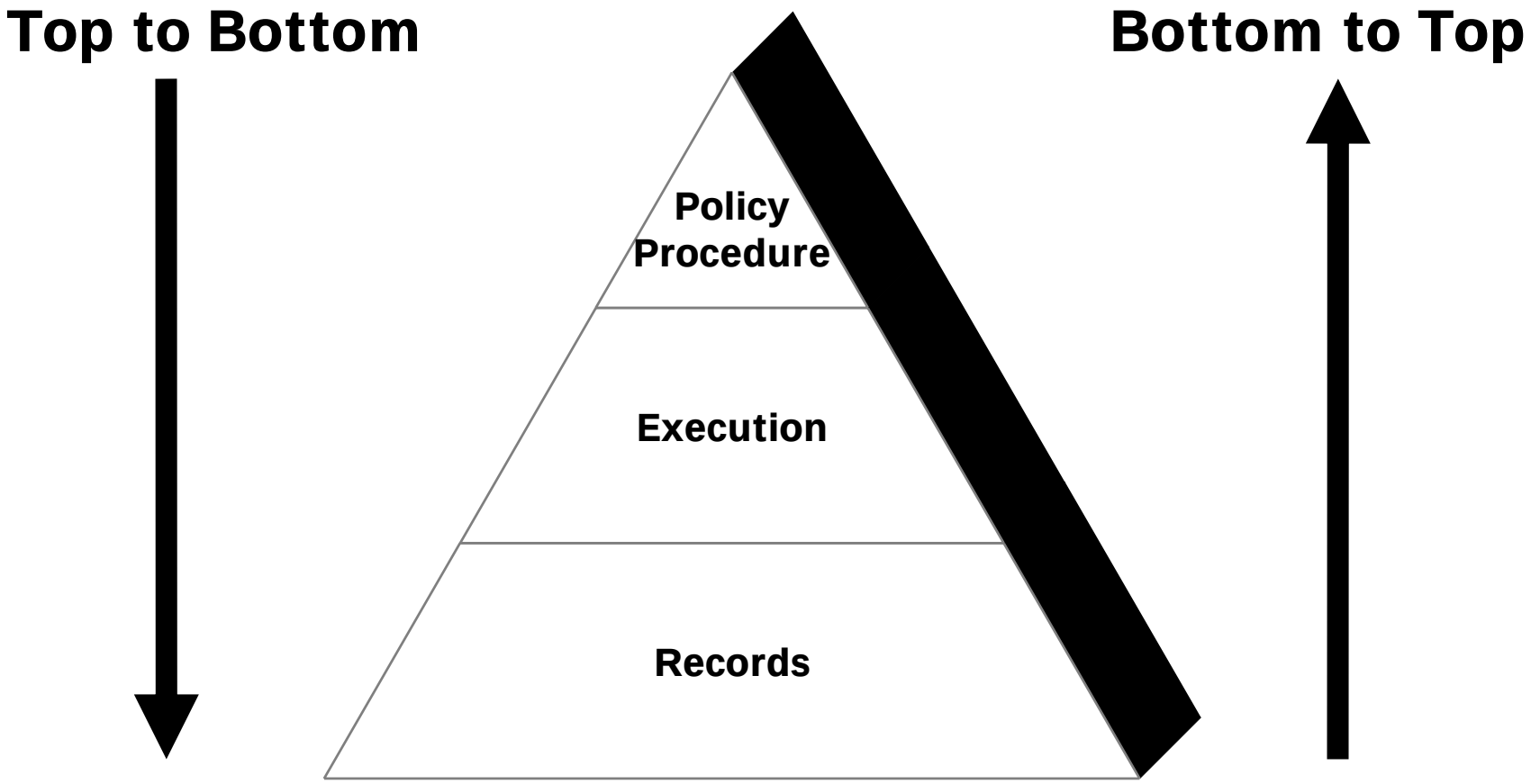
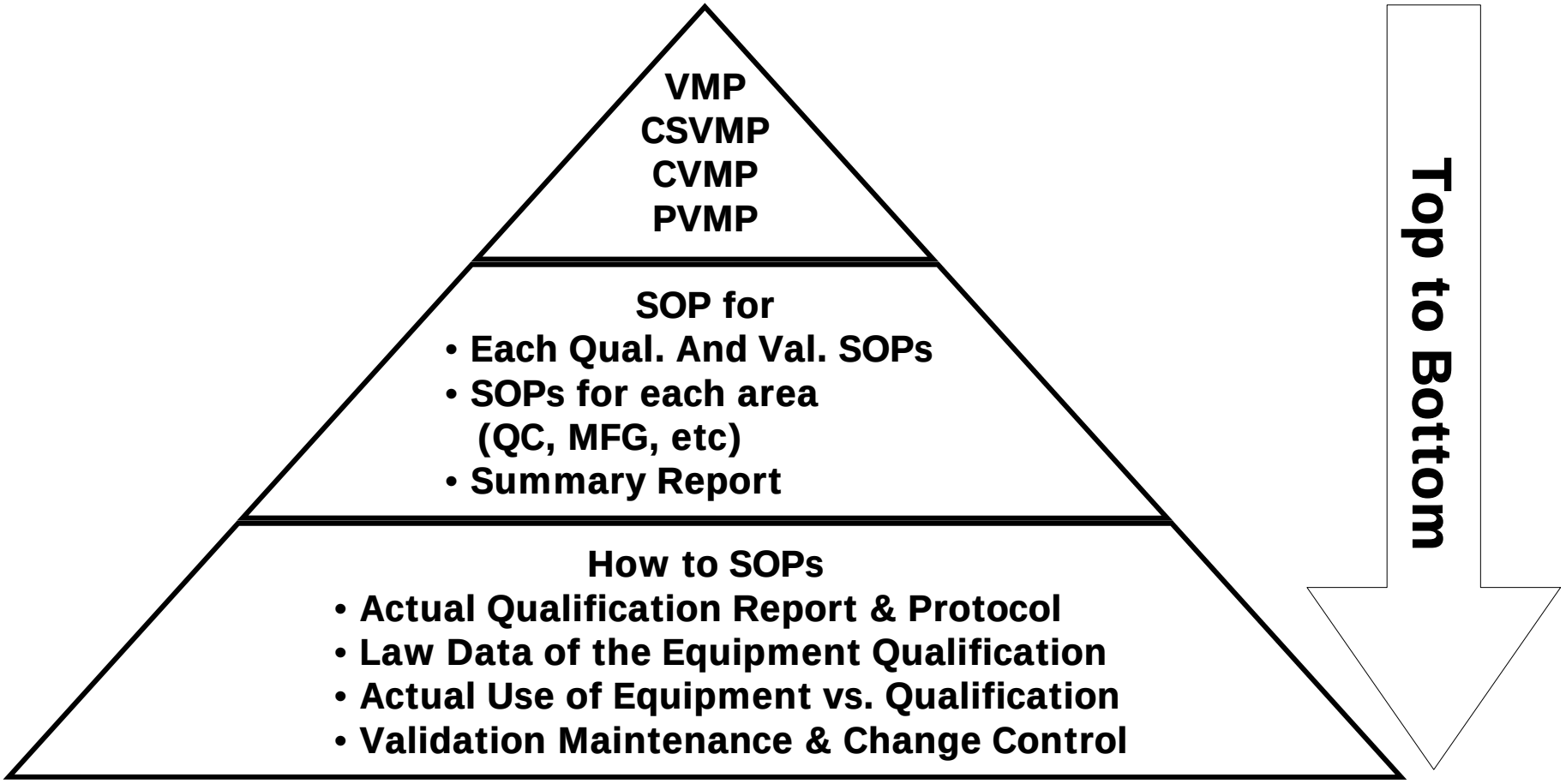
Inspection Approach



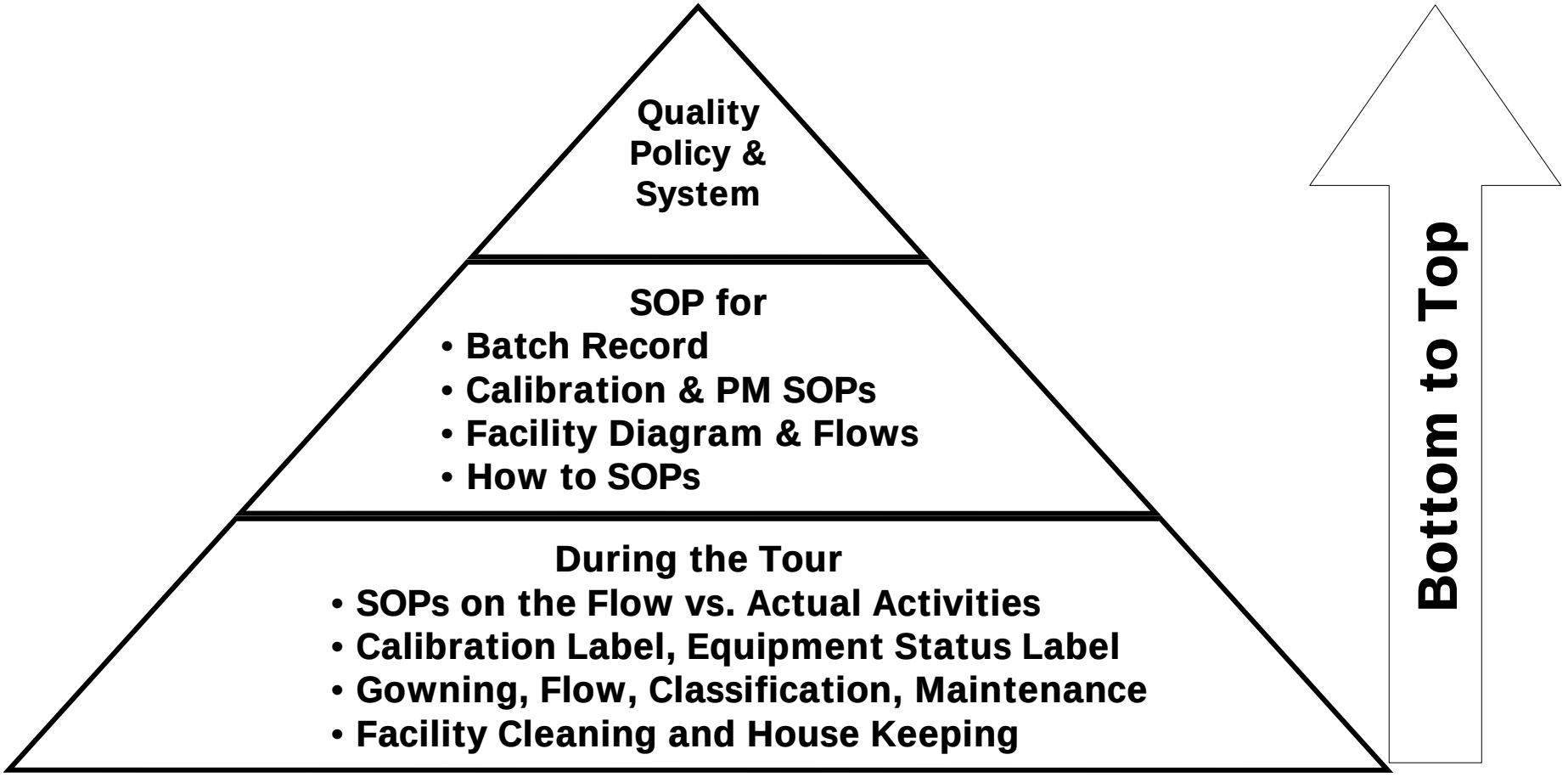
Inspection Approach (Top to Bottom)

Examples : Validation



Inspection Approach (Bottom to Top)

Examples : Facilities



Inspection Readiness

- **Always ready for the inspection**
- **Solid cGMP infrastructure**
  - Updated quality system - Understand the current GMP standards and expectations
    - ✓ FDA 21st Century Risk-Based cGMP Initiatives
    - ✓ PAT
    - ✓ ICH guidelines
    - ✓ FDA Compliance Program Manual
    - ✓ Various FDA Guidance for Industry
    - ✓ Pharmaceutical Inspectorate
  - Skillful employees
  - State-of-art technology
  - cGMP compliant facilities and utilities
  - Maintenance of control status

Inspection Readiness

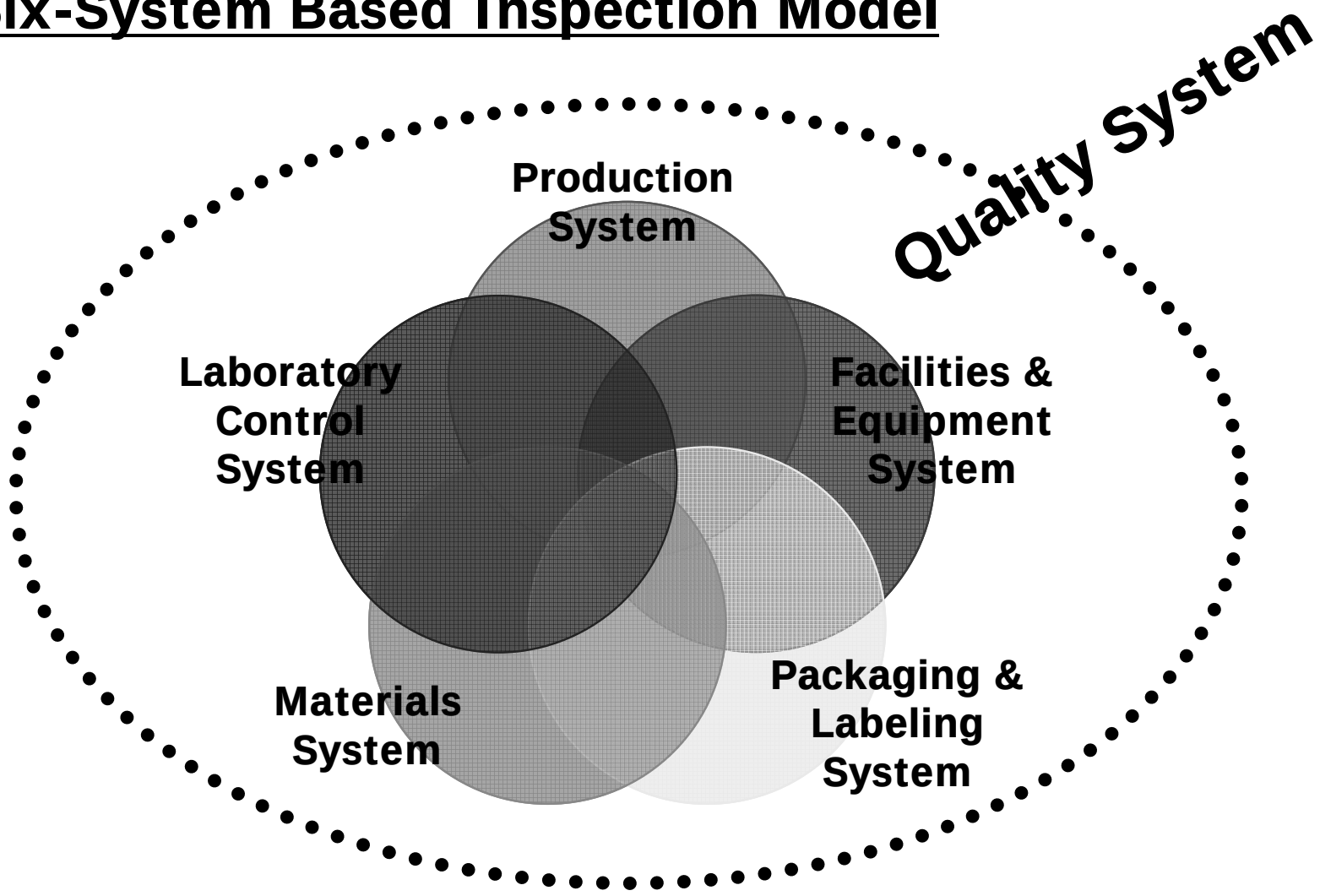
- **<u>Adaptation of cGMP as part of company business culture</u>**
  - The best way to prepare for inspections is diligently practicing cGMP regulations during daily operation.

Inspection Experience of Celltrion with System Based Inspection

II.	Quality Systems
III.	Production Systems
IV.	Facilities and Equipment Systems
V.	Materials Systems
VI.	Packaging and Labeling Systems
VII.	Laboratory Control Systems

System Based Inspections

- **Six-System Based Inspection Model**



Scope of Inspection

- **Quality System is always in the scope of inspection.**
- **If observations are found in Quality System and another system, FDA can take legal action.**

Inspection Scope at Celltrion

Quality System	Production System	Facilities & Equipment System	Materials System / Packaging & Labeling System	Laboratory Control System
• Document Control • Label & Form Reconciliation • Training • Deviation • CAPA • Change Control • Product Surveilance • Product Review • Internal Audit	• Batch Record • Trend Analysis • Process Parameters • Reprocessing • Hold Time • Bioburden • Column Packing • Media Transfer • Media Prep	• BSC • Bioreactor • Centrifuge • Depth Filter • UF/DF Skid • Media Tanks • Buffer Tanks • Pool Tanks • Autoclave • Glassware Washer/Dryer • Bulk Fill Study • Cleaning • Pest Control • Utility Monitoring • Environmental Monitoring • HVAC / Alarm • Calibration • Maintenance	• Receiving • Quarantine Area • Release • Label • Raw Materials • Material Review Board • Shipping • Supplier Qualification	• In-Process Sample • Retain Sample • Lab Monitoring • Test Method • Tech Transfer • Analyst Qualification • Data Control • OOS Handling • Test Control

Inspection Experience with System Based Inspection

- **Each six system will be presented from next page.**
  - Main focuses of each system during inspection
  - Company's experience of each system

II. Quality Systems

Quality System

- **Quality System is always in the scope of inspection.**
- **If observations are found in Quality System and another system, FDA can take legal action.**

- **Quality must be built into the process.**
- **Quality is not tested into the product.**
- **Assurance of Quality comes from :**
  - Design of robust process based on thorough knowledge of that process and the sources of variability
  - Effective Quality System in place

Quality System

- **In Quality System, management is responsible for insuring product quality, customer satisfaction and continuous improvement through :**
  - Organizational structure
  - All Processes
  - All Procedures
  - Facilities & Resources

Management Responsibilities

- **Assures overall compliance with cGMPs**
- **Review and approval duties for:**

1) Product Quality Reviews (at least annually)
2) Complaint Reviews
3) Discrepancy / Failure Investigations
4) Change Control
5) CAPA (Corrective Action & Preventive Action)
6) Reprocess / Rework
7) Validation / Revalidation
8) Rejects
9) Stability Failures / Out of Trend Data
10) Quarantine Products
11) Documented GMP & Job Related Training

Most Frequent Issues in Quality System

- **Non-compliance with SOPs**
  - Not following the SOPs
  - SOPs are written in the manner of non-compliance with CGMP regulations.
- **Training**
  - Repetitive errors and mistakes after training and follow-up training sessions.
- **Good documentation practice**
  - No explanation for certain changes; no subsequent verifications or approvals
  - Missing entry
  - Documentation fraud- e.g., back dating and unexplainable information entry

Most Frequent Issues in Quality System

- **Deviation handling / investigation**
  - Inadequate investigations
    - ✓ Inappropriate root cause analysis
  - Inadequate product impact assessment (justification)
  - Issues with timely closure
- **Change control**
  - Issues with timely closure
  - Inadequate assessment or follow up
- **Validation / Qualification**
  - Non-compliance with validation master plan
  - Inadequate justification of re-validation/re-qualification
  - Inadequate conclusions against the acceptance criteria
    - ✓ Conclude successful completion with failing results

Quality System – Experience

- **SOPs**
  - Routing, approval and distribution of SOPs
  - Reflection of modern concept in procedures
  - Tour of QA document storage room
- **Reconciliation of Forms and Labels**
  - Issuance and control of QC Forms for analysis
  - Reconciliation for raw material and BDS labels
- **Training Policy and Training Program**
  - Job description, training curriculum and training records
    - ✓ 1 Manufacturing operator
    - ✓ 4 QC analyst
    - ✓ 1 QA management
  - Checked by div. training coordinators and QA training team

Quality System – Experience

- **Internal Audit**
  - Internal audit program and audit schedule for last 3 months
  - To meet regulations and internal procedures
- **Product Quality Review**
  - To meet FDA regulation
  - To review and evaluate
    - ✓ The quality standards of each drug product
    - ✓ Manufacturing process
    - ✓ Deviations, change controls and all issues related to product

Quality System – Experience

❖ **Deviations and Change Control**

More than 40 deviations and 30 change controls were reviewed.

- Deviations and Change Controls were selected among
  - ✓ List of Deviations for last one year
  - ✓ List of Change Controls for last one year
- Major deviations and major changes were selected for review.
  - ✓ May have an impact on products and major equipment.
  - ✓ Re-occurred ones
- Those were reviewed with
  - ✓ Validation report of related equipment
  - ✓ Batch record of related production
  - ✓ Process parameter
  - ✓ Validation report and procedure related with utilities

Quality System – Experience

❖ Inspection focus of Deviation

- Investigations of deviation were reviewed thoroughly.
  - ✓ Decision tree
  - ✓ An aspect of finding root cause
  - ✓ Affected system / equipment and extended batch impact assessment
  - ✓ Timely closure of investigation (good – very timely manner)
- CAPA
  - ✓ Appropriate corrective actions for the deviation
  - ✓ Preventive actions to prevent re-occurrence in the future
- Trend analysis
  - ✓ Deviation quarterly reports
  - ✓ Main issues of deviation
    - Especially, personnel error

Quality System – Experience

- **Inspection approach of Deviation report (example)**
  - FDA inspector selected major one among the list.
  - Title was Sterility of Bioreactor (X-XXXX) was broken during inoculation.
  - Interviewed with Manufacturing supervisor and QA director
    - ✓ in that Root Cause was Personnel because the operator selected wrong message at dialog checking step of Transfer OP.
  - Reviewed CAPA and actions taken
    - ✓ Two OPs used for cell transfer were combined to prevent personnel mistake. (Procedure change)
    - ✓ Media was discarded and new media was prepared.
    - ✓ CIP, P-test and SIP of bioreactor were performed again.
    - ✓ The test result of in-process sample and cell growth parameter (VCD and Viability) were within acceptance range.

Quality System – Experience

❖ Inspection focus of Change Control

- Impact assessment
  - ✓ Justification of change
  - ✓ Affected system, equipment, product, document and etc.
  - ✓ Review of all related departments
- Implementation
  - ✓ Plan
  - ✓ Execution in a timely manner
    - Summary
    - Supporting documents
- Effectiveness evaluation of change
  - ✓ Monitoring after execution
  - ✓ Reviewed in batch release, and also in annual product review

Quality System – Experience

- **Inspection approach of Change Control report (example)**
  - FDA inspector selected change control report with review of downstream process description and related procedure.
  - Title was Change in assemble bag with filter for final product pool bag.
  - Reviewed Description of the change control
    - ✓ Manufacturing purification is currently using commercial Hyclone bag (XXXX-XX) for UF/DF pool operation and is planning to use a pre-assembled bag with capsule filter.
  - Interviewed with Manufacturing Director for Justification
    - ✓ It is difficult to prepare sampling bag with the related components for sampling and to sample from current cylindrical design. The assembly bag and filter, irradiated then shipped for used as delivered, no additional sterilization of capsule filter is required.

III. Production Systems

Production System

- Training (documented; job-related)
- Master production and control records
- Batch production and control records
- Change control procedure
- Contemporaneous, accurate and complete batch production documentation
- Implementation and documentation of in-process controls, tests, and examinations
- Adequate written procedures & practice for charge-in of materials
- Identification of equipment with contents, stage of manufacturing, status

Production System

- Equipment cleaning records
- Established time limits for completion of production step / stages
- Deviations investigated and documented contemporaneously with investigation
- Process validation based on knowledge of process (scientific basis for identifying critical steps / critical process parameters / control points)
- Justification and consistency of in-process specifications and final product specifications
- Data / information documented and available to Quality Unit for review (trending, investigations etc.)

Production System – Experience

❖ **Batch Record**

Series of Manufacturing were reviewed concisely.

- Upstream
  - ✓ Cell expansion in flask culture
  - ✓ Cell expansion in bioreactor operation
  - ✓ Production in bioreactor operation
  - ✓ Harvest and recovery
  - ✓ Media formulation
- Downstream
  - ✓ Initial purification
  - ✓ Final purification
  - ✓ Buffer solution

Production System – Experience

- **Trend Analysis and Review of Important Process Parameters**
  - Profiles of critical process parameter
  - Graphs of final data for all lots
    - ✓ Cell viability, cell density, bioburden, titer, culture hours
  - Overall yield and viability
    - ✓ For all PV and commercial lots
  - Bioburden and LAL test results
    - ✓ For all PV and commercial lots
  - Weekly process trend reports
    - ✓ Parameters relevant for each step have been monitored.

Production System – Experience

- Trend Analysis including graphs
  (All these were reviewed.)
  - ✓ QXL step yield
  - ✓ HIC pool HMW
  - ✓ HIC pool CHOP
  - ✓ HIC yield
  - ✓ VI agitation rate
  - ✓ rPA pool CHOP
  - ✓ QFF step yield
  - ✓ UFDF II pool bioburden
  - ✓ UFDF II process yield

Production System – Experience

- **Studies and Procedures**
  - Column lifetime studies
  - Reprocessing studies
  - Product and buffer hold time studies
  - Bioburden mapping study
  - Media transfer procedure
- **Column Packing and Repacking**
  - Manufacturing Solution Preparation records
  - Related logbooks for actual operations

IV. Facilities and Equipment Systems

Facilities and Equipment System

❖ Facilities

- Location, design, construction appropriate to facilitate cleaning, maintenance, operations
- Layout and air handling designed and constructed to prevent cross-contamination
- Flow of materials, personnel, air, waste and product designed to prevent mix-ups or contamination
- Defined areas or other control systems to prevent mix-ups or contamination
  - ✓ Incoming materials (ID, quarantine)
  - ✓ Sampling area (prevent contamination)
  - ✓ Quarantine (intermediates, APIs)
  - ✓ Released materials
  - ✓ Rejection

Facilities and Equipment System

- **Equipment**
  - Appropriate design, size, location, non-reactive product contact surfaces
  - Identification clearly marked
  - Qualification (DQ, IQ,OQ, PQ)
  - Calibration
  - Preventive Maintenance schedule and procedures
  - Cleaning procedures and validation
  - Records of use, cleaning, maintenance
  - Lubricants, heating fluids or coolants (not contact/alter product quality)
  - Closed or contained equipment
  - Inspection prior to use

Facilities and Equipment System

- **Utilities**
  - Qualified and appropriately monitored; drawings should be available.
  - Designed and constructed to prevent contamination or cross-contamination
  - Re-circulated air to production (same concern)
  - Permanently installed pipe work should be appropriately identified.
  - Drains of adequate size with air break

Facilities and Equipment System

- **Water System**
  - Process water at minimum meeting FDA program for potable water
  - Justify quality of water used to achieve stated product quality and establish specifications.
  - Water treatment facilities must be validated.
  - Product to be used for incorporation into sterile dosage form – water used in later stages should be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

Facility & Equipment System : Equipment – Experience

❖ Equipment Qualification (IQ, OQ, PQ Reports)

- Final validation reports were precisely reviewed rather than raw data.
- Variations during validation were reviewed.
- Generation of summary report for equipment qualification made easier to follow up and to review.
- Examples of equipment qualification reviewed
  - ✓ BSC, production bioreactor, harvest centrifuge, depth filter skid, UF/DF skid, harvest collection tank, media prep tank / hold tank, autoclave, glassware washer / dryer, buffer prep tank / hold thank, product pool tank

Facility & Equipment System : Equipment – Experience

❖ Bulk Fill Simulation Study

- Reviewed aseptic manipulations that occur during the bulk fill such that the bulk is assured of being contaminant free.
- Reviewed equipment qualification of LFB in ISO 5 environment inside ISO 7 room
- Manipulations
  - ✓ Equipment set-up, aseptic connections, product transfer, sealing and sampling
- Tests
  - ✓ surface microbial monitoring, airborne microbial particle monitoring, airborne non-viable particle monitoring, and settling microbial particle monitoring

Facility & Equipment System : Equipment – Experience

❖ **Cleaning Validation**

- Impressed about the extension of cleaning validation scope and scientific justification
- Cleaning Validation Master Plan well organized.
- Cleaning Validation Reports were reviewed.
  - ✓ Bioreactor
  - ✓ Centrifuge
  - ✓ Column

Facility & Equipment System : Facility – Experience

❖ Water For Injection (WFI)

- Routine WFI and clean steam monitoring program
- WFI Design and Construction (Drawings)
  - ✓ Sampling sites
  - ✓ Frequency
- WFI IQ/OQ/PQ validation reports
- WFI trending reports for 3 months
- Test items of WFI
  - ✓ TOC
  - ✓ Conductivity
  - ✓ Endotoxin
  - ✓ Microbial limit test
  - ✓ Heavy metals
  - ✓ Nitrates

Facility & Equipment System : Facility – Experience

❖ Clean Utilities

- Routine clean utility monitoring program
- Clean utilities design and construction (drawings)
  - ✓ Sampling sites
  - ✓ Frequency
- Clean utilities IQ/OQ/PQ validation reports
- Clean utilities trending reports for 1 year
  - ✓ Clean air
  - ✓ Clean gases
- Test items of clean air and clean gases (N_2, O_2, CO_2)
  - ✓ Water vapor
  - ✓ Hydrocarbons
  - ✓ Viable particulates
  - ✓ Non-viable particulates

Facility & Equipment System : Facility – Experience

❖ Environmental Monitoring Program

- EM procedures with sampling
- Diagrams including all bioburden sampling points
- Sampling plan
  - ✓ Monitoring type (operational, frequency)
  - ✓ Test type (surface, settling plate, air-viable, non air-viable)
  - ✓ ISO grades (ISO 9 through ISO 5)
- Recent 3 months trend results
  - ✓ Microbial count
  - ✓ Profiles of specific organisms
- Reviewed EM or personnel excursions occurred during Bulk Fill activities
  - ✓ Excursions over alert limit
  - ✓ Excursions over action limit
  - ✓ Deviations from excursions

Facility & Equipment System : Facility – Experience

❖ Power Interruption

- Power interruption procedure
  - ✓ Especially, data from power failure in Bulk Fill area
- Immediate notification
- Deviations from power interruption (electric supply)
  - ✓ Investigations
  - ✓ Especially, impact assessment of affected area
    - Including facilities and manufacturing equipment

❖ Facility Cleaning

- Cleaning and Sanitization procedure
- Manufacturing area cleaning logbooks

Facility & Equipment System : Facility – Experience

- **HVAC System**
  - Design and construction (Drawings)
  - Data of temperature, humidity and pressure in Bulk Filling Area
    - ✓ The data on specific date were requested and reviewed.
- **Alarm System**
  - Building Management System (BMS) alarms
  - Procedure for responding to alarms
- **Pest Control**
  - Pest Control procedure
  - Pest Control mapping plan
  - Quarterly trending reports

Facility & Equipment System : Calibration & PM – Experience

- **Calibration Program**
  - Calibration procedures
  - Deviations related to Out-of-Tolerance results of equipment
  - Calibration status
    - ✓ Calibration status (stickers) of each equipment in Manufacturing and Utility area were checked throughout the tour.
- **Maintenance Program**
  - Overall maintenance program and EAM system
  - Maintenance of vent filters on the bioreactors

V. Materials Systems

Materials System

- Written procedures for receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials
- System to evaluate suppliers (critical materials)
- Purchased against agreed specification
- Change control process for changing suppliers
- Upon receipt check for correct labeling, seals
- Before co-mingling bulk material, ID test
- Assurances obtained from non-dedicated tankers
- Identification on large storage containers and associated manifolds, filling and discharge lines
- Code given to received batches; status identity

Materials System

- At minimum, a specific identity test on incoming batches; COA
- Supplier evaluation should include three fully tested batches; one fully tested batch/year
- Written sampling plan with justification
- Prevent contamination of sampled containers
- Stored in manner to prevent degradation, contamination, no adverse effect on quality
  - Drums, bags, boxes off the floor
- First in, first out (or First expired, first out)
- Rejected materials identified and controlled under a quarantine system
- Established re-test / re-evaluation periods

Materials System – Experience

- **Receipt and Release of Material**
  - Tour of warehouse and QC sampling area
  - Receipt and quarantine of material at the warehouse
  - List of suppliers of critical raw materials
  - QC sampling and testing of material
  - Release or reject of material by QA
  - Control of labels
- **Lot History File of One Raw Material Release**
  - Assessment of the Material Specification, QC Testing Results and other related documents

Materials System – Experience

- **Material Review Board**
  - Role of the Board (SOP)
  - A meeting minute of MRB was reviewed.

- **Product Shipping (BDS)**
  - Relevant shipment documentation
  - Actual data from temptails
  - Chain of custody
  - Transportation of the product to customer after shipping
  - Verification of seal number of product shipment

Materials System – Experience

- **Supplier Qualification and Audit**
  - How the suppliers are qualified and controlled.
  - Supplier audit program
    - ✓ For critical raw materials
    - ✓ Interviewed with QA
    - ✓ And also with purchasing team
  - Annual supplier audit schedule
  - Interviewed with QA and also purchasing team

VI. Packaging and Labeling Systems

Packaging and Labeling System

- **Packaging**
  - Written procedures for receipt, identification, quarantine, sampling, examination and/or testing P&L
  - P&L should conform to specifications.
  - Records maintained for each shipment (showing receipt, examination & result)
  - Containers protective, clean, not alter product quality; if re-used, cleaned & labeling defaced.

Packaging and Labeling System

- **Labeling**
  - Access to label storage area limited
  - Written procedures for reconciliation; investigation if discrepancy
  - All excess labels with batch #, destroyed
  - Obsolete labels destroyed
  - Printing devices controlled to insure accuracy of label (against batch record)
  - Print labels checked against master and a copy placed into the batch record

Packaging and Labeling System

❖ Operation

- Documented procedures to assure correct packaging materials / labels used
- Operations designed to prevent mix-ups
- Labels : product name, batch #, storage conditions
- Shipped product : name / address manufacturer; special transport conditions; expiry / retest date
- Documented clearance before operations
- Packaged / labeled intermediates or products examined as part of packaging (documented)
- Seal employed to assure package integrity

Packaging & Labeling System – Experience

❖ Labeling System

- Raw material and BDS labels
- Investigation of appropriate label issue
- Reconciliation procedure
  - ✓ Logsheet of reconciliation with verification was reviewed.
- Information in product shipping label was reviewed.
  - ✓ Controlled by QA upon Manufacturing request
- During tour,
  - ✓ Labels on raw materials in warehouse were reviewed.
    - Especially, storage condition including temperature
  - ✓ Labels on samples in QC laboratory were reviewed.
    - Tracking system
    - Aliquot logsheet

VII. Laboratory Control Systems

Laboratory Control

- Written procedure (SOP) covering out of specification “OOS” results

- Investigation of “OOS” results conducted in a timely manner as per SOP and documented (complete records maintained). Conclusions from “OOS” investigations documented and corrective actions / need for addition investigation identified and implemented.

- “OOS” review included in Product Quality Reviews.

Laboratory Control

- **Laboratory records:**
  - Description of samples
  - Identification of method used
  - Raw data for sample/ standard preparation, reagents
  - Complete record of all data from testing
  - Record of all calculations
  - Statement of the test results; how compare with established acceptance criteria
  - Signature of the person who performed each test; dates tests performed
  - Date/ signature of second qualified person who reviewed original test records for accuracy, completeness and compliance with established standards

Most Frequent Issues in Laboratory Control

- **Laboratory compliance**
  - Inadequate laboratory data/records management
  - Inadequate laboratory investigations
  - Inadequate method validation
  - Equipment calibration
  - Material management

Laboratory Control System – Experience

- **QC Equipment Qualification and Lab Control**
  - IQ/OQ/PQ validation reports for Densitometer
  - Overall QC Equipment maintenance procedure
  - Temperature and humidity control of laboratories
- **Control of In-Process and Retain Samples**
  - Sample control procedure
  - Sample tracking sheet
  - Tour of retain sample storage room
- **Product Testing and In-process Testing**
  - SOPs for test methods
  - Those results and raw data

Laboratory Control System – Experience

❖ Tech Transfer of QC Testing Methods

- Method qualification protocols and reports
- Test method SOPs generated from method qualifications
- Tech Transfer documentation
- QC Analyst Qualification
  - ✓ With analyst training records
  - ✓ 4 analysts' training records on specific test methods were reviewed.
    - 1st employee's training record for Titer test
    - 2nd employee's training record for SEC test
    - 3rd and 4th employees' training records for Sialic test

Laboratory Control System – Experience

❖ Data Control and Security for QC Equipment

- How QC data is transferred from individual equipment to the server.
  - ✓ Server and back-up : QC equipment attached to the QC Network
  - ✓ Paper : QC equipment not attached to the QC Network
- How QC data are stored and maintained.
- Security and password management of laboratory computerized systems
  - ✓ Procedure of management of analytical data in QC computerized System
  - ✓ Procedure of configuration and management of QC Network
  - ✓ Analyst ID authorization control
  - ✓ Changing password

Laboratory Control System – Experience

- **Handling of Errors in QC Laboratory**
  - Procedure for investigating non-conforming test results
  - Deviations from non-conforming test
  - Handling of out-of-specification result by QC and QA
- **Control of QC Testing Forms**
  - QC testing forms issued and controlled by QA
  - Reconciliation and verification

Result from Inspection

Result

- **Successful Inspection with No Observation**
  - Company is in compliance with cGMP.
    - ✓ Facilities good shape in GMP perspective
    - ✓ Employees following SOP and Batch Records.
  - Documentations were very well written.

- **No CAPA was required.**

Inspection Follow up

- **Company had no observation and did not need to follow up any activity.**
- **Inspection follow up process overview**
  - Response within 20 days after inspection
    - ✓ Defensive justification (detail) : Studies, development reports, validation report or any other reports related to the observation.
    - ✓ Plan (detail)
    - ✓ Internal investigation – comprehensive and scientific methods
    - ✓ Corrective action (detail)
  - After response,
    - ✓ Re-inspection for evaluation or,
    - ✓ No response
  - After initial response, follow up progress report (detail)

Documents Carried Out – Experience

- ***These documents (SOPs, validation reports or other official documents) were permanently carried out and not to be returned upon FDA's request.***

Area	Number of Documents
Quality Assurance	9
Quality Control	5
Manufacturing	10
Facilities & Equipment	2
Validation	3