US FDA 수감
일반사항

CELLTRION

Global Biopharmaceutical Manufacturer

Hyuk Jae Lee

Regulatory Affairs

주의사항

- 본 자료는 ㈜셀트리온 내부절차 및 규정, 문서 등의 기밀정보를 포함하고 있으며 식약청 주관 “GMP **해외실사 대응전략 세미나** ”의 교육자료로 작성되었습니다.

- 본 자료는 최근 USFDA의 ㈜셀트리온에 대한 PAI의 준비, 실제 수행과정, 결과의 이해를 돕기 위한 교육자료로 작성되었으며, 다른 목적의 사용시 법적 책임을 질 수 있음을 명시 합니다.

Contents

Confidential Information

1. Celltrion Overview

Brief History of Celltrion

- Feb. 2002 Incorporation
- June 2005 1st BMS supply agreement
- July 2005 1st Facility Inauguration
- July 2006 2nd Facility Groundbreaking
- July 2006 2nd BMS supply agreement
- Nov. 2007 >30 Full-Scale runs, on-going

2. Legal Basis of the PAI by USFDA

1) 21CFR 601. 12(b) & 314.70(g)

Change requiring supplement submission and approval prior to distribution of the product made using the change (major change) *(1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.....* ***(3) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change..... (iii) The manufacturing site(s) or area(s) affected.....***

3. FDA Investigators

Inspector.1

- CDER, The Division of Therapeutic Protein
- Office of Pharmaceutical Sciences
- Biologist

Inspector.2

- CDER, The Division of Manufacturing and Product Quality
- Therapeutic Facilities Review Branch
- Microbiologist, Consumer Safety Officer

3. PAI Schedule Overview

1) sBLA Submission FDA Contact

2) PAI Duration Set-up

3) Receipt of requests for Pre-Sent Document

4) Receipt of requests for staging document

5) Arrival of US FDA Investigators

6) Inspection by US FDA :7 Days

   - Changed to 5 Days

7) Departure of US FDA Investigators

4. PAI Preparation Strategy

- **Establishing Responsibilities for PAI Readiness**

1) Regulatory Affairs Team

- sBLA Preparation and Submission
- Overall Authority of PAI Preparation Activities
  : Project Management
- Cooperation with Client PAI Readiness Team
- Coordination Between Every Department Within the Company
- Establishment of Procedures for PAI Hosting

4. PAI Preparation Strategy

- **Establishing Responsibilities for PAI Readiness**

2) Quality Assurance – Overall Compliance

- Compliance Review of Pre-existing Documents Including SOPs, IOPQ Protocols and Reports, Logbooks
- Development of Rationales Behind the Answers regarding Sensitive Issues Provided to the FDA Investigator
- Participation in the PAI as Key Players – QA Managers in the Inspection Room, Warroom Coordinator and Baseroom Coordinator

4. PAI Preparation Strategy

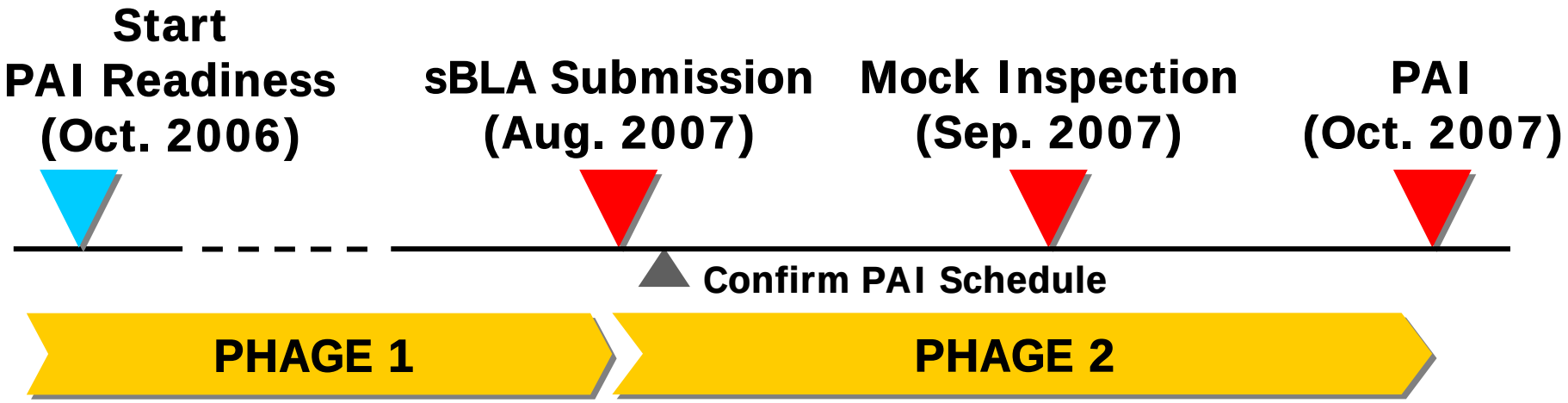
- **Establishing Responsibilities for PAI Readiness**

3) PAI TFT Team

- Responsible Representatives of Each Major Department (e.g. Quality Assurance, Manufacturing, Quality Control, Validation, Operation Service etc.)
- Regular Meeting: Once a Week
- Making Important Decisions for PAI Readiness
- Update Progress on Each Team's PAI Readiness Activities
- PAI TFT Audit

4. PAI Preparation Strategy

- **Progress of PAI Readiness**



- PHAGE 1: sBLA Submission
  and Consolidation of Company's Quality System
- PHAGE 2: Fine Tuning & Final Checks and Personnel Training

4. PAI Preparation Strategy

- **Area of Focus**

1) Document

2) Facility

3) Logistics

4) Personnel

Follow up of Internal/External Audit Results

5. Internal Preparation - Document Readiness

1) Document Readiness

- **Review and Improvement of Pre-existing Documents**
  - SOP Review and Revision
    : Translation in Korean, Compliance with Actual Practices
  - Review of Change Controls
  - Review of Engineering Drawings
  - Good Documentation Practice Review
- **Generation of New Documents**
  - Summary Reports for IQ and OQ
- **Follow-up of Internal/External Audit Observations Regarding Pre-existing Documents**

5. Internal Preparation - Document Readiness

1) Document Readiness

- **Preparation of FDA Requested Documents**
  - 21 Pre-requested Documents by FDA
  - Prepared by Individual Team and Reviewed by Quality Assurance
  - Staged in the Inspection Room
- **Preparation of Accessory Documents**
  - Prepared by Individual Team and Reviewed by Quality Assurance
  - Staged in the Inspection Room

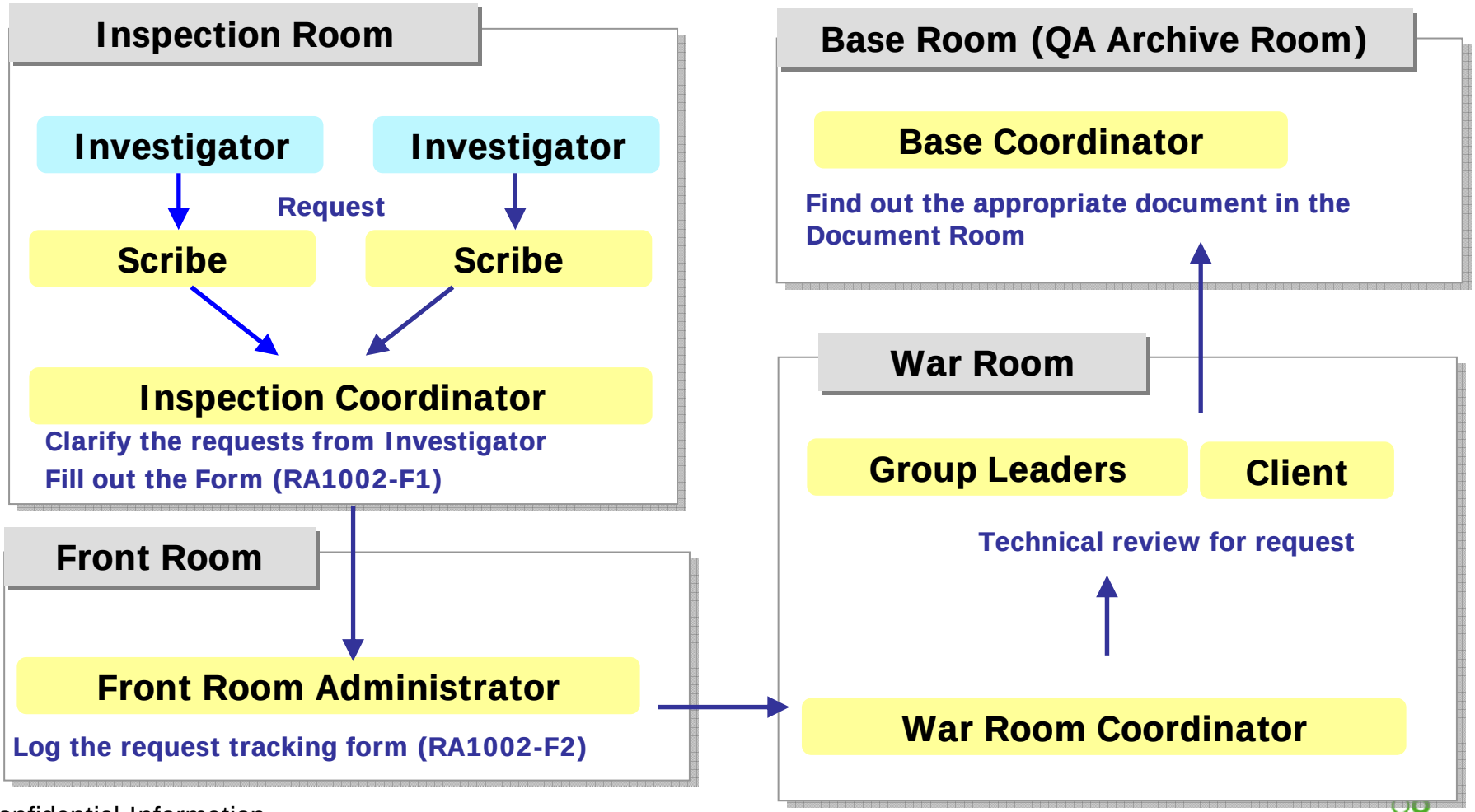
5. Internal Preparation - Facility Readiness

2) Facility Readiness

- **PAI TFT Audit**
  - Performed for Manufacturing Areas, Warehouse, Utilities and Laboratories
  - Corrective Actions for Observations: Completed before PAI
- **Facility Check**
  - Assignment of Room Owners and Area Supervisors
  - Preparation of Facility Checklist: Self-Inspection was Performed
  - Walk-throughs: Final Check by COO and Division Heads
- **Follow-up of Internal/External Audit Observations Regarding Facilities**

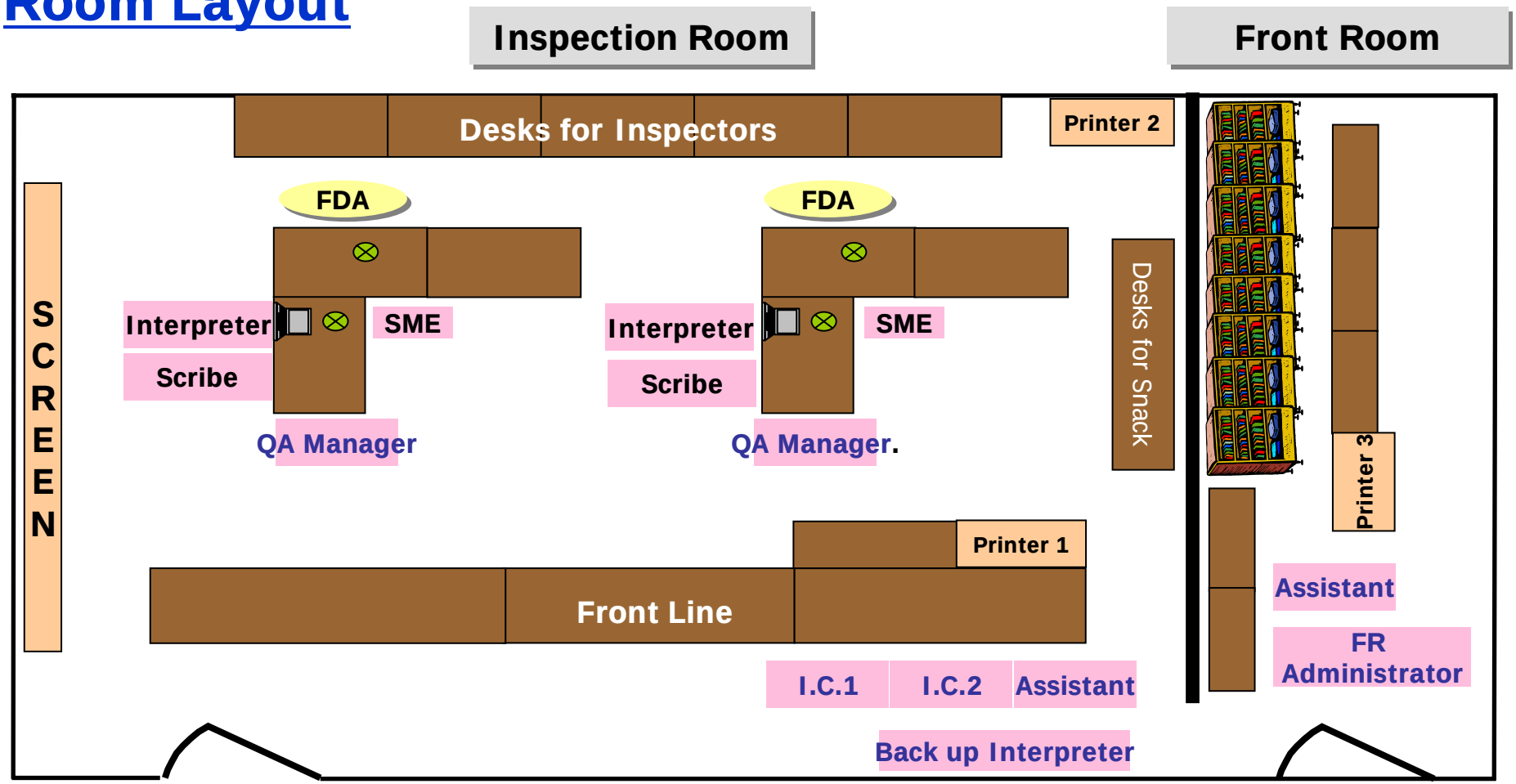
5. Internal Preparation - Logistics

3) Logistics – Request Flow



5. Internal Preparation (Cont'd)

Room Layout



5. Internal Preparation – Personnel Readiness

4) Personnel Readiness

- **Training Programs**
  - Training for All Employees on PAI
    : What is PAI and What are the Roles and Responsibilities for Individual Employee
  - Training for Key Players
    : Logistics and Behavior Trainings for PAI
  - Training for Subject Matter Experts
    : Interview Skills
- **Briefing Documents**
  - Sensitive Questions were Selected and the Answers were Prepared by Subject Matter Experts

5. Internal Preparation – Personnel Readiness

4) Personnel Readiness

- **FAQs**
  - Frequently Asked Questions from Previous Audits
  - Answers were Prepared and Practiced by Subject Matter Experts

5. Internal Preparation (Cont'd)

4) Key Players Assignment and Responsibilities

1. Inspection Coordinator
2. Interpreter / Scribe
3. QA Manager
4. Front Room Administrator
5. War Room Coordinator
6. Group Leader
7. Base Room Coordinator
8. Runner

6. Pre-Requested Documents

1) Electronic History of Business and Organizational charts
2) Production and Testing Schedule
3) SOP index with date of approval and revision number
4) Facility diagrams
5) List of major processing equipment
6) List of computer systems
7) List of Lab Testing Equipment
8) List of Lab assays
9) List of all change controls for the past year associated

6. Pre-Requested Documents (Cont'd)

10) List of testing and processing Out-of-Specification (OOS) investigations for the past year

11) Environmental monitoring and Clean Utility trend reports for the past year

12) Product batch records and a list of all deviations List of all Abatacept lots initiated, discarded or released

13) Process validation master plan

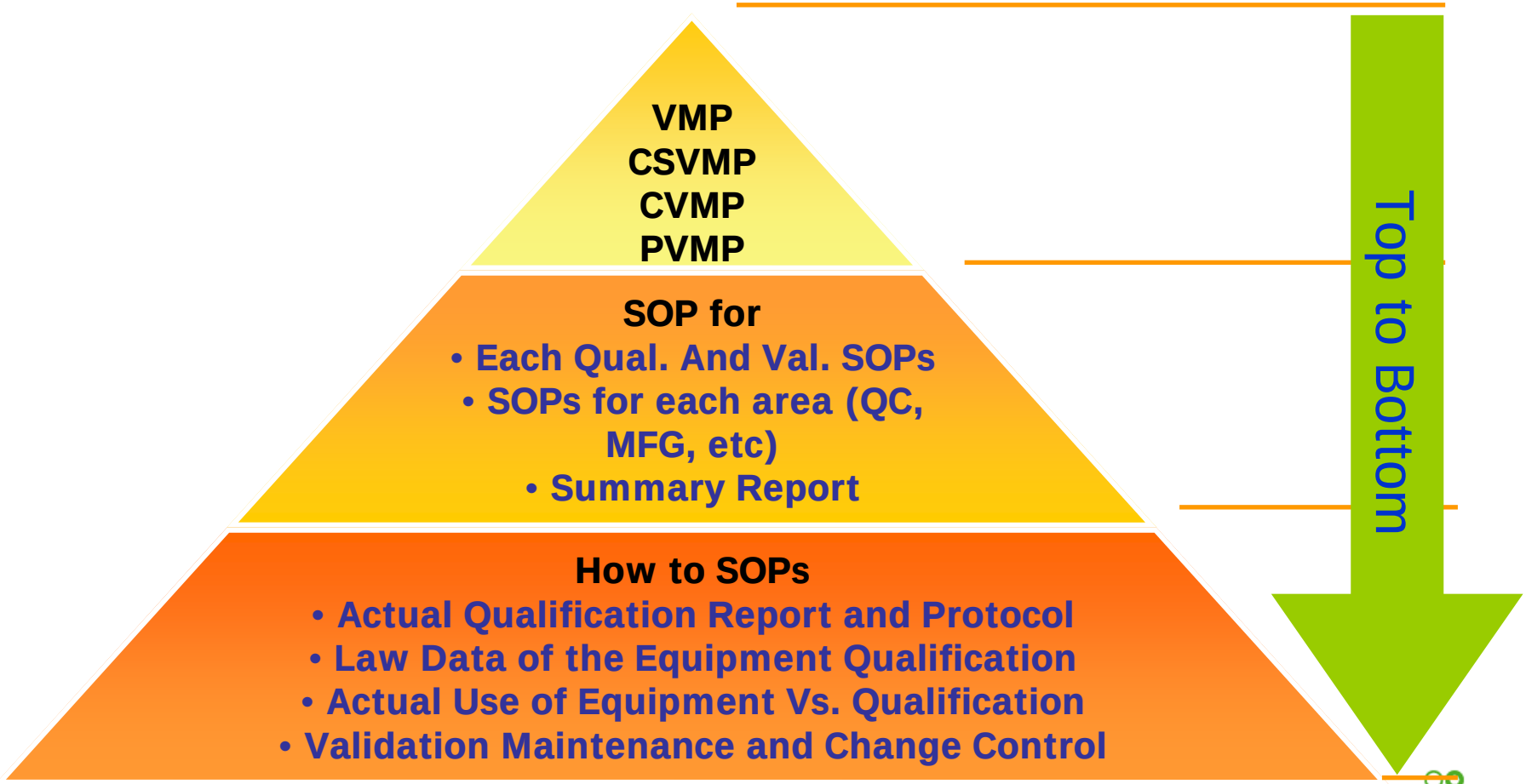
14) Working copy of the submission

15) Copy of the Training Procedure and the Recall Procedure

7. FDA Investigator's Approach (Top to Bottom)

Examples : Validation

Top to Bottom

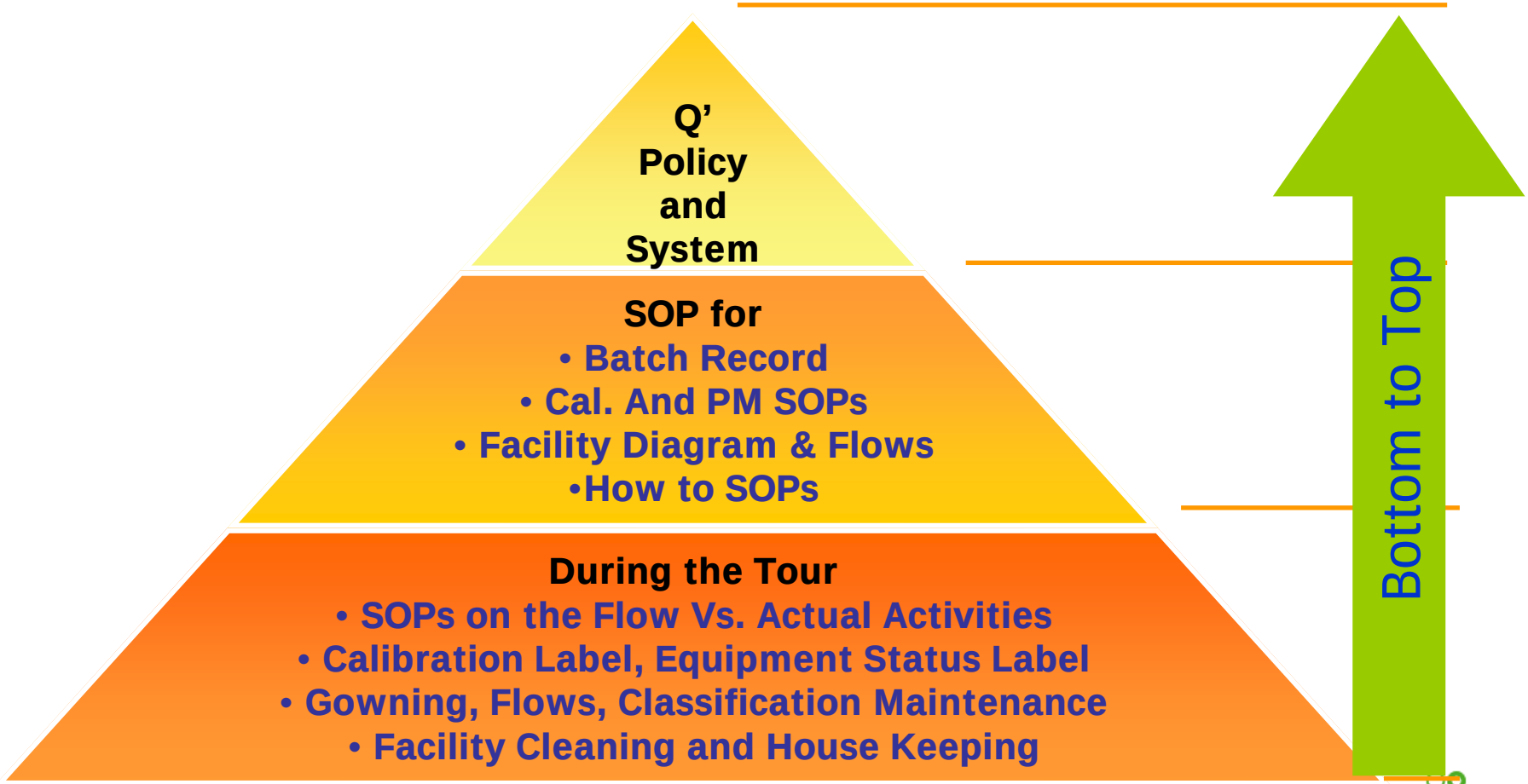


Confidential Information

7. FDA Investigator's Approach (Bottom to Top)

Examples : Facility

Bottom to Top



CELLTRION

7. FDA Investigator's Approach (Follow the Flow)

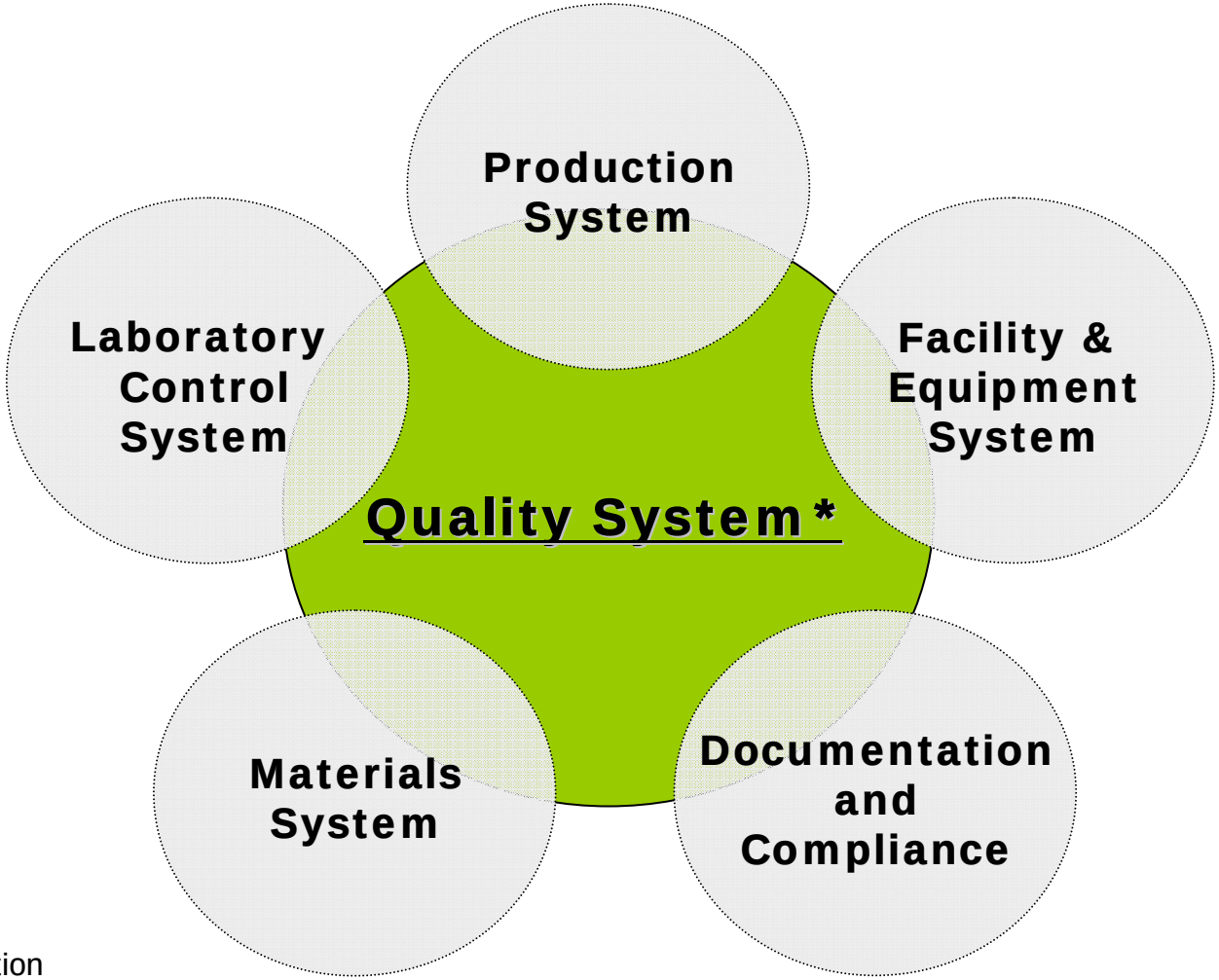
Areas	Accessed Equip. and Doc.
Material Receiving Dock	Receiving Document Check
QC Sampling Room in Warehouse	QC sampling Equipment, logbook, SOP
QC Raw Material Testing Lab.	Testing SOP, Lab. Equip., Raw Data
QA Office	QA Release SOP and Document
Material Storage Area	List of Material, SOPs, Investigation Report

Followed Raw Material Flow
To access overall material
Management system

Confidential Information

8. Inspection Coverage and Process

FDA's Approach is assessed based on 6 Quality Systems.



8. Inspection Coverage and Process (Con't)

FDA's Approach is assessed based on 6 Inspection Systems.

Susan Kirshner Ph.D.	Patricia Hughes Ph.D.
• Production System	• Quality System
• Laboratory Control System	• Facility & Equipment System
• Materials System	• Documentation & Compliance

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Quality System

1) **Recall Procedure / Product Surveillance**
2) **Training Policy and Training Program**
   - How it is implemented: Review of Training Curriculum and Training Records
3) **Product Quality Review by QA**
4) **Deviations and Corrective and Preventative Actions**
   - More than 40 Deviations (in 2006 – 2007) were Assessed
5) **Change Control**
   - 31 Change Controls (in 2006 – 2007) were Assessed

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Quality System

6) **23 / 45 QA SOPs were reviewed**

7) **11 / 24 Celltrion Policies were reviewed**

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Production System

1) Batch Record Review

- Upstream and Downstream Batch Record Review

2) Trend Analysis and Review of Important Process Parameters

- Profiles of critical process parameter
- Graphs of Final Data including Cell Viability, Cell Density, Bioburden, Titer, Culture Hours
- Overall Yield and Viability for All PV and Commercial Lots
- Bioburden and LAL Results for All PV and Commercial Lots

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Production System

2) Trend Analysis and Review of Important Process Parameters (Cont'd)

3) Review of Weekly Process Trend Reports

- Parameters Relevant for Each Step Have Been Monitored

4) Column Lifetime Studies

5) Reprocessing Studies

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Production System

6) Column Packing and Repacking

- Logs and Batch Records were Reviewed

7) Product and Buffer Hold Time Studies

8) Bioburden Mapping Study

9) Media Transfer Procedure

10) Observance of Media Prep Activities

11) Deviations and Corrective Preventative Actions Related to the Production were Closely Assessed

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Facility & Equipment System - Equipment

1) Equipment Qualification (IOPQ Reports)

- Biosafety Cabinet
- Production Bioreactor
- Harvest Centrifuge
- Depth Filter Skid and UF/DF Skid
- Harvest Collection Tank
- Media Prep Tank/ Media Hold Tank
- Upstream Autoclave
- Downstream Glassware Washer/Dryer
- Buffer Prep Tank/ Buffer Hold Tank

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Facility & Equipment System - Equipment

2) Equipment Qualification (IOPQ Reports) (Cont'd)

- Product Pool Tank

3) Bulk Fill Simulation Study

4) Cleaning Validation

- Cleaning Validation Master Plan
- Cleaning Validation Reports were Reviewed

  Bioreactor

  Centrifuge System

  Column

- Protocols for Sterile Hold of Small Equipment

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Facility & Equipment System – Facility

1) **Clean Utility Routine Monitoring Program**
2) **WFI IQ/OQ/PQ Protocols and Reports**
   - WFI Trending Report
   - Review of WFI Design and Construction (Drawings)
3) **Clean Steam IQ/OQ/PQ Protocols and Reports**
   - Clean Steam Trending Report
   - Review of Clean Steam Design and Construction (Drawings)

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Facility & Equipment System – Facility

3) Process Gas

- Handling Procedure and 1 Year Trend Results

4) Environmental Monitoring Program & Procedure

- Recent 3 Months (1st Quarter) Trend Results
- EM or Personnel Excursions Occurred During Bulk Fill Activities were Assessed

5. Pest Control Procedure & Reports

6. Procedures Regarding Power Interruption

- Including the Procedure and Data from Power Failure in Bulk Fill Area

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Facility & Equipment System – Facility

7) HVAC System

- Review of Design and Construction (Drawings)
- Temperature, Pressure & RH for Bulk Filling Area in August 07, 2007

8) Alarm System

- Building Management System Alarms
- Procedure for Responding to Alarms

9) Facility Cleaning

- Logs were Reviewed During the Tour of Manufacturing Area

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Facility & Equipment System – Calibration & Maintenance

1) Calibration Program & Procedure

- Deviations Related to Out of Tolerance Results of Equipments were Assessed
- Calibration Status were Assessed throughout the Tour of Utility and Manufacturing Area
- Calibration Procedures were reviewed

2) Maintenance Program

- Overall Maintenance Program + EAM System
- Maintenance of Vent filters on the bioreactors

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Documentation & Compliance

1) QA Documentation Control

- Routing, Approval and Distribution of Documents
- Tour of QA Documentation Center

2) Reconciliation of Forms and Labels

- Issuance and Control of QC Forms for Analysis
- Reconciliation for Raw Material and BDS Labels

3) QA Internal Audit

- QA Internal Audit Schedule for Last 3 Months

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Materials System

1) Receipt and Release of Material

- Tour of Warehouse and QC Sampling Area
- Receipt and Quarantine of Material at the Warehouse
- QC Sampling and Testing of Material
- Release or Reject of Material by QA
- Issuance of Material
- Control of Labels

2) Lot History File of One Raw Material Release

- Assessment of the Material Specification, QC Testing Results and other related documents

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Materials System

4) Material Review Board

- Role of the Board
- A Meeting Minute was Reviewed

5) BDS Shipping Procedure

- Relevant Shipment Documentation and the actual data from Temptails were Reviewed
- How the Product is Received at Client's End

6) Supplier Qualification and Audit

- How the Suppliers Are Qualified and Controlled

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Laboratory Control System

1) QC Equipment Qualification Policy/SOP

- IQ/OQ/PQ Protocols and Reports for Densitometer were Reviewed

2) Control of In-Process and Retain Samples

3) Drug Substance/Product Testing and In-process Testing

- 6 Testing Procedures and Results (Raw Data)

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Laboratory Control System

4) Tech Transfer of QC Testing Methods

- Method Qualification Protocols and Reports for BDS and In-process Testing were Reviewed

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Laboratory Control System

5) Qualification of QC Analysts

- Training Records for QC Analysts on Specific Testing Methods were Reviewed

6) Data Control and Security for QC Equipment

- How Data is Transferred from Individual Equipment to the Server

  QC Equipment Attached to the QC Network

  QC Equipment Not Attached to the QC Network

- How QC Data are Stored and Maintained
- Security and Password Management of Laboratory Computerized Systems

9. Inspection Focus in each System

FDA's Approach is assessed based on 6 Systems.

Laboratory Control System

8) Handling of Errors in QC Laboratory

- Procedure for Investigating Non-Conforming Test Results and a Related Deviation was Evaluated
- Procedure for Handling of Out of Specification Results was Assessed

9) Control of Testing Forms

- Control of Testing Forms in the QC Lab

10. Document List Taken By US FDA (Total 26 items)

- **Susan Kirshner**

	Document Title
1	• Supplier Qualification
2	• Insurance and Control of QC Forms for analysis
3	• peptide mapping
4	• Calibration Program
5	• Certificate of Manufacturer Authorization for Shipment
6	• Copy of Reprocessing data presented by Client
7	• Table of overall yield for PV + Commercial Lots • Table of bioburden & LAL results for BDS • List of Monitoring parameters for upstream • List of process monitoring parameters for purification
8	• Maintenance Program
9	• Copy of profiles of Glucose, pH, DO, Agitation for All lots • Copy of Graphs of Final Data for All Lots (Cell Viability, Cell Density, Bioburden, Titer, Culture Hours)
10	• Computers connected to QC network system • Monthly Trend Report

10. Document List Taken By US FDA

- **Patricia Hughes**

	Document Title
1	• List of Process Deviation • List of EM/Utility Deviation • List of OOT Deviation
	• List of Lots
2	• Material Review Board
3	• Environmental Monitoring Procedure in Celltrion Manufacturing Facility
4	• Cleaning Validation Master Plan for Abatacept
5	• Maintenance of Validation
6	• Open Cleaning Validation studies
7	• Certificate of Manufacturer Authorization for Shipment
8	• Copy of profiles of critical process parameter • Copy of Graphs of Final Data for All Lots
9	• Copy of Reprocessing data presented by Client

10. Document List Taken By US FDA

- **Patricia Hughes (cont'd)**

	Document Title
10	• Table of overall yield for PV + Commercial Lots • Table of bioburden & LAL results for BDS • List of Monitoring parameters for upstream • List of process monitoring parameters for purification
11	• Maintenance Program
12	•Survivability and Long-term preservation of bacteria in water and in phosphate-buffered saline
13	• List of Deviations and Investigations for the Past year for all product lots manufactured • Copy of the Training Procedure
14	• List of all change controls for the past year associated with production, equipment, utilities, and areas (Including date of occurrence, date of initiation, date of closure, and status)
15	• Material Review Board Meeting Minutes
16	• Amended and Restated Quality agreement

11. Wrap up Meeting

1) Area of Review

- **FDA Investigator Provided List of the Areas Reviewed for Each Day**
- **General Comments from FDA Investigators:**
  - Comprehensive Validation Master Plan and Cleaning Validation Master Plan
  - Quality of Equipment Qualification Studies and Cleaning Validation Studies: Scientifically Sound and Well Justified Approach
  - Thorough Deviation Investigations and Appropriate Corrective Preventative Actions
  - Documents Are Well Written and Easy to Understand

11. Wrap up Meeting

- **Celltrion Has Received A Lot of Complements Especially Regarding (Cont'd)**
  - Inspection Went Very Smooth and There were No Language Barriers
  - SOPs were Very Clear and Well Written
  - Analysts and Operators were Confident and Know What They are Doing
  - Facility in good shape in GMP perspective

11. Wrap up Meeting

2) Observations and/or Recommendations

- **No 483 Observation**
- **A Few Recommendations were Made:**
  - Moving Toward to More Electronic Systems for Overall Company's Data Management
  - Completing the Remaining Cleaning Validation Studies for Newly Installed Equipment
  - Completing Generation of IOQ Summary Reports
  - Completing the On-going Bioburden Study
  - Reconsidering the Excessive Gowning Strategy in ISO 9 Area
  - NO formal response is required regarding recommendations, Etc.

12. Conclusion

1) **Pre-Approval Inspection for Celltrion's MFG Facility was successfully completed.**
2) **There was NO 483 observation during Inspection.**
   - **All Celltrion Policies, SOPs and Validation Activities were well documented and in place.**
   - **Logistics for Request Handling was been working very well.**

Celltrion is in compliance with cGMP

Thank You