An Update on FDA’s New GMP Initiatives and PAT for Drugs

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Food and Drug Administration
Overview

- Drug Certification & Pharmaceutical Inspectorate
- GMP Initiative
- PAT
- Top 10 Drug Citations
Drug Certification
Drug Certification

- Level I
- Level II
- Level III
Level I

- A new hire investigator is someone not trained via traditional district provided ‘6-month’ new hire training program.
- Training completed within the first 12-months.
- Demonstration of competency by the new hire via a performance audit.
- Upon successful completion of the audit, investigators will have achieved Level I Investigator Certification.
- Mandatory
Level I Training

- Web based training courses and OJT experience
- Classroom training courses
  - Basic Food and Drug Law
  - Evidence Development
  - Investigative Interviewing
  - Quality Auditing
Level I Audit Criteria

- General Investigational Practices
- Evidence --- Recognize, Collect and Identify Appropriate Evidence to Support Findings
- Verbal Communication
- Written Communication
- Professionalism
Level II Drug Certification

- Not mandatory
- Specific to Drugs
- Candidate must spend at least 25% of time
- Candidate must submit packet to Level II Drug Certification Board
- Candidate must pass performance audit
- Candidate must be recertified every 3 years (18 CEU hours)
Level II Drug Investigator Certification

Prerequisites

- Must meet Level I
- Training courses
  - Drug Manufacturing & Quality Control Training Course
  - Pre-Approval Inspections Training Course
  - Industrial Sterilization of Drugs & Devices Training Course
  - Computer Systems Validation Training Course
  - Active Pharmaceutical Ingredient Manufacturing Training
- Performance Audit
Level II Certification Board

- 1 National Expert
- 1 Experienced Field Investigator
- 1 Expert from CDER
- 1 Expert from CVM
- 1 Field Manager
- 1 DHRD Specialist
Level II Audit Criteria

- Compliance assessment
- Evidence
- Verbal Communication
- Written Communication
- Professionalism
Level III Drug Certification

- Still under development
- “Pharmaceutical Inspectorate”
- Not mandatory
- Must be Level II Certified
- Candidates must submit packet to Level III Certification Board
- Course curriculum custom designed
- Expect to have some core training courses
- Planning for about 25 members (which is less than those in Level II) at the start.
Level III Drug Certification Board

- 2 Field Investigators operating at Level III in the area of certification being reviewed,
- 2 Experts from the CDER,
- 2 Experts from the CVM,
- 1 DFI Expert,
- 1 ORA Manager from the appropriate Field Committee and
- 1 Representative from DHRD, ORA.
Pharmaceutical Inspectorate
Pharmaceutical Inspectorate

- A group of Field Investigators with specialized experience and specific training in evaluating pharmaceutical manufacturing.
- Report directly to the management structure currently in place in the ORA District Offices.
- Spend a significant portion of their reportable time (80%) conducting drug quality inspections of domestic and foreign facilities and related activities.
Who is eligible for the PI?

- **CURRENTLY:**
  - Investigators with at least 3 years of experience in inspecting pharmaceutical manufacturing facilities.
  - Certified Level II Drug Investigators may apply to the Level III Drug Certification Board to enter the Level III drug certification program.
  - Once they have completed the Level III drug certification program, they will become members of the Pharmaceutical Inspectorate.
  - Expected to maintain their Level III certification.
Pharmaceutical Inspectorate

- An individual interested will submit their name to their supervisor for consideration.
- The initial nomination of an individual will then come from the District with concurrence through the management structure currently in place.
- The Level III Drug Investigator Certification Board will review certification packages and select candidates for Level III Drug Certification and membership into the PI.
In order to fulfill requirements & maintain their status as Level III Drug Investigators under the certification program, the PI will be authorized and encouraged to participate in professional activities that maintain, broaden, or enhance their knowledge in the area of certification.
Pharmaceutical Inspectorate

- Will continue to participate in additional activities to further their expertise in the area of drug quality inspection.
- May develop & implement formal training programs for FDA, industry, and state/local officials
- May develop and/or evaluate programs, policies, or procedures in their area of expertise, including serving as auditors for the Level II or III Drug Certification programs.
GMP Initiative
Steering Committee
Janet Woodcock, Chair
Maureen Hess, PM

Contracts Management
Theresa Mullin, Chair
Kate McEvoy, PM

International Activities
Janet Showalter, Chair
Ana Norris, PM

Part 11
Joe Famulare, Chair
Terry Martin, PM

Dispute Resolution
David Horowitz, Co-Chair
Helen Winkle, Co-Chair
Ted Shenwood, PM

Warning Letter Review
Fred Blumenschein, Chair
Erik Henrikson, PM

483 Communications*
Peter Beckerman, Co-Chair
Debbie Ralston, Co-Chair
Rose Cunningham, PM

Changes w/o Prior Review
Ajaz Hussain, Co-Chair
Jon Clark, Co-Chair
David Cummings, PM

Product Specialist on Inspection Teams
Ajaz Hussain, Chair
Bob King, PM

Work Planning & Risk Management
David Horowitz, Co-Chair
Theresa Mullin, Co-Chair
Khyati Roberts, PM

Pharmaceutical Inspectorate
Janet Woodcock, Co-Chair
Susan Setterberg, Co-Chair
Khyati Roberts, PM

Quality Systems Guidance Development
Joe Famulare, Co-Chair
Robert Sausville, Co-Chair
Anne Henig, PM

Quality Systems Framework
Lana Pauls, Co-Chair and PM
Pat Maroney-Benassi, Co-Chair and PM

GMP Harmonization Analysis
Kim Trautman, Co-Chair
Mary Malarkey, Co-Chair
Vikki Kinsey, PM

Evaluation of the Initiative
Janet Woodcock, Co-Chair
Theresa Mullin, Co-Chair
Maureen Hess, PM

GMP/Good Guidance Practice
Jane Axelrad, Chair
Susan Cohen, PM

* Project completed
5 New Guidance Documents

- **Part 11**, Electronic Records, Electronic Signatures - Scope and Application (final guidance)
- **Formal Dispute Resolution**: Scientific and Technical Issues Related to Pharmaceutical CGMP (draft guidance)
- Sterile Drug Products Produced by **Aseptic Processing**: Current Good Manufacturing Practices (draft guidance)
- **Comparability Protocols** - Protein Drug Products and Biological Products, Chemistry, Manufacturing, and Controls Information (draft guidance)
- **PAT** - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance (draft guidance)
Important changes to the inspections program

- Establishing a Pharmaceutical Inspectorate within ORA
- The Preapproval Inspection Compliance Program revised to give the field more opportunity to utilize a risk-based approach by allowing greater flexibility in determining whether a preapproval inspection is warranted.
Scientific Workshops

- FDA is actively seeking to improve international standards for drugs through efforts at supporting global harmonization, and collaboration with its public health counterparts in other nations.
Collaboration to promote innovative approaches to drug development

- McDonough School of Business at Georgetown University & Olin School of Business at Washington University, St. Louis to help FDA identify factors that predict manufacturing performance to further refine our pharmaceutical manufacturing risk-based assessment.
- National Science Foundation’s Center for Pharmaceutical Processing Research allowing FDA to expand its scientific foundation in the area of innovative pharmaceutical manufacturing technology.
- A Cooperative Research and Development Agreement with Pfizer, Inc., to research chemical imaging applications in pharmaceutical manufacturing and quality assurance.
Emphasizing a Risk-Based Approach

- FDA is developing a quantitative risk-based site-selection model for use in choosing sites for inspection.
- To be piloted for human drugs in October 2004.
- Will help FDA predict where its inspections are most likely to achieve the greatest public health impact.
- Will include risk factors relating to the facility, compliance history, the type of drugs manufactured, the manufacturing processes and the level of process understanding.
FDA has developed action plans for the review and revision of field compliance programs to incorporate risk-based approaches.

CVM and ORA will adopt a more systems based compliance program for its CGMP inspections to more closely parallel CDER's current program.

CDER and ORA have identified other compliance programs for revision toward a more risk-based approach, including the PAI program and API program.
Process Analytical Technology
Overview

- Process Analytical Technologies
  - Systems for **analysis** and **control** of manufacturing processes based on **timely measurements** of **critical parameters** and **performance attributes** of raw and in-process materials
  - Processes to assure acceptable end product quality at the completion of the process
Overview

- Process Analytical Technologies involve:
  - Optimal applications of process analytical chemistry tools
  - Feedback process control strategies
  - Information management tools and/or product/process optimization strategies
Why PAT?

• Paradigm shift from “testing to document quality” to “continuous quality assurance”
  - Quality “built-in” or “by design”

• Greater insight and understanding of processes

• At/on-in-line measurement of “performance” attributes
Why PAT?

- Real-time feedback controls
- Potential for significant reduction in production cycle time
- Minimize risks of poor process quality and reduce regulatory concerns
Regulatory Framework

- PAT not a requirement
- Research exemption
  - Continuous improvement without the fear of being considered non-compliant
- Regulatory support and flexibility during development and implementation
  - Eliminate the fear of delayed approval
  - Dispute avoidance/resolution
FDA Activities to Support PAT

- PAT subcommittee
  - Senior pharmaceutical and generic manufacturers
  - Government officials
  - Private and academic consultants
FDA Activities to Support PAT

- **PAT Review, Inspection and OPS Team (PATRIOT)**
  - Team of CMC reviewers, field investigators and compliance officers
  - Trained on PAT issues and new technologies to manage the review and inspection process
FDA Activities to Support PAT

- OPS PAT Policy Development Team
  - Pharmaceutical experts
  - Develop policy and guidance documents
  - Advise PATRIOT

- Training coordinators

- DRAFT guidance on PAT
  - (www.fda.gov/cder/guidance/5815dft.htm)
PAT Teams: ORA, CDER & CVM

**PAT Steering Committee**
Doug Ellsworth, ORA/FDA
Dennis Bensley, CVM/FDA
Mike Olson, ORA/FDA
Joe Famulare, CDER/FDA
Yuan-yuan Chiu, CDER/FDA
Frank Holcomb, CDER/FDA
Moheb Nasr, CDER/FDA
Ajaz Hussain Chair, CDER/FDA

**PAT Review - Inspection Team**

**Investigators:**
Robert Coleman (ORA/DFI)
Rebeca Rodríguez (ORA/DFI)
Erin McCaffery (ORA/NWJ-DO)
George Pyramids (PHI-DO)

**Compliance Officers:**
Albinus D’Sa (CDER)
Mike Gavini (CDER)
William Bargo (CVM)

**Reviewers:**
Norman Schmuff (CDER)
Lorenzo Rocca (CDER)
Vibhakar Shah (CDER)
Rosario D’Costa (CDER)
Raafat Fahmy (CVM)

**PAT Policy Development Team**
Raj Uppoor, OPS/CDER
Chris Watts, OPS/CDER
Huiquan Wu, OPS/CDER
Ali Afnan, OPS/CDER

**PAT Training Coordinators**
John Simmons, Karen Bernard
and Kathy Jordan
Possible PAT Applications to Pharmaceutical Manufacturing

- Characterization of amorphous versus crystalline materials (e.g., raw materials)
- Monitor crystallization reactions or polymorphic transformations during wet granulation or drying
- Monitor particle size, shape or density
- Blend uniformity monitoring
- Monitor moisture
- Monitor content uniformity and coating of tablets
- Cleaning validation
Possible PAT Technologies

- Infrared
- Near Infrared
- Chemical imaging
- X-Ray Powder Diffraction
- Laser Induced Fluorescence
- Nuclear Magnetic Resonance
- Raman Spectroscopy
Data Analysis Approaches for PAT Applications

- **Traditional**
  - Univariate analysis (peak height, peak area)

- **Chemometrics**
  - Pattern recognition
  - Principal component analysis
  - Multivariate analysis
  - Multivariate calibration
  - Neural networks
  - Others
Factors to Consider

- What variables are important for product performance?
- What variables are measurable?
- What is the most suitable method to measure the variables of interest?
- What are the possible issues or limitations of the candidate technologies?
Factors to Consider

- PAT method for FP release, stability or complaint sample analysis?
- Sample size
- Acceptance criteria or specifications
- Sample preparation
- Sampling techniques and sensors
Factors to Consider

- Process monitoring or feedback control?
- Decision making process
- Data requirements
- Multivariate analysis
- Comparing PAT method with referee method
References

- FDA’s PAT Webpage:
  
  http://www.fda.gov.cder/OPS/PAT.htm

- Some of the PATRIOT Training Resources
  - Ken Morris, Ph.D., Purdue University
  - Paul J. Gemperline, Ph.D., East Carolina University, MCEC
  - Brian Marquardt, Ph.D., University of Washington, CPAC
  - Mike McCarthy, Ph.D., University of California, Davis, CPAC
  - Steve Byrn, Ph.D., Purdue University
Top 10 Drug Citations
Citation References

- **211.100(b)**
  - Written production and process control procedures are not [followed in the execution of production and process control functions] [documented at the time of performance] (302)

- **211.22(d)**
  - The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. (235)
211.100(a)
- There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. (181)

211.165(a)
- Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. (172)
211.188
- Batch production and control records [are not prepared for each batch of drug product produced] [do not include complete information relating to the production and control of each batch]. (165)

211.110(a)
- Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. (163)
211.25(a)
- Employees are not given training in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations]. (156)

211.160(b)
- Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. (153)
211.198(a)
- Procedures describing the handling of all written and oral complaints regarding a drug product are not [established] [written] [followed]. (133)

211.192
- Drug product production and control records, are not [reviewed] [approved] by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. (132)