GMPs for the 21st Century

Steven Ostrove, Ph.D.
Ostrove Associates, Inc
www.ostroveassociates.com
Agenda

- Brief History of the FDA
- FDA Goals for 21 Century
- FDAs Current Approach to GMPs
  - Part 11
  - Modernization Act
  - PAT
  - QSIT
- Summary
The FDA Yesterday
History of the FDA and GMPs

- 1820 – US Pharmacopoeia formed
- 1848 – Drug Importation Act
- 1902 – Biologics Control Act
- 1906 – FD&C Act
- 1914 – Harrison Narcotic Act
- 1937 – Sulfanilamide Disaster
- 1938 – FD&C Revised
History Continued

- 1941 – Insulin Amendment
- 1944 – Public Health Service Act
- 1945 – Penicillin Amendment
- 1953 – Factory Inspections
- 1958 – Food Additives
- 1960 – Color Additives
1962 – Thalidomide
   ◦ Kefauver–Harris Amendment
1968 – Drug Efficacy Study Implementation
1970 – Patient Package Insert
1978 – Revised CGMP Regulations
1982 – Tamper Resistant Packaging
What Happened Next

- May 3, 1996
  - Revised GMPs published in Federal Register

- 21 CFR Part 11
  - August 20, 1997

- FDA Modernization Act – 1997
  - QSIT for CDRH Introduced

- 2000+ PAT, QSIT, and RISK Management
FDA Goals for the 21st Century
FDABidding Principles

- Risk-Based Orientation
- Science-Based policies and standards
- Integrated quality systems orientation
- International Cooperation
- Strong Public Health Protection
Vision for the Next Century

- Critical Path Initiative
  - Transform medical product development
  - Keep pace with expected medical advances
Risk

IGNORANCE IS RISK.
Types of Risk

- Equipment
  - Machine Failure
  - Cleaning
- Ingredients
  - API
  - Excipients
- People
  - Operator skills
  - Maintenance
  - Cleaning
- Understanding
  - Training
RISK

- IS
  - How severe is it?
    - Production – Environment – Personnel
  - How often CAN it occur?
  - How will it be detected?
  - How will the PATIENT be affected?

- IS NOT
  - The possibility of getting caught
FDA APPROACH TO RISK

- **PAT** – Process Analytical Technology
- **ICH Q9** – Risk Management
- **QSIT** – Quality Systems Inspections Technique
- The Quality System Approach
Science – Based

- Aseptic Process Guideline
- PAT Guidance
- Comparability Protocols Protein Drug Products ...
Improved Integration

- Quality Management System (QSIT)
- ICH Harmonization
- Process Validation Guideline
PAT = Process Analytical Technology

- Used in the Chemical industry for years
- Intended to make the process more accurate
- Need to FULLY understand the process before implementing

- Presents an automated control of a process
ICH Q9
ICH Q 9

- Prepared by the International Conference on Harmonization (ICH)
- Accepted by FDA
Initiate
Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Risk Communication
- Risk Communication

Output/Results of the Risk Management Process

Risk Review
- Risk Acceptance
- Review Events
Quality System Investigation Technology (QSIT)

- Started in the Device Industry
- Holds Management responsible
- Moved to Pharmaceuticals in 2006
INSPECTIONS – Old Way

- Bottom Up
INSPECTIONS – New Way

- QSIT
  - Top Down
Order of Systems

- Management
- Design
- CAPA
- Production & Process Controls
- Conclude with Management
Quality System’s Sub-systems

Design Controls

Corrective & Preventive Actions

Production & Process Controls

Material Controls

Management

Equipment & Facility Controls

Records, Documents, & Change Controls

Corrective & Preventive Actions
The Inspection Approach

- Top-down (versus Bottom-up)
- Sampling records (use tables)
- Pre-inspection activities (ask for and review documents)
- Start and end with Management
Definition of Quality in the Context of Mfg & Control of Products

- Fitness for intended use
  - Safe
  - Effective
  - Available
- Consistency
  - Process
  - Product
- Increased process and product knowledge leads to increased assurance of quality
- Must include customer (patient) expectations
Benefits of a Risk Based System

- **Patients**
  - Increased availability
  - Faster approval of new products
  - Continue to receive quality products

- **FDA**
  - More product and process knowledge shared by industry
  - More efficient resource allocation for review and inspection
  - Increased trust and understanding of industry decision making
Benefits of a Risk Based System

- Industry
  - Fewer, more efficient, science based inspections resulting in increased consistency
  - Faster, more consistent reviews
  - Potential for reduced regulatory burden
  - Less FDA oversight
  - Focuses resources on critical issues
  - Flexibility to focus on what should be done, not what can be done
QSIT Findings In-Plant Time

Average Hours

- Mgmt.: 4.2
- Design: 5.2
- CAPA: 10.7
- PAPC: 8.1
- QSIT Total: 28.2

Coverage

OAI
What Does this Really Mean
How to Conduct Analysis

1. Identify potential failure i.e. ways in which the system might fail.
2. Identify potential causes.
3. Rate severity, occurrence, and detectability.
5. Multiply the numbers together to determine the risk of each failure mode.
6. Identify ways to reduce or eliminate risk.
Identify areas of potential risk based on probability of occurrence and severity.
Qualification of Equipment

- Low probability of failure, severity if it fails
  - Minimal Qualification
  - Preventive Maintenance needs to be maintained (PMs)
- Medium probability of failure, medium severity
  - More extensive Qualification
  - More monitoring between PMs
- High probability of failure, high severity
  - Extensive Qualification
  - Continuous monitoring
Process Validation

- Low risk to patient
  - Minimal testing – NOT ELIMINATED

- Medium risk to patient
  - More complete testing

- High risk to patient
  - Extensive testing
Common Risk Management Tools

- FTA (Fault Tree Analysis)
- FMEA (Failure Mode Effect Analysis)
- FMECA (Failure Mode, Effect and Criticality Analysis)
- HACCP (Hazard Analysis Critical Control Points)
- Risk Ranking and Filtering
Role of Science

USE IT
Role of Management

- Management is responsible for Implementing Quality System
- Start & Finish with Management
- All product, process, design & CAPA problems can be tied to management
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THANK YOU

QUESTIONS?