Pharmaceutical cGMPs for the 21st Century
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Chairperson: Rob Sample
FDA GxP Regulations Along the Drug Life

Basic Research  →  Disease Discovery  →  Drug Discovery  →  Drug Development → Clinical Trials I, II, III → Manufacturing

No GLP/GMP!!!  →  GLP  →  GCP  →  GMP

21 CFR Part 11

21 CFR:
- GLP: Part 58
- GCP: Part 50
- GMP: 210/211

Product Safety
+ Availability
+ Affordability

Agilent Technologies
Pharmaceutical cGMPs for the 21st Century

- Announced August 21, 2002
- Two year program
- Merges science-based risk management with an integrated quality system approach
- Will not interfere with current enforcement - no deregulation!
- To be implemented in multiple steps
- First results in 2003

Risk based system inspections

Optimize FDA resources
Background: Significant Changes Occurred in the Last 25 Years

• Increase #of pharmaceutical products and a greater role of medicine in health care
• Decreased frequency of FDA manufacturing inspections

Domestic non-medical gas GMP inspections

Source: FDA
21st Century GMP Initiative - Three Goals

Goal #1
• Enhance focus of agency’s cGMP requirements more on potential risks to public health. Focus on those aspects of manufacturing that pose greatest potential risk

Goal #2
• Help ensure that FDA’s enforcement practices does not slow down innovation and introduction of new manufacturing technologies in the pharmaceutical industry

Goal #3
• Enhance consistency and predictability of FDA’s approach for inspections

Use FDA resources more efficiently

Source

Agilent Technologies
First Results

- Guidance on **Comparability protocols** for non-protein drugs and biological
  - allows certain manufacturing changes without submission of prior approval supplement

- Guidance on **Process Analytical Technology**
  - helps to modernize manufacturing

- **Electronic records/signatures (part11)** based on “justified and documented risk assessment” makes electronic records and signatures affordable and manageable

- Review of Warning Letters by Centers and guidance on dispute resolutions helps with **consistency and predictability of enforcement**
FDA Guide
Process Analysis Technology (PAT)

Advantages
- Less recalls
- Less waste

Previous problems
- Validation

FDA working with industry on how to optimize validation/compliance vs. risk

DCS = Distributed Control System
Review of Warning Letters

- Inspection
  - Deviations?
    - No → No action
    - Yes → 483 Observation
      - Severe deviations?
        - No → No action
        - Yes → Warning Letter Review by Center
          - In line with FDA’s thinking?
            - No → No action
            - Yes → Warning letter to inspected site

Fewer warning letters but Higher impact on industry
Audit Trail and OOS

• Confirmed OOS results for … were invalidated by Quality Assurance, that concluded that the chromatographs were incorrectly integrated.

• The Chromatographs were reprocessed with adjusted baseline parameters, yielding acceptable results, and the lots were released for distribution.

• However, the laboratory investigation concluded that the results could not be invalidated and that no problems were observed during the chromatographic run.

Recommendation: keep all integration results, document changes

Ref.: www.fdagoodmanufacturingpractice.com
Rationale Behind Systems Inspections Approach

What does change?
• The way how inspections are done and evaluated
• Time for inspections may go down

Requirements do not change !!!

• If the quality system and one or more other systems are adequate all profiles covered by the system are adequate
• If one site is not in compliance, other sites may not be in compliance!!!
New Approach: System Inspection - Top Down

- Management controls
- SOPs
- Capa

Quality System

- Change control
- Validation
- Records
- Training

Material Systems

Production Systems

Laboratory Control

Labeling & Packaging

Facilities & Equipments

LIMS

HPLC

Others e. Ph meter

Impact on direct product quality? Complexity?

- People (staffing, training)
- Validation
- Raw data
- E-records (part 11)
- Data audit
Recommendation for System Based FDA Inspections

Study FDA’s Compliance Policy Guide 7356.002

COMPLIANCE PROGRAM
GUIDANCE MANUAL PROGRAM

• Guidance for inspectors on how to conduct inspections
• Describes all six systems
• Includes checklist items for each system

Download from:
http://www.labcompliance.com/agilent/gmp
How Does this Impact Part 11?

- The concept of risk based inspections will be applied to GMP AND part 11
- Ensure latest technology can be used
- Part 11 implementation based on documented risk management
- Narrow the scope of part 11

First guidance Feb/Aug, '03

Guidance for industry
21 CFR Part 11;
Electronic Records;
Electronic Signatures
Maintenance of
Scope and Applications

Draft Guidance for Industry – Not for Implementation –
New Part 11 Approach

1. Determine Predicate Rule Requirements

2. Narrow Scope - Identify Electronic Records that Require Part 11 Compliance

3. Part 11 Records | Not Part 11 Records

4. Assess Risk - Evaluate Level of Controls Appropriate to Risk

5. Implement Appropriate Part 11 Controls

Ref: Famulare - Murray - McIntire
Risk Assessment

We suggest that you base your decision on … a justified and documented risk assessment

- Develop risk assessment strategies and SOP
- Identify, evaluate, and prioritize risks for Part 11
- Document risk assessment
- Define consequences for systems as defined high, medium or low risk
- For long term: develop and implement risk management
Risk Management

- Identify the system
- Identify hazards and possible threats
- Estimate, justify and document risk level (probability/severity)
- Estimate costs of mitigation vs. non-mitigation
- Define and take actions for mitigation
- Monitor for new threats
- Monitor risk levels
- Update plan and take actions

Key criteria: product quality (public health), business continuity
Start With a Risk Management Master Plan

1. Approach
2. Steps for risk analysis/evaluation
3. Steps for risk mitigation/control
4. Inputs for risk assessment
5. Risk categories
6. Examples for risk levels
7. Appropriate controls for different risk levels
8. SOP with Templates

Risk Matrix

<table>
<thead>
<tr>
<th>Risk descript.</th>
<th>Severity</th>
<th>Probability</th>
<th>Risk factor</th>
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<tbody>
<tr>
<td>computer systems - networks - spreadsheets - legacy systems</td>
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</table>
Documenting Risk Assessment

- Use tables with description of risks, severity, probability and the rationale behind
- Calculate overall risk factor
- Classify factors in high, medium and low

<table>
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<tr>
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<th>Justification</th>
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<th>Risk factor</th>
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There are many other ways to do this
Example: QC Laboratory Data System

Sample from plant

Sample receipt and log in → Sample analysis → Review and approval

Release Packaging Labeling

High Risk

Direct impact on product quality
Computer performs regulated action

Agilent Technologies
Example: Word Processing System for SOPs

Inputs

- Users
- Archive

Draft → Review → Approval Release

No direct impact on product quality
Computer = type writer
What’s Next?

Part 11 Re-examination and new rule making
• First public hearing in 2004
• Final release not expected before 2006

Quality system guide
• FDA develops Quality System Guide
• Agency wide concept
• Encourages industry to use quality system principles
• Release expected in late 2004
• Risk management expected to be a key element

www.agilent.com/chem/eseminars-compliance
Recommendations

- Start risk management/risk assessment process
  - master plan - SOPs - ranking criteria -
  - assessment for Part 11

- Monitor warning letters

- Start implementing quality system principles
  - quality by design
  - ongoing process monitoring and improvement
Further Information

To attend the Agilent e-seminar series, please visit our WEBSITE:

http://www.agilent.com/chem/eseminars-compliance

For further information on our products and services please contact your local Agilent Office.