

FDA-Systems based Inspection Approach

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Profile Class Codes

CCS	CHEMICAL SYNTHESIS CRUDE
CHG	CAPSULES - PROMPT RELEASE
CRU	CRUDE BULK - (NON-SYNTHESIZED)
CSN	NON-STERILE API BY CHEMICAL SYNTHESIS CRUDE
CTL	CONTROL TESTING LABORATORIES
LIQ	LIQUIDS-INCLUDES NON-STER SOL, SUSP, ELIX,
TINCT	
SVS	STERILE-FILLED SMALL VOLUME PARENTERAL
DRUGS	
TCM	TABLETS - PROMPT RELEASE
TTR	TABLETS – EXTENDED RELEASE
NEC	NOT ELSEWHERE CLASSIFIED

Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

Introduction

FDA oversees the quality of drug products* using a two-pronged approach involving review of information submitted in applications as well as inspection of manufacturing facilities for conformance to requirements for current Good Manufacturing Practice (cGMP).

Now, as we approach the 25th anniversary of the last major revision to the drug cGMP regulations, it is time to step back and evaluate the currency of these programs so that:

the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality;

the latest scientific advances in pharmaceutical manufacturing and technology are encouraged;

FDA resources are used most effectively and efficiently to address the most significant health risks.

To these ends, FDA is undertaking an initiative, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach."

Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

Merging Science-Based Risk Management with an Integrated Quality Systems Approach

Over the last two decades, significant changes in the environment of pharmaceutical regulation have occurred and have resulted in incremental adjustments in FDA's regulatory approach to product quality. These changes include:

- Decreased frequency of FDA manufacturing inspections as a result of fewer resources available for pharmaceutical manufacturing inspections
- FDA's accumulation of experience with, and lessons learned from, various approaches to the regulation of product quality
- Advances in the pharmaceutical sciences and manufacturing technologies
- Application of biotechnology in drug discovery and manufacturing
- Advances in the science and management of quality
- Globalization of the pharmaceutical industry

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The cumulative impact of these changes has been greater than the sum of the parts, and warrants a systematic reappraisal of FDA's approaches to product quality regulation. The following principles will guide implementation of the reappraisal:

Risk-based orientation In order to provide the most effective public health protection, FDA must match its level of effort against the magnitude of risk. Resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.

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Science-based policies and standards Significant advances in the pharmaceutical sciences and in manufacturing technologies have occurred over the last two decades. While this knowledge has been incorporated in an ongoing manner into FDA's approach to product quality regulation, the fundamental nature of the changes dictates a thorough evaluation of the science base to ensure that product quality regulation not only incorporates up-to-date science, but also encourages further advances in technology. Recent science can also contribute significantly to assessment of risk.

Integrated quality systems orientation Principles from various innovative approaches to manufacturing quality that have been developed in the past decade will be evaluated for applicability, and cGMP requirements and related pre-approval requirements will be evaluated according to applicable principles. In addition, interaction of the pre-market CMC review process and the application of cGMP requirements will be evaluated as an integrated system.

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International cooperation The globalization of pharmaceutical manufacturing requires a global approach to regulation. FDA will collaborate with other regulatory authorities, via ICH and other venues.

Strong Public Health Protection The initiative will strengthen the public health protection achieved by FDA's regulation of drug product manufacturing and will not interfere with strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

To accomplish the reappraisal, FDA will carry out the following broad actions:

- Perform an external review of the existing cGMP program and product review practices, including evaluation of potential inconsistencies in implementation
- Reassess and reevaluate our current scientific approach to both the product review process and the cGMP program to achieve a consistent, integrated systems approach to product quality regulation
- Enhance the scientific approach of cGMPs to emphasize risk-based control point analysis and to facilitate the latest innovations in pharmaceutical engineering

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Intermediate Steps

- Use emerging science and data analysis to enhance compliance programs to target the highest risk areas
- Evaluating the feasibility of establishing dedicated cadres of pharmaceutical inspectors

Long term Steps

- Enhanced training of agency staff on new scientific approaches and innovative pharmaceutical manufacturing technology
- Develop and publish policies and procedures reflecting a science-based, risk management approach
- Educate industry on new regulatory approaches encouraging innovation

Approach

- **Systems based Inspection Approach
(no classic PAI – Approach)**
- **Risk based Inspection Approach
(e.g. Steriles vs. Solids)
according to "Pharmaceutical cGMPs
for the 21st Century" initiative**

Strategy

- **Global QA – System (top-down)**
- **QA – Lead**
- **Management Involvement**
- **Presentations**
- **Right Experts**
- **Summary Reports**
- **"Issue" - Presentations**

Strategy

**80 percent of the success
of an inspection is the preparation**

**➔ Proactive behaviour against reactive!
(Victim or predator)**

PAI – Inspection Approach

- **Product related**
 - development / justification of ranges
 - process validation
 - product related deviations
 - **Facility related**
 - plant tour
 - specific equipment
- **Bottom-up**
- **High involvement of production / development**

System Based Inspection Approach

**(Compliance Program 7356.002,
effective February 1st, 2002)**

- **System Related**
 - **Quality System!**
 - **Facilities and Equipment System**
 - **Materials System**
 - **Production System**
 - **Packaging and Labeling System**
 - **Laboratory System**
- **Full (≥ 4 systems) vs. Abbreviated Inspection (≥ 2 systems; mandatory coverage of Quality System)**
- **GMP-Compliance for whole operation / whole profile class**

System Based Inspection Approach contd.

Quality System:

- Evaluate whether the QC unit has fulfilled their regulatory responsibilities
- Assess data collected to identify quality problems and may link to other major systems for inspectional coverage
 - Top down
 - High Involvement of QA / Compliance

Compliance Program

Pros and Cons

PRO:

- **Conserves FDA resources**
- **Inspections will likely be shorter duration**
- **Prevents redundant site inspections**

CON:

- **Failure in one quality system will cause the entire facility to be regarded as non-compliant for all profile classes**

Examples of Significant Deviations

Quality System:

- 1) **Pattern of failure to review/approve procedures.**
- 2) **Pattern of failure to document execution of operations as required.**
- 3) **Pattern of failure to review documentation.**
- 4) **Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints.**
- 5) **Pattern of failure to assess other systems to assure compliance with GMP and SOPs.**

Quality System

Areas covered:

- Annual review under 211.180(e)
- Complaints (quality and AE)
- Deviation and failure investigations
- Change control
- Product improvement projects
- Reprocess / Rework

Quality System

- **Returns/Salvages**
- **Rejects**
- **Stability failures**
- **Quarantined products**
- **Qualification and validation**
- **Training and qualifications of employees**

Project NOVIS (GQO-Project)

Local Implementation

- **Site Overview Presentation**
- **Quality System**
- **Facilities + Equipment**
- **Materials**
- **Production**
- **Packaging + Labelling**
- **Laboratory**

Laboratory

- **Reference standards**
- **System suitability checks**
- **Specifications, standards, sampling plans**
- **Methods**
- **Validation of methods**

Laboratory

- **Change control**
- **Testing of the correct sample**
- **Investigations/documentation**
- **Complete records**
- **Retention of raw data**
- **Data reviews**

Laboratory

- **OOS**
- **Reserve samples**
- **Stability**

Laboratory Control System

Pattern of Failures leading to Regulatory Actions

- 1. Failure to establish/follow a control system for implementing changes in the laboratory operations**
- 2. Failure to document investigation of discrepancies**
- 3. Lack of validation of computerized and/or automated processes**
- 4. Inadequate sampling practices**
- 5. Lack of validated analytical methods**
- 6. Failure to follow approved analytical procedures**
- 7. Failure to follow an adequate OOS procedure**
- 8. Failure to retain raw data**
- 9. Lack of stability indicating methods**
- 10. Failure to follow stability programs**

Topics

- **Trending (deviations, complaints, APRs)**
- **Process Validation covered only for Certican**
- **Plant tour to identify "issues"**

→ **QA – system rather than product - focused**

Topics contd.

Deviations (AWMs):

- trending (i.e. quarterly reports)
- single Discrepancy System / Consistency
- root cause / failure investigation
- other products affected?
- measures / corrective actions / follow-up
- risk assessment / QA-decision

examples:

- production failures (e.g. labeling)
- (re) - qualification failures (e.g. air velocity)
- physical monitoring failures (particle, pressure, humidity, disk-crash)
- utility failures (e.g. vent filters, sterile filters)
- (re) - calibration failures (e.g. wrong requirements)

Topics contd.

Complaints

- **trending (i.e. quarterly reports)**
- **recalls**
- **field alerts**
- **critical / major complaints**

Topics contd.

Annual Product Review (APR):

- no PAI – product (Aredia, Miacalcin, Lioresal)
- Profile classes
- high volume US – products
- examples / consistency checks for:
 - OOS
 - deviations
 - complaints
 - changes
 - analytical
 - production (e.g. Field Alert for Aredia in 2000)

Topics contd.

Microbiological Monitoring:

- **environmental (quarterly reports)**
- **sterility failures (summary)**
- **Media Fill Concept & Failures (summary)**
- **Water (trending & failures)**

Sampling by FDA for fingerprint analysis (biobatch)

Follow-up of Previous FDA-Inspection(s)

- **PAI-Inspection Glivec, Diovan by C. Ahn (April/May 2001)**
- **Deviation Handling System**
- **Consistency between qualification / validation ranges**

Outlook / Actions

- **Keep / Enforce strong Quality Unit**
- **Focus on QA - Systems**
- **Concentrate on Deviation Handling!**
- **Focus on Trending / Corrective Actions for System Failures**
- **Focus on Timelines / Deadlines**
- **Apply consistent GMP-Standard for US-profile classes –"legally vs. trust"**
- **Enforce lead of QA TechOps in Validation / Launch Process**