Corrective and Preventive Action (CA/PA)
cGTP Quality Program

1271.160(a) - General

Functions

Audit

Computer Validation

CA/PA

1271.160(b)(1) Method for SOPs – Core Requirements
1271.160(b)(2) Procedures to Evaluate Info. RE: Core Req.
1271.160(b)(3) CA/PA
1271.160(b)(4) Training & Education
1271.160(b)(5) Monitoring Systems
1271.160(b)(6) Investigate & Doc. Deviations & Trends

1271.160(b)(4) Training & Education
1271.160(b)(5) Monitoring Systems
1271.160(b)(6) Investigate & Doc. Deviations & Trends

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Quality Program Requirements

- HCT/P establishments are required to “establish and maintain a quality program that is appropriate for the specific HCT/P manufactured and the manufacturing steps performed.”

- All of the “foundational” elements of the cGTP Quality System are ubiquitous to all Quality Management Systems models.
Six Specified Requirements of a cGTP Quality Program

- §1271.160 presents the **foundation** for development of a cGTP Quality Program

- §1271.160 sets forth the **basic functional requirements** of a cGTP Quality Program

  - Four (4) specified requirements that ensure the performance of six (6) basic QMS functions
§1271.160  Foundation of cGTP Quality Program

![Diagram of cGTP Quality Program Functions, Audits, and Computer Validation]

- **Functions (of cGTP Quality Program)**: 1271.160(d)
- **Audit (RE Core Req.)**: 1271.160(d)
- **Computer Validation**: 1271.160(d)

- **FUNCTIONS**
  - 1271.160(b)(1) SOPs for Core Requirements
  - 1271.160(b)(2) Procedures to Evaluate Info. RE: Core Req.
  - 1271.160(b)(3) CA/PA
  - 1271.160(b)(4) Training & Education
  - 1271.160(b)(5) Monitoring Systems
  - 1271.160(b)(6) Investigate & Doc. Deviations & Trends

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CA/PA System

- The **heart** of an effective quality management system

- The **key quality system element** under FDA’s QSIT approach to auditing Medical Device Quality Management Systems
CA/PA in cGTPs

- 18 times CA/PA guidance in Preamble
- 14 times CAPA “specified” in the body of the regulations

- 1271.150 – “Appropriate” Quality System – allow for C/A
- 1271.160 (b)(3) C/A a function of a cGTP Quality Program
- 1271.160 (b)(7) Investigation of HCT/P deviations require effort to determine cause and implement C/A
- 1271.195 Inspection of Environmental Monitoring systems requires appropriate C/A.
- 1271.200 Equipment Calibration and PM system must provide for C/A
- 1271.250 Labeling Controls – investigation must allow for C/A
- 1271.260(d) – Storage procedures must provide for C/A when storage conditions not met
- 1271.320 – Complaint investigations require provision for C/As
- 1271.350 – Reporting Product deviations must include proposed C/As
Purpose of CA/PA

“…collect information, analyze information, identify and investigate product and quality issues, and take appropriate and effective corrective and/or preventive action to prevent recurrence of a problem.”

*FDA’s Guide to Inspections of Quality Systems (August, 1999)*
Corrective & Preventive Action (CA/PA)

Terms and Definitions

“Correction” or “Remedial Action” – Immediate containment action taken to eliminate a detected nonconformity

- refers to repair, rework, or adjustment and relates to the disposition of the nonconformity.
- A “correction” is a “short-term” action to address an immediate problem.
- “Remedial Action” can be taken in conjunction with “corrective action.”
Corrective & Preventive Action (CA/PA)

✧ Example of “Remedial Action”

- Your QC Inspector has discovered a packaging problem, and you can rework it to correct the error.

- It is important to recognize that this is a “short-term” action to address/fix the immediate problem.

This is not “corrective action”.
Corrective & Preventive Action (CA/PA)

Terms and Definitions:

- "Corrective Action" – Action taken to eliminate the cause(s) of an existing non-conformity, defect, or other undesirable situation.
  - There can be more than one cause for a nonconformity
  - Corrective action is taken to prevent recurrence

[ISO 9000:2000]
Corrective & Preventive Action (CA/PA)

- You investigate to determine the root cause of the packaging problem and take appropriate action to ensure that this problem does not re-occur.
  - Implement Corrective Action
  - You perform a subsequent follow-up audit to determine that the action you took was effective (close the loop) and now have a high level of confidence that the problem will not re-occur.
Corrective & Preventive Action (CA/PA)

- **Terms and Definitions:**
  - **“Preventive Action”** – Action taken to eliminate the cause of potential nonconformity, defect, or other undesirable situation in order to prevent occurrence.

[ISO 9000:2000]
Corrective & Preventive Action (CA/PA)

Example of Preventive Action:

- Trending of environmental monitoring indicates that your cleanroom is drifting toward your alert limit...
  - Investigation indicates that a small tear in a HEPA filter is the root cause of the drift.
  - Replace the HEPA filter
  - Verify/validate that the process meets specification.

What you do not document, did not happen!
CAPA System

Review: Your CAPA system/SOPs need to specify how you:

- Document deviations and nonconformances;
- Correct nonconformances and deviations and other quality problems *(short term correction)*;
- Prevent recurrence of deviations, nonconformances and other quality problems *(long-term action)*;
- Eliminate the cause of potential deviations, potential nonconformances and other undesirable conditions before they become deviations or nonconformances *(preventive action)*
cGTP CA/PA Requirements

Documentation of corrective actions must include where appropriate:

i. Identification of the HCT/P affected and a description of its disposition;

ii. The nature of the problem requiring corrective action;

iii. A description of the corrective action taken; and

iv. The date(s) of the corrective action.
Elements of a Sound CA/PA Program *(checklist)*

- Documented procedure
- Method for documenting *(Form or software)*
- Inputs *(data sources)*
- Method for analyzing inputs
- Method for prioritizing
- Containment
- Investigation *(determine root cause)*
- Disseminate Information
- Identify solutions *(corrective or preventive)*
- Verification or validation
- Impact assessment *(risk analysis)*, where appropriate
- Corrective Action Plan
- Implement and Monitor
- Effectiveness verification
- Management Review
Establish CA/PA Responsibility

- It is management’s responsibility to ensure that all nonconformance issues (in cGTPs, these are defined as deviated product) are handled properly.
- Management is responsible to ensure that all procedures in an HCT/P Quality Program are “designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease through the use of HCT/Ps by ensuring that the products do not contain relevant communicable disease agents; that the products do not become contaminated during manufacture; and that the function and integrity of the products are not impaired through improper manufacturing.”
Establish CA/PA Responsibility

- Management should appoint a Management Representative of the Quality System.

- Management is responsible to allocate adequate resources and provide organizational structure and authority.

- Procedures should delegate responsibility for implementation and maintenance of the CA/PA system.
Identify CA/PA Inputs

- Product, process and quality data sources must be identified;
- All Quality System processes that can potentially identify a deviation or a nonconformance need to interact with the CA/PA System

[I believe every organization should map their processes and understand the inter-relationships of those processes.]
Quality Data Sources that Should Feed into CA/PA System

Internal Data Sources

CA/PA System

External Data Sources
Internal Data Sources Feeding into CA/PA

- Deviations & Nonconformances
- Internal Audits
- 3rd Party Audits
- Supplier Evaluations
- Inspection & Test
- Process Monitoring
- Equipment Monitoring
- Design Controls
- Change Control
- Material Review Board

CA/PA System

Management Review
External Data Sources Feeding into CA/PA

CA/PA System

- Complaints & Adverse Events
- Tissue Recovery Organizations
- Distribution Partners
- Product Returns
- Suppliers
- Recalls
- Legal Claims
- Management Review
Development of the CA/PA System

- Multi-Tiered Approach:
  - Tier I: SOP and Method for documenting and Investigating Deviations (evaluation of impact on tissue/product.
  - Tier II: SOP and Method for documenting and Investigating Nonconforming Product
  - Tier III: SOP and Method for Corrective Action Request (when Deviations, Nonconformances, and other quality problems are identified as repetitive, systemic, or critical (impact PIDSCD))
Define Method for Documentation of CA/PAs

- Define in procedure
  - Develop a form (*use a standard form or develop*)
  - CA/PA Software
- Define how you identify actual/potential deviations and nonconformances
- How do you document the investigation
- Formulation of a CA/PA Action Plan
- Implementation of CA
- Follow-up Activities to ensure effectiveness (*re-audits*)
Failure Analysis

Failure Investigation Procedures

- Confirm failure mode
- Determine root cause
- Verify controls for preventing distribution of nonconforming HCT/Ps

Intent

- Conduct investigations to a degree commensurate with the significance and risk of the nonconformance
The Thought-Process of Failure Investigation

1. Failure
2. What Needs To be Done?
3. Problem Definition
   - What actually Happened?
4. What Records Available?
5. What Failed?
6. What Changed?
7. Who Knows?
8. Data Collection
   - Gather as many details and as much data as possible
9. Data Evaluation
10. Determine Failure Mode
11. Determine Root Cause
12. Define outcome of investigation
13. Document actions to be taken
14. Communicate to appropriate persons
Multiple “WHYs”

✓ What happened? → Determine Sequence of events
✓ Why did it happen? → Define causal factors (proximate cause)
✓ Why did that happened? → Analyze each causal factor’s Root Cause
✓ Why did that happened? → Analyze each root cause’s generic cause

Develop Action Plan
6 Phases of Failure Investigation

**Review:**

- **Phase I:** Problem identification and definition
- **Phase II:** Investigation
- **Phase III:** Root Cause Analysis
- **Phase IV:** Solution Development
- **Phase V:** Solution Implementation
- **Phase VI:** Solution Verification
Symptoms vs. Causes

Causes: Problems are undesirable results caused by structural relationships among system components.

- When these relationships are complex and hidden, traditional problem solving is not effective and another technique is needed.
- Root Cause problem solving consists of discovering and correcting these structural relationships.
Differentiating Between Symptoms and Root Causes

1. Identify the undesirable condition that needs to be corrected...or the events associated with this condition.

2. Use the “multiple why” process to identify the causes underlying this undesirable condition.

3. Continue the “multiple why” process until fundamental or root cause is apparent.
Typical Resolutions to Causes

- Procedural changes / updates
- Process Changes
- Engineering changes
- Process validation
- New training programs

Typical Resolutions to Symptoms

- Fix it…re-work it…correct it
- Re-Training
- Disciplinary action
FDA’s Road Map to CAPA Assessment

1. **CAPA system procedures**
   - Do they address the requirements of the regulations?
   - Has management defined responsibilities?
   - Are CA/PA results trended and submitted for Management Review?

2. **Do you identify existing problems?**
   - Is there objective evidence of Corrective Actions?
Inspector’s Road Map (continued)

3. Have you identified potential problems?
   - Is there objective evidence of action taken to prevent recurrence?
   - Were quality data sources identified?
   - Is data from sources analyzed?

4. Inspector will then challenge your data
   - Is your data complete?
   - Is your data accurate?
   - Was the data analyzed in a timely manner?
5 Statistical and Non-statistical techniques (trending)

- Were recurring quality problems detected?
- Were results of analysis compared across different data sources?
- Were the results of analysis used to identify and develop extent of problems?
Failure Investigation

- Were your internal procedures followed?
- Was the investigation commensurate with the significance and risk of the nonconformance?
- Was root cause identified, where possible?
- Was product controlled to prevent contamination and/or cross/contamination, and to prevent the distribution of nonconforming product?

Was *appropriate* corrective or preventive action taken?
Inspector’s Road Map (continued)

8 Actions

- Were the actions effective?
- Were the actions verified or validated?
- Was it confirmed that the actions did not adversely affect the product?

9 Were corrective and preventive actions implemented and documented?
Inspector’s Road Map (continued)

10 Was CAPA information disseminated to individuals directly responsible for assuring product quality and prevention of quality problems?

Was CAPA information submitted for Management Review?