Setting up deviation, incident, non-conformance systems

Presented by Debbie Parker
4 July, 2016
Introduction

This session will cover:

- Regulations
- Definitions
- Process
- Case Study
- Setting up a new system
- Common issues
Deviations, incidents, non-conformances, discrepancies…

What is a deviation?

Or a non-conformance?

What about an incident?

And a discrepancy?
**Definitions**

**Non-conformance**

- A deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate, or not according to specified requirements

**Non-conformity**

- The nonfulfillment of a specified requirement (820.3)
Definitions

**Discrepancy**
- Datum or result outside of the expected range; an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend

**Deviation**
- Departure from an approved instruction or established standard.

**Incident**
- Operational event which is not part of standard operation (GAMP)
PIC/S Expectations

- Significant deviations are fully investigated
- QC – any deviations are fully recorded and investigated
- Assessment of deviations from specified procedures
- Incorporate risk assessment
- Reviewed in PQR
- Signed authorisation for deviation from manufacturing formula, processing instructions and packaging instructions
PIC/S Expectations

- Written policies, procedures, and the associated records of actions taken or conclusions reached of any deviations or non-conformances
- Should be avoided as far as possible; should be approved in writing
- Any deviation from expected yield should be recorded and investigated
- Include stability program
FDA expectations

- Quality Systems staff are effectively integrated into manufacturing and involved in non-conformance investigations.
- The investigation, conclusion and follow-up must be documented.
- Any deviation from the written procedures recorded and justified.
FDA expectations

Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. (211.192)
The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow up. (211.192)
Key steps: System

- Create the tools – SOP, form, register, process flow
- Incorporate risk assessment into process
- Train staff in whole process, including risk processes
- Ensure procedure is understood and followed
- Track progress of each deviation
- Ensure timely closure
- Periodically review raised deviations
- Look for trends, repeat events
Key steps: Process

Raise ASAP → Complete initial details → Assess criticality → Identify immediate actions / corrections

Investigate → Assess risks → Identify corrections → Conclude

Raise CAPAs → Close
In a quality system, it is important to develop and document procedures that define who is responsible for halting and resuming operations, recording non-conformities, investigating discrepancies, and taking remedial action. Under a quality system, if a product or process does not meet requirements, it is essential to identify and/or segregate the product so that it is not distributed to the customer.

**Remedial action can include any of the following:**

- Correct the non-conformity
- With proper authorization, allow the product to proceed with justification of the conclusions regarding the problem’s impact
- Use the product for another application where the deficiency does not affect the products’ quality
- Reject the product
When to raise a deviation

As soon as it is known that an unexpected event, deviation from a process or failure to meet a limit or specification has occurred

• QA should be involved as early as possible
• Record the issue in the deviation register at the time it is raised
• Track progress
Initial information

You cannot re-create a point in time so your initial deviation information and entries are critical

Review:
• Sufficient detail
• All technical details
• Critical process (e.g. 5 why)
Investigating deviations

- Establish what happened
- Seek understanding of events
- Use investigation tools e.g.
  - Fishbone / cause and effect diagram
  - 5 whys
  - Fault tree analysis
- Identify likely causes
- Is there a common cause?
- Might other batches, components, materials, equipment also be affected?
Root Cause Analysis – Methods/Tools for identifying Causes

- 5 whys
- Cause and effect
- Tree diagram
- Factor analysis
- Brain storming
Root Cause Analysis – Methods/Tools for identifying Causes

Fishbone diagrams

Pareto chart

Failure Mode & Effect Analysis

Change Analysis

Flow charting
Closing deviations

- Write up the investigation
- Explain what happened and why
- Identify & document root cause(s)
- Review by QA
- Ensure CAPAs are raised as needed
- Detail corrections and any corrective actions
- Final closure by QA
- Update register
Case Study
Raising a deviation

<table>
<thead>
<tr>
<th>Dev ID:</th>
<th>DEV-14-01-003</th>
<th>Date initiated:</th>
<th>22 Jan 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation level:</td>
<td>Proposed date completed: 05 Mar 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deviation type:</td>
<td>□ Non-conforming material/product/result/data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Deviation from procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Deviation from regulations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Planned deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Deviation within facility/services/environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Adverse trend detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linked deviations – Dev IDs:</td>
<td>Extension - New data:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escalated – Escalation date:</td>
<td>Cancelled - Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escalated to:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Section 1: Deviation details** (Completed by the investigator/Department Manager as the ‘Owner’)

**Investigator’s name:** Jack Sprat  
**Department:** Production

**Description of the deviation:**

A piece of plastic was found in the sifter, after milling batch # ABC-1234, Product X. Manufacture commenced at 10:00 on 22 Jan 2014 on manufacturing line 3 (Room P3) using freeze drier No. 3.

The plastic was found by Peter Pan, Milling Technician, on 22 Jan 2014 at 15:25, and brought to the attention of the Production Coordinator (Jack Sprat).

**Has product been quarantined?** □ No  □ Yes - Location: Quarantine store #1

**Batch numbers/codes quarantined:** ABC-1234 (Product X)

**List other immediate/containment actions taken:** Line clearance and cleaning not started before inspection by Production Coordinator. All inspection samples held.

**QA Manager (Elliot Ness) and Engineering Manager (Leo Da Vinci) notified immediately.**

**Is this deviation linked to an audit citation?** □ No  □ Yes. Audit ID:  

**Does this deviation affect registration?** □ No  □ Yes. Products/countries:

**QA initial reviewer:** Lucy Liu  
**Signature:**  
**Date:** 22 Jan 14
Assigning deviation level

<table>
<thead>
<tr>
<th>Section 2: Assigning deviation level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a risk assessment been completed for the deviation?</td>
</tr>
<tr>
<td>No. Justification for no risk assessment:</td>
</tr>
<tr>
<td>Deviation level assigned:</td>
</tr>
<tr>
<td>QA Manager: Elliot Ness</td>
</tr>
</tbody>
</table>

All critical deviations must be escalated

<table>
<thead>
<tr>
<th>Dev ID: DEV-14-01-003</th>
<th>Date initiated: 22 Jan 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation level: Critical</td>
<td>Proposed date completed: 05 Mar 2014</td>
</tr>
<tr>
<td>Deviation type:</td>
<td>□ Non-conforming material/product/result/data</td>
</tr>
<tr>
<td>Deviation from procedure</td>
<td>Deviation from regulations</td>
</tr>
<tr>
<td>Deviation within facility/services/environment</td>
<td></td>
</tr>
<tr>
<td>□ Linked deviations – Dev IDs:</td>
<td>□ Extension - New date:</td>
</tr>
<tr>
<td>□ Escalated – Escalation date: 22 Jan 2014</td>
<td>□ Cancelled - Date:</td>
</tr>
<tr>
<td>Escalated to: Senior Sam (Executive Production Manager)</td>
<td></td>
</tr>
</tbody>
</table>
## Investigating the event

### Section 3: Complete the investigation

(Complete each subsection as required by SOPXXX – Managing Deviations)

<table>
<thead>
<tr>
<th>Investigation plan</th>
<th>Investigation plan/approach</th>
<th>Resp.</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not required</td>
<td>Review batch record, associated equipment &amp; cleaning logs, staff training records</td>
<td>Prod. Coord.</td>
<td>23 Jan 14</td>
</tr>
<tr>
<td></td>
<td>Review maintenance records</td>
<td>Eng. Mgr.</td>
<td>23 Jan 14</td>
</tr>
<tr>
<td></td>
<td>Supplier histories – raw material &amp; consumables</td>
<td>QA Mgr</td>
<td>23 Jan 14</td>
</tr>
<tr>
<td></td>
<td>Complete root cause analysis - fishbone</td>
<td>All</td>
<td>23 Jan 14</td>
</tr>
<tr>
<td></td>
<td>Impact assessment based on root cause</td>
<td>QA Mgr</td>
<td>24 Jan 14</td>
</tr>
<tr>
<td></td>
<td>Propose corrections &amp; corrective actions</td>
<td>All</td>
<td>24 Jan 14</td>
</tr>
<tr>
<td></td>
<td>Implement as per raised CC &amp; CAPA</td>
<td>Prod. Coord.</td>
<td>As per CC/CAPA record</td>
</tr>
</tbody>
</table>

**Sources of information to review:**

- Batch record, staff training records, staff interviews, related procedures, equipment logs, cleaning records, facility/service maintenance logs, material and consumable supplier histories.

**Detailed investigation plan attached?**

- Yes
- Not required

**Copies of relevant records attached?**

- Yes
- Not required
# Investigating the event

<table>
<thead>
<tr>
<th>Trend analysis &amp; historical assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date range of historical review: 3 years (entire deviation database)</td>
</tr>
<tr>
<td>List any previous events related to this deviation (include frequency &amp; impact):</td>
</tr>
<tr>
<td>There have been no previous events related to this deviation for any product.</td>
</tr>
<tr>
<td>List any trends related to this deviation:</td>
</tr>
<tr>
<td>There are no trends associated with this deviation or associated with this product/product type</td>
</tr>
<tr>
<td>Other comments: NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Determine-root-cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of root-cause analysis tool used: Fishbone analysis</td>
</tr>
<tr>
<td>Root-cause category:</td>
</tr>
<tr>
<td>Equipment</td>
</tr>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>Summary of root-cause analysis:</td>
</tr>
<tr>
<td>Multiple root-causes:</td>
</tr>
<tr>
<td>1. Design — process does not include preparing trays, raw material testing did not detect plastic film, and inspection did not detect contamination, supplier did not provide notification of tray film addition</td>
</tr>
<tr>
<td>2. Personnel — did not seek approval for additional preparation step</td>
</tr>
<tr>
<td>Detailed root-cause analysis attached?</td>
</tr>
</tbody>
</table>
Root cause – Fishbone diagram

Problem statement = Plastic contaminant was found in batch ABC-1234 during milling.

• What was different to normal conditions?

People
- Manufacturing staff performed an additional step without approval

Methods
- Batch record does not include all preparation instructions
- In process checks may not be good enough or completed correctly

Machines
- No changes in plant
- No maintenance performed

Materials
- New freeze drying trays used

Environment
- No changes in environment

Plastic contaminant
Root cause – Fishbone diagram

Of the possible causes, what’s different?

- Staff made a mistake – possible contributing action
- New freeze drying trays – how are these different to normal? Inspect new stock.

Most probable root cause:

- Plastic film on new trays not removed completely prior to use– no instructions to do this or specifications
- Staff did not seek approval for extra preparation step with the trays
Root cause – Fishbone diagram

- **People**: 
  - Manufacturing staff performed an additional step without approval

- **Methods**: 
  - Batch record does not include all preparation instructions
  - In process checks may not be good enough or completed correctly

- **Machines**: 
  - No changes in plant
  - No maintenance performed

- **Materials**: 
  - New freeze drying trays used
  - No changes in environment

- **Environment**: 
  - No changes in plant

- **Plastic contaminant**
Investigating the event

<table>
<thead>
<tr>
<th>Impact Assessment</th>
<th>List any impacts of the deviation on related batches or products (including those in the marketplace), results, locations or systems not already included. □</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Batches using the same trays should be included in the scope of the investigation &amp; placed on hold — include CDE-998 Product Y and CDE-999 Product Y. No released batches impacted. □</td>
</tr>
<tr>
<td></td>
<td>Batches manufactured immediately after the impacted batches include — FGH-356, FGH-357 and FGH-358 (Product Z). Retention samples to be inspected for contamination. Confirm that line clearance and cleaning procedure would remove any plastic contamination. □</td>
</tr>
<tr>
<td></td>
<td>List supplier(s) of suspect raw materials. □</td>
</tr>
<tr>
<td></td>
<td>Freeze drier trays supplier by Tray Masters — current supplier history acceptable. Minor changes to trays to help distribution quality made without notifying tray customers. □</td>
</tr>
<tr>
<td></td>
<td>Detailed impact assessment report attached? □ Yes □ Not required □</td>
</tr>
</tbody>
</table>
# Investigating the event

<table>
<thead>
<tr>
<th>Corrections &amp; Corrective actions</th>
<th>List the proposed corrections required to address the outcome of the deviation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Investigate quality of other impacted batches to determine their batch disposition.</td>
</tr>
</tbody>
</table>

List the proposed corrective actions to prevent the deviation from reoccurring:

1. **Raw material specification updated to include presence of plastic film**
2. **Create preparation & cleaning instructions for trays and validate cleaning step passes requirements.**
3. **Preparation instructions for trays added to batch record, to include cleaning step and ensure product is covered at all times. Include line clearance of preparation step before trays are loaded.**
4. **Update freeze drying SOP to include a mandatory line clearance and 2nd check of tray condition before loading is allowed to commence.**
5. **Review inspection SOP and batch record sampling details to determine if inspection/sampling was non-conforming. Confirm that inspection procedure is adequate.**
6. **Production staff notified of the deviation, its origin and outcomes. Staff involved in the batch manufacture advised of responsibility to seek approval for additional tasks and GMP record keeping. Staff involved in the sampling and inspection downstream notified of the need to follow inspection instructions.**
7. **Complete site-wide GMP refresher training.**
**Effectiveness & QA review**

**Effectiveness check**

<table>
<thead>
<tr>
<th>Not required</th>
<th>List any measures required to check the effectiveness of the corrective actions:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The following 3 batches using new trays will have additional visual inspection</td>
</tr>
<tr>
<td></td>
<td>samples after freeze drying stage.</td>
</tr>
<tr>
<td></td>
<td>Date/frequency that the effectiveness check is to be completed:</td>
</tr>
<tr>
<td></td>
<td>Review routine batch manufacture after 2 months to determine any trends.</td>
</tr>
</tbody>
</table>

**Section 4: QA review of the investigation** (completed by the QA Manager)

<table>
<thead>
<tr>
<th>Approved to implement</th>
<th>Approved to implement with the following additional actions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rejected. Justification:</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
</tr>
</tbody>
</table>

Any QA-related comments: **Confirm that line clearance and cleaning procedure would remove any plastic contamination and followon batches are not impacted.**

**QA Deviation Register status updated? Date:** **24 Jan 14**

**QA Manager:** **Elliot Ness**

**Signature:** **Elliot Ness**

**Date:** **24 Jan 14**
Implementing actions

<table>
<thead>
<tr>
<th>Description or Quality System reference (e.g. CAPA or CC)</th>
<th>Date initiated</th>
<th>Closed (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPA-14-01-001: Notifying Production staff of the deviation, origin and outcomes. Notifying staff involved with the batch on appropriate GMP responsibilities.</td>
<td>24/01/14</td>
<td>Yes</td>
</tr>
<tr>
<td>CAPA-14-01-002: Refresher GMP training for the site.</td>
<td>24/01/14</td>
<td>No</td>
</tr>
<tr>
<td>CAPA-14-01-003: Review inspection procedure for appropriate level of control</td>
<td>24/01/14</td>
<td>Yes</td>
</tr>
<tr>
<td>CAPA-14-01-004: Effectiveness check</td>
<td>24/01/14</td>
<td>Yes</td>
</tr>
<tr>
<td>CAPA-14-01-005: Confirm new tray preparation/cleaning instructions are appropriate (process/cleaning validation)</td>
<td>24/01/14</td>
<td>Yes</td>
</tr>
<tr>
<td>CC-14-01-023: Update tray spec, batch instructions for Product X and Product Y, SOPXXX Using the Freeze Driers</td>
<td>24/01/14</td>
<td>Yes</td>
</tr>
<tr>
<td>Copies of reports, data or records attached?</td>
<td>Yes</td>
<td>Not required</td>
</tr>
<tr>
<td>Any samples or rejects have been disposed of or placed in appropriate storage?</td>
<td>Yes – Date: 03/3/14</td>
<td>Not required</td>
</tr>
<tr>
<td>Retention samples have been returned to the retention store?</td>
<td>Yes – Date: 03/3/14</td>
<td>Not required</td>
</tr>
<tr>
<td>Date effectiveness check(s) completed (if required): 04/03/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were the corrective actions effective?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If no, describe the outcome and proposed further actions to eliminate the deviation: NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Closing out the deviation

## Section 7. Closeout

**Final batch disposition status:** Product X, Batch #ABC-1234 rejected. Destroyed 03 Jan 14.

Product Y, Batches #CDE-998 & CDE-999 quality was acceptable, manufactured before new trays used – scheduled for release according to current site procedures.

Product Z, Batches #FGH-356, FGH-357 and FGH-358 quality was acceptable, manufactured before new trays used – scheduled for release according to current site procedures.

<table>
<thead>
<tr>
<th>CAPA or CC have been initiated and approved to commence?</th>
<th>Yes</th>
<th>Not required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the risk class still appropriate?</td>
<td>Yes</td>
<td>No – Propose actions:</td>
</tr>
</tbody>
</table>

**Comments:** NA

**QA Manager:** Elliot Ness  
**Signature:** Elliot Ness  
**Date:** 05 Mar 2014
Setting up a deviation system

Basic elements
- SOP
- Process flow
- Deviation form
- Deviation register

Decisions
- Manual, electronic or hybrid?
- Approval process – who, when?
- Timeframe
- What triggers a CAPA?
Basics

- Follow SOP
- Raise ASAP
- Investigate quickly
- Investigate thoroughly
- Find route causes
- Address route causes – raise CAPAs
- Close ASAP, within target timeframes
**Tips**

- **Do**
  - Make sure the SOP, form and process flow are aligned
  - Have a few staff trained as site experts in investigations

- **Don’t**
  - Don’t over-complicate the process
  - Don’t expect everyone to be good at investigating
<table>
<thead>
<tr>
<th>Common problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor investigations</td>
</tr>
<tr>
<td>Not addressing all facts / Ignoring evidence</td>
</tr>
<tr>
<td>Only considering one route cause</td>
</tr>
<tr>
<td>Poor scientific basis</td>
</tr>
<tr>
<td>Making assumptions</td>
</tr>
<tr>
<td>Not addressing issues / not raising CAPAs</td>
</tr>
<tr>
<td>Repeat deviations – failure to address</td>
</tr>
<tr>
<td>Failure to consider the impact on other batches</td>
</tr>
</tbody>
</table>
References

• Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations, FDA, Sep 2006

• PIC/S guide to good practices, for the preparation of medicinal products in healthcare establishments, PE-010-3, Oct 2008
In Conclusion

This session covered:

- Regulations
- Definitions
- Process
- Case study
- Setting up a new system
- Common issues
Thank you for your time.
Questions?

Debbie Parker
Senior Consultant
Debbie.parker@pharmout.net
www.pharmout.net