Data of Exceptions

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Outline of Presentation

- Understanding Data of Exceptions
  - Deviations, Non-Conformances, Out of Specifications (OOS), Out of Trend (OOT), Out of Frequency (OOF)
- How to Manage Data of Exceptions
- Deviations & Non Conformances
  - Biological Product Deviations (BPD)
- Out of Trend
- Out of Tolerances
- Out of Frequency

Data, Observations & Results

Analysis or Monitoring of Data, Observations & Results for Compliance with Standards/Specifications

- Data of Compliance
  - Meeting Standards/Specifications
  - Used to Release Product
  - Trending, Tracking, Periodic Review
- Data of Exception
  - Not Meeting Standards/Specifications
  - Includes Deviations, Non-Conformances, Out of Specifications (OOS) Results, Invalid Results
  - Needs Immediate Attention/Notification & Investigation

Deviations/Non-Conformances

- Deviation – Action of Departing from an Accepted Standard, Procedure or Established Course
  - Biological Deviations – A Requirement to Report to FDA for a Distributed Product
- Non-Conformance – Failure to Conform to Accepted Standards of Behavior or Nonfulfillment or Failure to Meet a Requirement
  - OOS, OOT and OOF are Examples of Non-Conformance
- Both Deviations and Non-Conformances are Regulatory Non-Compliance
  - May have Impact on Quality of Drugs (Safety, Purity, Potency)
  - Need Immediate Attention

Deviations/Non-Conformances

- Not following, deviating or not meeting cGMP Regulation Requirements, Quality Management Systems, Regulations, Standards, Specifications
- All Deviations and Non-Conformances Need Immediate Attention
  - Notification to QA, Management and also to FDA if Product has been Distributed (Biological Deviations)
  - Need to be dealt with as per SOPs, Requirements
  - May need Immediate Corrective Action, Re-work, Re-Processing, Re-test, as per Approved Procedures
  - Investigation for Root Cause
  - CAPA, may lead to a Change (Change Control Procedure)

Biological Deviations

- 21 CFR 600.14 Reporting of biological product deviations by licensed manufacturers
- FDA Guidance for Industry – Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components, October 2006
- Earlier referred as “Errors and Accidents”
- For Products that are Distributed. In Addition to Reporting to FDA
  - Evaluate & Investigate, as appropriate, Unexplained Discrepancies & Failures to meet Specifications, & to Maintain Complaint records, including Records of investigations & Follow-up (21CFR 211.192, 211.198, 820.90, and 820.100)

What to Report for Biological Deviations?

- Any Event & Information relevant to the event, associated with
  - Manufacturing, to include Testing, Processing, Packing, Labeling, or Storage, or Holding or Distribution, of a Licensed Biological Product
- Event Involving All Following Conditions
  - Deviation from cGMP, Applicable Regulations, Applicable Standards, or Established Specifications Affecting Safety, Purity, or Potency of Product; or
    an Unexpected or Unforeseeable Event affecting safety, purity, or potency of product
  - Occurs in your facility or another facility under contract with you
  - a Distributed Biological Product

What is Required for Biological Deviations?

- Report ASAP, but must be within 45 Calendar Days, Additionally you should Perform
  - A Timely Investigation
  - an Appropriate Corrective Action Plan to Prevent Recurrence;
  - Procedures to Gain Control of Unsuitable Products in a timely Manner;
  - Appropriate Disposition of all Affected Products (in-date and expired)

What is Not Required to Report for Biological Deviations?

- Products Not Distributed Regardless of the Event
- Event did not actually affect the Safety, Purity, or Potency
- Prior to Distribution Appropriate Corrections, or Reprocess or Rework Done following Appropriate Procedures
- Late Reporting of an event
- Minor Recordkeeping Deviation not affecting the Safety, Purity, or Potency of the Product
- Product was not a US Licensed Product

Examples of BPD Reporting

- Incoming Materials
  - Containers or Closures, Source or Raw Materials did not Conform to Specifications
- Process Controls
  - Manufacturing Performed using Incorrect Parameters, such as Incorrect Temperature, Not following SOPs
  - Improper Storage of Raw Materials, Intermediates, etc.
  - Equipment or Power Failure
- Testing
  - Not Performed or Performed Incorrectly
- Labeling
  - Incorrect Package Insert, Incorrect or Missing Information
- Product Specifications were not Met
  - At Release and during Stability
- Issues with Quality Control and Distribution Procedures

OOT – Out of Trend

- Out of Trend – A set of Results that Falls Outside Expected Values or Fails Statistical Process Control or Results not Following Expected Trend
  - Specified Number of Data Points outside Alert Limits
  - Specified Number of Consecutive Data Points outside Alert Limits
  - Statistical Trends in Stability Data Over Time
- Not Necessarily OOS
- Indication of a Potential Problem
- Need Investigation
- Need Corrective and Preventive Action

OOT – Out of Tolerance

- Out of Tolerance – Not Within Specified Limits
  - Equipment during Verification and/or Calibration
  - Manufacturing Process
- Non-compliant Event
- Needs Immediate Attention
  - Reporting
  - Correction
  - Investigation & Root Cause Analysis
  - Corrective & Preventive Action

Out of Tolerance – As Found

- Many Equipment, Instruments & Pipettes Evaluated for Accuracy and Precision Before Periodic Maintenance and Calibration – As Found
  - Out of Tolerance (OOT)
  - Serious Quality Implications
  - When, Where and How the OOT Equipment Used?
  - All Testing and Data Using OOT Equipment since last Verification Need Review on Impact on Product Quality
  - Risk Analysis of All Implicated Data
  - Example of BPD Notification to FDA
  - May Lead to Product Recall

Out of Frequency

- When Equipment or Instrument missed Periodic Calibration, Verification & Maintenance
  - Good Equipment Maintenance Program Ensures that All Equipment get Periodic Calibration/Maintenance (Service) on a Timely Basis (On or before Due date)
  - OOF Equipment Need Tagging – “Not For Use”
  - Many Equipment, Balances, pH Meter, etc. Verified on the Day of Use for their Accuracy
  - Such Equipment Missing Periodic Service Still Need Tagged
  - Equipment may be used “At Risk” if Urgently Needed with Notation on Worksheet “Don’t Release Data Until Equipment Successfully Completes Periodic Maintenance” - Deviation

Changing Frequency of Calibration

- As More Experience is Obtained with Performance of Equipment, Frequency of Periodic Calibration may need Changes
  - If New Schedule Involves Decreasing Intervals between Service and More Parameters for Calibration – A Simple Notification
  - If New Schedule Involves Increasing Intervals between Service and Removing Certain Parameters – A Change Control Required with Full Justification and Impact on Quality

Summary

- Data of Exception Need Immediate Attention, i.e. Notification, Correction, as appropriate, Investigation for Root Cause Analysis and CAPA
- Biological Product Deviations
  - For Distributed Products only
  - Notification to FDA
  - May Require Product Recall
- Out of Trends – Need to be Defined and How to Handle these?
- Out of Tolerance – may have Serious Implications for As Found Equipment
- Out of Frequency should be avoided with a Good Equipment Maintenance & Calibration Program
- Change Control for Maintenance & Calibration Program


Thank You!
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