

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

3

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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

4

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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)

5

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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)

6

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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**

7

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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)

8

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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

9

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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

10

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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

11

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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

12

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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

13

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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

14

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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

15

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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

16

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