FDA Regulations and Recommendations for Failure Investigations

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Regulations

- **21 CFR 211.192, Product Record Review**

  All drug product production and control records…shall be reviewed … before a batch is released or distributed. Any unexplained discrepancy or failure … shall be thoroughly investigated… The investigation should extend to other batches … that may have been associated with the specific failure or discrepancy. A written record of the investigation … shall include the conclusions and followup.

Regulations (continued)

- **21 CFR 606.100(c), Standard Operating Procedures**

  All records pertinent to the lot …shall be reviewed before the release or distribution … of final product. The review … may be performed at appropriate periods during or after collecting, processing, or compatibility testing and storing. A thorough investigation, including the conclusions and followup, of any unexplained discrepancy or failure…shall be made and recorded.

Examples of manufacturing process deviations that warrant investigation

- **Equipment validation**
- **Donor suitability/eligibility**
- **Device**
- **QC**
- **Components not meeting product specifications**

What is a Thorough Investigation?

An investigation of the critical steps or areas where an unexplained discrepancy or failure resulted.

- **What's the problem?**
- **When / where did it happen?**
- **Why did it happen?**
- **How to prevent it from recurring?**
- **Documentations**

Examples of critical steps or areas

- Donor
- Operator
- Supplies and reagents
- Device
- Components
- Environment
- SOPs
- Samples

Examples of critical steps or areas
(continued)

- **Donors**
  - **characteristics**
  - **specifications**

- **Operator**
  - **performance**
  - **training/competency**

Examples of critical steps or areas
(continued)

- **Supplies and reagent**
  - **lots**

- **Device**
  - **performance**
  - **operation**
  - **controls**
  - **device validation / calibration**
  - **maintenance**

Examples of critical steps or areas
(continued)

- **Components**
  - **specification**
  - **collection**

- **Environment**
  - **storage**
  - **shipping**

Examples of critical steps or areas
(continued)

- **SOPs**
  - **adherence to**
  - **adequacy of**

- **Samples**
  - **type**
  - **collection**
  - **storage / shipping**

Closing Notes

- **Any unexplained discrepancy may have more than a single cause.**
- **An apparent deviation may have multiple impacts on the final products.**
- **Shifts and trends enable the detection of unexplained discrepancies or failures.**