Compounding Quality Center of Excellence 2023 Conference

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Quality Essentials: Case Studies

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CASE STUDY PART 1

Setting the Stage

- VP of Quality for a registered outsourcing facility
- Produce sterile injectable drug products distributed in pre-filled syringes and IV bags
- Products made from commercially available drug products and bulk drug substances
- Produce drug shortage products when feasible

The Scenario

- Over the last month your firm has received multiple ADE reports related to Fentanyl Citrate 50mcg/mL, lot 20230630@0015, BUD 9/28/2023; product distributed in 10mL syringes
  - 12 reports of severe respiratory depression requiring medical intervention

The Investigation (1 of 20)

Possible potency issue with at least 1 batch of fentanyl citrate

- What Happened?
  - How did super-potent batch get produced?
  - How did super-potent batch get released?

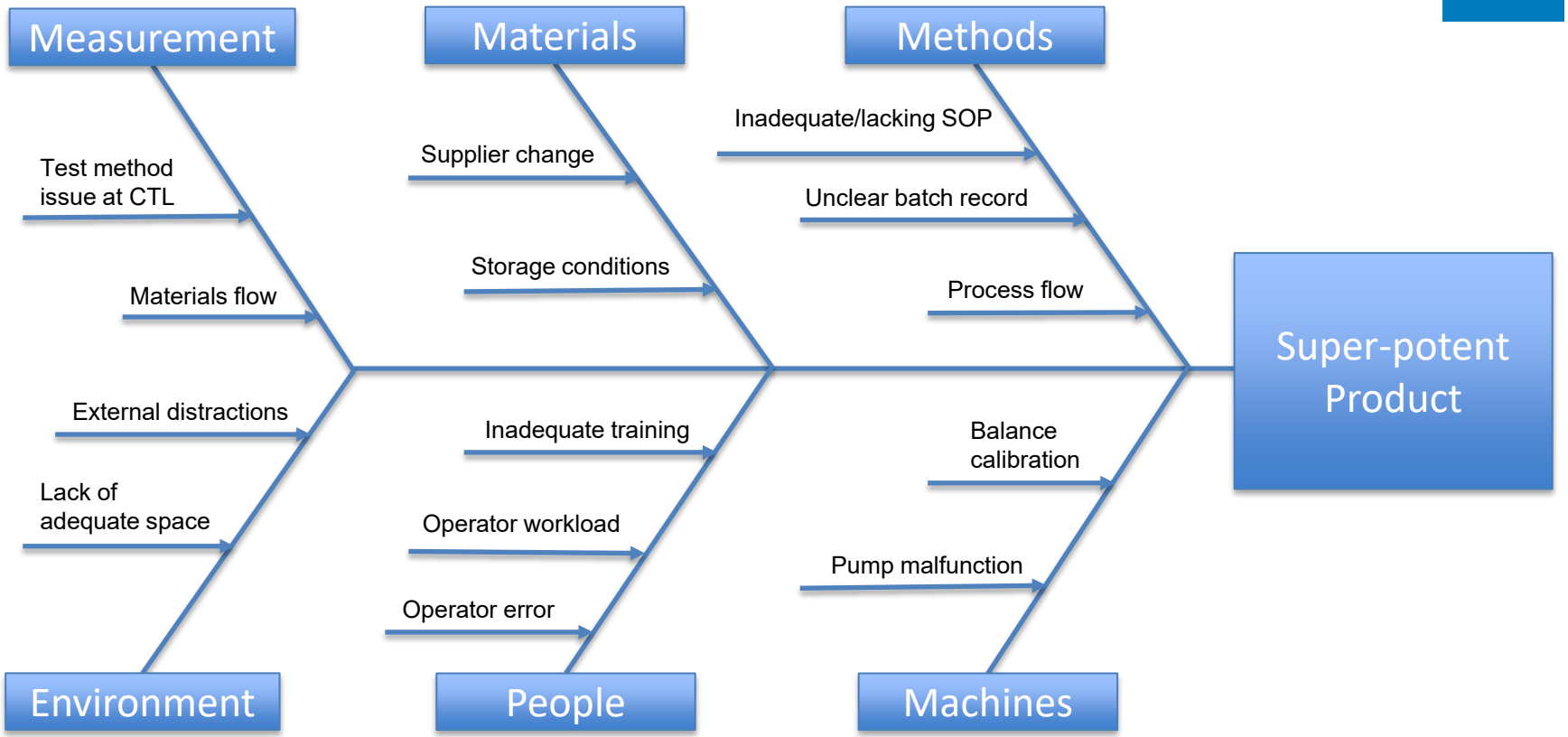
The Investigation (2 of 20)

Where do you start?

Root Cause Analysis

- Quality Risk Management Tools
  - Cause and Effect Diagrams (Ishikawa or fish bone diagram)
  - Fault Tree Analysis (FTA)
  - Failure Mode Effects Analysis (FMEA)
  - Failure Mode Effects Criticality Analysis (FMECA)
  - 5 Why tool

The Investigation (3 of 20)



The Investigation (4 of 20)

- Review of batch record reveals nothing out of the ordinary
  - Quality's batch release checklist was completed; line stating, "Any OOS results for finished product testing? Yes or No" was marked "No"
  - Batch record looked complete; no issues found with calculations
- Call Contract Testing Lab (CTL) for results of expedited retain testing results

The Investigation (5 of 20)

CTL confirms Fentanyl citrate batch is super-potent… by 10-fold

What is your next step?

The Investigation (6 of 20)

- After initiating recall of affected batch, start talking to production
- Have production walk you through the process
- Follow along in the batch record and look for places where errors could occur
- Ask lots of questions
- Pull batch records for other products made same day

The Investigation (7 of 20)

- General formulation/filling process includes:

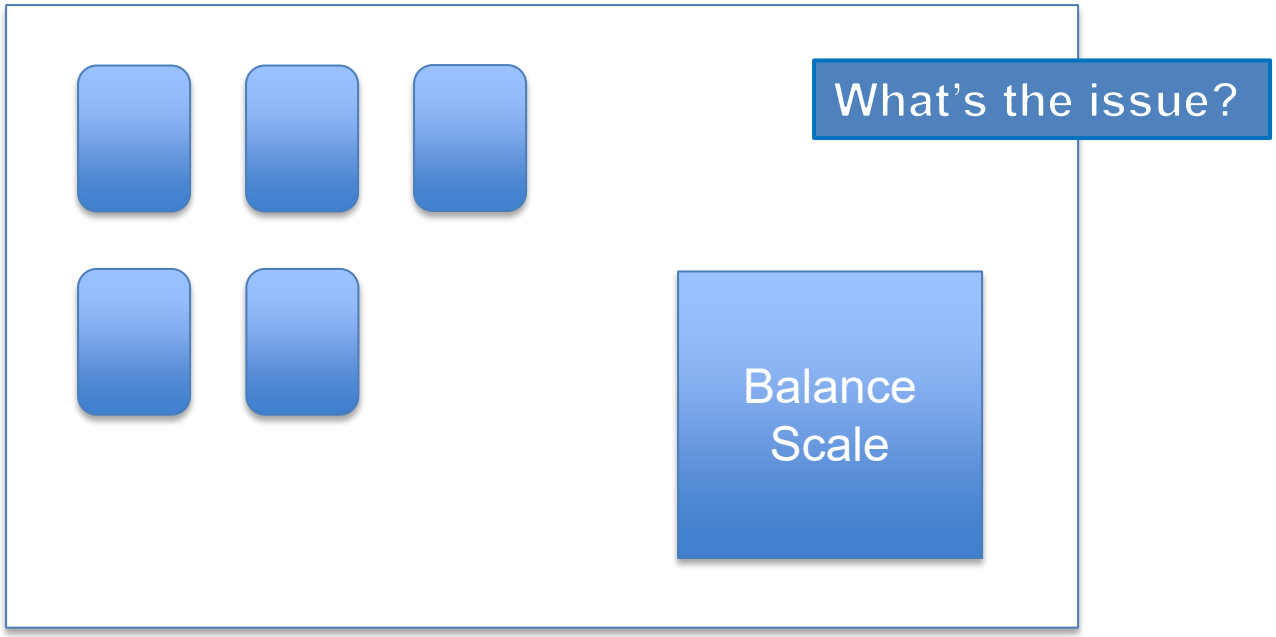
The Investigation (8 of 20)

- Five lots of Fentanyl citrate 50mcg/mL injection were scheduled to be made that day:
  - 20230630@0002, 10mL syringes, batch size: 1000 syringes
  - 20230630@0007, 10mL syringes, batch size: 1000 syringes
  - 20230630@0012, 10mL syringes, batch size: 100 syringes
  - 20230630@0015, 10mL syringes, batch size: 100 syringes
  - 20230630@0021, 10mL syringes, batch size: 100 syringes

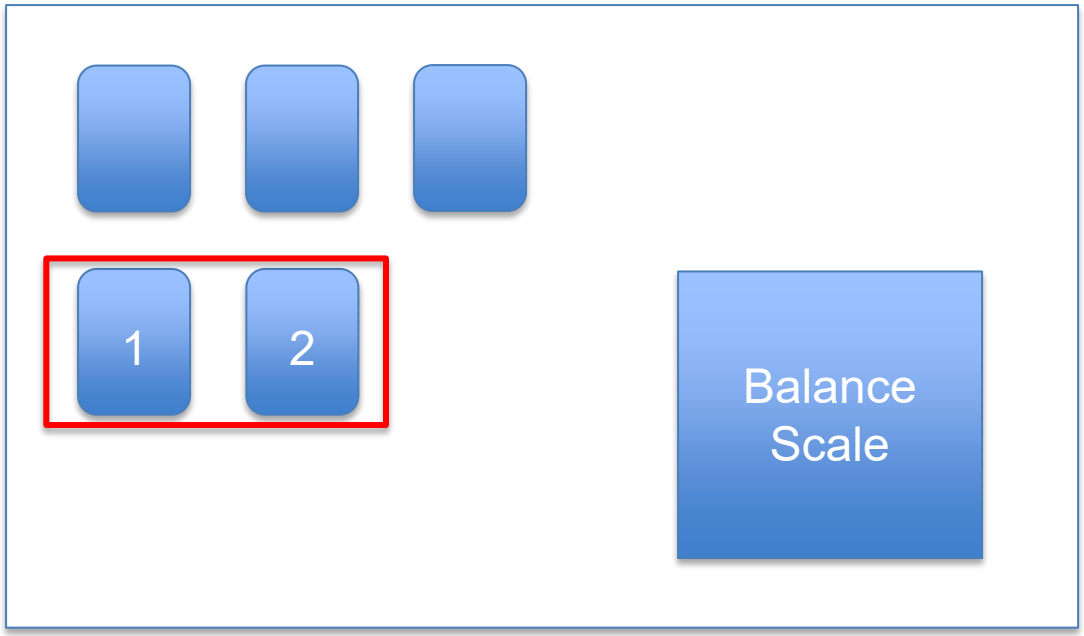
The Investigation (9 of 20)

- In an effort to be efficient, Technician 1 weighed the bulk drug substances for all 5 lots at the same time then was pulled away to take care of something else
- Technician 1 told Technician 2 the first two were the large batches, the other 3 were the smaller batches

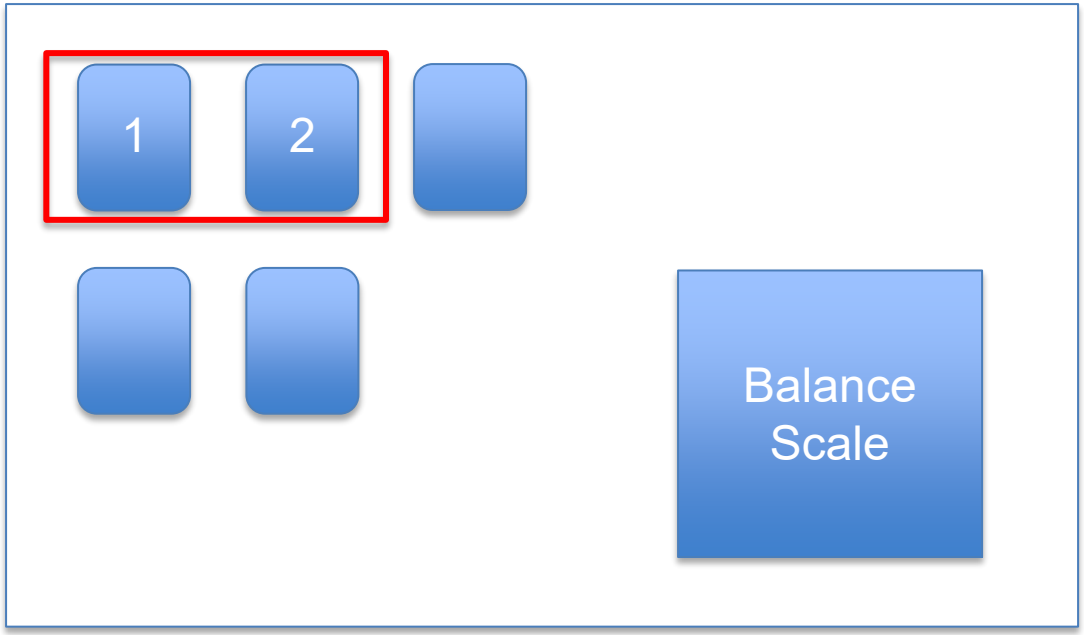
The Investigation (10 of 20)



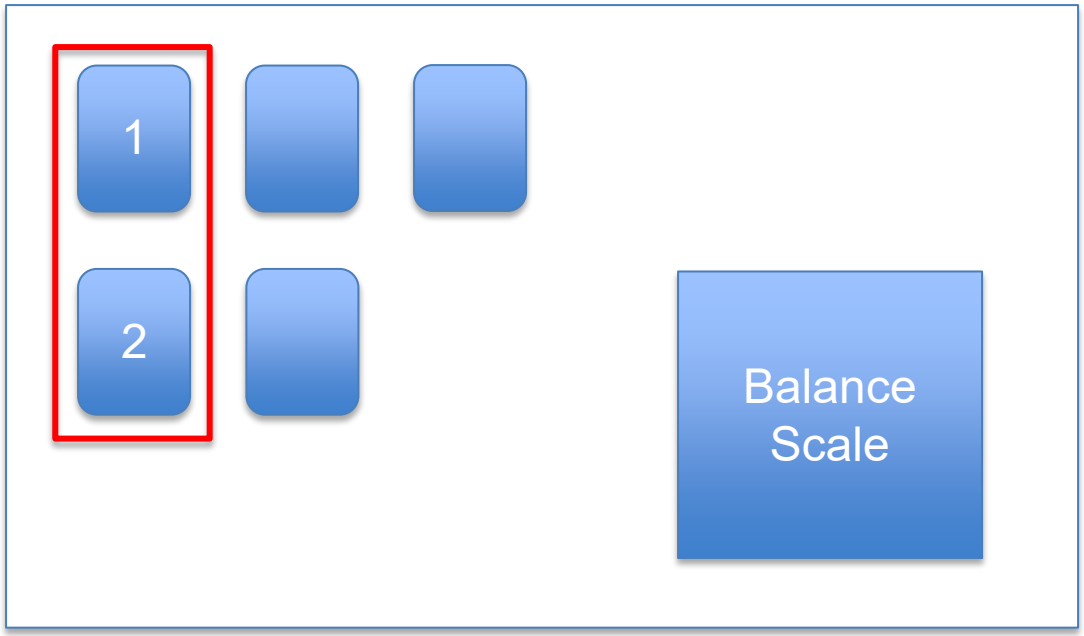
The Investigation (11 of 20)



The Investigation (12 of 20)

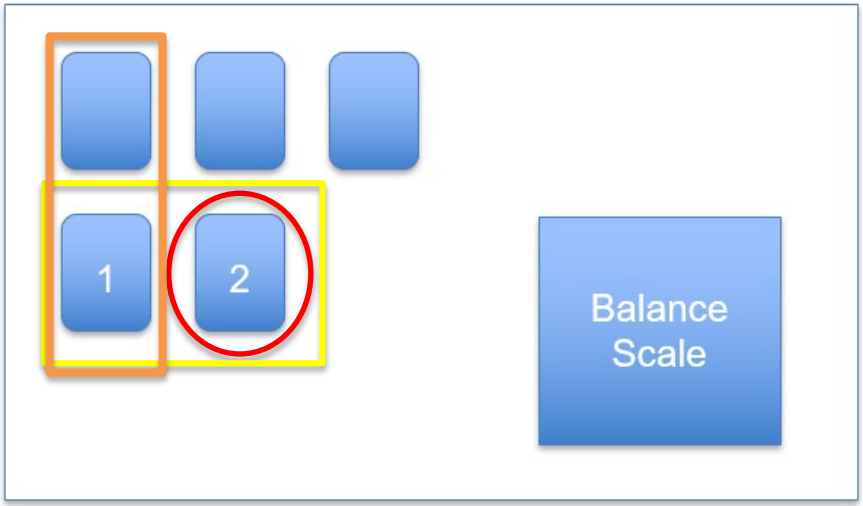


The Investigation (13 of 20)



The Investigation (14 of 20)

- Technician 1 meant the front two
  - But Technician 2 assumed the first of each row when matching up BDS and supplies for formulation and filling
- Resulted in BDS intended for 1000 syringes was formulated into 1L bulk solution and filled into 100 syringes



The Investigation (15 of 20)

But wait…. Shouldn’t Technician 2 have known which BDS was which? They did sign as the second weight verification in the batch record after all.

Should have but didn’t - batch records were pre-signed before weighing even started

The Investigation (16 of 20)

- Contributing factors to error:
  - Multiple lots of same product filled on same day
  - Technician weighed out BDS for multiple batches at once
    - Found that procedure requires separation of batches for different drugs, but not for multiple batches of same drug
  - Second technician pre-signed for weight verification (data integrity issue)
  - Inadequate training of personnel

The Investigation (17 of 20)

Why wasn’t this error caught prior to release of the batch?

The Investigation (18 of 20)

- Batch release checklist – yes or no boxes for OOS results
  - Did not specify testing results should be included
  - No testing results in batch documentation
- Where are the test results?

The Investigation (19 of 20)

Contract lab uses online portal for results

OF is not contacted directly for OOS results

SOP does not assign responsibility for checking portal

No cross training of personnel

Quality Agreement vague and not reviewed

The Investigation (20 of 20)

What Systems/Processes Failed?

- Personnel Training
- Procedures
- Quality Agreement with CTL
- Batch Release Process
- Quality Oversight

The Repercussions (1 of 2)

- At least 2 batches known to be affected by production error
- No review of finished product testing for last 10 weeks; number of batches involved TBD; unknown number of OOS results from those batches

The Repercussions (2 of 2)

What now?

Where do you go from here?

The CAPAs

(*list is not all inclusive*)

- ❑ Pull finished product testing results from all batches produced in last 10 weeks
- ❑ Determine if any other batches had OOS test results
- ❑ Quarantine all products still on site until review complete
- ❑ Immediate recall of batches affected by known production error
- ❑ Consider recall of other batches (if any) found to have OOS test results
- ❑ Cross-training of personnel
- ❑ Revise batch release process to require review of finished product testing results; form revision
- ❑ Update procedures (production controls to prevent mix-ups (e.g., labeling weigh boats), review of testing results, batch release process, etc.)
- ❑ Conduct data integrity risk assessment
- ❑ Documented personnel training/re-training on procedures and data integrity principles
- ❑ Update Quality Agreement with contract testing lab

CASE STUDY PART 2:

The FDA Inspection

- Prompted by the receipt of multiple MedWatch reports for significant ADEs
- At the time of inspection, firm's investigation was initiated and still ongoing; root cause of super-potent batch (production error) had not yet been determined

Which observations might you see on a Form FDA 483?

211.22	•Failure of QCU to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity
211.100(a) and (b)	•Failure to establish and follow adequate written procedures designed to assure drug products have the identity, strength, quality, and purity they purport or are represented to possess
211.165(a)	•Failure to have appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient
211.165(f)	•Failure to reject drug products that did not meet established standards or specifications and any other relevant quality control criteria
211.188	•Failure to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced
211.192	•Failure of QCU to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed
211.194(a)	•Failure to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards
211.198(a)	•Failure to establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product

FDA 483 Observation #1

211.165(f)

Your firm failed to reject drug products that did not meet established standards or specifications and any other relevant quality control criteria.

Specifically, your firm released and distributed two batches of fentanyl citrate 50mcg/mL inj., 10mL pre-filled syringes (lots 20230630@0007 and 20230630@0015) that had out of specification potency results. The finished product testing results included potency assays of 10% and 1000% of labeled strength, respectively.

FDA 483 Observation #2

211.22

Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity. Specifically,

Your firm does not have written procedures for retrieving and reviewing test results provided by your contract testing lab (CTL) prior to the release of sterile drug products. Additionally, there are no written procedures requiring a review of all drug product testing results by your firm's Quality Unit before releasing and distributing finished drug products. A review of your firm's records found that 952 batches of sterile drug products were released without reviewing the finished product testing results provided by your CTL between June 5, 2023, and August 17, 2023. However, your firm's signed QA batch release documentation indicates there were no out-of-specification results for each of these batches. This lapse and inaccuracy in your firm's quality review resulted in the distribution of at least one (1) super-potent and one (1) sub-potent batch of fentanyl which led to 12 adverse drug events.

FDA 483 Observation #3

211.188

Your firm failed to prepare batch production and control records with complete information related to the production and control of each batch of drug product produced.

Specifically, your procedures do not specify that finished product testing results be included in the batch records prior to batch release. Batch records for all sterile drug products produced by your firm between June 5, 2023 and August 17, 2023 (approximately 952 batches) do not include the finished product testing results for those batches.

The Response

In general, what kind of information do Outsourcing Facilities provide to the Agency?

The Response – Observation 1

Actions Taken or To Be Taken

- Affected lots of drug products have been recalled; all unused product has been accounted for
- Updated procedure and batch release form to require review and inclusion of testing results prior to release
- Quality staff retrained on updated procedure, form, and batch release process requirements

Supporting Documentation Submitted

- Reconciliation of recalled product vials (amount used, returned, destroyed)
- Updated procedure and batch release form
- Documentation of staff retraining (trainer, who was trained, what was included in training, date completed)

FDA Response Evaluation (1 of 6)

What is good about this response?

Did you notice anything missing?

FDA Response Evaluation (2 of 6)

- Observation 1
  - Failed to include update on root cause investigation for the super-potent drug product lots and any related CAPAs (implemented or planned) based on findings
  - Failed to include product impact assessment
  - Failed to include update on any additional ADEs received related to recalled lots (since there were known ADEs at time of inspection)

The Response – Observation 2

Actions Taken or To Be Taken

- Review of testing results from lots cited on 483 is underway; results for approximately 375 of the 952 lots have been reviewed; estimated time for completion of review: 30 days
- Three additional lots with OOS test results have been identified (2 OOS for low potency, 1 OOS for pH); individual investigations and risk assessments are ongoing for these lots
- Updated batch release procedure and batch release form to require review of testing results prior to release
- Created procedure that outlines process and assigns responsibility to review contract testing lab's online portal daily for test results to one specific Quality Associate and requires designee be assigned in the event of their absence
- All Quality staff will be cross-trained on accessing and review of testing results in online portal; estimated completion date: 10/1/2023

Supporting Documentation Submitted

- Updated procedure and batch release form
- New procedure for retrieval and review of testing results from contract testing lab

FDA Response Evaluation (3 of 6)

What is good about this response?

Did you notice anything missing?

FDA Response Evaluation (4 of 6)

- Observation 2
  - Timeframe specified for completion of review of CTL test results is inadequate
  - Response does not address the data integrity issues with this observation
  - Response does not address any revisions that may have been needed to the Quality Agreement with the contract testing lab following implementation of new procedure
  - Missing supporting documentation (testing results; initiated investigations/risk assessments for additional OOS results)
  - Should provide anticipated date of next response update

The Response – Observation 3

Actions Taken or To Be Taken

- Updated batch record procedure to require inclusion of all test results
- Updated batch release procedure and batch release form to require review and inclusion of testing results prior to release
- Trained Quality staff on updated procedures and documentation control expectations

Supporting Documentation Submitted

- Updated procedures and batch release form
- Documentation of staff training (trainer, who was trained, what was included in training, date completed)

FDA Response Evaluation (5 of 6)

What is good about this response?

Did you notice anything missing?

FDA Response Evaluation (6 of 6)

- Observation 3
  - Response does not specify that the test results for the 952 batches cited on the 483 will be added to those batch records and the estimated time of completion
  - Does not specify that procedure for retrieving and reviewing test results also requires that results be printed and included with the batch record

Case Studies Takeaways

- Cooperation between Quality and Production is key for successful investigations; talk to your operators
- Well-defined procedures, roles, and responsibilities are imperative so critical processes are not missed
- Documentation, documentation, documentation – it is important to send supporting documentation with your 483 (and WL) responses so FDA can fully evaluate your response.

Questions?

Thank you!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