

Laboratory OOS Investigations The Missing Link

**India Pharmaceutical Alliance
Carmelo Rosa, Psy.D
Director Division of Drug Quality I**

**November 6-17, 2017
Indian Pharmaceutical Alliance**

DISCLAIMER: The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of the Food and Drug Administration

OOS Investigations What's Missing and Why ?

Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

<http://www.fda.gov/cder/guidance/3634fnl.htm>

PROBLEM STATEMENTS

1. For at least 10 years, inadequate or the absence of thorough investigations has been among the most top 5 CGMP violations/deficiencies cited during FDA inspections.
2. Deficient OOS investigations may represent a significant risk to patients and thereby compromise the safety or efficacy drugs/pharmaceuticals

PROBLEM STATEMENTS

3. FDA continues to see lack of scientific rationale to support investigation conclusions.

- knowledge to support conclusions and decisions is not readily available or is not clearly communicated
- No additional understanding or insight into why the problem may have occurred and thus no hope for prevention.
- CAPAs are not evaluated and are often ineffective

These failures suggest a quality management system that is **insufficiently empowered** or **resourced** to adequately carry out its essential functions.

OOS GUIDANCE

A BRIEF HISTORY

Long-standing Principles include:

- ✓ OOS results cannot be disregarded or negated without a documented investigation that clearly demonstrates the cause to be laboratory error

- ✓ If retesting is performed because the original OOS result is suspect (not confirmed) the number of retests needs to be specified before the analyses begin

- ✓ Resampling should be performed only if evidence indicates that original sample was compromised or not representative

OOS GUIDANCE

A BRIEF HISTORY

Long-standing Principles include (continued):

- ✓ Averaging should not be used to hide variation in individual test results
- ✓ Relying on the average of OOS and in-specification results is misleading
- ✓ The invalidation of results obtained from Biological assays of high variability via use of outlier tests is to be used sparingly, can introduce “a serious source of bias,”* and is not applicable to chemical assays.

**Source: United States Pharmacopoeia*

FINAL GUIDANCE, GENERAL

Scope

- **Chemistry-based** laboratory testing of CDER-regulated drugs, including CDER-regulated biologic drugs, as applied in traditional methods of batch testing and release (includes contract laboratories)
- All test results that fall outside specifications or acceptance criteria, including in-process laboratory tests (one exception: guidance does not address PAT approaches to testing and release).
- APIs, excipients, in-process materials, components as well as finished drugs
- Does not apply to biologic assays, Although recommendations are intended for OOS results, the same investigation principles may applied to Out-of-Trend (OOT) results

GENERAL COMPONENTS: OOS INVESTIGATION

- OOS test result
- Root cause analysis-laboratory/production (process)
- Acceptance criteria/specifications
- Test conducted
- Information about batch or products potentially affected
- Timeliness, unbiased, well documented, scientifically sound
- Invalidation or acceptance of OOS results
- Disposition- release or rejection of batch

GENERAL COMPONENTS: OOS INVESTIGATION

- Compendia versus filed unmet specification
- Incoming material tested, in-process, testing of API, finished drug/release testing, stability testing, complaint f/u testing of product
- Examination or testing procedure
- Examination of retain samples
- Robustness of test method
- Qualifications and testing of personnel
- Suitability of the equipment
- Adequacy of procedures

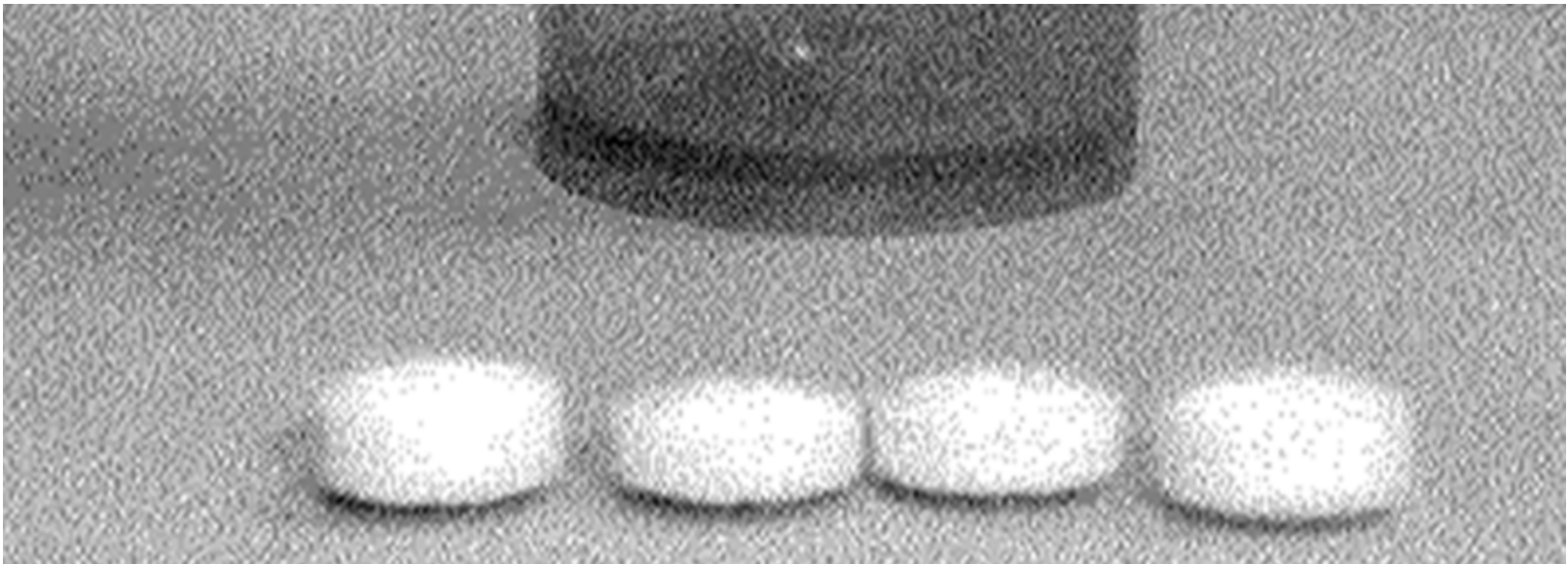
FINAL GUIDANCE, GENERAL

Recommended procedures for OOS investigations are divided into two phases to reflect that the OOS result can be caused by either:

- An aberration of the measurement process (i.e. laboratory error)
- An aberration of the production process (i.e. the product is OOS)

CASE STUDY 3: INADEQUATE INVESTIGATION

- Complaint for “thick and shiny” tablets and a second complaint for hospitalization
- How do you start your investigation ?



CASE STUDY: INADEQUATE INVESTIGATION

Does your Investigation consider the following ?

- Risk to patient
- Result of this lot
- Other similarly handled lots
- Other products affected
- How do you justify that only 1 lot was affected?
- What are the regulatory options?

FINAL GUIDANCE, PHASE I AND PHASE



Phase I: Laboratory Investigation

- Is initial assessment for possible laboratory error

Phase II: Full Scale OOS Investigation

- Review of manufacturing process and production events as possible root causes
- May also require additional laboratory work (i.e. retesting or resampling)

PHASE I: LABORATORY INVESTIGATION

GENERAL

- Data from analysis should be compared with test specifications before discarding sample preparations. If result is OOS, sample preparations should be retained, if stable, for further examination.
- **Contract** laboratories should convey all data, findings, documentation to manufacturing firm's QCU which should take overall responsibility for conducting the investigation.

PHASE I: LABORATORY INVESTIGATION

ANALYST RESPONSIBILITIES

- Use suitable instruments
- Verify proper instrument function
- Document any errors (spills, etc.) at time of occurrence.
- If error is likely to impact outcome of analysis, do not continue.
- If result is OOS, retain sample preparations and inform supervisor.

PHASE I: LABORATORY INVESTIGATION

SUPERVISOR RESPONSIBILITIES

- Discussion with analyst
- Examine all Data for anomalies
- Verify that calculations (and algorithms) used for converting raw data into final result are correct.
- Confirm performance of the instruments
- Appropriate standards, reagents, solutions used
 - in date? prepared correctly?
- Method performance meets standard established by validation?
- Fully document assessment (§§ 211.192, 211.194)

PHASE I: LABORATORY INVESTIGATION *SUPERVISOR RESPONSIBILITIES*

- Invalidate a result only in the event that investigation shows that OOS is due to a clear assignable cause.* Otherwise, go to phase II.
- Respond to identified laboratory errors with corrective and preventive action(s)
- Should be alert to developing trends that may indicate systemic problems with method, analyst training, lab quality assurance
- Ensure that QCU provides oversight of laboratory investigation

**as always, all records still need to be retained by the firm*

PHASE II: FULL-SCALE OOS *PRODUCTION REVIEW*

- Inquiry should be conducted by QCU and extend to all departments implicated. With **contract** and other off-site manufacturing, all sites potentially involved should be included.
- When the inquiry finds identifiable cause in manufacturing events (OOS confirmed), it is critical that firm then assess impact on other batches, including those already distributed.
- Confirmed OOS should be followed by corrective and preventative action. May indicate need for process adjustments.

PHASE II: FULL-SCALE OOS *PRODUCTION REVIEW*

Written record of review should include:

- Reason for the investigation
- Possible root causes in the manufacturing process
- Results of a documentation review, including assignment of actual or probable cause
- Results of review to determine impact on other lots as well as whether problem has occurred in the past
- Description of corrective action

PHASE II: FULL-SCALE OOS

ADDITIONAL LAB TESTING

Retesting, key points:

- Retesting procedures, including the number of retests **should be specified in advance (e.g., SOP)**. This can allow for additional retests after an initial round. A point needs to be set at which retesting ends and batch release decision is made.
- Retest results can substitute for original OOS results in case of **clear lab error** but all data should be retained (§211.194)
- If no clear lab error, no scientific basis for invalidating OOS result and this, as well as passing retest results, should be considered in the QA (QCU) batch release decision

PHASE II

RETESTING CONCERN

- Repeated testing until a passing result is obtained is unscientific and objectionable under cGMPs
- The practice of repeated testing until a passing result is obtained is considered **Testing into Compliance**

PHASE II: FULL-SCALE OOS *ADDITIONAL LAB TESTING*

Resampling, Key Points:

- Should be done in accordance with predetermined procedures (§ 211.165(c)). Procedures should specify sample size large enough to accommodate additional testing on original sample. If not feasible, new sample can be collected
- All other cases: Is appropriate only when evidence indicates improper sample collection or preparation, or that sample is otherwise not representative.

PHASE II: FULL-SCALE OOS

REPORTING RESULTS, DATA ANALYSIS

When reporting and interpreting results, what is the applicability of the following practices?

- Averaging
- Outlier tests

PHASE II: FULL-SCALE OOS

REPORTING RESULTS, DATA ANALYSIS

Averaging, appropriate uses:

- Final analytical batch result can be defined as an average of several determinations or replicate measurements.
- If this approach is taken it should be defined in the written test methodology. Limits on replicate analysis or measurement variability should be specified. If these limits are not met, do not use result.
- Any retests should be by the same defined method.
- Can provide a more accurate result, assuming sample is homogenous.

PHASE II: FULL-SCALE OOS *REPORTING RESULTS, DATA ANALYSIS*

Averaging, *inappropriate_uses*:

- When intent of test is to measure variability within the product (e.g., content, blend uniformity)
- OOS results and in-spec retest results should not be averaged together to hide or “bury” the OOS result. All results should be evaluated by the QCU.

PHASE II: FULL-SCALE OOS *REPORTING RESULTS, DATA ANALYSIS*

Outlier Tests:

- May have legitimacy as a way to **infrequently** invalidate extreme observations in highly variable **biological** assays.
- For chemistry-based testing within the scope of this guidance:
 - Might be used occasionally as an auxiliary part of the investigation
 - The finding from an outlier test that a result is discordant does not identify the source of the OOS and would **not** be cause to invalidate the result

CONCLUDING THE INVESTIGATION: *THREE BASIC SCENARIOS*

1. If the OOS result can be attributed to a clear assignable cause (i.e. lab error), it can be invalidated.
2. If the investigation confirms the OOS result, batch should be rejected and in accord with 211.192:
 - investigation extended to any other batches affected
 - further investigation into root cause of failure (may include additional testing for diagnostic purposes)
 - corrective and preventative action

CONCLUDING THE INVESTIGATION: *THREE BASIC SCENARIOS*

3. Inconclusive:

- If investigation reveals no cause for the OOS result and does not confirm the result, the OOS result should be considered in any batch release decision.
- Infrequently, a very thorough investigation may produce information that shows that the source of the OOS result was a cause unrelated to the manufacturing process. See example provided in the guidance.
 - *Note that any decision to release a batch, in spite of an initial OOS result that has not been invalidated, should come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. In making such a decision, the QCU should always err on the side of caution. If such a decision is made, scientific rationale should be thoroughly documented.*

NOTE: OOS results for APIs – possibility that the API can be reprocessed or reworked based on a **defined validated process**

CONCLUDING THE INVESTIGATION

-
- Cautions:
 - Results that are “borderline:” When a series of assay results are averaged as per the test procedure and one or more individual values are OOS while others are within specification, and all are within the known variability of the method, “the passing results are no more likely to represent the true value for the sample than the OOS results. Firm should err on the side of caution.”
 - Assay results that are low but within specification should raise a concern. For example, may indicate formulation error or other problem.

MANAGEMENT RESPONSIBILITY

- Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, and that roles, responsibilities, and authorities are defined, communicated, and implemented throughout the company. This includes outsourced activities and quality of purchased material

OOS INVESTIGATIONS & LABORATORY CONTROLS ALSO DISCUSSED IN...

Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

<http://www.fda.gov/cder/guidance/7260fnl.htm>

QUALITY SYSTEMS GUIDANCE

EXCERPT

Under a quality systems approach, procedures should be in place to ensure the accuracy of test results. Test results that are out of specification may be due to testing problems or manufacturing problems and should be investigated. Any invalidation of a test result should be scientifically sound and justified.

QUALITY SYSTEMS GUIDANCE

EXCERPT

Under a robust quality system, sufficient resources should be allocated for quality system and operational activities. Under the model, senior management, or a designee, should be responsible for providing adequate **resources** for the following:

- To acquire and receive **materials that are suitable** for their intended purpose
- For **laboratory analysis** of the finished drug product, including collection, storage, and examination of **in-process, stability, and reserve** samples

CONTRACT LABORATORIES

QS Guidance:

- Quality systems call for contracts (quality agreements) that clearly describe the materials or service, quality specification responsibilities, and communication mechanisms.
- Under a quality system, the manufacturer *should ensure that a contract firm is qualified* before signing a contract with that firm.

OOS Guidance:

- In addition, when investigation by a contract laboratory does not determine an assignable cause, all test results should be reported to the customer on the certificate of analysis
- “The Agency also recommends that OOS investigation reports be provided to the customer”

OOS GUIDANCE

INVESTIGATIONS

OOS results **may indicate a flaw in product or process design.** For example, a lack of robustness in product formulation, inadequate raw material characterization or control, substantial variation introduced by one or more unit operations of the manufacturing process, or a combination of these factors can be the cause of inconsistent product quality. In such cases, **it is essential that redesign of the product or process be undertaken to ensure reproducible product quality.**

OOS GUIDANCE

FIELD ALERT REPORTING

- If OOS results occur post-distribution on products covered by full or abbreviated applications (for example, from stability tests), then field alert reporting requirements also apply.
- Also applies to batches of APIs used in the finished pharmaceuticals

RECENT FDA 483 EXAMPLE

- The FDA 483 also mentioned that the firm had invalidated a high number of assay results in the first 6 months of 2016, mostly attributed to sample preparation; however, the firm did not implement any investigation or CAPA to address or correct the issue

REGULATORY ACTION

WARNING LETTER

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

“From January 1 to June 30, 2016, your firm invalidated 101 out of 139 (about 72 percent) initial out-of-specification (OOS) assay results without sufficient investigation to determine the root cause of the initial failure.”

“For example, you opened laboratory investigation report PR 908027 for an initial OOS six-month stability assay result of (b)(4) percent (specification (b)(4)–(b)(4) percent) for (b)(4) mg tablets, lot (b)(4). You invalidated the initial failing result without adequate investigation, performed re-testing, and then reported the (b)(4) results of these replicate re-tests ((b)(4) percent). Your investigation did not reach an assignable cause, nor did you take appropriate corrective actions and preventive actions to ensure that the significant “analytical bias” to which you ultimately attributed the initial failure would not affect other analytical work in your laboratory.”

ADDITIONAL NOTE IN THE WL

- Warning Letter also noted:
 - The firm failed to determine how to eliminate or mitigate the laboratory error repeatedly noted in these investigations (no CAPA plan)
 - The invalidated results were not included in the analysis of laboratory investigation trends (only confirmed OOS results were included)
 - Laboratory trending excluded a large amount of data based on the frequent practice of invalidating initial failures
- Agency requested the firm to re-evaluate all OOS results, and update their procedures so that **ALL** OOS investigations are included in the trending

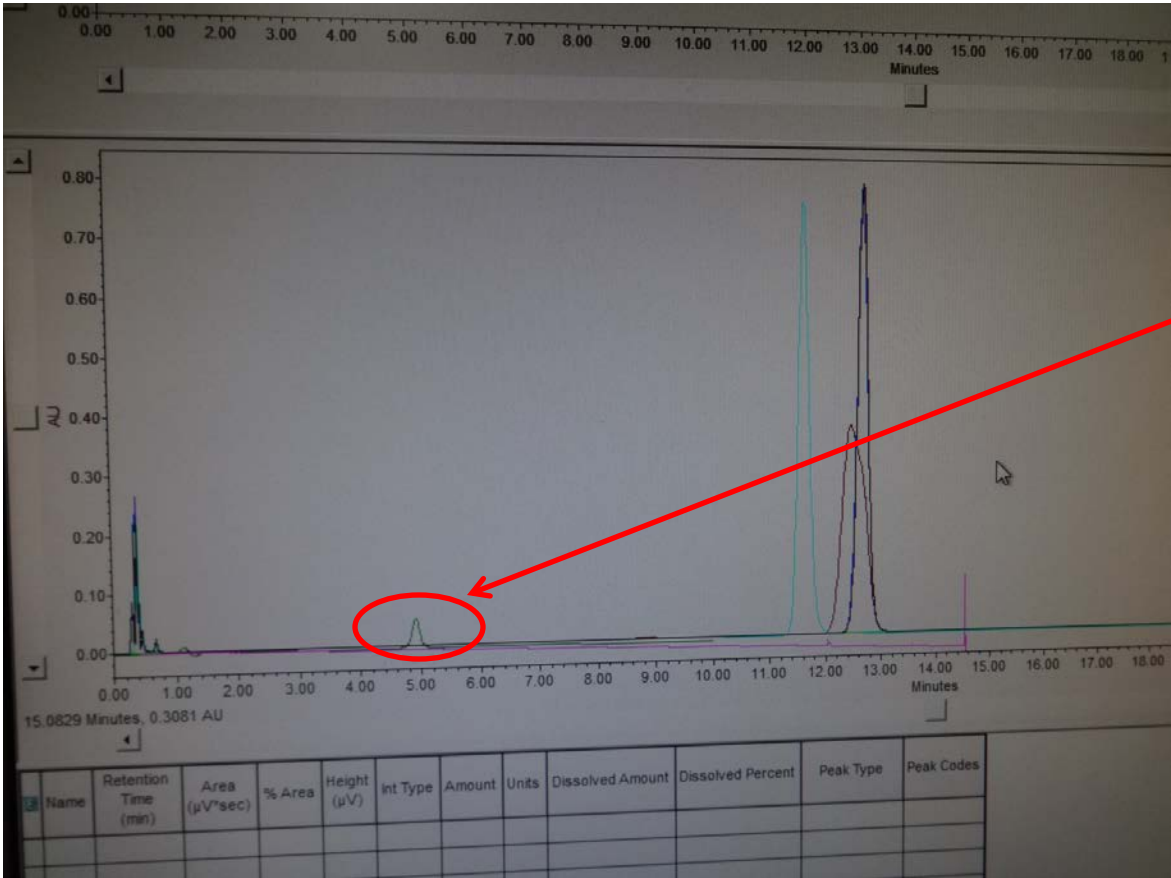
CASE STUDY #1

- Assay Testing

- Duplicate samples of a product are tested for assay
- Duplicate samples are 89.5% and 90.8%
- Average = 90.2%
- Specification is 90.0% - 110.0%
- Phase I OOS Investigation finds no attributable error
- Phase II Retesting: Results are 91.0% and 91.4%
- Average = 91.2%
- Product is released based on retest results

- Is this acceptable?

CASE STUDY #2



Anomalous Peak Observed

CASE STUDY #2

- Phase I Investigation
 - Root Cause: glassware contamination
 - Not fully dried; hypothesis is that the anomalous peak is residual cleaning solvent
- Phase II Investigation
 - Retesting by a second analyst
 - Anomalous peak is not present
 - Product is released based on the retest
- What is this investigation missing?

FINAL THOUGHTS

- OOS investigations can be time-consuming, but are necessary
- Robust OOS Investigation SOP is critical
- Need for employee training **and** understanding
- Investigation plans must be pre-defined
- Multiple departments may be involved
- Scientific rationale needs to be used at each step
- QA needs all data in order to make the right (*conservative*) decision
- Implement CAPAs
- Testing into compliance is “*bu hao*” (not good)
- Potential significant consequences for improper OOS investigations

CONTRIBUTORS

- Rick Friedman, Deputy Director, Office of Manufacturing Quality, CDER, OC, US FDA
- Atul Agrawal. Senior Policy Advisor, Office of Regulatory Affairs, US FDA
- Brooke Higgins, Senior Policy Advisor, CDER-OC/OMQ, Division Drug Quality 1
- Rebecca Parrilla, Senior Policy Advisor, CDER-OC/OMQ, Division Drug Quality 1