Handling OOS Investigations: Regulatory Expectations India June 2023

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The OOS Guidance: Why are we still talking about this?

Recent Warning Letter Trends

- Testing into compliance
- Inadequate investigations and CAPA

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2006
Pharmaceutical CGMPs

https://www.fda.gov/media/71001/download

OOS Guidance

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

Long-standing principles include:

- Averaging should not be used to hide variation in individual test results
- Relying on the average of OOS and in-specification results is misleading
- 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

OOS Guidance

- Conducting/concluding the investigation
- Interpretation of results
- Handling inconclusive results
- Retesting
- Appropriate use of averaging
- Appropriate use of outlier tests

Scope of Guidance

- Chemistry-based lab testing of drugs
- Traditional methods of testing and release (includes contract labs)
- All test results that fall outside specifications or acceptance criteria, including in-process lab tests
- APIs, excipients, in-process materials, components as well as finished drugs
- Does not apply to PAT approaches, biological assays (immunoassays, in vivo)
- Although recommendations are intended for OOS results, the same investigation principles may be applied to Out-of-Trend (OOT) results

OOS Guidance

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

1. An aberration of the measurement process
   - Laboratory error
2. An aberration of the production process
   - Product fails specification

Guidance Phase I and Phase II

Phase I: Laboratory Investigation

- Initial assessment for possible laboratory error

Phase I: Laboratory Investigation

- Thorough, timely, unbiased, well-documented and scientifically sound
- Data from analysis should be compared with test specifications.
- If result is OOS, sample preparations should be retained for further examination.
- Contract laboratories should convey all data, findings, documentation to owner's QCU which should take final responsibility for reviewing the investigation and making the appropriate batch release decision.

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 calculations and algorithms are correct
- Confirm instrument performance
- Ensure appropriate standards, reagents, and solutions are used
- Ensure method performed as intended, meets validation
- Fully document the assessment

Phase I Investigation

- Examination and reinjection of solutions may be helpful to evaluate:
  - Equipment errors
  - Incomplete extractions
  - Dilution errors
- If a conclusive lab error is identified:
  - Respond with CAPAs appropriately
- Invalidate only when the investigation shows the OOS is due to a clear assignable cause. Otherwise, go to Phase II.
- Look for trends that may indicate systemic problems with the method(s), analyst training, SOPs
  - Lab error should be infrequent

Warning Letter Example

Your firm's investigations of out-of-specification (OOS) results were closed without adequate scientific justification.

For example, you opened an OOS investigation for **(b)(4)** USP active pharmaceutical ingredient (API) for an unknown impurity which exceeded your specification. Your investigation identified an "old reagent" as a root cause, despite your inability to reproduce the unknown impurity. You subsequently retested a new sample with fresh reagents and used the passing results to release the API for use in producing your **(b)(4)** USP drug product. You did not evaluate the original failing API sample. Your root cause determination and investigation were not scientifically justified.

Phase II: Full-Scale OOS Investigation

When the initial assessment does not demonstrate lab error as the root cause and testing appears to be accurate

Include a thorough review of production and typically additional lab testing

Phase II: Full-Scale OOS Investigation

Investigation should be conducted by QCU and extend to all departments implicated.

- Contract and other off-site manufacturing sites involved should be included.

It is critical to assess impact on other batches, including those already distributed, once the investigation confirms an identifiable cause in manufacturing.

Confirmed OOS should be followed by CAPA. 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
- A thorough review of the product
  - Process performance and product quality
- Description of corrective action

Warning Letter Example

E. You obtained an OOS impurity result during the 18-month stability test of ciprofloxacin ophthalmic solution, 0.3%, lot [redacted], performed on November 29, 2017. Testing was conducted at 20 months: two months after the drug product had expired. Previous stability results for the nine- and 12-month time points were at the upper specification limit (not more than **(b)(4)**%). You did not appropriately evaluate signals of potential quality problems. Your investigation determined the OOS impurity result would have occurred at 14 months. At the time of our inspection, approximately nine months after the initial OOS, your investigation remained open, and you had not yet determined a root cause for the impurity failure.

Phase II: Full-Scale OOS *Additional Laboratory Testing*

Retesting, key points

- Retesting procedures, including the number of retests, should be specified in advance. A point needs to be set at which retesting ends and a 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: Full-Scale OOS *Additional Lab Testing*

Resampling, key points

Should be done in accordance with predetermined procedures.

- Procedures should specify sample size large enough to accommodate additional testing on original sample. If not feasible, new sample can be collected.

Appropriate when evidence indicates improper sample collection or preparation, or when 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*

Appropriate Use of Averaging

- Final analytical batch result can be defined as an average of several determinations or replicate measurements.
- Any averaging should be pre-defined in test method. 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*

Inappropriate Use of Averaging

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*

Outliers

- May be a valid way to infrequently invalidate extreme observations in highly variable biological assays
- Minimal value in chemical testing; for information purposes
- 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.
- Not applicable in cases where variability is being assessed

Phase II: Full-Scale OOS Concluding the Investigation

Three Basic Scenarios:

1) Invalidate: OOS result can be attributed to a clear assignable cause (i.e. lab error)

2) Confirm OOS: batch should be rejected/recalled and investigate in accord with 211.192

- Extend investigation to other batches
- Additional testing may be performed
- Scientifically sound CAPA

3) Inconclusive: Investigation does not confirm or reveal a cause for the OOS result, the OOS result should be given full consideration in batch disposition decision.

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.

General Principles

- 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”

NOTE: The manner in which OOS results are handled; how root cause(s) are identified and supported; and effectiveness of CAPA, are all indicators of either a healthy or unhealthy Quality System

Warning Letter Example

You failed to conduct adequate investigations into out-of-specification (OOS) test results for critical product attributes, such as assay, for your **(b)(4)** drug products. Your investigations into the OOS results did not determine root causes and include effective corrective action and preventive action (CAPA) to prevent their recurrence. In addition, your rationales for invalidating the testing failures lacked a substantive scientific evaluation.

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.

Common Problems Cited by Regulators

- No evidence to support root cause or probable root cause
- Failure to evaluate impact on other batches, process, systems
- Continuously failing to identify root cause.
- Repeated unconclusive OOS investigations, failures
- OOT retest results on lower side not evaluated carefully with the OOS result
- Investigation not scientifically sound
- Failure to conduct risk assessment
- Failure to implement appropriate CAPA with timelines; Ineffective CAPA
- Inadequate retrospective review
- Fixes seem quick, not a systemic and holistic approach
- Ineffective or lack of training
- Data not reviewed appropriately by QU
- Field Alert Reports not submitted

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

NOTE: An OOS does not need to be confirm in order to submit a FAR

Investigations should include a QRM principles and assess risk to the quality of the drug through the product lifecycle

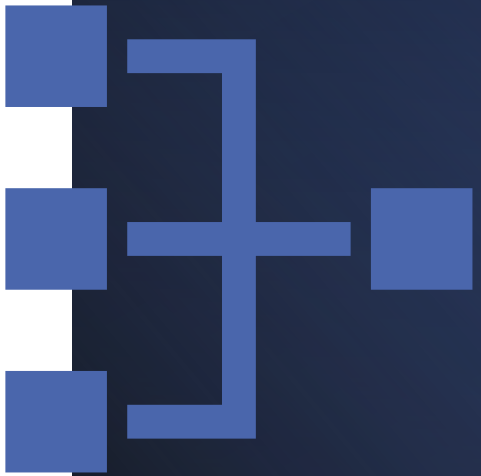
- How was the root cause determined? Evidence/Supporting Data
- Determine the systems and products affected?
- Determine people involved
- How did you determine probability of recurrence?
- Evaluate Product Lifecycle
- How severity determined?
- Is process reliable?
- How do you know your root cause was correct?
- Relevance and Effectiveness of CAPA
- Are there appropriate controls in place?
- Does the Quality agreement specify (Communication- internal, customers/client/regulatory)reporting requirements?

FACTORS TO CONSIDER

Is the investigation scientifically sound?

Are you able to "connect the dots"?

- Connecting the dots before and when a problem occurs translates into better process understanding: process changes, product variability and correlation or impact on quality attributes (OOS, OOT, OOL, complaints, unexpected events/results, variation of suppliers).
- Reactive vs Preventive and predictable



Signals of Ineffectiveness

- Repeated and recurrent OOS results at a site or within a corporation
- OOS Investigations handled in a reactive mode
- No accountability or transparency
- No evidence to support conclusions
- Delayed, absence or ineffective CAPA
- Are alternate systems, SOPs, reliable approaches being used to handle OOS results(e.g., data integrity and risk to patients)

Determine Effectiveness

- When did the OOS or deviation/events occur?
- How was timeline established?
- How was extent or scope determined?
- What quality attribute was affected (impurity test, assay, dissolution, CU…and possible correlation with other quality issues found)
- Systems impacted or affected by the questionable practices or bad CGMPs?
- Was process re-examined and will CAPA ensure sustainable compliance?

Ineffective CAPAs pose a risk of further process variation and may impact product quality.

For example,

- Presence of unknown impurities found.
- The Impurity is found and detected, but no further work is done to understand the associated risk until an OOS is obtained (often the CAPA relates it to laboratory error because the dots are not connected on time to prevent impact on product quality)

Impact Assessment: Management Strategy

A management strategy that includes:

- Detailed global CAPA plan: describe how you intend to ensure reliability and completeness of all data you generate.
- Comprehensive description of the root causes of your GMP lapses
  - Evidence the scope and depth of the current action plan is commensurate with investigation findings and risk assessment.
  - Indicate whether individuals responsible for GMP lapses remain able to influence CGMP-related or drug application data at your firm.

Warning Letter Examples- Inadequate Investigations

Warning Letter Examples- Inadequate Investigations

- Our investigators identified your practice of performing trial sample injections for HPLC analyses. For example, trial injections of (b)(4) stability samples (lot (b)(4) and (b)(4)) were acquired in the “Test” folder prior to official testing. Immediately after the trial injections were completed, the official samples were analyzed. The trial injection raw data, captured in the backup files, were deleted from the test folder.
- Your response indicates that the “Test” folders were used to equilibrate the analytical columns and to determine when the system was ready for analysis. It is your responsibility to follow validated methods that include specific procedures to assess the suitability of your instruments. Neither the ICH document Q2R, "Validation of Analytical Procedure: Text and Methodology," nor the United States Pharmacopoeia (USP), General Chapter , "Analytical Instrument Qualification," provides for use of “trial” injections as part of a validated method. Your rationale that you retested failing samples on different analytical instrumentation to evaluate system suitability is inadequate.

Warning Letter Examples- Inadequate Investigations

- Your OOS investigation procedure 036/—/QS/QA permits an analyst to abort a chromatographic run if an apparent OOS is observed prior to completing analysis of all samples scheduled to be injected in the sequence. Your quality control (QC) manager confirmed that analysts abort HPLC analyses if they "expect to invalidate" them later for an assignable cause. For example, you aborted the HPLC sequence of **(b)(4)** API batch **(b)(4)** while observing the chromatographic run on the screen ("online monitoring") in which an individual unknown impurity tested at **(b)(4)**% (specification: NMT **(b)(4)**%). There was no machine malfunction (e.g., unstable system) that would justify aborting the automated analysis.

- Your SOP was inadequate. When performing a sample preparation, it may be possible to identify an obvious manual error at the time of the mistake. In such a limited instance, it can be appropriate to discontinue the sample preparation, immediately document the deviation, and justify a new sample preparation. However, it is not appropriate to stop an in-progress automated analysis because of an assumption that an earlier error may be causing an OOS result.

Case Studies- OOS Results/Investigations

Quality Expectations

- The commercial manufacturing process can consistently produce a quality product over lifecycle.
- Appropriate controls are essential to assure that the information used for making decisions is trustworthy, accurate, and reproducible
- The data submitted to support applications, assess quality of drugs and release batches- should be reliable.
- To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification (***Investigation***) for its exclusion.

Materiality of Inadequate Investigations

- Regulators must be able to rely upon the accuracy and completeness of data generated to meet applicable regulatory requirements.
- Assurances of product safety, identity, strength, purity, and quality are dependent on the validity of data and information obtained.

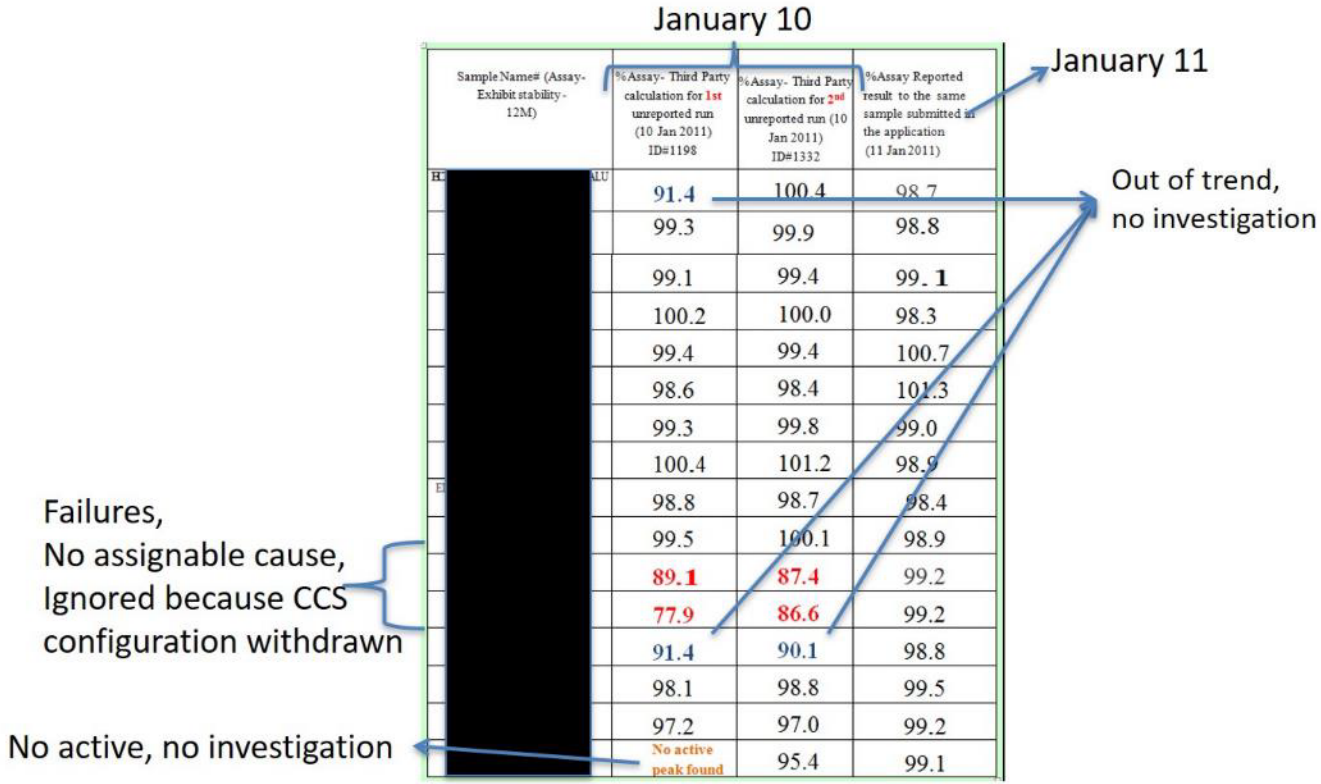
Materiality

A fact is ***material*** if there is a substantial likelihood that a reasonable reviewer would consider the statement or fact to be ***significant or important*** in evaluating the application.

This is an objective test: it measures what facts a hypothetical reasonable reviewer would probably think is important, not what any individual reviewer actually considers to be important.

You do not need to find that the misrepresented or omitted fact would have changed the decision to approve an application, only that the fact would be considered significant or important.

Example of Testing into Compliance and Unexplained Failures (Stability)



Sample Name# (Assay-Exhibit stability-12M)	%Assay- Third Party calculation for 1st unreported run (10 Jan 2011) ID#1198	%Assay- Third Party calculation for 2nd unreported run (10 Jan 2011) ID#1332	%Assay Reported result to the same sample submitted in the application (11 Jan 2011)
[redacted]	91.4	100.4	98.7
	99.3	99.9	98.8
	99.1	99.4	99.1
	100.2	100.0	98.3
	99.4	99.4	100.7
	98.6	98.4	101.3
	99.3	99.8	99.0
	100.4	101.2	98.9
	98.8	98.7	98.4
	99.5	100.1	98.9
	89.1	87.4	99.2
	77.9	86.6	99.2
	91.4	90.1	98.8
	98.1	98.8	99.5
	97.2	97.0	99.2
	No active peak found	95.4	99.1

Case Study

- A Facility observed OOS results for the In process samples for uncoated tablets during the manufacturing of the tablets for a registration batch intended for submission to the Agency.

Parameter/ Batch	Uncoated tablets (IPC)	Coated Tablets (FP)	Specification
Assay AB/123	70.5%	97.3%	95.0-102.0%
Assay CD/345	90.0 %	101%	95.0-102.0%

- **Facility did not perform the investigation of the OOS results and no root cause** is identified. The firm closes the investigation and simply performs the final release testing and claiming acceptability of the finish product since it is within the acceptance criteria.
- Facility's strategy to application submission data for agency review focused on single passing results to select a full data set and failed to account for and justify all information available on batches to support applications.

Case Study

Common thinking:

Investigations of "OOS-results" have to be done only in cases of batch release testing and testing of excipients .

- ✓ API
- ✓ Excipients

? In-process control-Is an investigation of IPC – OOS results really necessary?

- ✓ Final product

-OOS investigation is necessary. The data are unreliable to support application review as Agency cannot determine whether the data variability and failures are due to manufacturing issues, method issues, and/or product design issues

- Inability to invalidate the failures with scientific justification leaves the application with inconsistent data results which cannot be ignored in determining manufacturing capability and product quality.- **Material for review**

Case Study

- Submission registration batch AB 123 Cd Assay result observed **OOT** from result at **T= 3 M** had 101.6% (5.0 % difference than T=0)
- Facility hypothesis stated that T= 3 month OOT assay results were due to lower initial assay result and investigation was performed.

Initial Assay Testing for AB123Cd T=0			
Original result for T=0 (09/15/2015)	OOS investigation result for T=0 (10/08/2015)	Retested result for T=0 (01/26/2016)	Specification Limit
94.2%	97.1%	99.0%	90.0- 105.0%

  - Replacement/retested of the original T=0 assay result.
  - No root cause identified. Retested and invalidated initial result
  - Concluded analyst error- error occurred more than 3 months ago and no other justification was provided

Case Study

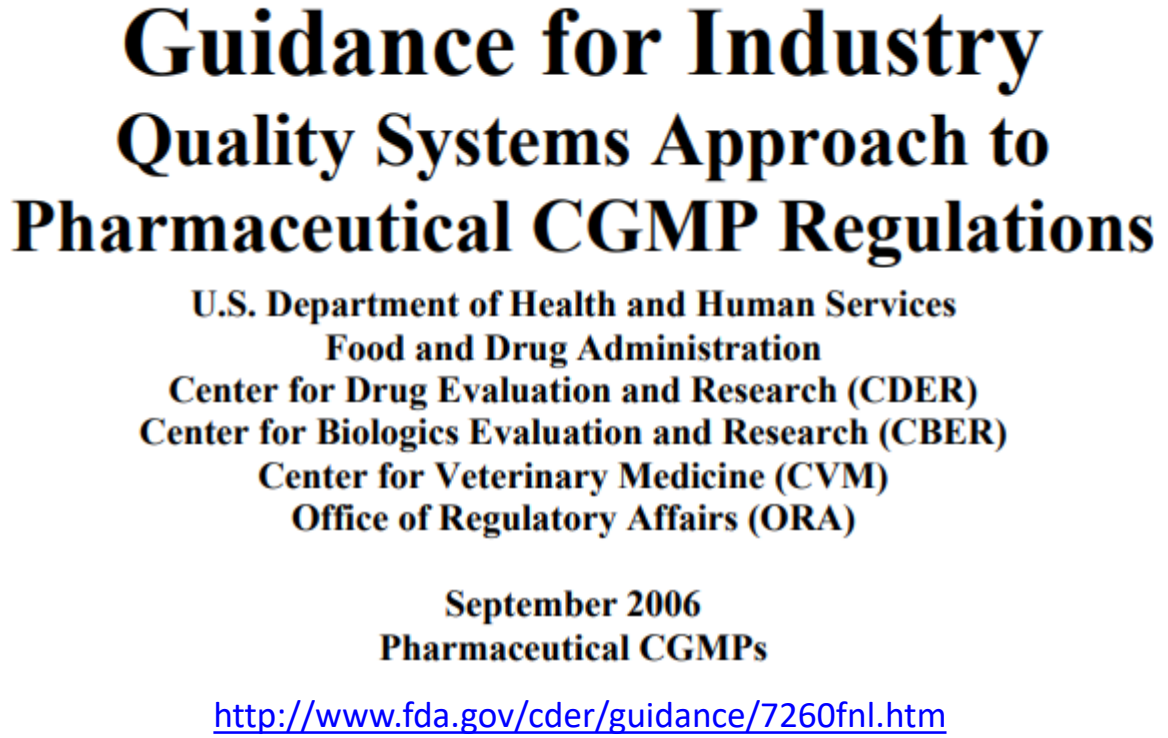
- **BU Testing**
  - BU samples of a product were tested for Biobatch
  - Samples test results range within 60.7% and 98%
  - Average = 92.4%
  - Specification is 90.0% - 100.0%
  - Phase I OOS Investigation finds no attributable error
  - Phase II Retesting: Results are 91.0% and 91.4%
  - Average = 91.2%
  - Product is released based on retest results
  - Firm discredited the 1 failing BU location
- **Is this acceptable?**

Case Study

- Lab investigation found no root cause and supported the OOS result.
- Manufacturing investigation also found no root cause but summarized likely lab error.
- Lot was released for use in the trials before this stratified sample investigation was completed.
- Investigation resulted in conclusion that event was **low risk** and batch acceptable for submission.
- However during the retrospective analysis the firm could not establish root cause and was found to be inconclusive.

Under a quality system approach, appropriate 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 thoroughly investigated. Any invalidation of a test result should be scientifically sound and justified.

OOS Investigations and Laboratory Controls are also discussed in…



Guidance for Industry

Quality Systems Approach to Pharmaceutical CGMP Regulations

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

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