實驗室調查報告及有效執行CAPA

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Disclaimer

- This presentation contains a summary of opinions and perspectives from industry representatives on the topic of OOS and the associates.
- This presentation does not necessarily represent the opinion of the presenter or its employers.
- All the material included in this presentation was obtained from publicly available sources.

實驗室調查報告及有效執行CAPA Ⅰ& Ⅱ

- Barr case （OOS的起因）
- MHRA/ FDA OOS 相關法規
- Investigation Quality 重點提醒
- Check list for Lab Investigation
- Case study
- Take Home Message

Barr case

Some Definitions

- What is an OOS Result?
- What is a test result?
- Definition of reportable value

- "A reportable value is the end result of the complete measurement method as documented. It is the value compared with the specification, the values collected when the term replicates is used, the values used for official reports, and the values used for any statistical calculation or analysis."
- Torbeck (February 1999, Pharmaceutical Technology)

Before Barr – Current Practice

- Prior to 1993 and the court decision – it was COMMON practice to retest once or in exceptionally good companies twice
  and to release the batch if the retest result was within the specification
- Companies had not really thought about the practice
- But then…nor had the regulators

The Barr Court Case and Judge Wolin

From the New York Times

February 6, 1993, Saturday

(AP); Financial Desk

COMPANY NEWS; Judge Rules On Barr Labs

A generic drug manufacturer must recall batches of some of its medicines and stop distributing others until the company completes studies of its manufacturing process, a Federal judge ruled on Thursday. But United States District Judge Alfred M. Wolin refused a request by Federal pharmaceutical regulators to order a complete shutdown

Barr and OOS

- Faced with potential closure, the company took FDA to court
- The judge went into great details as to the meaning and implications of OOS results
- The outcome: FDA draft guidance: 1998
- FDA final guidance: 2006

Barr: What happened in court

- The judge heard experts on behalf of FDA and Barr regarding the practice of retesting
- FDA wanted retesting to be banned under all circumstances
- After a long hearing at which five industry experts, an FDA investigator, and several company employees testified, Judge Alfred M. Wolin, U.S. District Judge for the District of New Jersey, issued a 79-page opinion

The Barr Court Case 1993

- Reported problems include
  - misplaced records
  - test data recorded on scrap paper
  - failure to control manufacturing steps such as those governing products' physical properties
  - release of products not meeting their specifications
  - inadequate investigation of failed products

Barr: "Testing into Compliance"

- Barr had numerous failures
- Performed retests with
  - no investigations
  - no regard for process and product history
- Tested until results met specifications
- Then irrespective of previous OOS results for the batch, released product **reporting only the passing results**

Q: How do you report passing OOS's on COA?

Reading the Judgment

- Reading the Barr Court Judgment is like reading FDA's draft guidance and pretty similar to the final guidance
- Judge Wolin preferred to use the term "out-of-specification" (OOS) laboratory results rather than the term "product failure" which was more common to (preferred by?) FDA's investigators
- Ruled that an OOS result identified as laboratory error by a failure investigation or an outlier test, or overcome by retesting is not a product failure BUT
- Limited situations where laboratory error could be used

Guide to Inspection: QC Labs

- Issued July 1993 (must have been working on it while the court case was ongoing)
- Addresses OOS results and instructs inspectors to be alert
- "Evaluate the company's system to investigate laboratory test failures. These investigations represent a key issue in deciding whether a product may be released or rejected and form the basis for retesting, and resampling "
- (Most of the information is in FDA's guide)

Guide to Inspection: QC Labs

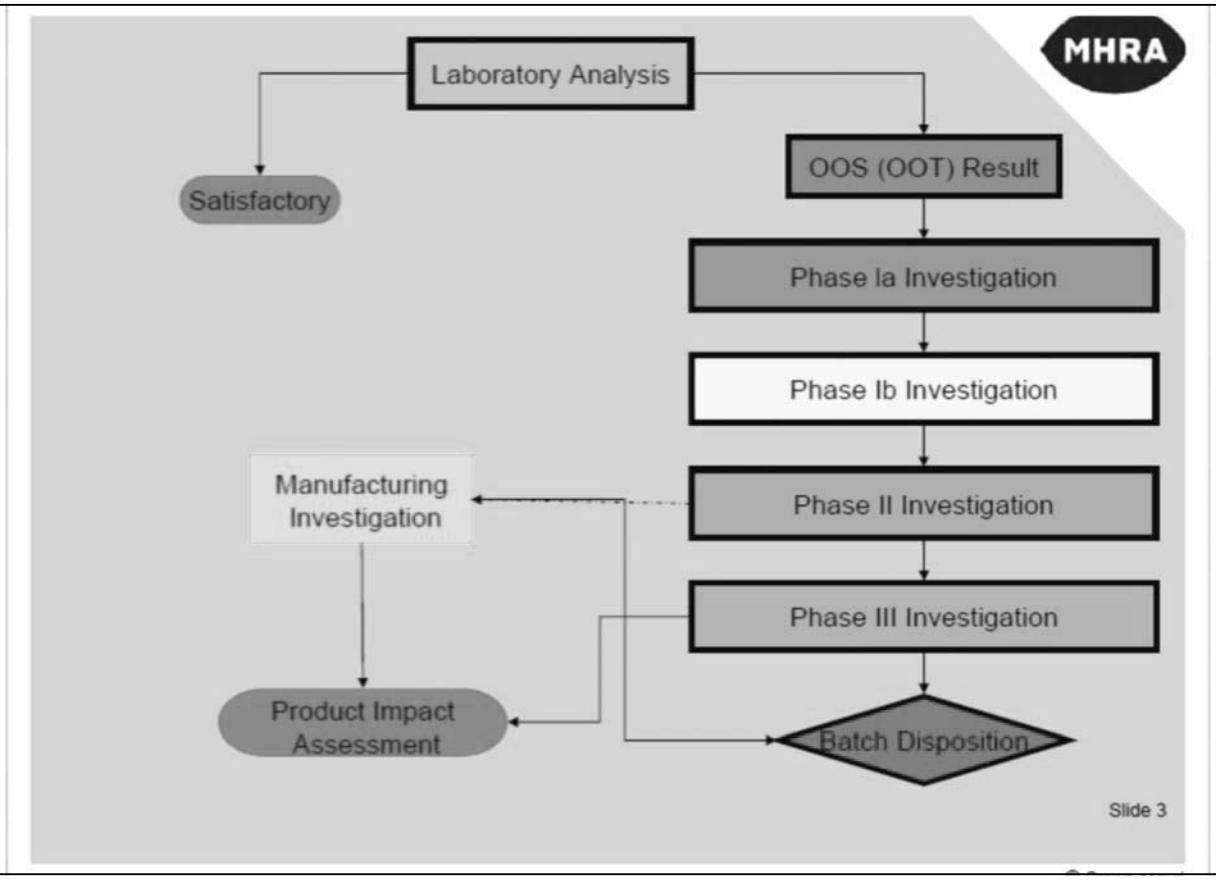
- OOS results fall into three categories:
  - laboratory error
  - non-process related or operator error
  - process related or manufacturing process error
- Evaluate the company's retesting SOP for compliance with scientifically sound and appropriate procedures
- A very important ruling sets forth a procedure to govern the retesting program
- The court ruled that a firm should have a predetermined testing procedure and should consider a point where testing ends and product is evaluated. If results are not satisfactory, product is rejected.

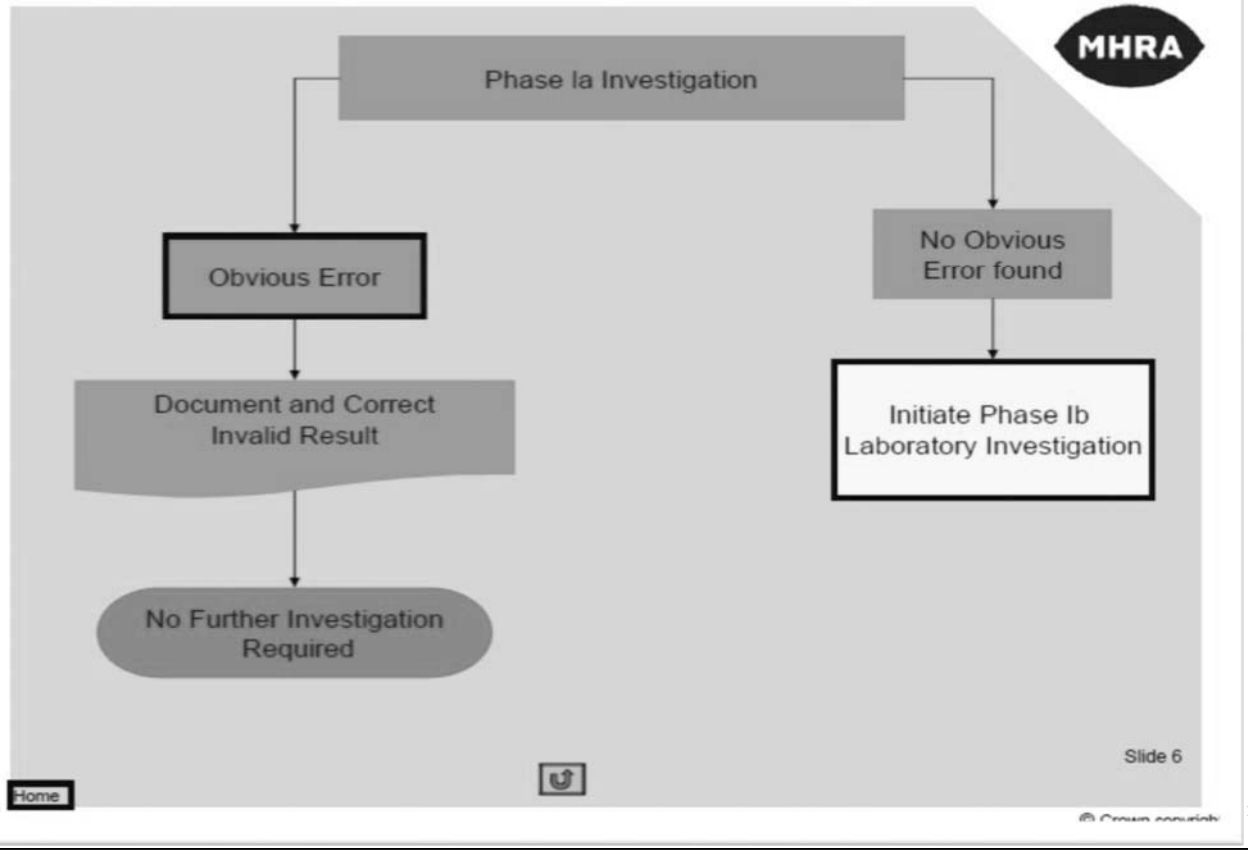
After Barr – Current Industry Practice

- ALL pharmaceutical companies have SOPs for handling Out of Specification results
- There are still many investigational findings concerning out of specification results
- There are still numerous issues, particularly with transparency:
  What do you report on the COA?

OOS Flow Chart

MHRA/ FDA (OOS highlights)




MHRA
Phase Ia Investigation
Obvious Error
No Obvious Error found
Document and Correct Invalid Result
Initiate Phase Ib Laboratory Investigation
No Further Investigation Required
Slide 6
Home

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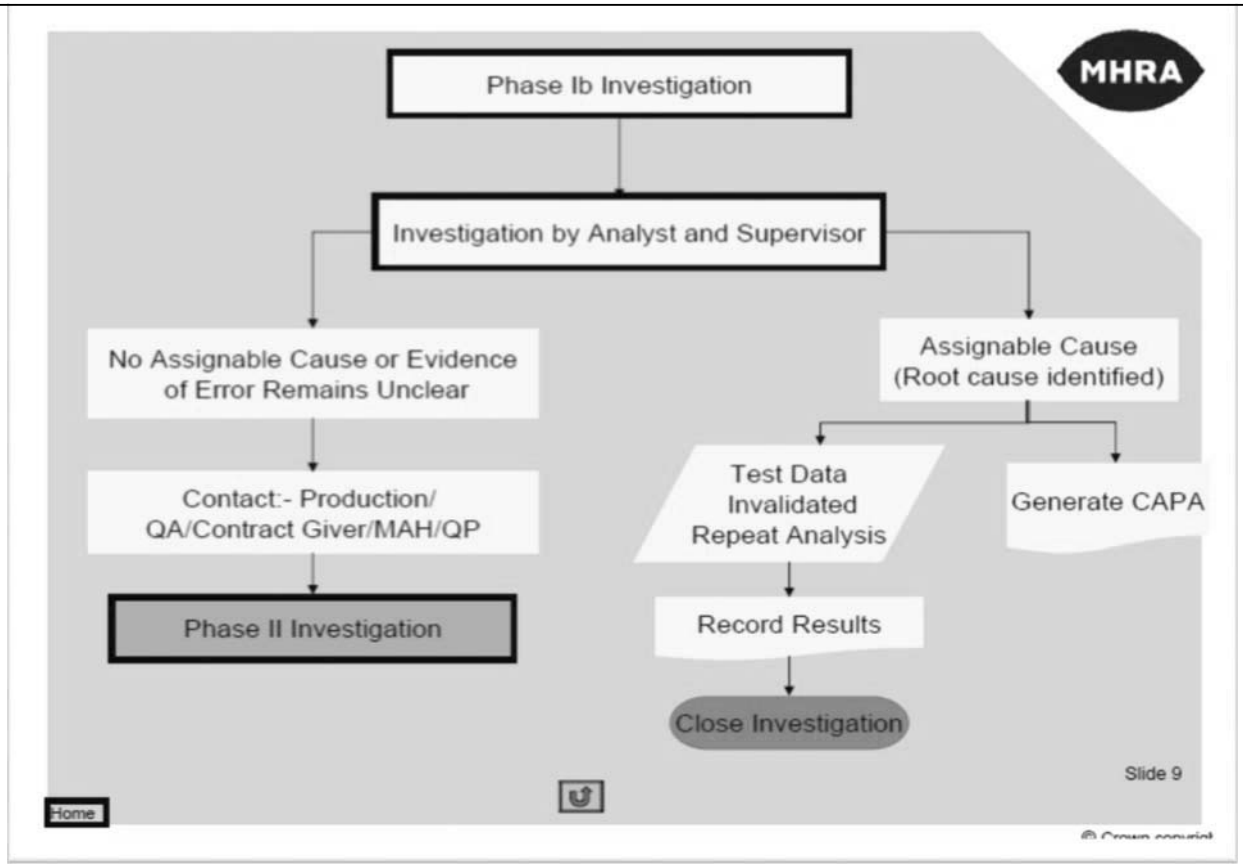
MHRA
Phase Ib Investigation
Investigation by Analyst and Supervisor
No Assignable Cause or Evidence of Error Remains Unclear
Assignable Cause (Root cause identified)
Contact:- Production/ QA/Contract Giver/MAH/QP
Test Data Invalidated Repeat Analysis
Generate CAPA
Phase II Investigation
Record Results
Close Investigation
Slide 9
Home

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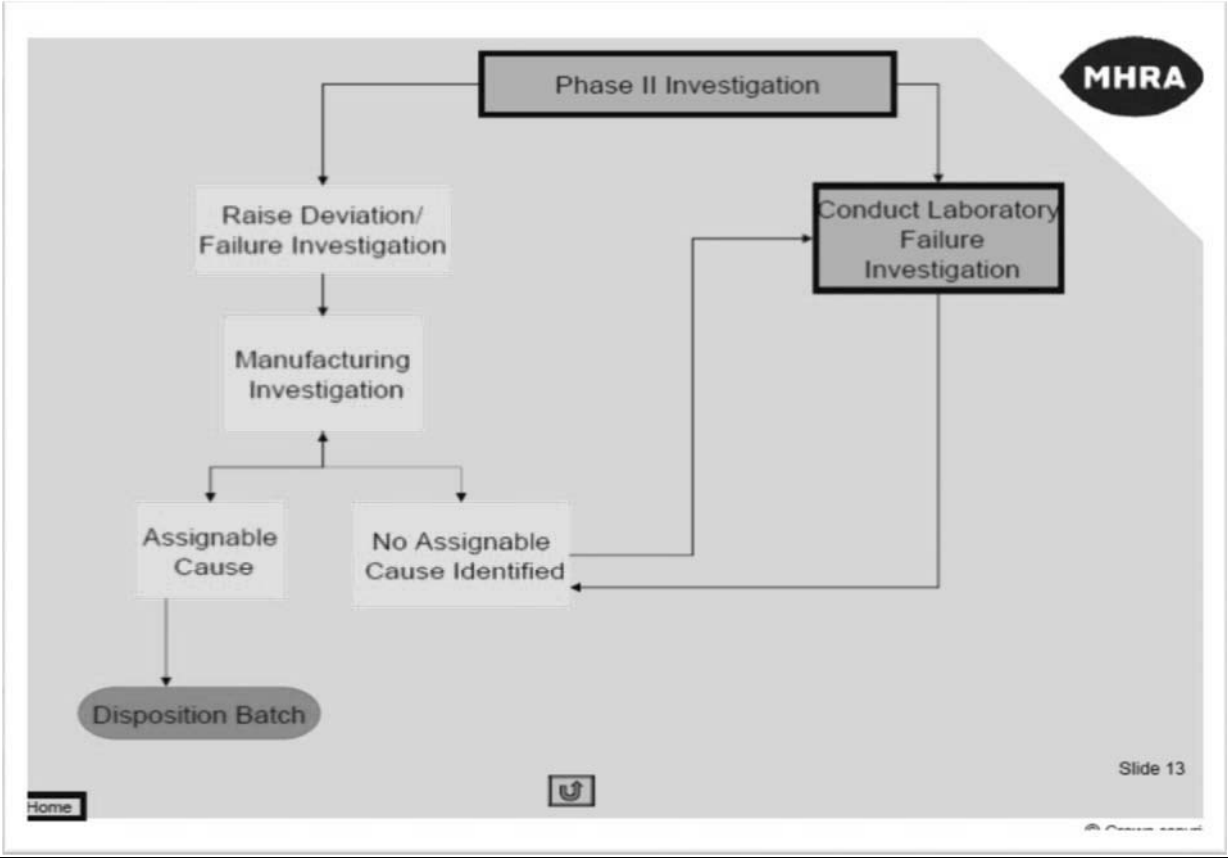

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OOS Investigation –(Phase I)

Laboratory Investigation

Check list to identify obvious Laboratory error

1. Analyst qualification and training on intended work
2. Correctness Test specification and Method
3. Instrument calibration or performance
4. Preparation test solutions and dilutions
5. Validity of Reagents and standards
6. Performance of system suitability
7. Correctness of calculation and etc….

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OOS Investigation –(Phase I)

Laboratory Investigation

- If Analyst Error identified, it should be
  - logical and appropriate
  - not on hypothetical basis
- Identify appropriate assignable cause for Laboratory error
- Correct the error, and repeat the analysis to invalidate the OOS.
- Suggest the Corrective and Preventive actions e.g. training to the Analyst, Requalification of Analyst etc. whatever the scientifically appropriate.

OOS Investigation – (Phase II)

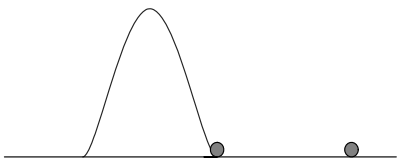
Extended Investigation

- If No assignable cause found in phase I investigation, Phase II investigation should be initiated
  - Retesting of Material with other analyst (n≥ 3?)
  - Resampling and testing
  - Investigation at Plant
  - Further Extend investigation (upon rejection)

Investigation Quality

Outliers – Judge Wolin

- Extreme values vs outliers:
- "The USP expressly allows firms to apply this test (outlier) to biological and antibiotic assays, ..., but is silent on its use with chemical tests."
- "In the Court's view the silence of the USP with respect to chemical testing and outliers is prohibitory."



Outliers - Investigation

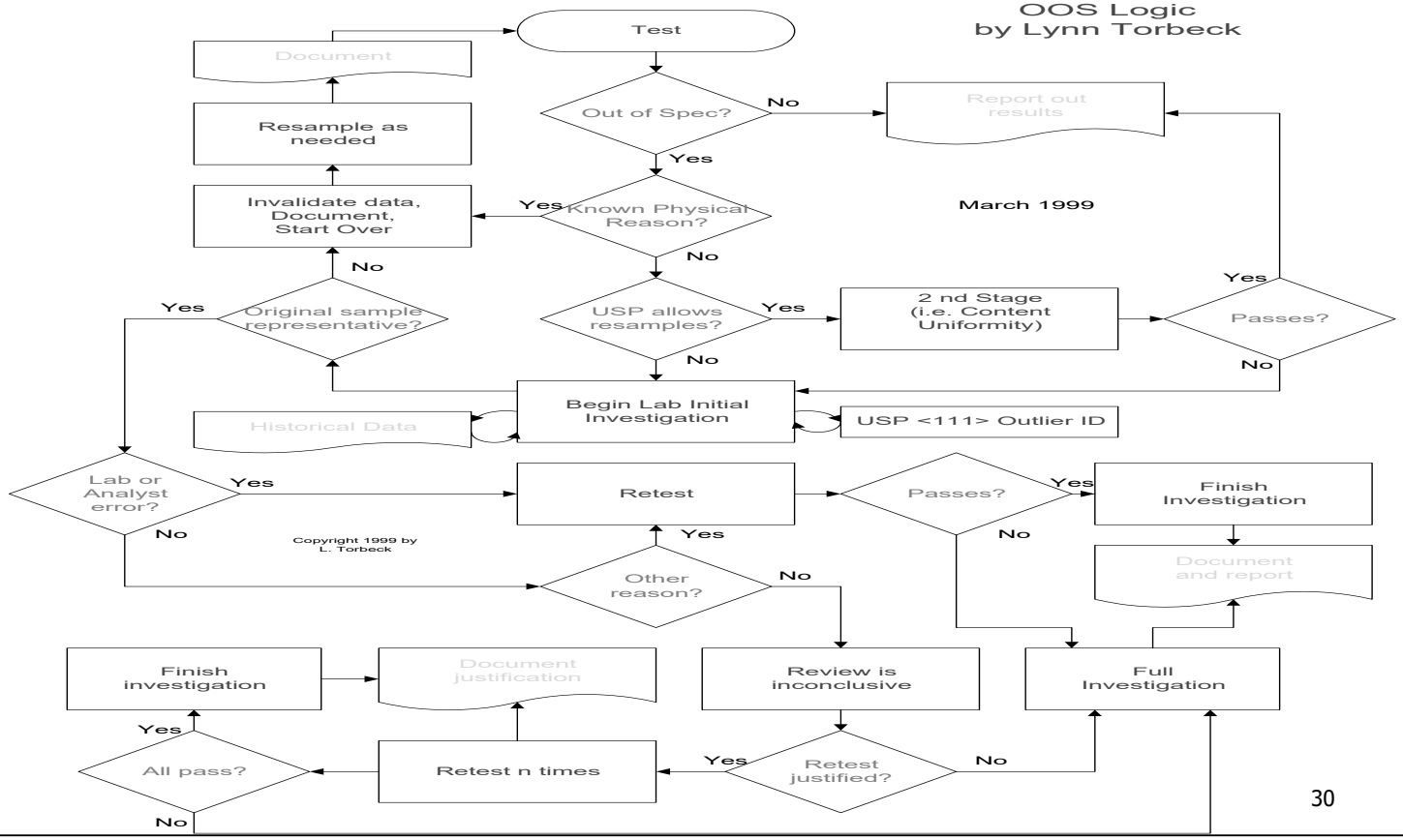
- *"In chemical procedures, where method accuracy variation is small, an outlier test may be appropriate as part of an OOS investigation, provided the sample and test procedure assumes homogeneity ... as in the composite strength assays. Our current thinking is that outlier tests are never appropriate where the purpose of the sample is to measure uniformity" Paul Vogel, September 10, 1993.*

Outliers - Recommendations

- Don't use any outlier rejection test for rejection of chemical test results. But it can be used as supporting information in an OOS investigation to consider retesting.

- Keep all data, especially suspect data, for future review. Unusual data when seen in context and with other historical data often is not unusual at all, but in fact forms a known and well-behaved statistical distribution.

- "Reportable Values for Out of Specification Test Results"
  - Lynn Torbeck
  - Pharmaceutical Technology
  - Vol. 23, No. 2, February 1999
  - Special Supplement



FDA R.V. Definition

- "It should be noted that a test might consist of replicates to arrive at a result. For instance, an HPLC assay result may be determined by averaging the peak responses from a number of consecutive, replicate injections from the same preparation. The assay result would be calculated using the peak response average."

- "This determination is considered one test and one result."

Implications of FDA Definition

- A reportable value is the end result of the complete measurement method as documented.
- It is the value compared to the specifications.
- It is the value used for official reports.
- It is usually the value used for statistical analysis.

Figure 1

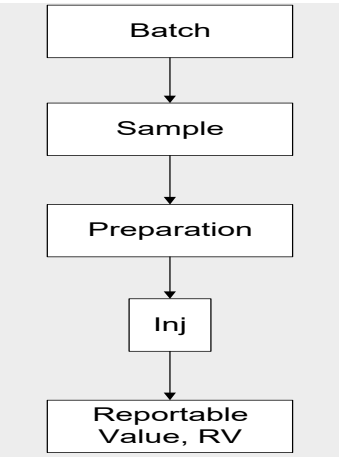


Figure 1

Figure 2

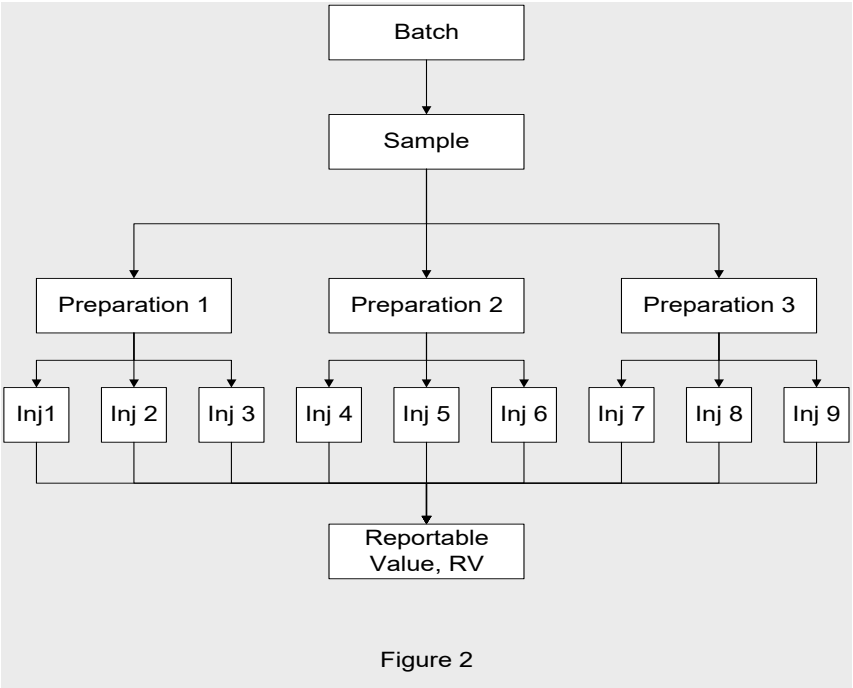


Figure 2

Figure 3

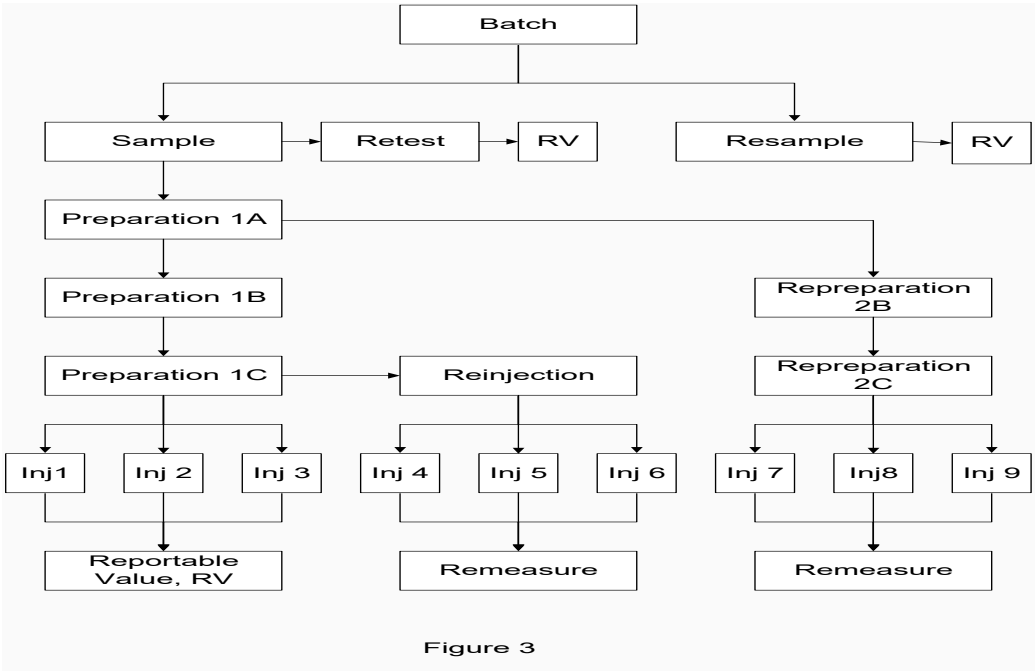


Figure 3

Interpretation

- The individual determinations have to meet the specification?
- Individual determinations are not reported out of the lab?
- However the variability of the determinations is a system suitability issue?
- Set a limit on the standard deviation or %RSD?

R.V.: OOS Prevention

- Record in writing the operational definition of the Reportable Value for each test method in the method documentation, any protocols and any reports.
- Add "Only this reportable value can be compared to the specification criteria."

Averaging

- Specifically, the arithmetic mean; the sum of all of the numbers divided by the count of the numbers.
- More generally, it is a value that represents the central point of a data set. (In this sense, it can include the arithmetic average, the median, the *mode*, the *geometric mean* or the *harmonic mean*.)

Averaging

- "... as a general rule, firms should avoid this practice, because averages hide the variability among individual test results.“
- "[Averaging] is particularly troubling if testing generates both out-of-specification and passing individual results which when averaged are within specification.
- "Here, relying on the average figure without examining and explaining the individual out-of-specification results is highly misleading and unacceptable."

Averaging

- *"Averaging the results of tests intended to measure the uniformity of the test article is not current good manufacturing practice ...*
- *because it may hide the variability of the sample the test procedure is intended to detect. For this reason, all individual test results must be reported and evaluated on an independent basis"*

  Paul Vogel, September 10, 1993.

Averaging: OOS Prevention

- Do not average out of specification reportable values within specification reportable values to get an in specification result.
- Do not average reportable values for QA to make a decision. QA must see all individual reportable values, OOS and retests.

Testing Into Compliance

- Torbeck, L., "Preventing the Practice of Testing into Compliance", Pharmaceutical Technology, Oct 2002.
- Testing into compliance is the practice of ignoring valid information that should be used to make decisions.
- Such a practice is at best not scientific and at worst is fraudulent, illegal, and immoral.
- Such practices if found must be stopped.

Testing Into Compliance

- Averaging OOS results with in specification results to get an in specification result.
- Physically averaging powers, granulations and liquids to get in specifications results.
  - If not part of the validated process.
- Discarding data or not recording data until is known to be in specification.
- Missing samples and rejected cans.
- Overwriting HPLC chromatograms.

Not Testing Into Compliance

- Large initial sample sizes are acceptable if all data generated is reported.
- Large number of retests are acceptable if all data generated is reported.
- Failing system suitability is not an OOS.
- Out of limits for an in-process adjustment is not an OOS.

Compliance: OOS Prevention

- Train all laboratory personnel, analysts, supervisors and managers to be able to identify specific situations of testing into compliance.
- Train to be able to defend situations that are not testing into compliance during an audit.

Full Consideration

- First, all QA decisions are made with the Reportable Values, both OOS and retests.
- Second, QA looks at the magnitude of the retest values compared to the specifications.
- If the retest values are close to the target, the lot can be released.
- If the retest values are close to the limit that the OOS exceeded, technically the lot can be released, but QA should consider further investigation to determine why the retests are not at target.
- QA should detail and document the logic and rational for decisions based on retesting results after a OOS result is found.

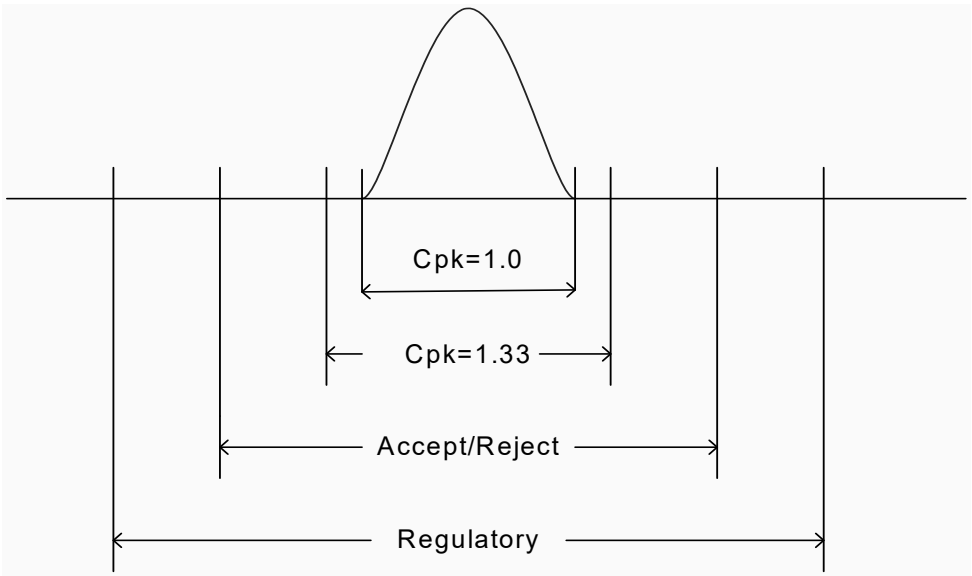
Unresolved Issues

- Specification Limits for OOS?
- What size the retest sample?
- Second analyst?
- Statistical treatment of data?

Specification Limits for OOS?

- Regulatory Limits
- Release: accept/reject
- Action limits, Cpk=1.33
- Alert, Cpk=1.0
  - Warning limits
  - Trend
  - Validation limits

Specification Limits



Specification: OOS Prevention

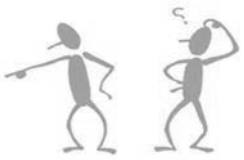
- Define in writing the levels of specification criteria.
- Justify in writing which specifications are considered applicable to OOS and why or why not.

What Size the Retest Sample?

- "… a matter of scientific judgment,"
- "… retesting cannot continue ad infinitum."
- "Such a conclusion cannot be based on 3 of 4 or 5 of 6 passing results, but possibly 7 of 8."
- "… will vary on a case by case basis … "
- "… an inflexible retesting rule … is inappropriate

OOS Investigation Purpose

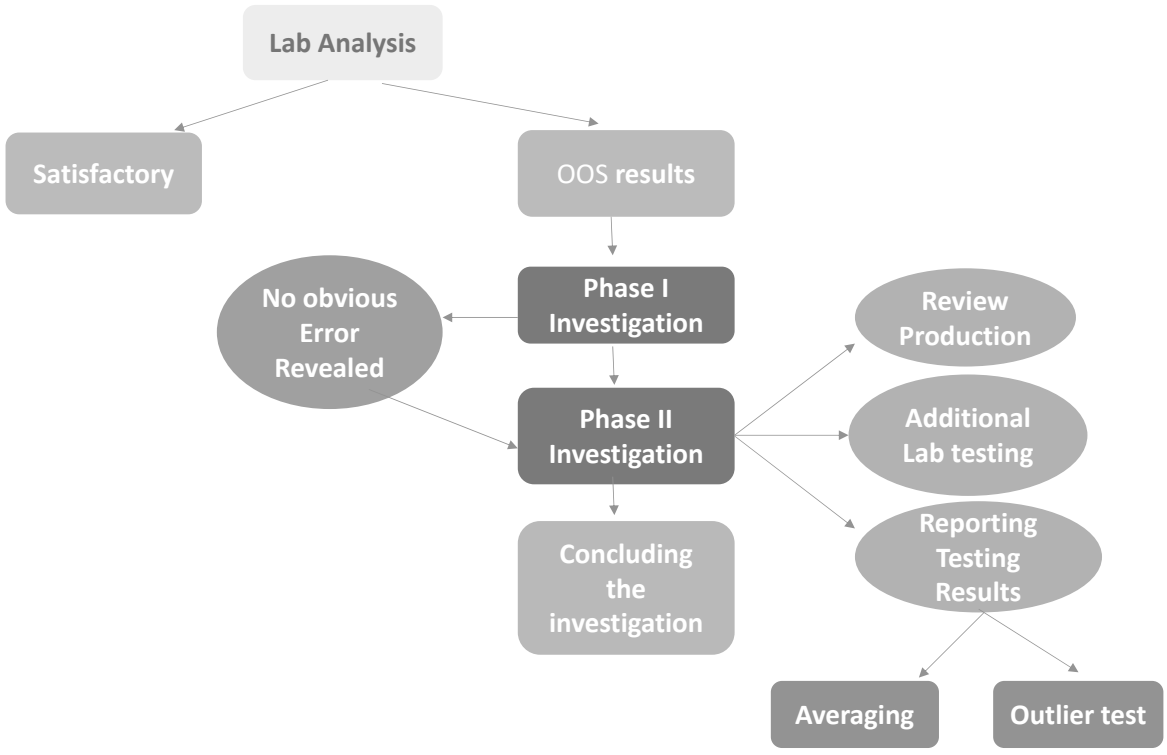
- To determine whether the cause of OOS is from aberration of measurement or from manufacturing process.
- If the batch is rejected the investigation should be continued to determine the root cause of OOS and a corrective action can be taken.
- The investigation should determine if the results is associated with other batches of the same product or other products.

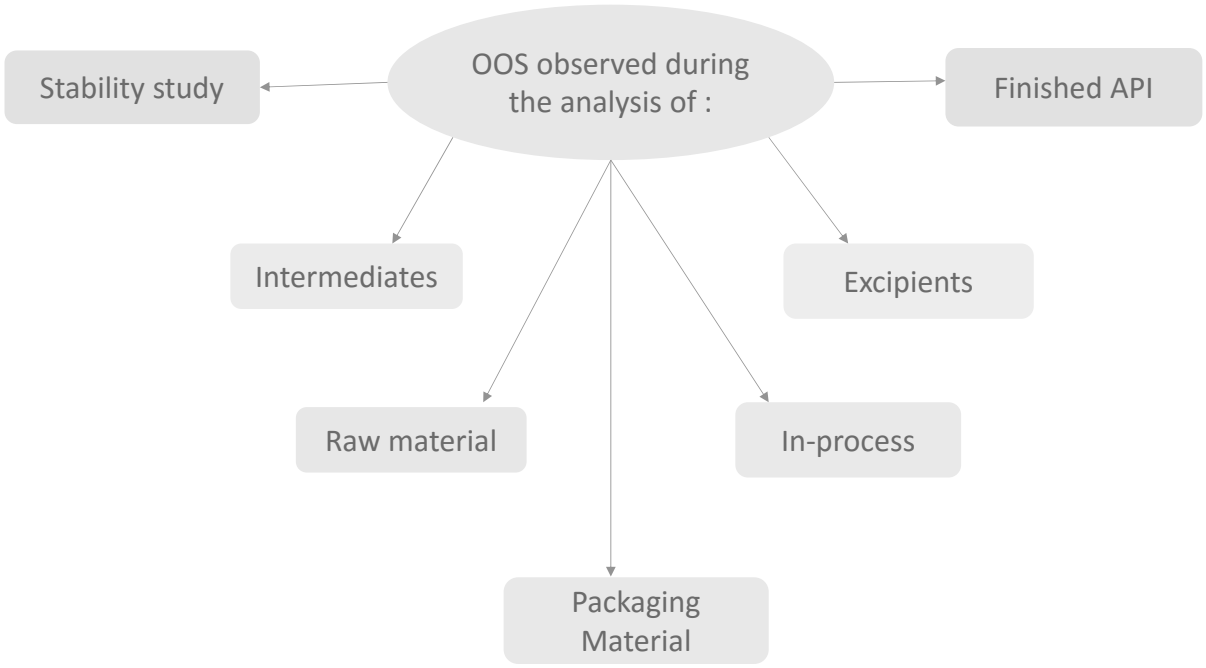


Definitions

- OOS : Is the test result that fall out side the acceptance criteria established in SOP
- OOT ：Result that may be within specs but show significant variation from the historical results.

OOS	OOT
Comparison results vs. a predetermined specs criteria.	Comparison of many historical data values vs. time.
e.g.: specs limit for assay 98.0 ~ 105.0% w/w of HPLC Result : a particular batch has 97.2% w/w	e.g.: same one. Result: 98.8% w/w, although the results are within the specs, analyst should compare results with previous batch trend. If the average value of the trend as 99% w/w, then the batch 98.8% is OOT





OOS investigation CDER/FDA

Phase I investigation (Lab investigation)
Analyst observed OOS result
Verify calculations, if the results are the same. QC supervisor shall be informed.
Log OOS
Start Phase 1
Review documents, instruments, RS, reagents
Ambient Temp., storage conditions
If there's no abnormality observed, then report results as valid OOS and report to QA officer
Repeat the analysis n=3 if the QA officer permits, with different analyst.
If results complies, then invalidate OOS and release batch. If not report to QA and continue OOS investigation

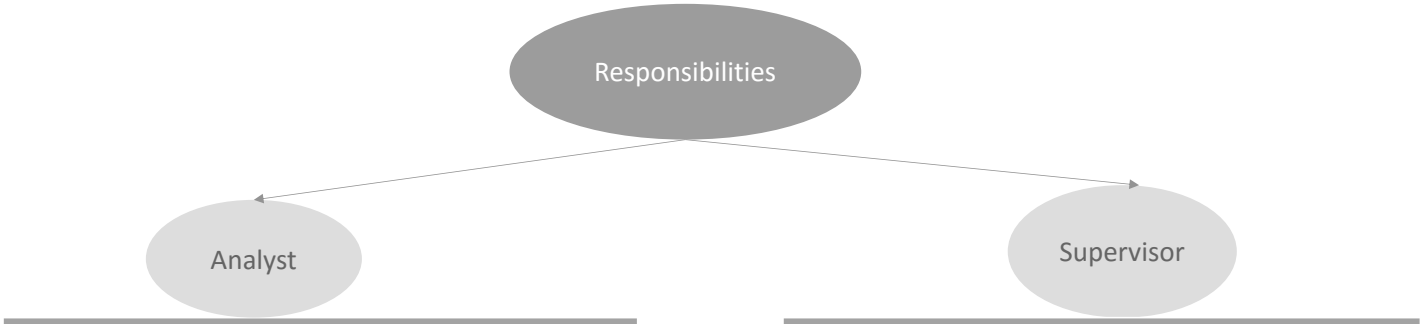
Pass

Define CAPA & Release Bath

Fail

Reject Batch & Transfer to T&D

Phase II investigation (Manufacturing)
Begins if an error assignable to the testing lab can't be identified in phase I
Recommended by QA
Production personnel should investigate raw material
Process parameters
Calibration and PM of equipment
Contamination investigation
Ambient environment check
If there is no assignable cause observed, then report to QA
QA, QC and production will evaluate the situation. The QA may request resampling
QC shall analyze the sample as per SOP. Report results (pass/fail)

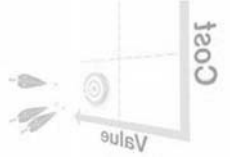


Verify paperwork is in order & matches label info.
Verify proper test method is used
Retain original test prep until data and results have been checked.
Discontinue testing and notify supervisor if a problem is suspected.

Ensure each analyst is properly trained
Ensure proper sample management within the lab.
Notify the QAU when an OOS result arises.
Ensure documentation and implementation of the retesting protocol.
Ensure investigation is conducted within the specified timeframes.

Why is it important to improve the qulity of investigations?

- Patient Risk
- Compliance
  - Health Authority Requirement
  - Continual Quality improvement
  - Effectiveness
    - Eliminate recurrence – (focus on deviation reduction)
    - Identify root cause / most probable cause
    - Identify adequate / appropriate Corrective and Preventive Actions
  - Efficiency
  - Economics



Quality of Investigations

- *Guidance for Industry: Investigating Out of Specification (OOS)*
- " *FDA Regulations require that and investigation be conducted whenever on OOS test result is obtained* ……Even if the batch is rejected based on the OOS result, the investigation is necessary to determine if a result is associated with other batches of the same drug product or other products. Batch rejection does not negate the need to perform an investigation. *The regulations require that a written record of the investigation be mad, including conclusions and follow-up* .

Quality of Investigations

There is an expectation:

- Action
  - To investigate deviations from procedures, process, etc.
- Demonstrate " due **diligence**"
  - Dig " deep" enough
  - Ensure and understanding as to why the "event" occurred and how to prevent recurrence
  - Identify the root cause or most probable cause
  - Identify , implement and monitor effectiveness of corrective and preventive actions
- Quality Oversight
- Notification to Quality in a timely manner
  - When to notify, how to notify, what information to document
  - Appropriate Site Management / Quality ….review and approval

Quality of Investigations
Definitions (1/2)

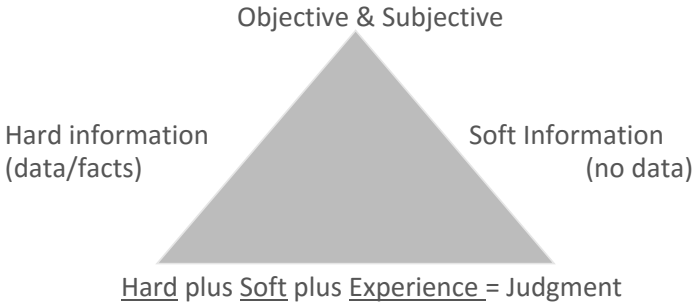
- **Deviation**: *Unplanned departure* from an approved instruction or established standard or an *unexpected observation*.
- **Nonconformity**: Non-fulfillment of a requirement.
- **Out-of-Expectation Results (OOE)**: A test result that *falls outside historical*, expected or previous trends/limits.
- **Out-of-Specification Results (OOS)**: A test result that *does not meet established specifications* or acceptance criteria. In stability testing the test result does not meet *shelf life specifications*.
- **Out of Trend (OOT)**: A stability result that does not follow the expected trend, either in comparison with other stability batches or with respect to previous results collected during the stability study.
- **Human Errors** are errors or mistakes caused by humans in the GMP environment or which may have effect on GMP. Errors and mistakes might or might not lead to a GMP related incident.

Quality of Investigations
Definitions (2/2)

- **Incident** is an event that may adversely affect the quality, safety, identity, strength, purity, availability (supply) or efficacy of a commercial product or clinical trial material and/or may compromise the Quality System and the global reputation. Any such incidents must be brought to the attention of the management through a system of sequential or concurrent notifications.
- **Unintentional errors** against approved and communicated norms. The action (or lack of action) can be accidental or caused by lack of correct knowledge or be a consequence of incorrect knowledge. This category also includes situations where the approved norms were communicated but for some reason the individual was not aware or capable of properly executing the process or using the machine (for example not understanding the training, disturbing environment or complicated interface).

- ***In order to determine if the conclusion is appropriate, we must first review the objective evidence (data) that supports the conclusion.***

Data Collection and Analysis

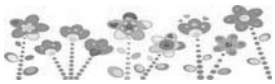


- **Manufacturing Records (examples)**
  - Batch records
  - Applicable SOPs
  - Equipment records
  - Temperature Charts , etc.
  - Training Records
  - Other?

- **Laboratory Records (examples)**
  - Notebook pages/data sheets
  - Test Methods
  - Applicable SOPs
  - Sample Receipt
    - What do I look at?
    - Sample characteristics
  - Chromatograms, data printouts, temperature charts, etc.
  - Training Records
  - Equipment/Instrument Records
  - Other?

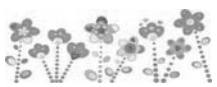
Quality of Investigations
Root Cause Analysis seeks to identify the CAUSE of the deviation

- There are generally three types of causes:
  - **Physical** - Tangible, material items failed in some way (for example, an equipment failure occurs).
  - **Human** - People do something incorrectly, or did not doing something that was required. Human error typically leads to physical causes (for example, no one checked the fluid level, which led to the failure).
  - **Organizational** - A system, process, or procedure is faulty (for example, no one person was responsible for maintenance, and everyone assumed someone else had performed the required maintenance).



Quality of Investigations
Human Factor

- Human error is typically ***not*** the root cause
- Human errors are symptoms of deeper causes (symptom versus the disease)
- We must perform in depth investigations to determine the cause of the "Human Error"
  - Interviewing is the most critical step in the investigation
- Key points to consider:
  - ✓ ***Poor*** design of facility and/or equipment
  - ✓ ***Inadequate*** procedures and processes
  - ✓ ***Ineffective*** training
  - ✓ ***Inadequate*** supervision
  - ✓ ***Inadequate*** staff and resources
  - ✓ ***Ineffective*** communication
  - ✓ Roles and responsibilities ***not clearly defined***



Quality of Investigations

Contributing factors of Human Error

- **Processes**
  - Inadequate checks, verification, control
  - Change in process
  - Lack of robust design
  - Not user tested
  - No user centered design
- **People**
  - Fatigue
  - Lack or loss of focus
  - Stress
  - Automatism
  - Superman syndrome (It won't happen to me)
  - Not understanding the impact of their actions
  - State of mind
  - Ignore a suspected issue
  - Disregards established procedures
  - Circumvents the process (workarounds)
- **Organization**
  - Training
  - Right people in the right roles
  - Peer Pressure
  - Proper Resourcing
- **Governance / Metrics**
  - Speed is more important than right
  - Quantity over Quality
  - Performance Pressures
  - Unclear accountability and responsibility
  - Deadlines
  - Budget
  - Unclear / insufficient communication
- **Procedures**
  - Unclear Instructions
  - Procedure doesn't match the process
  - Overly complicated
  - No user-centered design
- **Tools**
  - Improper tools and equipment
  - Unnecessarily complex
- **Physical Environment**
  - Noise
  - Climate
  - Lighting
  - Interruptions & Distractions
  - Workspace design
  - Cleanliness / Order
- **Product**

Quality of Investigations

Human Factor

- Stepwise approach for Human Factor investigations:
  - **Detection** of potential HFs including evaluation
    - Skill Based Errors
    - Rule Based Errors
    - Knowledge Based Errors
  - **Investigation** leading to identifying most probable root cause and contributing factors.
    - Individual
    - Environmental
    - Process/interface
    - Non Human Factors
  - **Consequences** including CAPAs and disciplinary or administrative actions
  - **Follow-up**

- Key elements of an Error Free Workplace:
  - Speak up about errors
  - What behaviors are we driving (and how) that increase human error?
  - Strive for perfection in order to achieve excellence
  - Eliminate repeat human errors
  - Personally recognize and reward success

Checklist for Lab Investigation

Investigation Checklist

- Evaluation of Raw Data:
  - System suitability acceptable?
  - Standards / controls results acceptable?
  - Calculations verified and acceptable?
  - Adverse trend observed?
  - Anything unusual observed during testing (prep/analysis)?
- Evaluation of analyst:
  - Training records verified?
  - Has analyst performed this assay previously?
  - Previous OOS with this analyst?
- Evaluation of Analytical Procedure:
  - Correct method no..?
  - Current version?
  - Was procedure followed exactly?

Investigation Checklist (continued)

- Evaluation of Standards / Controls:
  - Standard / Control condition acceptable?
  - Standard / Control prepared per procedure?
  - Standard / Control within expiration?
  - Stored and handled properly?
  - Dilutions performed correctly?
  - Mixed correctly?
  - Containers acceptable?
  - Weighing performed properly?
- Evaluation of Equipment
  - Equipment Malfunction?
  - Calibration verified and acceptable?
  - PM verified and acceptable?
  - Any error messages?

Investigation Checklist (continued)

- Evaluation of Sample:
  - Sample condition acceptable upon receipt?
  - Sampled prepared according to procedure?
  - Sample tested within expiration?
  - Were dilutions prepared correctly?
- Evaluation of Reagents :
  - Reagents condition acceptable ?
  - Reagents prepared according to procedure?
  - Reagents within expiration?
  - Stored and handled properly?
  - Used previously?
  - Freshly prepared?
- Data Analysis:
  - Trends reviewed?

Case study

OOS Case Study #1

- Complex substance assay: 6 replicates
- Inherent variability allows for wider than usual specification of 80 – 120%
- Results: 45, 50, 46, 52, 65, 69%

- What would you think if it happened to you?
- The lab technician has 20 years seniority
- No other technician is familiar with the test

OOS Case Study #1 - continued

- "Must be my mistake!"
- WRONG
- Analyst retested (not in accordance with SOP)
- Results: 72, 69, 81, 80, 82, 81%

- NOW what would you think?

- "Results: 72, 69, 81, 80, 82, 81%
- 72 and 69% must be "OUTLIERS"
- Average 81, 80, 82 and 81 and result passes
- Batch can be released
- Report only this set of results

- The outcome…..
- Product complaints from patients and doctors: Product is sub-potent
- Litigation
- Product recall
- Investigation reveals weighing error in production

What is the purpose of testing?

- To find out the value of a specific parameter
- To assess if that parameter meets the pre-determined specification for each lot
- So as to make a sound scientific judgment regarding product release or rejection
- What happens in your company when there is an OOS result?
- IDEALLY the analyst doesn't know the specification because of "BIAS."

Is it possible to ensure a correct result?

- Not at a 100% certainty level
- Just as it is not possible to prevent an incorrect result (at the 100% certainty level)
- What is a correct result?
- A result that is identical to the true result…. BUT
- When testing, we NEVER know the true result

Consequences of an Incorrect Test Result?

- FALSE NEGATIVE

  Product declared fit for use when not

  Side Effects → Death

- FALSE POSITIVE

  Product declared unfit for use when fit

  Rejection → Financial Loss

Is it possible to ensure a correct result?

- It is possible to ensure a result as close as possible to the true result
- Using a quality assurance program in the laboratory
- Validate methods
- Qualify analysts
- Follow methods as written
- Qualify, calibrate and maintain equipment
- Report deviations / malfunctions

Types of Tests

- Quantitative: assays and some limits tests
- Qualitative: e.g. sterility test, appearance
- Chemical
- Physical
- Microbiological

Chemical Testing

- Inherently reliable
- Precision is usually considerably better than for microbiological and biochemical testing
- Outlier testing is forbidden by the FDA guide for chemical testing
  (usually have less replicates anyway)
- Don't forget case study #1 – How NOT to handle OOS results

Physical Tests

- Black spots in powder
- Fill volume are particularly problematic, since results are almost certainly correct.
  Is there any place for retesting?
- Is there any place for resampling?

Hypothesis Testing, Case Study #2

- LAL test on radioactive product (short half-life) is positive
- Product history – no previous failure
- Other products tested in same series passed
- Initial laboratory investigation: no evidence of lab error
- Dilution used: 1:70
  specification allows up to 1:140 dilution

Hypothesis Testing, Case Study #2

- Perform retest in parallel with production investigation because of short half-life
- Production investigation included sampling glassware and equipment for LAL residues NO positive results
- Repeat test at 1:70 and 1:140 dilutions Results were in spec i.e. no positive LAL
- New LAL reagent prepared and same sample tested with old and new reagent:
  - Old: failed
  - New: passed

Out of Specification Results

- If the laboratory investigation is ***conclusive***
  - Document findings
  - INVALIDATE original test
  - Perform NEW test on same sample
  - Report original result with investigation as well as new result in batch record for QA review prior to release
  - COA carries new result only; some companies use an asterisk and indicate that there was an OOS
- If the laboratory investigation is ***NOT*** conclusive inform QA (or customer for contract lab)

Out of Trend Results

- If the laboratory investigation is conclusive or inconclusive, consult with QA
- In most cases, DO NOT perform any additional testing or sampling
- Make product disposition judgment based on:
  - Original result
  - Product history (e.g. stability data – statistical analyses of particular use here)
  - Batch history (e.g. review indicates that there were no processing errors / there were errors)
  - Other investigational findings

And now some work for you.....

- Specification is 90.0 – 110.0% for an oral suspension
- Three batches are tested simultaneously, each sample in duplicate
- Two batches show (average) 98.2% and 99.7% respectively
- Third batch gives one result of 88.2% and a second result of 89.3%

PREPARE A CHECKLIST OF QUESTIONS TO REVIEW AS PART OF THE LABORATORY INVESTIGATION

FDA: Concluding the Investigation

- Example given shows seven retest results which gives the only indication in the guide regarding numbers of retests
- The example given is also extreme:
  89.5% OOS
  99.0, 98.9, 99.0, 99.1, 98.8, 99.1, 99.0%
- Consider method precision and validation data in making release / reject decision

OOS Case Study #3

- BN 200602 gave an assay result for 3 month stability study: 89.2% (long term / RT)
- Limits: 90.0 – 110.0%
- Test performed at a contract laboratory using an internal instrument control
- BN 200701 tested at the same time gave a result of 95.4% (i.e. in spec. – release test)

DO YOU INFORM THE REGULATORS?

OOS Case Study #3 – cont/

- The samples have to be diluted during preparation and as far as records showed there was no evidence of laboratory error
- Calculations were satisfactory
- No evidence that reagents were outdated or faulty technique
- Control sample showed a 3.5% difference at beginning and end of run: usually around 1%; NMT 5% allowed by method

OOS Case Study #3 – cont/

- Batch number 200701; in-process result: 98.2%
- Batch number 200602; time zero result: 92.8%
  i.e. an apparent difference of 3.5% between results in both cases
- Hypothesis formulated:
  problem is with the control sample / equipment and this can be tested using both batches
  i.e. in-spec and OOS

OOS Case Study #3 – cont/

- Retesting Protocol (before start of retesting):
  - BN 200602: OOS on inverted stability sample at 3 months
    Perform retest at three dilutions in duplicate on:
    - Same sample = 6 results vs 2 original
    - Upright sample = 6 additional results
  - BN 200701: In spec. but 3.5% lower than IPC
    Perform retest at three dilutions in duplicate
    - Same sample = 6 results vs 2 original

OOS Case Study #3 – cont/

- Outcome:
  - BN 200602: All retest results in specification
    average result: 92.2%
  - BN 200701: All retest results in specification
    average result: 97.9%
  - Control sample: difference of 1% beginning and end of run

OOS Case Study #3 – cont/

- Original OOS result for BN 200602 is invalid
- Original OOT result for BN 200701 is invalid ?
- CAPA required regarding external laboratory as follows:
  - Tighten allowed limits for control sample (NMT 5% is too high)
  - Revalidate method? Investigation showed validation last done 15 years ago and a new instrument had been introduced since then!
  - Closely follow BN 200602 at additional stability stations

Take Home Message
Data Integrity and Culture

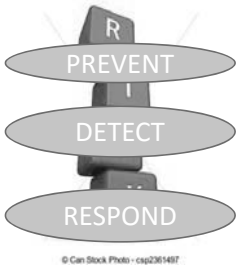
Data Integrity and Culture

- You can fix systems
- You can fix processes
- You can fix procedures

- Can you “fix” people?
- How do you change behavior?
- How do you create “Culture”

Why DI Issues Happen?

- Time Pressure
- Insufficient education & understanding (WHY)
- Fear for mistakes
- Performance Pressure
- Am told by leader
- Reputation
- Money
- Culture or accepted behavior

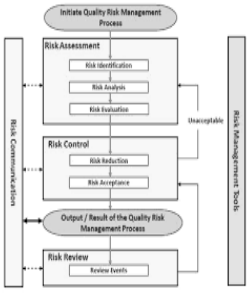


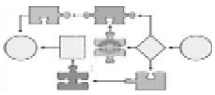
Personnel

Not aware, not trained, culture

Data Review

Insufficient, not done, not in SOP





Processes

Not validating for intended use

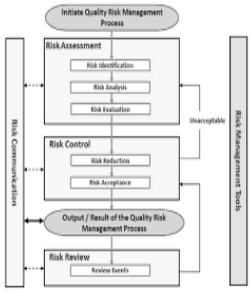
Outsourcing

QC Lab, Manufacturing

Data Integrity Risk Factors

PREVENT

- Personnel (Internal /External)
- Validation
- Security Controls
- External Sources
- Documentation Control



DETECT

- Audits
- Data Review

RESPOND

- Governance/Findings/Actions

PREVENT

- Personnel (Internal /External)

  - State and enforce high standards of ethics and integrity by :
  - Training employees on proper data handling and reporting
  - Company Values and Code of Conduct
  - Emphasize that everyone in the company is responsible for data

- Validation

  - Computerized systems should be validated for intended use
  - Identify the Risks: what are the controls to Prevent Data Integrity Issues? What are the controls to Detect Data Integrity Issues?
  - Include Data Life Cycle requirements
  - Identify Critical Data and Records
  - Backup and Recovery

PREVENT

- Security Controls

  - Protect at both the physical level (building / room) and the information level (network and application)
  - Access Controls: users, password controls, segregation of duties
  - Include Cyber Security (be protected from the outside)

- External Sources

  - Contractors and vendors for variety of GxP services
  - Audits and Inspections should include reviews for data integrity controls
  - Quality Agreements should include data integrity controls

- Documentation Controls

  - Managing the life of the data (initial carton, review, approval, storage, obsolete)
  - Ensure policies and procedures define the requirements for both patper and electronic data and their usage.

DETECT

- Audit

  - An independent audit program that utilizes auditors who are qualified by education, experience and training to evaluate the quality systems used for collecting , analyzing, reporting and retaining information and data.
  - The audit program will include periodic audits to confirm adherence to establish requirements for data integrity.

- Data Review

  - Good Documentation Practices
  - System Audit Trail: Tracks actions of System Administrator, Reviewed periodically based on risk, Defined in Administrators SOPs
  - Data Audit Trail (Tracks actions of users, reviewers, and approvers; Reviewed when the data is reviewed; Defined in User Operational SOPs

RESPOND

- Governance /Findings /Actions

  - Develop Data Integrity Policy and Procedures to address data ownership throughout the lifecycle
  - Consider the design, operation and monitoring of processes / including control over intentional and unintentional changes to information
  - Investigate / Correct / Prevent
  - If warranted, conduct and in-depth documented investigation of any alleged instance of falsification, fabrication, or other misconduct involving data integrity issues.

- A Strong Quality Culture is best indicated by what it is done when Nobody is Looking

- Culture is the Cornerstone of Qulity

"the **printed chromatograms** used in drug manufacturing and testing **do not satisfy** the predicate rule requirements in 21 CFR Part 211.

The electronic record must be maintained and readily available for review by, for example, QC/QA personnel or the FDA investigator"

Thank You For Your Attention