



FAILURE INVESTIGATION



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10/13/2011



Topics

- Defining failure & investigation
- Need for investigation
- Regulatory outlook
- Investigation methodologies
- Investigation tools
- Data to be reviewed
- CAPA
- Investigation report
- Case studies



What is Failure & Failure Investigation?

- **Failure** refers to the state or condition of not meeting a desirable or intended objective, and may be viewed as the opposite of compliance.
- **Failure** in other words is a Non-conformity which may include
 - Product failure (Release testing / In-process testing / stability testing)
 - Failure of Utility
 - Quality System failure
 - Market complaints
 - Deviation
- **Failure investigation** is the process of collecting and analyzing data to determine the cause of a failure.



Why investigate failures?

- To prevent reoccurrence
 - Failures are cost to company
 - Failures can have adverse health impact on the consumers if go undetected
- To identify the cause and take corrective actions
- To identify other similar situations and take preventive actions
- Continuous improvement
- Regulatory requirement



Regulatory requirements

□ 21 CFR 211 – cGMP for Finished Pharmaceuticals

□ Subpart B--Organization and Personnel

- Sec. 211.22 - Responsibilities of quality control unit in investigation of errors observed during testing.
- 211.125 - Investigation of discrepancies in label reconciliation
- 211.170 – Investigation of deterioration observed in Reserve samples



Regulatory requirements

- ❑ **21 CFR 211 – cGMP for Finished Pharmaceuticals**
 - ❑ **Subpart J--Records and Reports**
 - **211.180 General requirements - A review of complaints, recalls, returned or salvaged drug products, and investigations.**
 - **211.186 Master production and control records – Investigation of yield deviations;**
 - **211.192 Production record review – Investigation of 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.**
 - **211.198 Complaint file – Investigation of market complaints**
 - **211.204 Returned drug products - Investigation of returns**

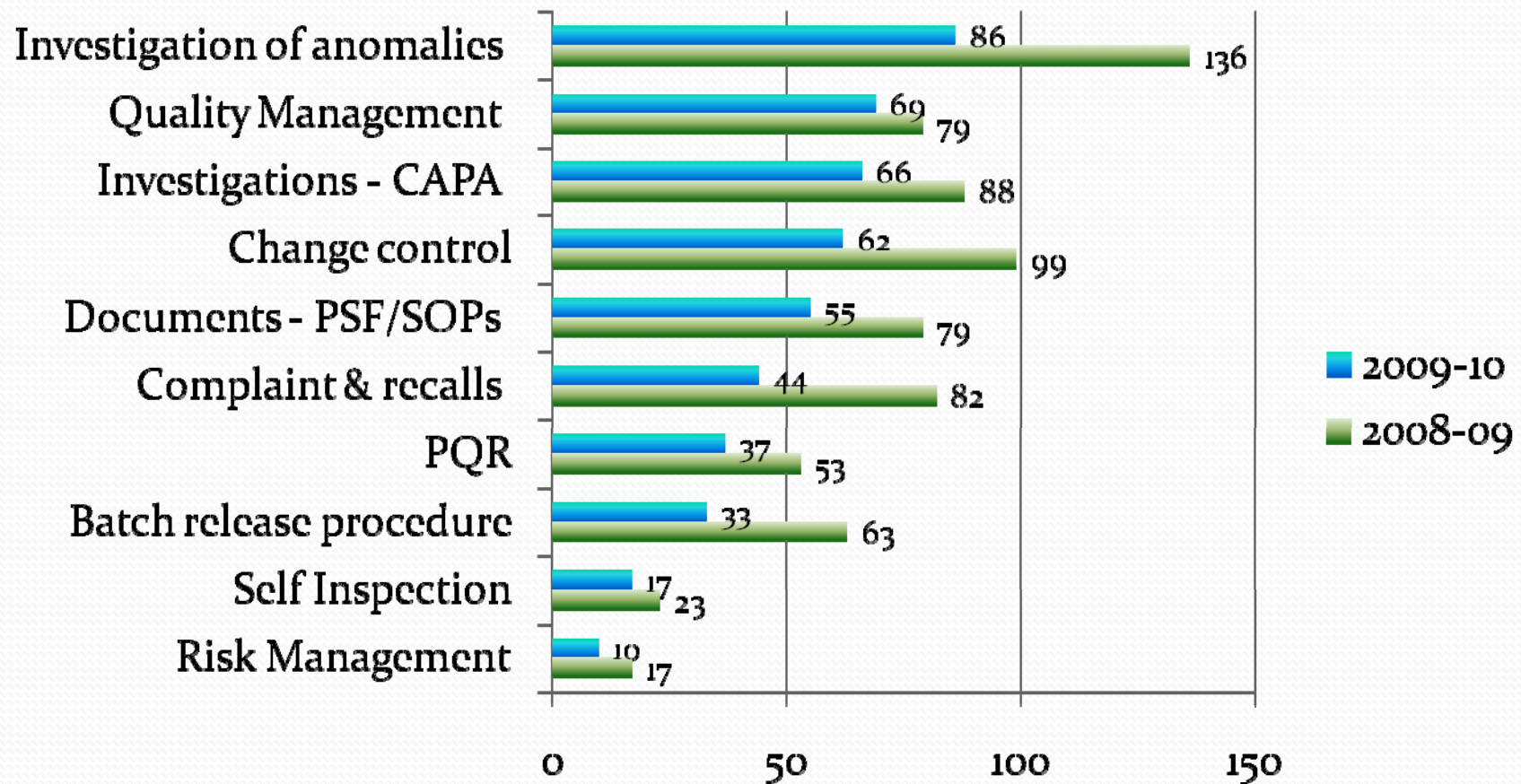


Regulatory requirements

- **EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines**
 - **Good Manufacturing Practice for Medicinal Products (GMP)**
 - (iv) Documentation and investigation of any significant deviations in sampling, inspecting and testing;
 - (vi) Documentation and investigation of any significant deviations in the manufacturing;
 - (x) Investigation of complaints
 - **Product Quality Review**
 - (iii) A review of all batches that failed to meet established specification (s) and their investigation.
 - (iv) A review of all significant deviations or non-conformances, their related Investigations.
 - (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.



Investigations top MHRA deficiency list





Failure Investigation



Causes of failure or variation

- **Assignable causes**

- Causes can be identified and eliminated
 - Human error
 - Machine problem
 - Material problem
 - Deviation from process
 - Environment
 - Measurement error (Laboratory error)

- **Common causes**

- Random causes that we cannot identify
- Unavoidable
- Related to process capability
 - Poor design or robustness issue

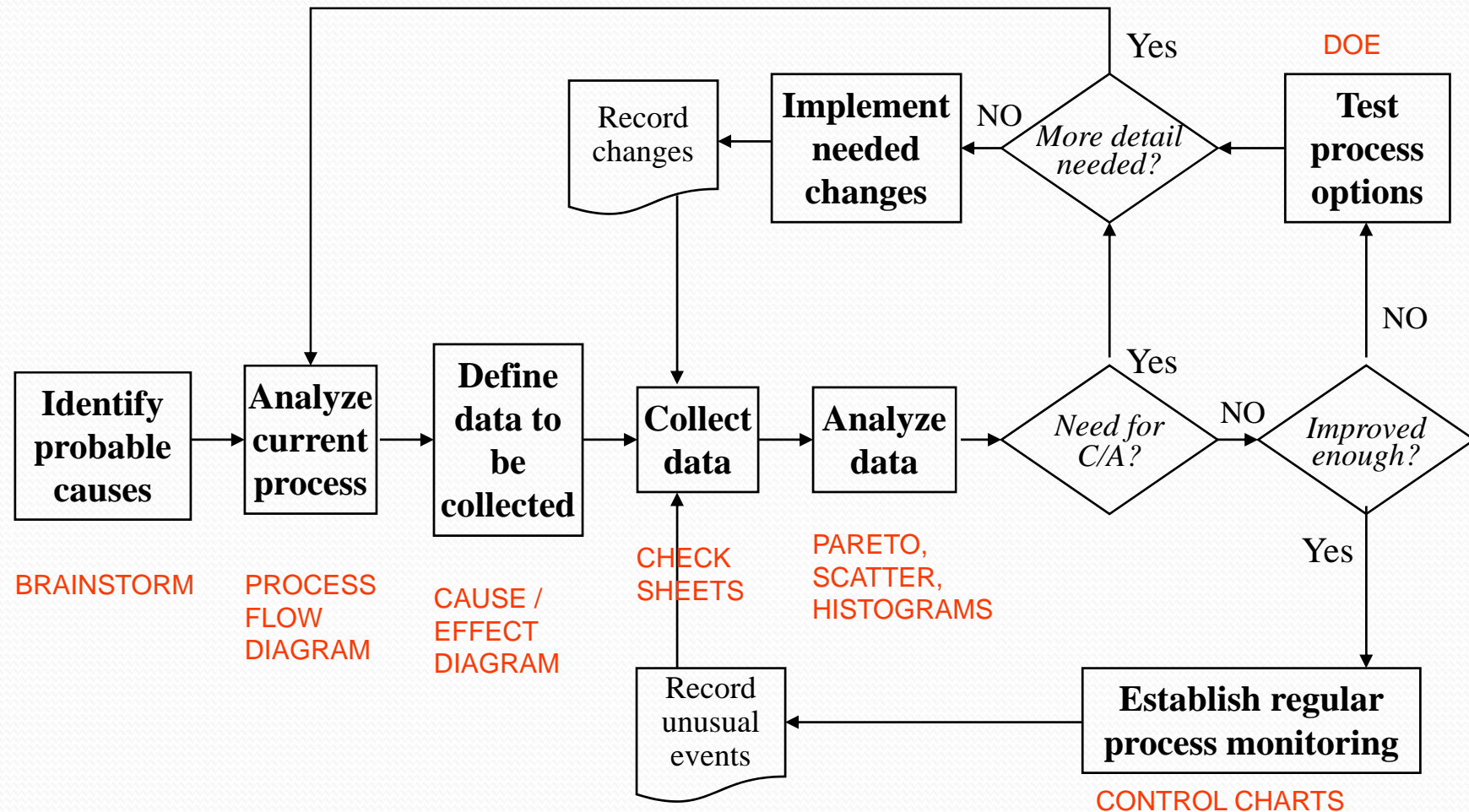


SQC Tools for investigation

1. Brain storming
2. Cause and Effect Diagram
3. Five Whys?
4. Check Sheet
5. Histogram
6. Pareto Chart
7. Defect Concentration Diagram
8. Scatter Diagram
9. Fault tree analysis
10. Design of Experiments
11. Control Charts



Investigation using SQC tools

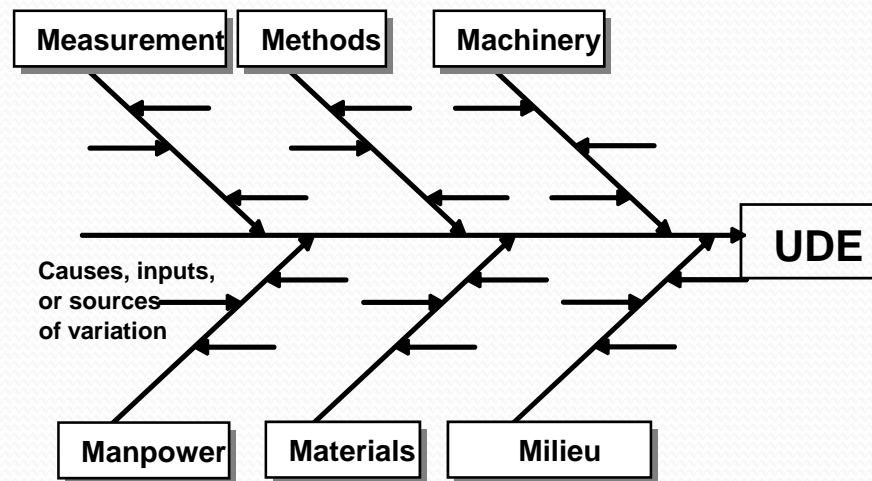




Cause & Effect Diagram

Ishikawa / Fishbone Template

- Developed by Kaoru Ishikawa
- Used to explore potential causes (6 M's) that can result in single undesirable effect (UDE).
- Potential causes arranged according to hierarchy
- Helps in identifying potential problem areas under each of 6 M's



UDE is an **Un-Desirable Effect**



Factors to be explored for 6 M's

- **Man Power**
 - Skill, knowledge, competency and attitude
 - Adequacy of supervision & support
 - Clarity about job role
 - Experience, training
 - Shift in which the activity was done
 - Conducive work environment?
 - Availability of tools / equipment

- **Machine**
 - Age of equipment or machine
 - Maintenance history
 - Was machine operating correctly?
 - Machine capability
 - Operating parameters
 - Recent changes





Factors to be explored for 6 M's

- **Material**

- Change in Source of material
- Change in process
- Age of material v/s stability
- Test results at incoming stage / re-test
- Material packing
- Storage condition
- Correctness of Quantity
- Quality trends



- **Method**

- Is the process well defined?
- Critical control points
- Adequacy of control parameters
- Robustness of the process
- Process capability
- Recent changes if any
- Deviations in execution
- Trend analysis of process parameters
- Safety mechanisms & challenges





Factors to be explored for 6 M's

- **Milieu (Environment)**

- Control of Environmental conditions (Temp / RH)
- Impact of environmental conditions on the processes
- Impact of environmental conditions on the materials



- **Measurement**

- Method validation- Specificity & robustness
- Analyst training
- Equipment calibration
- Standards used
- Frequency of inspection
- Other analysis done along with the failing batch
- Execution of methodology

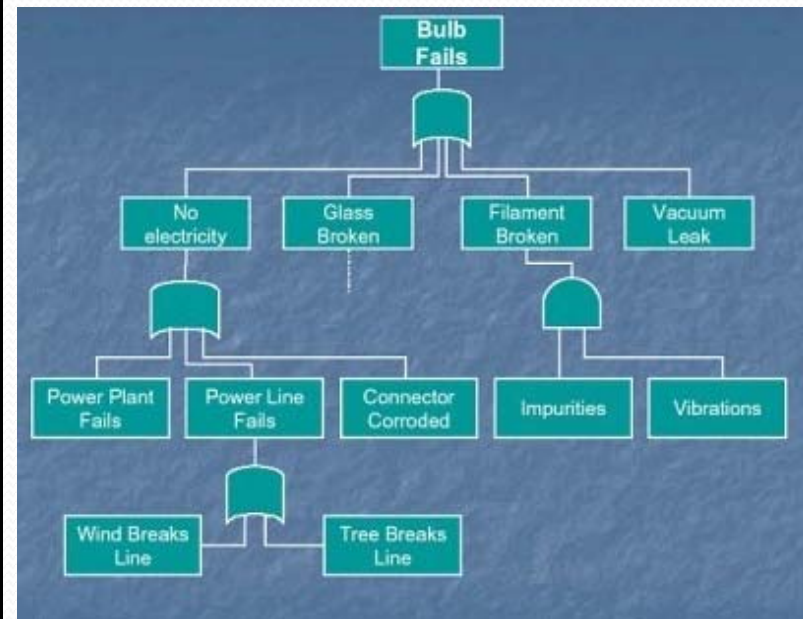




Fault Tree Analysis

Fault tree analysis is a graphical representation of the major faults or critical failures associated with a product, the causes for the faults, and potential countermeasures. The tool helps identify areas of concern for new product design or for improvement of existing products. It also helps identify corrective actions to correct or mitigate problems. Fault tree analysis is useful both in designing new products/services or in dealing with identified problems in existing products/services. As part of process improvement, it can be used to help identify root causes of trouble and to design remedies and countermeasures.

FTA Template





Five Whys?

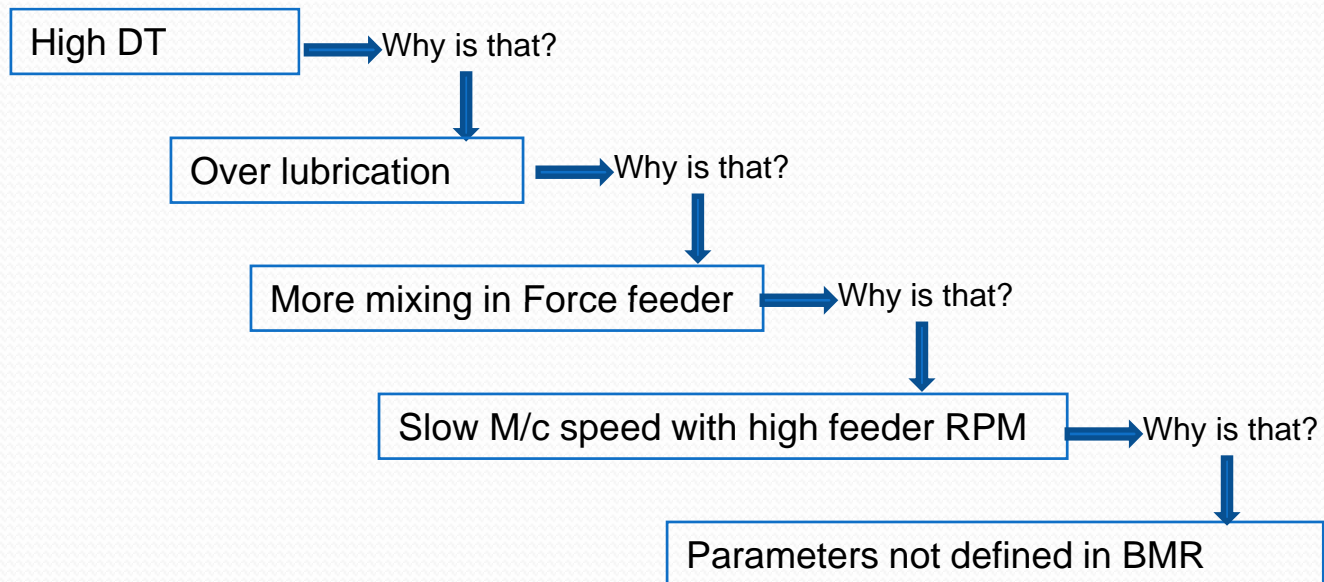
- The **5 Whys** is a questions-asking method used to explore the cause/effect relationships underlying a particular problem.
- Ultimately, the goal of applying the 5 Whys method is to determine a root cause of a defect or problem.
- Keep asking Why till you reach root cause



Five Why example

Problem : Dissolution failure in tablets

Why it has happened ?





Critical information to be reviewed

- Process flow
- Development report
- Forced degradation study & degradation profile
- Past history
- Material usage / left over stock reconciliation
- Critical process parameters & controls
- Trends of process parameters, process timing, hold time
- Yields
- Machine logs
- Distribution records
- Quality trends
- Stability data (exhibit & commercial batches)
- Method validation & transfer data



Corrective & Preventive Actions



What is CAPA?

- CORRECTIVE ACTION
 - Action to eliminate the cause of a detected non-conformity or other undesirable situation
 - Corrective action is taken to prevent recurrence of non-conformity
- PREVENTIVE ACTION
 - Action to eliminate the cause of a potential non-conformity or other undesirable potential situation.
 - Preventive action is taken to prevent occurrence of potential non-conformity

(ISO 9000:2005, ICH Q-10)



CAPA [21CFR 820.100] Includes Actions Needed To:

- Correct (“correction”) nonconforming product and other quality problems
- Prevent recurrence (“corrective action”) of nonconforming product and other quality problems
- Eliminate the cause of potential (“preventive action”) nonconforming product and other quality problems



Examples

- Problem : Twinning of tablets
- Correction: Sorting of twin tablets by inspection
- Corrective action: Standardization of coating parameters and fixing recipes to eliminate the root cause of improper rolling of tablets during initial spray.
- Preventive action : Modification of shape of tablets which require coating to eliminate flat surfaces



Regulatory requirements

- ❑ **ICH Q10: Pharmaceutical Quality System**
 - ❑ **3.2.2 Corrective Action and Preventive Action (CAPA) System**
 - **CAPA preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.**



Investigation report



What should be included?

- Header information
- Problem definition
- Discussion on analytical results / observations
- Summary of data reviewed
- Conclusions based on data review
- Experimental plan
- Summary of results of experiments
- Discussion & Conclusion of experiment results
- Final conclusion about root cause
- Corrective & Preventive actions
- Batch disposition



Problem definition

- Use correct technical terminology
- Describe observed results along with the limits
- Include extent of the problem



Discussion of analytical results and observations

- Original Test results
- Repeat analysis results
- Results of experimental testing
- Results of related samples (control samples, other batches analyzed together etc)
- Observation of the complaint samples
- Discussions and conclusions based on analysis of results



Summary of data review

- Trend data of quality parameters
- Stability data
- Trend of Manufacturing parameters
- Process timings and hold times
- Equipment usage
- Cleaning history / line clearances
- People deployed in operations
- Materials used
- Environmental conditions



Conclusions of data review

- Provide data analysis
- Scientific justification
- Include both positive and negative conclusions
- Collect more data if data collected earlier is not resulting definite conclusion or suggest review of some other parameters not seen earlier.



Experimental Plan

- Scientific rationale & purpose of experiment
- Description of experiments and measurement methods
- Expected outcomes



Discussion of results & evaluation

- Compare the results with expected results
- Discussion of the findings
- Conclusions based on the evaluation of the results and scientific rationale
- Need for additional experimentation if conclusion is not reached
- Conclusion about root cause or probable causes



CAPA

- Identification of corrective actions to eliminate identified root cause or probable causes
- Identification of Preventive actions to eliminate other potential non-conformities
- Target dates of completion
- Evaluation of effectiveness of CAPA



Actions on the batch/es

- Impact assessment
- Decision about the involved batch/es
- Actions to salvage if any
- Actions for safety of the consumers



Failure investigation

Case study



Problem definition

- All six units failed in dissolution test



Collection & evaluation of the data

- Analytical data
- Changes, deviation and incidents
- Other test results
- Equipment calibration
- Analytical solution stability
- Process parameters (granulation end point & time)
- Review of key raw materials
- Quality data trend of key raw materials



Data analysis

- Dissolution results
- Disintegration result – higher side
- Cause of failure
 - Change in key raw material vendor – lactose
 - Particle size distribution is out of trend
 - Ampere load achieved early, when compared to recommended procedure in granulation stage
 - Operator run the machine manually to meet the recommended time mentioned in the procedure
 - Over kneading in granulation stage resulting in hard granules



Improvement & control measure

- CAPA
 - Manual run option removed
 - Procedure changed from recommended time for granulation to ampere load achievement
 - Trial run before proceeding for change in key raw materials



Failure investigation

Case study -2



Problem definition

- Microbial failure in finished product
- Submerged colonies observed in soya bean casein agar plates
- TNTC in bacterial count



Collection & evaluation of the data

- Review of microbial data
- Physical examination of plates
- Examination all raw materials for microbial contamination
- Review of environmental data & personal count
- Enrichment to isolate the microorganism
- Identification of the culture
- Verification of standard and reagent used
- Simulation experiment results



Data analysis

- Microbial growth appeared by pour plate technique
- No growth in enrichment media
- No microbial growth if it is filtered
- Cause of failure
 - Method not suitable for the formulation
 - Reaction of product residue with media ingredient gives colony like growth structure



Improvement & control measures

CAPA

- Change of method
 - Selection of suitable/compatible media with the product



Any Questions?

