Batch failure investigation

Conference Document| February, 2018

Investigation is an important element of pharmaceutical quality

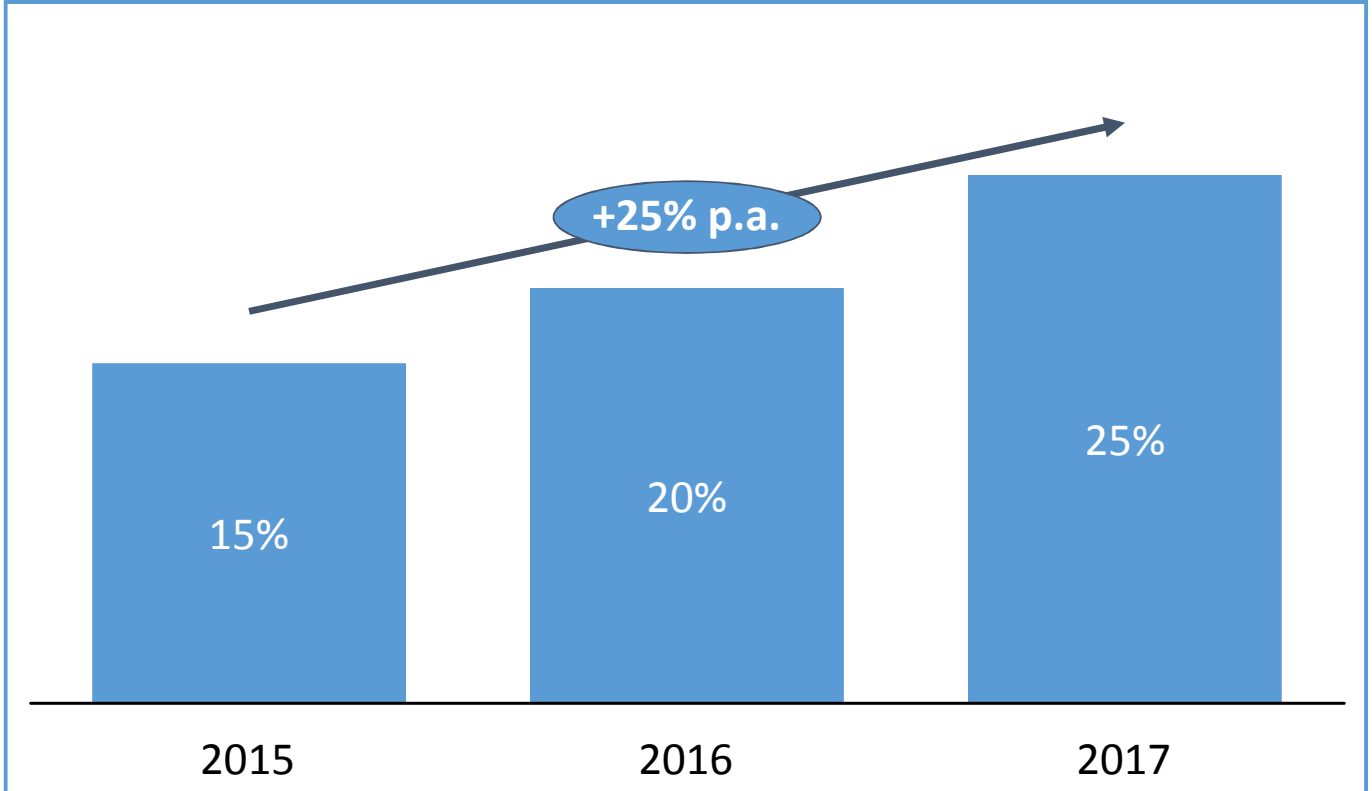
> To be meaningful, the (OOS) investigation should be ***thorough, timely, unbiased, well-documented, and scientifically sound***
>
> **– US FDA Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production**

> 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
>
> **– ICH Pharmaceutical Quality system Q10**

> Among the essential elements of a well established Quality Management System (QMS), deviation handling plays a ***key role in assuring quality in products and by contributing to continuous improvement***
>
> **– WHO guidelines for deviation handling and quality risk management**

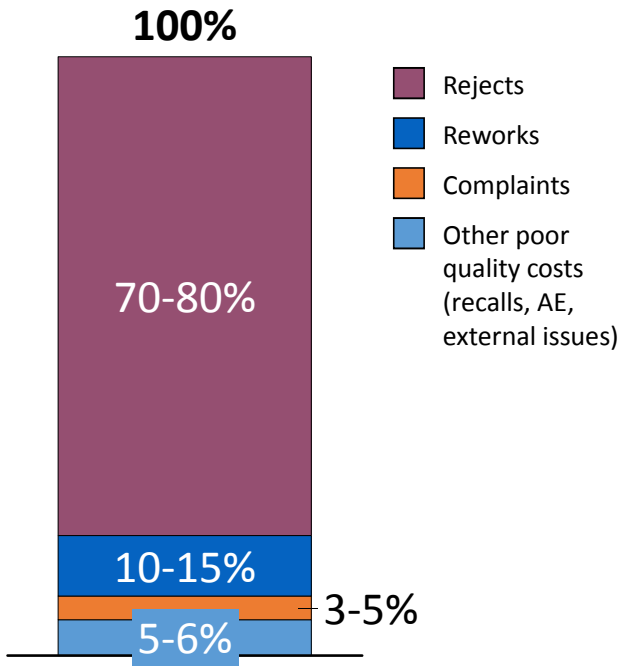
Product quality related investigations have been one of the leading contributors to non-compliance observations and poor quality costs

Contribution to Warning Letter observations *(approx %)*



Contribution to poor quality cost[2] *(%)*

Indian pharma site example

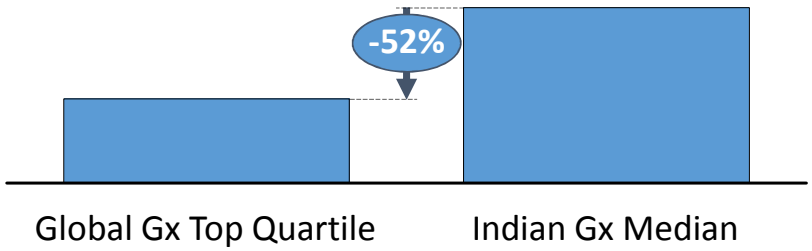


1 Analysis of FDA WL over the last 3 years

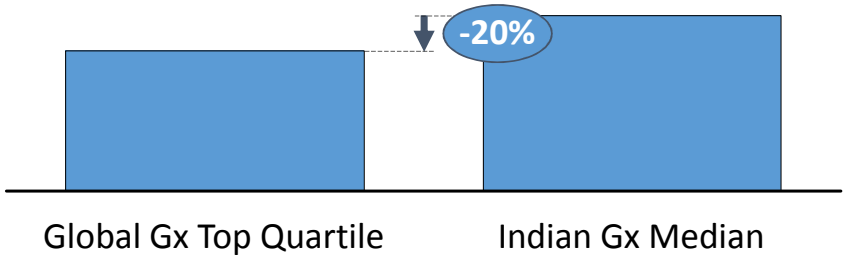
2 Poor Quality costs are costs related to rejects, reworks, complaints, adverse events, recalls and other related to production failure or external issues

Indian pharmacos lag behind global benchmarks in batch failures & quality of investigations

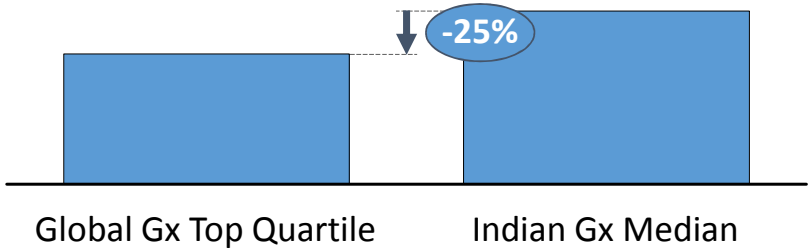
Total rejected batches (%) - Formulations



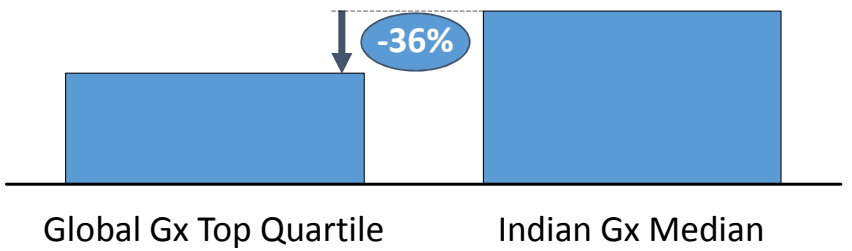
Investigation cycle time (days)



CAPAs with PAs (%)



Investigations over 30 days (%)



SOURCE: McKinsey POBOS benchmarks

Indian pharmacos have face several challenges in batch failure investigation

NOT EXHAUSTIVE & DISGUISED

Fundamental gaps in product quality	Gaps in investigation process	Inability to determine root cause	Managerial & Cultural issues
Illustrative observations in audits/inspections			
"Attributed the failures to product degradation from the process, but you failed to identify the specific impurities or their root causes"	*"…written procedures do not adequately address the need to investigate anomalies, unexpected events, or out-of-trend results"*	*"…ignored aberrant analytical test results rather than investigating them, determining the root cause, & implementing appropriate corrective actions"*	*"The management review process was deficient, the meetings stated that results were satisfactory; despite there being an obvious adverse trend increase"*
"Multiple batches of product failed to meet finished product specifications, including active ingredient content"	*"Investigations did not include hypothesis for test failure before retesting"*	*"Firm invalidated many out-of-specification (OOS) assay results without sufficient investigation to determine the root cause of the initial failure"*	*"… gloves are worn during these critical interventions, using non-integral gloves for aseptic processing is an unacceptable practice. It is a direct risk to product sterility"*

SOURCE: MHRA GMP inspection deficiency data trend 2016; Analysis of FDA WLs from 2015-2017

5 major areas to improve batch failure investigations

NOT EXHAUSTIVE

1. **Improve fundamental product quality by taking an end-to-end lifecycle approach**
2. **Establish a harmonized best practice process, roles & responsibilities, and investigation tool-kit**
3. **Improving fundamental understanding of unit operations and root-cause assessment capabilities in the organization**
4. **Use the right combination of leading & lagging indicators coupled with a strong governance mechanism**
5. **Build a culture of Right-First-Time and getting to the root-cause**

1 Lifecycle approach is critical to product quality

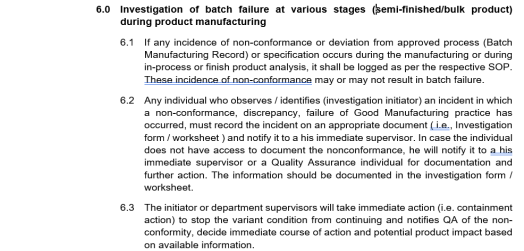
Stage 1: Process design	Stage 2: Process Qualification	Stage 3: Continuous process verification
Commercial manufacturing process defined based on knowledge gained through development & scale-up activities	Process design **evaluated to determine if it is capable of reproducible** commercial manufacture	**Ongoing assurance** gained during routine production that the process remains in a state of control

Covered in detail in the Process Validation guidelines to be released on Day 2

SOURCE: Process validation guidelines by regulatory agencies

2 Best practices in batch failure investigations need to be implemented

Key areas	Description
1 Best practice guideline	• Developed overall guidance on batch failure investigation for laboratory and manufacturing
2 Investigation checklist	• Standardized the investigation criteria for common test failures through 13 checklists
3 Governance mechanism	• Defined RACI matrices for defining governance and escalation mechanism

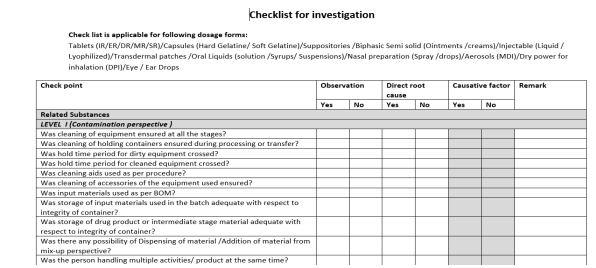


6.0 Investigation of batch failure at various stages (semi-finished/bulk product) during product manufacturing

6.1 If any incidence of non-conformance or deviation from approved process (Batch Manufacturing Record) or specification occurs during the manufacturing or during in-process or finish product analysis, it shall be logged as per the respective SOP. These incidence of non-conformance may or may not result in batch failure.

6.2 Any individual who observes / identifies (investigation initiator) an incident in which a non-conformance, discrepancy, failure of Good Manufacturing practice has occurred, must record the incident on an appropriate document (i.e., Investigation form / worksheet) and notify it to a his immediate supervisor. In case the individual does not have access to document the nonconformance, he will notify it to a his immediate supervisor or a Quality Assurance individual for documentation and further action. The information should be documented in the investigation form / worksheet.

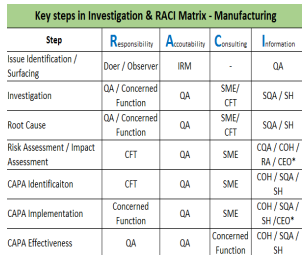
6.3 The initiator or department supervisors will take immediate action (i.e. containment action) to stop the variant condition from continuing and notifies QA of the non-conformity, decide immediate course of action and potential product impact based on available information.



Checklist for investigation

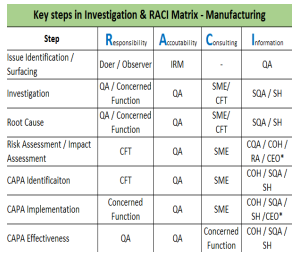
Check list is applicable for following dosage forms:
Tablets (IR/ER/DR/MR/SR)/Capsules (Hard Gelatine/ Soft Gelatine)/Suppositories /Biphasic Semi solid (Ointments /creams)/Injectable (Liquid / Lyophilized)/Transdermal patches /Oral Liquids (solution /Syrups/ Suspensions)/Nasal preparation (Spray /drops)/Aerosols (MDI)/Dry power for inhalation (DPI)/Eye / Ear Drops

Check point	Observation		Direct root cause		Causative factor		Remark
	Yes	No	Yes	No	Yes	No	
Related Substances							
LEVEL I (Contamination perspective)							
Was cleaning of equipment ensured at all the stages?							
Was cleaning of holding containers ensured during processing or transfer?							
Was hold time period for dirty equipment crossed?							
Was hold time period for cleaned equipment crossed?							
Was cleaning aids used as per procedure?							
Was cleaning of accessories of the equipment used ensured?							
Was input materials used as per BOM?							
Was storage of input materials used in the batch adequate with respect to integrity of container?							
Was storage of drug product or intermediate stage material adequate with respect to integrity of container?							
Was there any possibility of Dispensing of material /Addition of material from mix-up perspective?							
Was the person handling multiple activities/ product at the same time?							



Key steps in Investigation & RACI Matrix - Manufacturing

Step	Responsibility	Accountability	Consulting	Information
Issue Identification / Surfacing	Doer / Observer	IRM	-	QA
Investigation	QA / Concerned Function	QA	SME/ CFT	SQA / SH
Root Cause	QA / Concerned Function	QA	SME/ CFT	SQA / SH
Risk Assessment / Impact Assessment	CFT	QA	SME	CQA / COH / RA / CEO*
CAPA Identificaiton	CFT	QA	SME	COH / SQA / SH
CAPA Implementation	Concerned Function	QA	SME	COH / SQA / SH /CEO*
CAPA Effectiveness	QA	QA	Concerned Function	COH / SQA / SH



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CAPA Implementation	Concerned Function	QA	SME	COH / SQA / SH /CEO*
CAPA Effectiveness	QA	QA	Concerned Function	COH / SQA / SH

3 Need to build fundamental understanding of unit operations & root cause assessment capability in middle managers

Gaps in fundamental understanding & investigative capabilities in unit operations

> *Unable to get to the root cause of deviations…they know what they need to do but in case of deviation do not know "why"*
>
> *– Head of Ops*

> *Do not understand the critical process parameters and their impact on quality*
>
> *- Head of Quality*

> *Unable to get to the root cause…do not have the analytical & investigative mindset*
>
> *- Site Head*

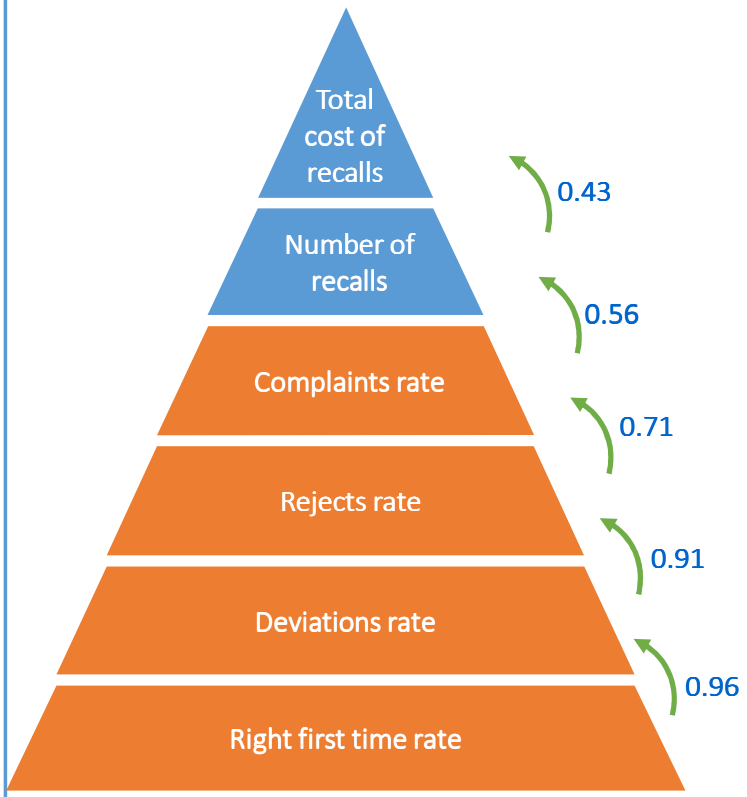
> *Do not get the right guidance from supervisor when we face issues. Who do we ask?*
>
> *~ Shopfloor operator*

Skills to be developed

- ***Understanding of Critical Process Parameters (CPPs)*** for the unit operations and their linkage to Critical Quality Attributes (CQA)
- Ability to resolve complex **issues that lead to non-conformances and non-compliances**
- **Conducting Root cause assessment through application of Problem solving tools, and methodologies**

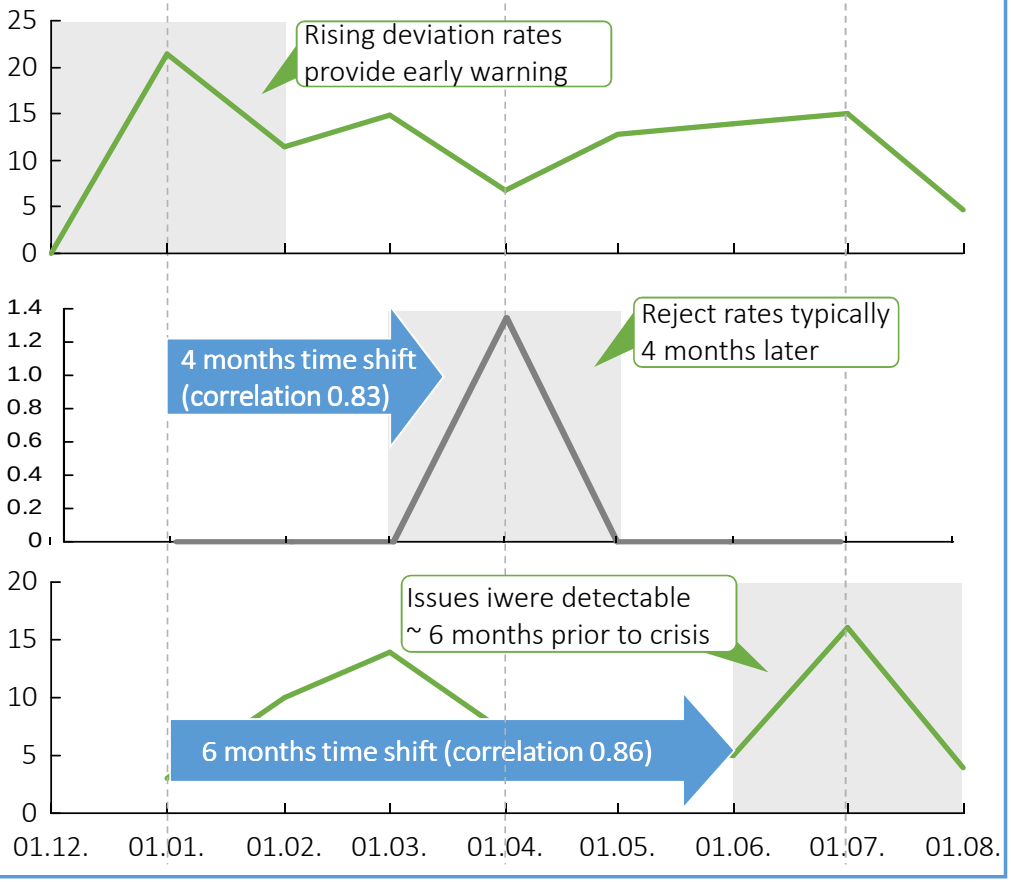
4 Leading indicators help us connect operations fundamentals and their influence on Quality & Compliance outcomes

High degrees of correlations found along pyramid of incidents…



1 Correlation coefficients based on data samples from 14 production sites

… allowing management to launch remediation efforts before business / customer impacting



SOURCE: McKinsey POBOS benchmarks

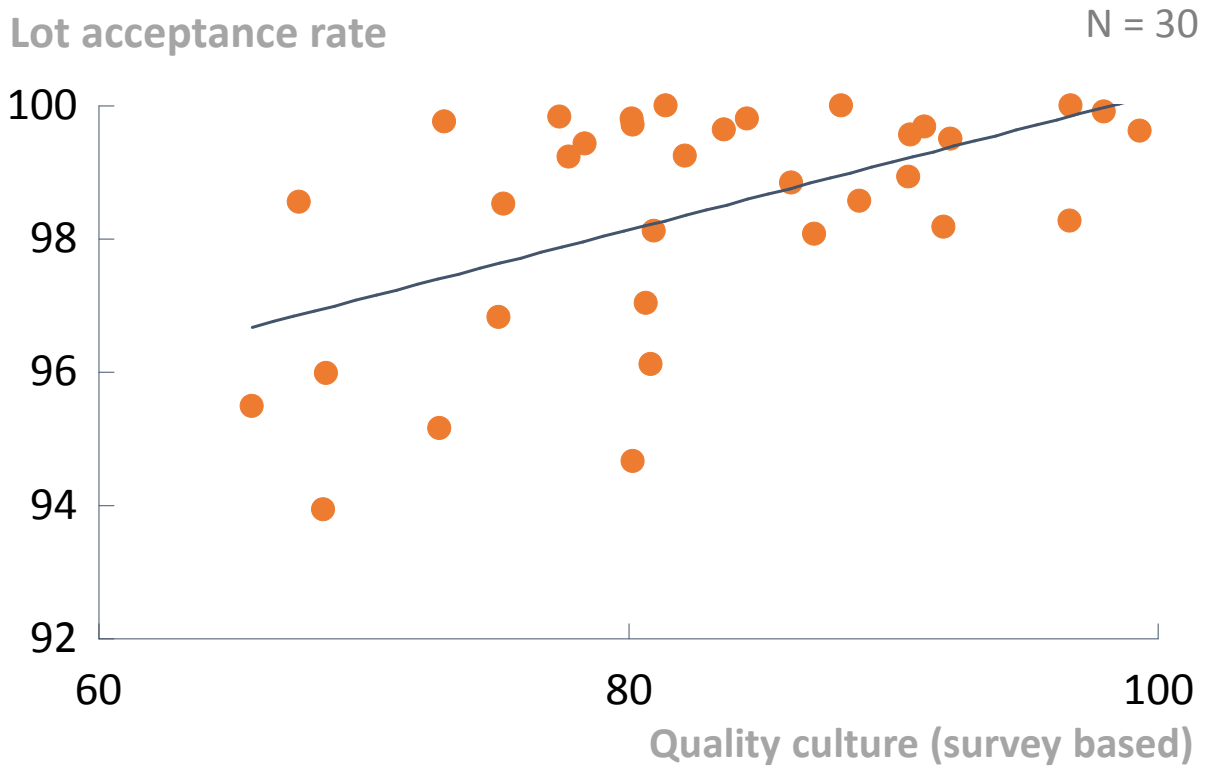
5 Culture matters: Quality culture drives ~30% of lot acceptance rate

Cost of poor quality vs. quality culture

$R^2 = 0.29$

$P = 0.001$

Similar associations seen with complaints, rejects & reworks etc.



Need to build a Right-First-Time mindset & Focus on identifying the root cause

SOURCE: McKinsey POBOS benchmarks

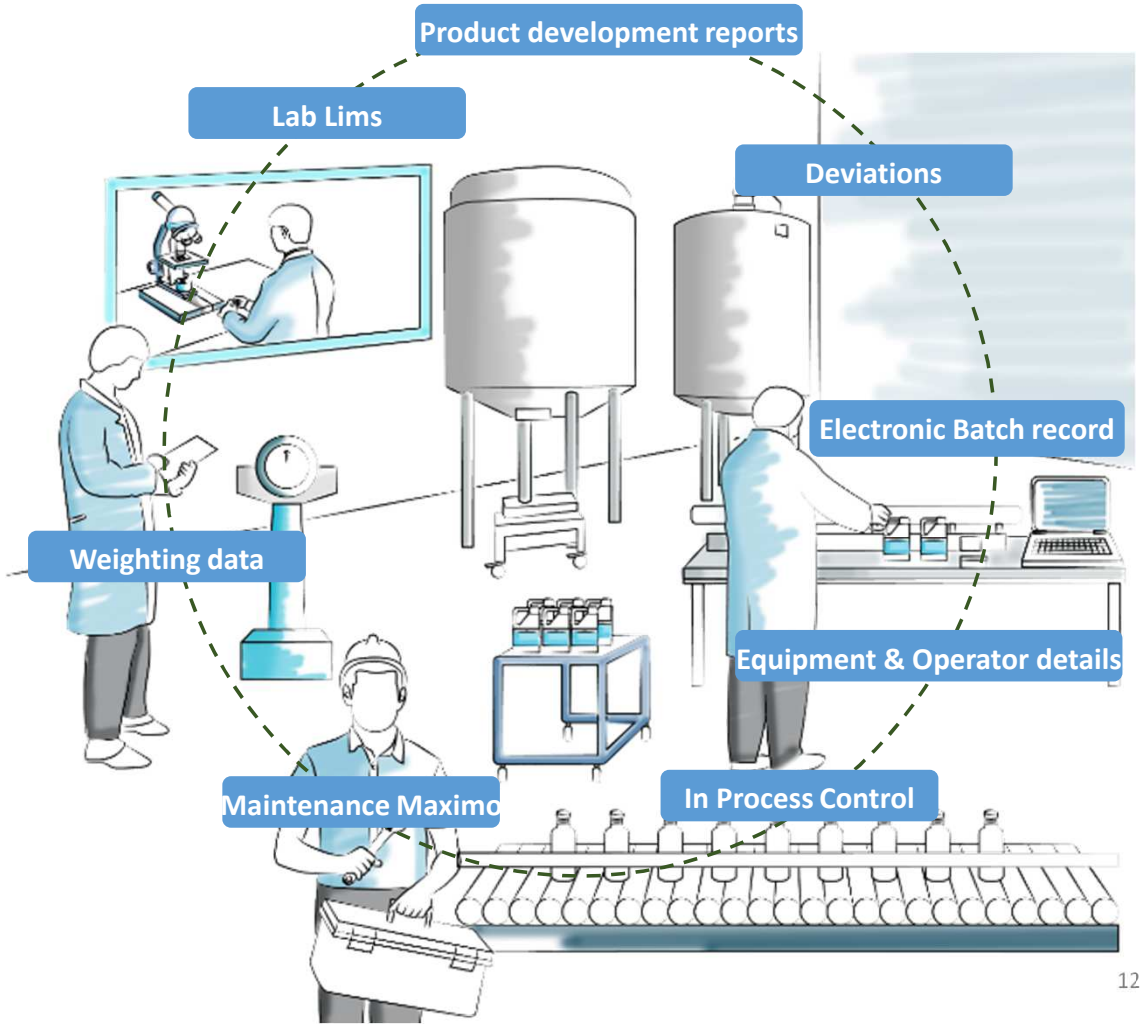
Use of Advanced Analytics: By connecting & analyzing existing data, we can identify risk factors for deviations / OOS

10+ data sources,
can potentially be tapped to capture manufacturing / quality data / product development data

2,000+ variables
- primary and secondary, can be analysed

10+ algorithms
can be use to identify key drivers & root causes

25+ risk factors
can be generated from the machine learning algorithm

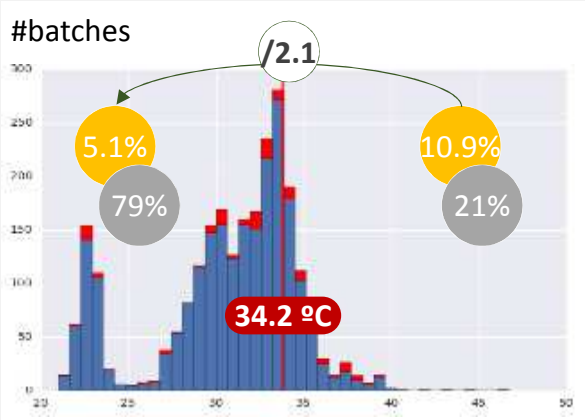


Example: Granulation Temperature correlated with deviations

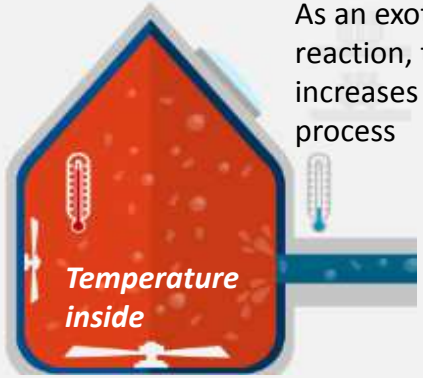
NUMBERS ANONYMISED

x% Probability of deviations x% Number of batches x Risk ratio

Statistical analysis



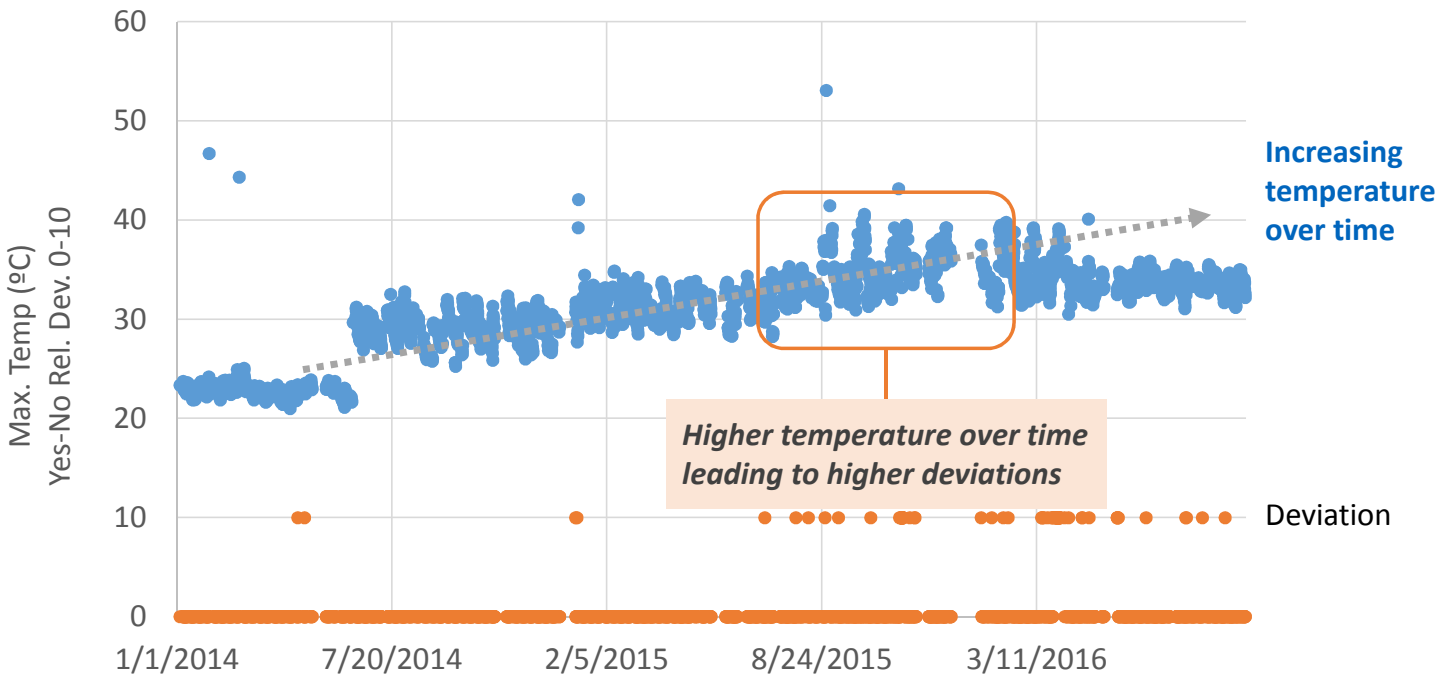
Granulation step



As an exothermic reaction, temperature increases during the process

Example of deep dive with experts & Next steps

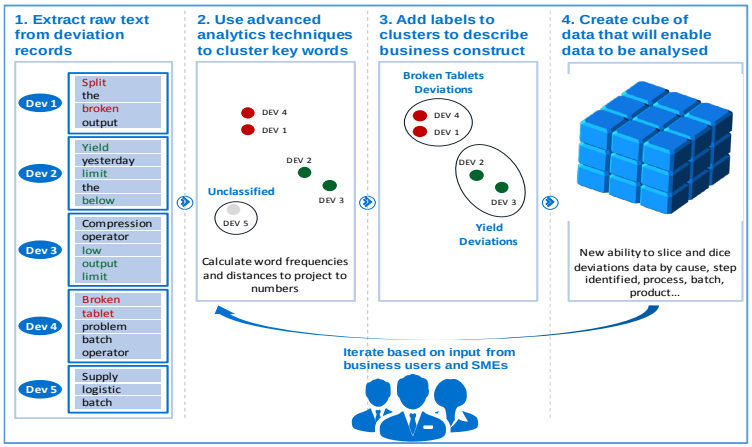
Maximum temperature



Example: Natural Language Processing (NLP) enables reconstruction of free text from available data to help in investigations

Data captured in system Insight after NLP

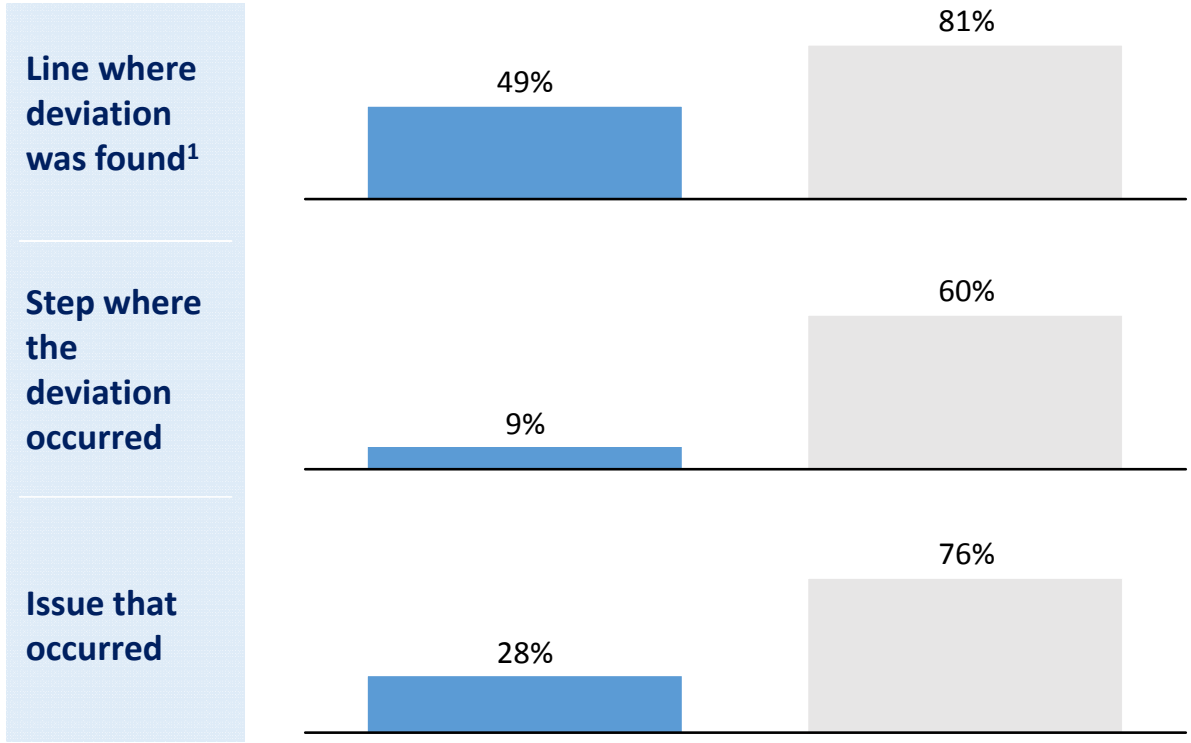
Use of NLP on Dev@com information logged in free text in local language



Iterative process used

- **Clean text** to prepare for processing
- Calculate **word frequencies** and **similarity between words**
- **Cluster and label deviations** based on similarity between words

Reconstruction of complete deviation data-cube



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Batch failure investigation

Sub-group 4

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IPA QF sub-group 4 focused on Batch failure investigations

Company name	Name	Pic
LUPIN	Pradeep Chakravarty	
Zydus dedicated to life	S V Gopalakrishnan	
Dr.Reddy's	K V Raghu	

Company name	Name	Pic
torrent PHARMA	Jayendra Tripathi	
Cipla	Sanjay Gorana	
SUN PHARMA	Sanjay Deshmukh	

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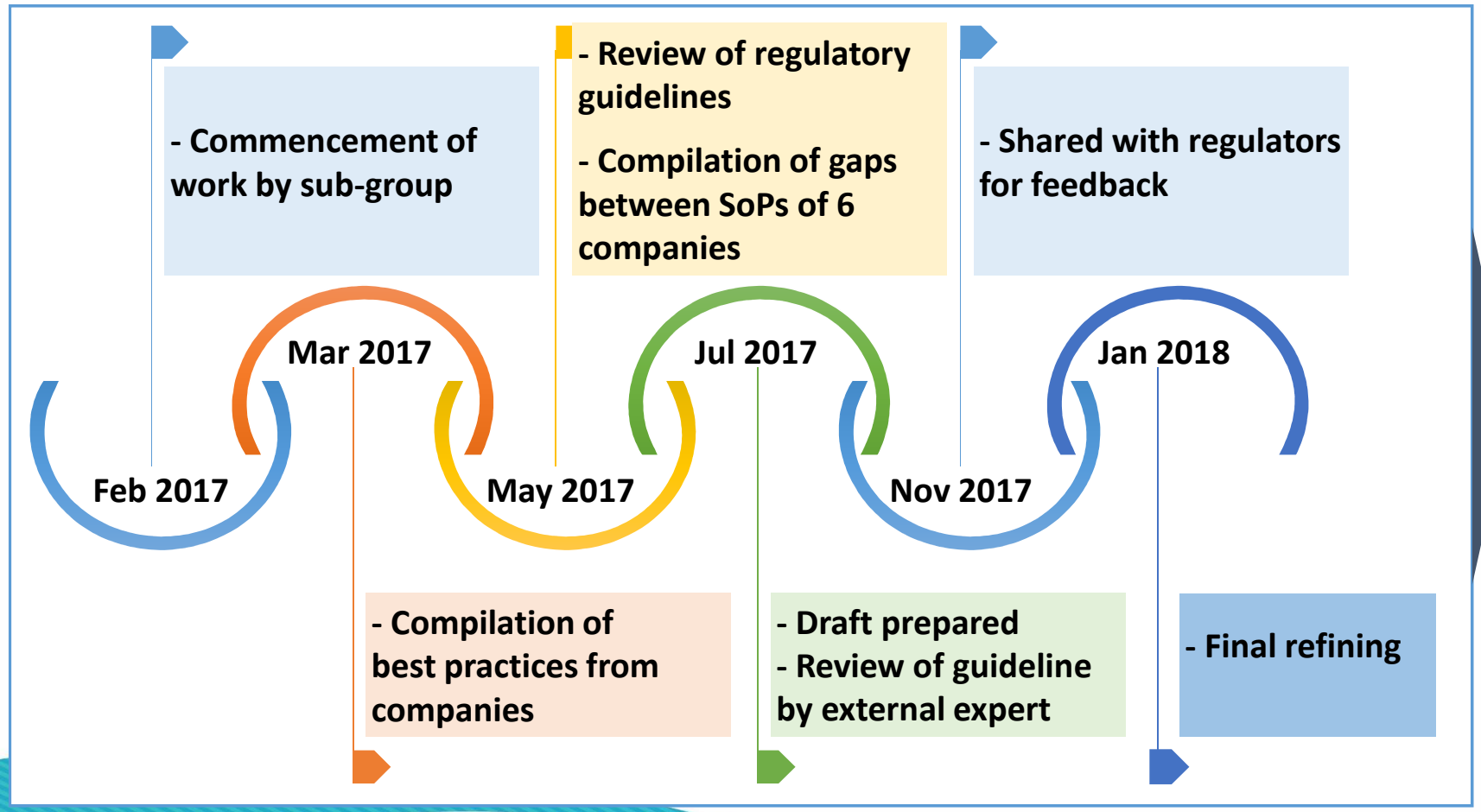
IPA subgroup 4 followed a structured process to develop the guideline



- 6+ individuals directly involved in writing the guidelines
- Extensive expert involvement for review and refinement

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A comprehensive guideline is designed covering the entire investigation process

Guidance for batch failure investigation

- Includes all potential batch failure causes at "**any stage of manufacturing**" (deviations) & **"quality control"** (OOS) and **post distribution** including stability failures and those coming from market complaints etc.
- Provides guidance for best practices for **both laboratory and manufacturing investigation**

All processes for investigation considered

Batch Failure Investigation

- Lab Error
- Manufacturing Process Issue

Phase I

- Obvious lab error

Phase II

- Hypothesis based Lab Investigation
- Manufacturing Investigation

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Laboratory Investigation							
Investigation outcome	**Company-1**	**Company-2**	**Company-3**	**Company-4**	**Company-5**	**Company-6**	**Proposal**
Root Cause Identified (Obvious Laboratory Error definitevely attributable)	Retesting in Triplicate	Retesting in 5 replicates for most of the tests	Retesting in duplicate	Single analysis	Retesting in duplicate	Retest in single as per standard analytical test procedure	Re-tesing in single.
Probable/Assignable Cause Identified	Phase-I: Re-testing in triplicate by first analyst. Phase-II: Re-testing in triplicate by two analysts.	Retesting in 5 replicates for most of the tests.	No such direct provision	Re-testing in triplicate by two analysts.	Retesting in duplicate	Retesting in 3 replicates each by two analyst.	Re-testing in triplicate by 2 anlaysts only if it's based on sound scientific rationale and proved through hypothesis studies. For commercial batches, err on the side of caution.
No root cause identified	Reject batch	Reject batch	Retesting in six replicates and decision to be taken by QA if all results pass	Re-testing in triplicate by two analysts. QA will take final decision.	For tests with numeric results - 3 replicated For qualitative Tests 7 replicates	Reject batch	Reject the batch.

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Guidance document consists of 3 areas to standardize the approach batch failure investigation across the industry

Best practice document on batch failure investigation

1

Overall guidance on batch failure investigation for laboratory and manufacturing

Generalized procedure for end-to-end handling of batch failure by standardizing approach for responding to common issues as well as situations outside SOPs

2

Dosage form wise checklists defining investigation criteria for common test failures

13 checklists to standardize the investigation criteria for dosage form specific common test failures, for e.g tablets, liquid sterile products

3

Governance and escalation mechanism

RACI matrices for defining governance and escalation mechanism both in lab and manufacturing

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1 Key highlights from guidance document for laboratory investigation

- FDA is very critical of any re-testing for batch release decisions without root cause identification. Thus, it's proposed that the **batch where root cause of failure is not identified will be rejected**
- Wherever **probable / assignable cause is identified through experimental/hypothesis testing, re-testing is allowed**. We have added a specific criteria that apart from retest results meeting acceptance criteria, there should also be closeness among the results observed. Specific guidance of RSD of the replicate results for various tests is provided
- The **decision making process for batch disposition is described separately for the commercial batches and exhibit batches**. This is based on the risk and amount of information available for these two types of scenarios

Important: Err on the side of caution in case of commercial batch disposition decision whenever probable or assignable cause is identified

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1 Key highlights from guidance document for manufacturing investigation

- The Critical Process Parameters **(CPP)** & Critical Quality parameters (**CQA)** must be defined during product development for faster & accurate investigation.
- The **checklist driven approach** will help in preserving the line of action to be taken during investigation
- The **process of investigation to become structured** by ensuring **investigation is conducted by a separate group** who will be a set of SMEs brought together depending on the type of investigation
- In-depth **review of batch data report / alarm report / event report (audit trail)** should be done in order to help evaluate any failure in phase II investigation
- **Brain storming and personal interview** must be completed and documented at an earliest i.e. in level I investigation
- **On site visit by the investigation team** preferably on the same day will be helpful to collect first-hand information of failure

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1 Batch Failure Investigation - Laboratory

Commercial batch

- Root cause identified – Remove the cause and re-analyze. Initiate CAPA to eliminate root cause in further testing.
- Probable cause identified – Verify if probable cause is clearly proven and attributable to OOS. If yes, re-analyze. Always err on the side of caution. Initiate CAPA to eliminate probable cause in further testing.
- No root/probable cause identified – OOS stands valid. Assess if this is one off case. If repetitive, method shall be looked into.

Stability batch

- Root cause/probable cause identified – If not concluded within 3 days, inform concerned regulatory agency (FAR). Investigate whether cause is applicable to other batches. Further action is based on this assessment. May add additional time points to stability program for further monitoring. Initiate CAPA to eliminate cause.
- No root/probable cause identified – All above actions. Consider additional testing of retention samples. Take market action as warranted based on all available data. Initiate CAPA based on outcome of overall investigation.

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1 Batch Failure Investigation - Manufacturing

Commercial batch

- Root cause identified – Reject the batch. Initiate CAPA and proceed with further manufacturing.
- Probable cause identified – Reject the batch. Initiate CAPA and closely monitor further batches to ensure CAPA effectiveness.
- No root/probable cause identified – Reject the batch. Assess if this is one off case. Manufacture further batches under close monitoring and extensive analysis.

Stability batch

- Root cause/probable cause identified – Inform concerned regulatory agency (FAR). Investigate all batches within expiry at site and on the market whether the same cause is applicable. Consider additional testing of retention samples. Take market action as warranted based on all available data. Initiate CAPA based on outcome of overall investigation.
- No root/probable cause identified – All above actions. Stop further manufacturing. Refer product to R&D.

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2 The consolidated final guidance lays out investigation approach both for manufacturing and lab along with 13 detailed checklists

List of checklists included in the guidance

- **Checklist for common test failures across all dosage forms:**
  - Assay
  - Relates Substance
- **Checklist for common test failures for tablets:**
  - CU – Tablets/capsules
  - Weight variation
  - Disintegration
  - Dissolution
  - Hardness
  - Thickness
  - Friability
- **Checklist for common test failures for liquid sterile products (Eye/Ear Drops/ Injectable):**
  - Content uniformity
  - Foreign particles
  - Glass particles
- **Separate checklist for lab investigation**

Sample checklists

Checklist for investigation

Check list is applicable for following dosage forms:
Tablets (IR/ER/DR/MR/SR)/Capsules (Hard Gelatine/ Soft Gelatine)/Suppositories /Biphasic Semi solid (Ointments /creams)/Injectable (Liquid / Lyophilized)/Transdermal patches /Oral Liquids (solution /Syrups/ Suspensions)/Nasal preparation (Spray /drops)/Aerosols (MDI)/Dry power for inhalation (DPI)/Eye / Ear Drops

Check point	Observation		Direct root cause		Causative factor		Remark
	Yes	No	Yes	No	Yes	No	
Related Substances							
LEVEL I (Contamination perspective)							
Was cleaning of equipment ensured at all the stages?							
Was cleaning of holding containers ensured during processing or transfer?							
Was hold time period for dirty equipment crossed?							
Was hold time period for cleaned equipment crossed?							
Was cleaning aids used as per procedure?							
Was cleaning of accessories of the equipment used ensured?							
Was input materials used as per BOM?							
Was storage of input materials used in the batch adequate with respect to integrity of container?							
Was storage of drug product or intermediate stage material adequate with respect to integrity of container?							
Was there any possibility of Dispensing of material /Addition of material from mix-up perspective?							
Was the person handling multiple activities/ product at the same time?							

Checklist for Content Uniformity/Weight Variation

Check list is applicable for following dosage forms:
Tablet/Capsule

Check point	Observation		Direct root cause		Causative factor		Remark
	Yes	No	Yes	No	Yes	No	
Content uniformity							
LEVEL I							
Was input materials used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
Were the quantities of all the APIs used as per BOM?							
Were all the manufacturing steps followed as per BMR?							
Were Process parameters in line with the specified range in BMR?							
Were the Environmental conditions and control (Temperature/RH/) as per requirements? (During manufacturing and storage)							
Was storage of input materials used in the batch as per requirement?							
Was the storage condition of product at intermediate stage satisfactory?							
Was the storage container of product at intermediate stage satisfactory?							
Was there any possibility of spillage of Dispensing of material especially binders?							
Were granulation parameters, viz. mixing time, granulation end point within validated limit?							
Was Compression/Filling M/c machine speed run at validated speed?							

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2 Checklists

Check point	Observation		Direct root cause		Causative factor		Remark
	Yes	No	Yes	No	Yes	No	
Assay							
LEVEL I							
Was input materials used as per BOM?							
Was quantity of API used as per BOM?							
Were the quantities of all the excipients used as per BOM?							
LEVEL II							
Was there any deviation related to this product? If so, was this deviation a cause for failure?							
Sampling							
• Was right sampling technique used?							
Was right sampling tool used?							
LEVEL III							
Human Errors							
Is there clarity of instructions in procedures?							
Was training adequate?							
Was supervision adequate?							
Was person experienced?							
LEVEL IV							
Was Potential cause of segregation during manufacturing process and handling							
Was there any modification in the equipment?							

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3 RACI matrices have been defined for governance and escalation mechanisms in lab and manufacturing

Key steps in Investigation & RACI Matrix - Laboratory				
Step	**R**esponsibility	**A**ccoutability	**C**onsulting	**I**nformation
Issue Identification / Surfacing	Analyst	Section Head	-	QA
Investigation	QA & QC	QC Head	ARD/ SME	SQA / SH
Root Cause	QA & QC	QA	ARD/ SME	SQA / SH
Risk Assessment / Impact Assessment	QA & QC	QA	ARD/ SME	CQA / COH / RA / CEO*
CAPA Identificaiton	QA & QC	QA	ARD/ SME	SQA / SH
CAPA Implementation	QC	QC Head	ARD/ SME	COH / SQA / SH /CEO*
CAPA Effectiveness	QC	QA	-	SQA / SH

Key steps in Investigation & RACI Matrix - Manufacturing				
Step	**R**esponsibility	**A**ccoutability	**C**onsulting	**I**nformation
Issue Identification / Surfacing	Doer / Observer	IRM	-	QA
Investigation	QA / Concerned Function	QA	SME/ CFT	SQA / SH
Root Cause	QA / Concerned Function	QA	SME/ CFT	SQA / SH
Risk Assessment / Impact Assessment	CFT	QA	SME	CQA / COH / RA / CEO*
CAPA Identificaiton	CFT	QA	SME	COH / SQA / SH
CAPA Implementation	Concerned Function	QA	SME	COH / SQA / SH /CEO*
CAPA Effectiveness	QA	QA	Concerned Function	COH / SQA / SH

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3 step process that can be followed when root cause of failure is not identifiable

Stop

- When to stop?
  - Root cause of failure can not be identified
  - Consecutive batches fail
  - % of batches failed cross the threshold limit

Start

- How to start again?
  - Reach out to R&D to understand potential reasons for batch failure
  - Plan experiments with R&D help and take trials to understand the causes
  - Manufacture and monitor the batch if process parameters are not changed
  - Go through process validation if there's a change in process parameters

Improve

- How to improve?
  - Continuous evaluation of batches.
    - Continued Process Verification
    - Trending CQAs
  - Close monitoring of CPP (Critical process parameters) and Cpk of CQAs (Critical Quality Attributes) to take preventive actions against batch failures

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The group has also drafted a set of open questions for inputs from the regulators

- At what point during the investigation one should consider immediately stopping production?
- What action should be taken in case no root cause is identified eg. Batch rejection?
- What is guidance to understand the impact of investigation results of experimental batches on previous batches and validations?
- What is the impact of batch failure with no root cause on validation status of product?