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Batch Failure Investigations

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Agenda

- Reliable Manufacturing
- Current trends/issues
- Management of incidents
- Case Studies/Example

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Reliable Manufacturing

- The output/results of the risk management process should be reviewed to take into account new knowledge and experience.
- Lifecycle events might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall).
- Risk review might include reconsideration of risk acceptance decisions (section IV.D.4).

[ICH Q9]

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Reliable Manufacturing

- Robust Product Development
- Process Understanding
- Process Capability
- Periodic Evaluation of Process
- Preventive Measures
- Effective Pharmaceutical Quality System (PQS)
- Quality Oversight

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Preventing Adverse Quality Impact

- Identify Signals
  - internal signals (e.g., OOT) before there is a drug quality consequence
  - external (voice of customer) signals, especially complaints
- Prevention
  - Implement upstream process controls to monitor output throughout operations, robust statistical sampling plans, operational supervision, and recording of anomalies as deviation
  - Such a quality culture will generally identify problems during process, before final QC stage

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Preventing Adverse Quality Impact

- When a meaningful manufacturing issue is emerging/occurring…
  - *Know when Management Escalation is needed → ensure timely communication*
  - *Prevention/Correction may require obtaining resources for root cause determinations and reinvestment in facilities.*
- Use the CAPA Program Effectively
  - Catch leading indicators of quality or production problems internally & deal with them early to help avoid external failures (e.g., complaints, FARS/BPDR, recalls)

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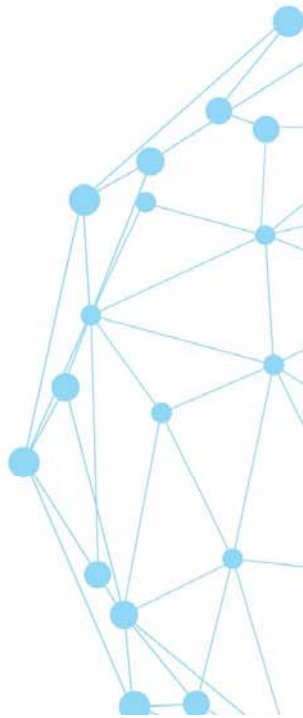
Current Trends/Findings



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Some Common Investigation-Related Findings

- Failure/OOS SOPs usually good, but not followed
- OOS's are tested into compliance
- Complaints not substantively investigated (rote process)
- Adverse complaint trend not detected or investigated
- Scope of Investigations : *isolated issue or recurring?*
- Appropriate expertise (SMEs) to investigate/diagnose/correct

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Some Common Investigation-Related Findings

- Addressing failures at contracted sites (CMO, contract lab
- Handling stability failures
- Root Cause identification and correction
- Effectiveness Checks
- Resources to make lasting correction, not patchwork
- Technology choice at launch was not really capable enough

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Moving from QC to QA

A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality. **Management's** daily decisions on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will ultimately determine the quality of the drugs that are shipped from a given facility.

[Woodcock, J and M. Wosinska, Clinical Pharmacology & Therapeutics, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage," Jan 2013

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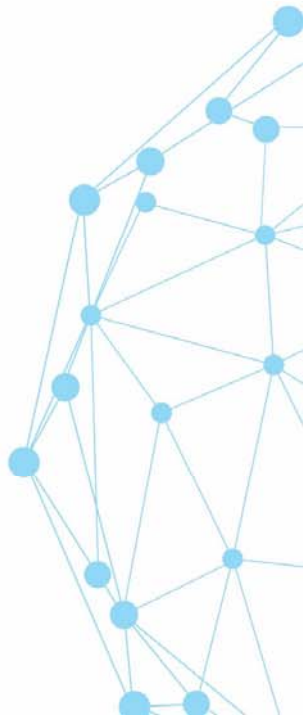
Management of Incidents



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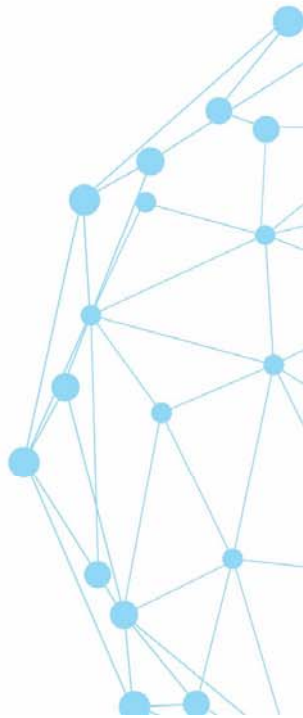
Basics of incident management

- Tools
  - ICHQ9 principles
  - CAPA
  - Kepner-Tregoe
  - 5 Whys
  - Ishikawa / fish bone
  - Failure Mode Effect Analysis
  - Fault Tree Analysis



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Successful management of batch failure investigation

- Strong Senior Management Engagement and Commitment to:
  - surface issues
  - review potentially adverse information and inquire into cause of problem
  - oversee overall adequacy of CAPA program
  - remediate identified areas of deficiency by allocating all appropriate resources

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Successful management of batch failure investigation

- Senior management
  - Is a defect viewed as ‘inconvenience’ / ‘learning opportunity’
  - ‘we are a high quality organisation, therefore we don’t have problems’ (really? – and therefore the number of issues reported is low)

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Successful management of batch failure investigation

- Senior management
  - If senior management view defects as inconvenient, shop floor will view as ‘not my problem’ / ‘bury it’.
  - Impacts patient, and ultimately impacts business
- These behavioural themes apply to other aspects of the conference – equally applies to DI and Quality culture

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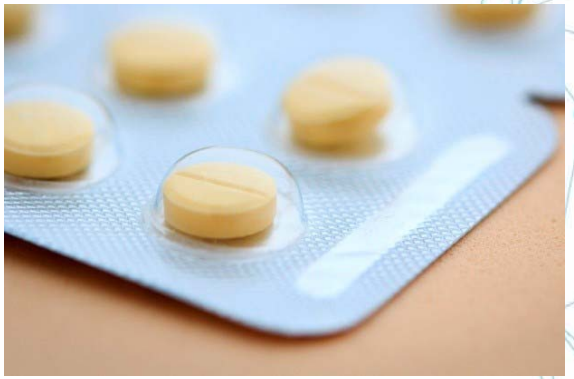
Successful management of batch failure investigation

- Shop floor
  - Do they understand their role in protecting patient health?
  - Can they ‘see the patient’ in what they do?
  - If not – that’s a training issue



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Successful management of batch failure investigation

- A written program that defines the CAPA system and its interactions with other systems
- Well qualified staff (training, education, experience) who understand the technology and failure modes. Incorporate the right SMEs into each evaluation.
- Evaluating effectiveness of the change
- Process for monitoring progress of change, & closing out once effectiveness is confirmed

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Successful management of batch failure investigation - Metrics

- Are **metrics** based on performance, or what matters to the patient?
  - ‘right first time’, ‘number of deviations over 30 days’ ‘number of open change controls’ etc – of no interest to the patient
  - ‘right before released’, quality issues which are identified, investigated and result in learning (with quality improvement as a result) are of interest to the patient
  - Learning which improves consistency, reduces risk of failure, reduces shortage are metrics which benefit both company and patient

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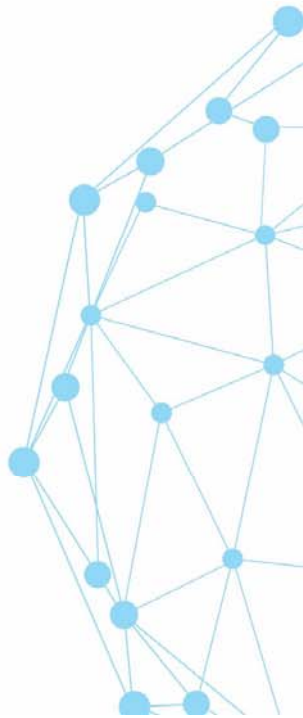
Potential Barriers



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Barriers to a QRM focussed batch failure investigation:

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<u>Not knowing your product</u>

- Can't apply QRM to a process or product which you know little about – because you don't know what is important and what is not.
  - Can be a particular problem for generics – low margins, tech transfer from other sites; may not have access to much development data (if any)
- Making assumptions, lack of critical thinking
  - 'human error' aspects
  - Failure to identify trends

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Barriers to a QRM focussed batch failure investigation:

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<u>Not understanding why the batch is failing</u>

- Need tools to do the job
  - good product development (or access to the data if transferred)
  - validation which tests boundaries of proven acceptable ranges
  - data recorded in a way which enables investigation
    - (i.e. more data, not less data - which doesn't show the problem)

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Barriers to a QRM focussed batch failure investigation:

<u>Not understanding why the batch is failing</u>

- Process capability
  - are we operating on the edge of failure (poorly developed product, poor validation)?
  - If so, there are likely to be other batches on the market which have also failed, but passed their low statistical power) QC tests.
  - This is not an assumption – population statistics tells us this.

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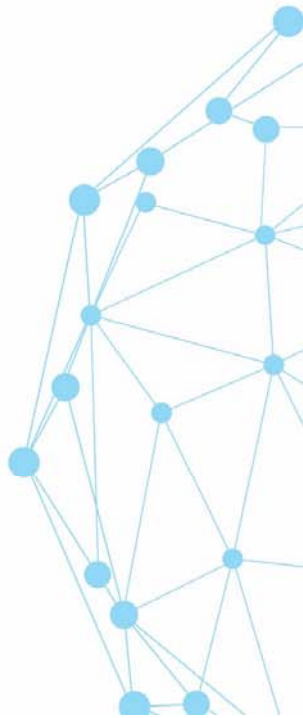
CASE STUDY



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Manufacturing Problem

- Manufacturer - sterile inhalation solutions
- Manufacturing Process – Aseptic Fill
- Filling Operations – 4 days to complete
- Manufacturing Equipment – Blow/Fill/Seal Machines (5)
- Issue – black stains observed around necks of vials during manufacturing (pallet #11) on Line 3

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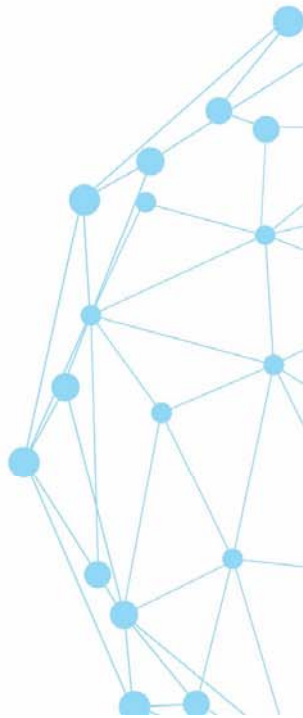
When It Goes Wrong



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Some examples of poor investigation

Unsupportable risk assessment, which led to no action:

- Black contamination in product: RPN score was low, on basis of Detectability score of 1 (highly detectable) – “because the patient would see it”
- Stability failure of hygroscopic tablets in the market. Cause: product packaging issues; not addressed because company culture didn’t want to hear ‘bad news’. Tablet turned yellow on exposure to moisture (degradant). Tablets released ‘in spec’ as ‘off-white’ when they were actually yellow (OOS). Assumption that patient would notice if serious issue

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Some examples of poor investigation

Unsupportable risk assessment, which led to no action:

- **Cracked vials (sterile lyophilised product).**
  - RPN score low, on basis of Detectability score of 1 (highly detectable) –because:
  - Cracked vials will ‘probably’ let in moisture
  - Moisture will ‘probably’ cause lyo cake to discolour
  - Healthcare professional will ‘probably ‘ notice and ‘probably’ decide not to use that vial. (all ‘probably’ quotes from the actual investigation)
  - No consideration given to loss of sterility assurance.
  - Example cracked vials shown to inspector, where the lyo cake was not discoloured.
  - No investigation into defect over a period of several months (with risk to patient, and critical medicine based on market share).

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Acknowledgements

Rick Friedman – FDA

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