BioPhorum

GUIDE TO IMPLEMENTING A RISK-BASED DEVIATION MANAGEMENT SYSTEM

CONNECT
COLLABORATE
ACCELERATE™

Contents

List of tables

List of figures

Contributors

This guide was created from best practice documents and case studies authored and shared by representatives of the BioPhorum Drug Substance Deviation Management System (DMS) Workstream. It intends to guide companies through the process of implementing its risk-based approach to deviation management. The guide outlines the main factors to consider during implementation and shares the benefits that have been realized by several member companies.

The BioPhorum Drug Substance Phorum comprises 29 member companies. Subject matter experts from 18 of these companies collaborated on this document.

Amgen

Astra Zeneca

Bayer

Biogen

Boehringer Ingelheim

Brammer Bio

BMS

Eli Lilly

Merck

Fujifilm Diosynth

Janssen

Lonza

Merck & Co Inc., Kenilworth, NJ

Novo Nordisk

Regeneron

Roche

Sanofi

Takeda

BioPhorum
Elaine Speirs

About BioPhorum

BioPhorum's mission is to create environments where the global biopharmaceutical industry can collaborate and accelerate its rate of progress, for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum now comprises over 90 manufacturers and suppliers deploying their top 3,500 leaders and subject matter experts to work in seven focused Phorums, articulating the industry's technology roadmap, defining the supply partner practices of the future, and developing and adopting best practices in drug substance, fill finish, process development and manufacturing IT. In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

1.0

Introduction

BioPhorum has developed a risk-based deviation management system (DMS). 13 member companies have implemented this approach, and summary data from these companies shows improved quality performance plus an average time saving of 22,200 work hours per site per year, which is equivalent to a $888k cost saving.

An effective deviation management process is one that identifies and removes risk from processes using root cause analysis (RCA) principles and a corrective and preventive action (CAPA) program. The current model used by many biopharmaceutical companies considers all deviations or events are equal and require a 30-day closure, known as the '30-day rule'[1]. Treating all events as equal and following the '30-day rule' drives an inefficient process and wasteful behaviors.

This guide outlines the work of the BioPhorum DMS Workstream in defining and creating a simplified and effective risk-based deviation management system with advanced RCA methodologies, and a track-and-trending process of low-risk events. It includes everything required to build a risk-based approach to DMS, including the business case for change, the new process, risk-based tools, and a detailed sharing of post-implementation benefit.

Elaine Speirs
Facilitator, BioPhorum

2.0

The business case for change

The business case for change was developed by the BioPhorum DMS Workstream using blinded survey data. The survey was completed by 13 member companies covering 20 sites and was based on their existing DMS process, which is described in Figure 1. The survey data was used to create a simplified DMS process, as shown in Figure 2.

The business case is based on data for an 'average' site drawn from the DMS survey, as described in Table 2 and more detail in Section 2.3. Each company can, of course, calculate the business case at site and company level, using their actual figures. The DMS Workstream strongly recommends that the time saved using the improved process is invested in deviation prevention and assuring quality at source. Member companies have shared case study benefits of having 'quality on the floor' in Section 8.2.

2.1 Annual savings

An annual time saving of 16,700 hours per average site was calculated based on 60% of deviations being categorized as events that do not require investigation and should be monitored as track-and-trend events.

The current and future DMS features and expected benefits of the future DMS are summarized in Table 1.

Table 1: Current DMS versus future DMS

Current DMS	Future DMS	Future DMS benefits
98% of events are investigated	40% or less of events are investigated (100% of major and critical items continue to be investigated)	18 hours saved per event that is track-and-trended (60% or more of all events)
100% have quality assurance (QA) assessment	40% or less of all events have QA assessment, the rest are track-and-trended	Reduced workload for QA and faster release of product
30-day rule and standard methods for investigations	As much time as needed and an advanced RCA method toolkit for investigations	More efficient RCA, leading to more effective CAPA and fewer instances of recurrences
Event closure duration ca. 29 days minor, 53 days major and 68 days critical	Minor event closure duration <5 days, 50-day target for major and critical	Reduced workload due to less coordination/follow-up work and reduced release times
Manual reoccurrence assessment	Track-and-trend process for assessment	Better risk and reoccurrence detection. System improvements through better CAPAs

While there are financial and time savings when implementing a risk-based DMS process, there are associated costs in training, project managing and running a track-and-trend process. The costs and benefits are summarized in Table 2. There is a $648k per site per year saving for the average drug substance site.

Table 2: Cost of the current DMS process versus implementation of a risk-based approach

Cost of the current process	
Average deviations per site per year	1,542
Low-risk deviations per site per year	925
Time spent investigating low-risk deviations	18.1 hours each = 16,700 hours total per site per year
Cost of investigating low-risk deviations ($40 per hour assumed)	$668k per year per site
Cost of implementing the new approach	
Project management, training and support costs	300 hours = $12k
Ongoing cost of track-and-trending	200 hours = $8k
Benefits less costs	$648k per site per year

For companies using TrackWise, for the vast majority of BioPhorum members, there should be little or no IT costs. There may need to be an addition of some user-defined fields, but existing systems can support the DMS proposals.

Some member companies who implemented the risk-based approach were already planning a major corporate-wide upgrade to TrackWise or equivalent system, and they used this system change to ensure better support for the new process.

There are two major implementation costs.

1. **Project management and implementation support at an average site, which is estimated as:**
   - Training – 2-hour face-to-face sessions, 4–8 per week over a 13-week period for the target audience (mainly supervisors and managers, higher-level manufacturing associates, logistics and support groups)
   - Post-implementation support (using existing forums as much as possible, such as shift exchanges and daily operations meetings)
   - Project and change management (planning, supporting site leadership team, etc.) using a small team of a project lead and 2–4 QA and operations representatives.

For an average site with 656 operations staff, the assumption is that 35% (230) will need training, which will require:

- 100 trainer hours, including preparation
- 80 hours of post-implementation support
- 80 hours of project management
- 40 hours coaching/mentoring/on-the-floor support
- A total of 300 hours per average site over a 13-week timeframe.

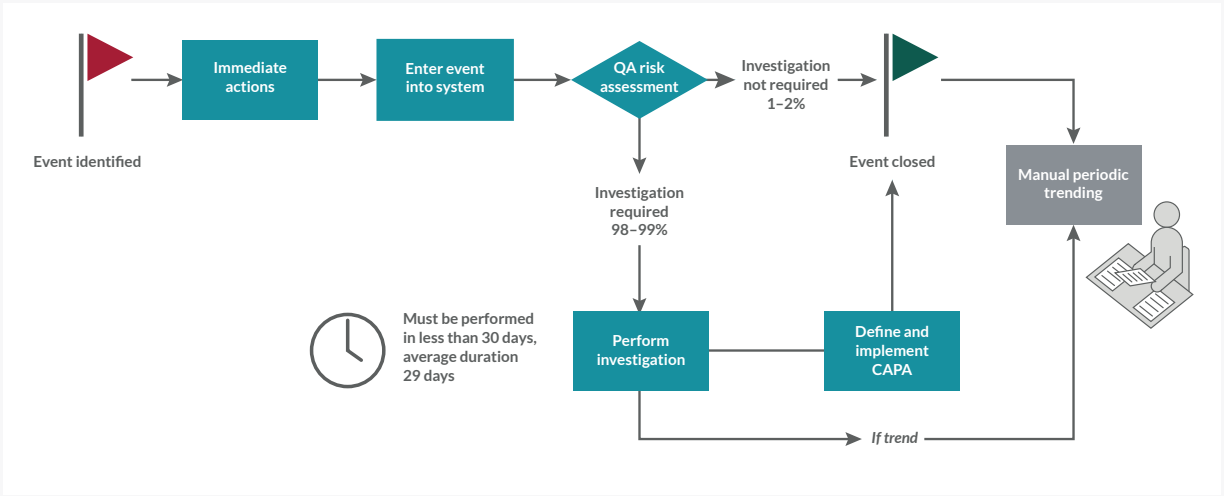
Appendices 1 and 2 give example milestone and activity schedules for the rollout of this change.

2. **Ongoing costs, including 'deep-dive' investigations of significant trends that emerge from track-and-trend data analysis, which is estimated as:**
   - Equivalent to four major investigations per site (a major investigation takes 46.4 hours, so 186 hours per average site)
   - A $40 per hour staff cost is estimated (operations and QA combined).

2.2 Old process

The old process is shown in Figure 1. The survey showed that events were entered into the quality management system (QMS) often after extensive discussions asking, *Is this a deviation?* There was a reluctance to log deviations since 98% of these led to an investigation. A risk assessment was carried out by QA and an investigation was triggered with a 30-day completion target. A CAPA was normally created for each deviation. Periodic trending was performed by the QA department.

Figure 1: The old process



The survey data describing the old process indicates that:

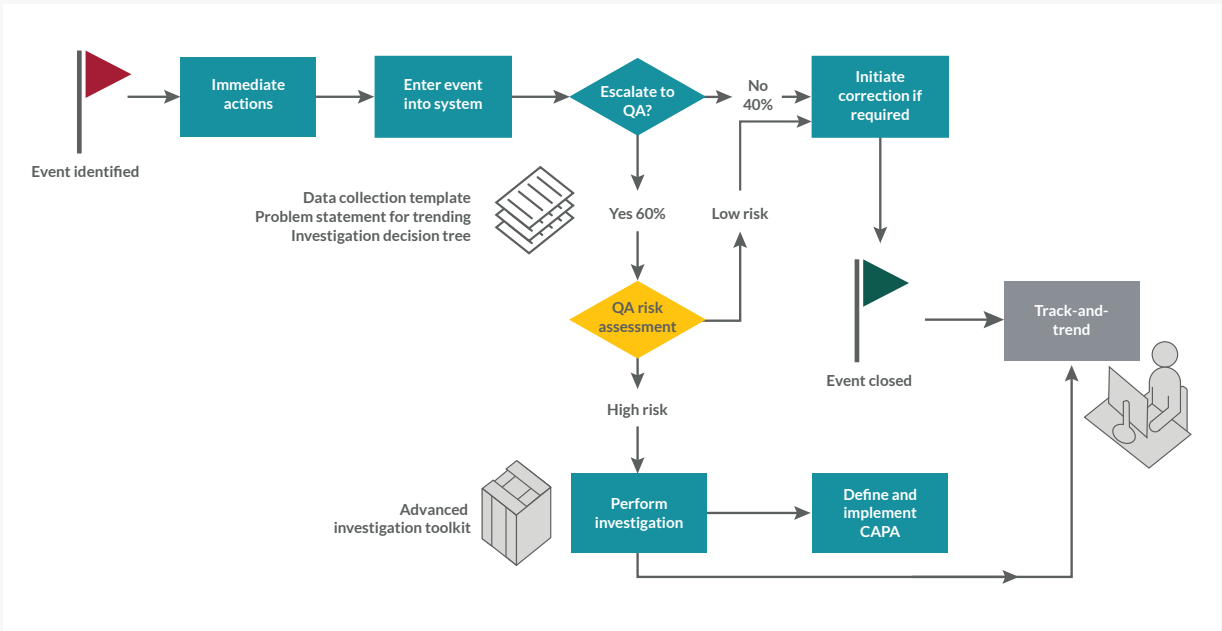
- The current systems are based on a small-molecule pharmaceutical compliance model that dates back to the 1980s, with the '30-day rule' and a process that is not risk-based
- Companies still tend to use a compliance-driven system
- A '30-day rule' leads to an average minor investigation duration of 29 days, causing prolongation of release times and additional coordination work
- There is pressure to close an investigation without finding the real root cause
- 24% of deviations are repeats, pointing to an ineffective investigation and CAPA process. Investigations fail to address and eliminate true root causes and systemic issues
- Average number of deviations by site per annum: 1,542
- 98% of deviations are investigated. There is little or no track-and-trending, i.e. no risk-based analysis of what should and should not be investigated
- For every 100 deviations, 72% are classed as minor, 26% major and 2% critical
- Average number of operational staff by site: 540 (range: 120–3,777)
- Average number of QA staff per site: 101 (19% of operational staff)

- A minor deviation involves 18.1 hours of activity time, 5.3 hours of which are spent by operations staff involved in the investigation, i.e. time they are not supporting product manufacturing
- A major deviation involves 46.4 hours of activity time, of which 12.7 are spent by operations staff. A critical deviation involves 92 hours of activity time, of which 28 hours are spent by operations staff (note: this is for information only as the team assumes no reduction in the time spent investigating major and critical deviations. This is not a factor in the business case)
- Less than 50% of companies measure deviations by batch, but the range is wide for those that do: 3.8–12.7 deviations per batch
- The target for release is 50–60 days, no figures were available for 'on-time-in-full' for batch release (anecdotally, the suggestion is 20–25% do not meet that target)
- Human error is often a root cause category in the DMS, which means there is no drive to investigate human factors.

2.3 New process

The new risk-based process is shown in Figure 2.

Figure 2: The new process



Key features of the risk-based process:

1. Every excursion is logged – operations staff are encouraged to log potential problems and issues. Time is not wasted asking, *Is this a deviation?* Open reporting is actively encouraged. This moves the focus towards finding opportunities to solve issues before they become deviations
2. An open reporting culture – the goal is to proactively uncover potential issues and near-misses that would otherwise remain unseen until discovered during an investigation process. This is a proactive measure that reports low-risk issues before they are linked to failures when processing
3. Decision to be made by operations staff whether an excursion is an event that should be track-and-trended or a deviation that should be investigated. The decision is made in real-time, on the same shift where possible, by the staff who have the information. Frontline workers are closest to the process and therefore in the best place to identify the problems
4. A risk-based approach is more than just using the current leveling systems (e.g. 1/2/3 or critical/major/minor) used by nearly every company
5. Fundamentally, it is a question about acceptable risk, not simply level of risk i.e. *Is this a risk that we can accept recurrence of or not?*
6. Operations staff are trained and follow set criteria to make the decision. QA is available to advise and challenge so that quality oversight is maintained
7. Better quality investigations using an advanced investigation toolkit. Better trained, more professional investigators are equipped with a bigger toolkit than the few tools that are often overused or misused in the old process (which relies on the 5-whys and fishbone analyses)
8. Guidance on this advanced RCA methodology can be found in Appendix 5 (members-only access)
9. Several companies are using a 45- and 90-day rule rather than the '30-day rule'. Deadlines are set according to the scale of the investigation and the speed of learning required (note that the average time to complete major deviations investigations is 50–60 days and up to 180 days for critical (28% of all investigations))
10. Track-and-trending of events provides an opportunity to reduce the 29 days for analysis of a minor deviation, reducing it by half or more is possible
11. Common definitions and risk assessments, which reduce variation
12. A decrease in the time it takes to analyze issues and an increase in the amount of usable information, building a smarter investigation
13. A strong track-and-trend program supports this risk-based approach by looking at aggregated system defects.

3.0

System implications

Many companies use commercial software packages to manage their deviations. These packages can continue to be used once a track-and-trend program has been introduced but they should be adapted for the new process.

In an ideal situation, the software process flow will be changed to match the new track-and-trend process. Some companies in the collaboration have redesigned the software process flow so it guides users through the stages of the process – from discovery, through to the decision points in the process and then finally to closure. In these cases, input fields only become available once a previous field has been completed. The available fields may also depend on the answers to the classification questions that companies use to decide whether the deviation goes straight to track-and-trending or whether it requires an investigation. If the event is classified for track-and-trending, then the fields leading to closure become available; if it needs to go through the investigation route, then those fields become available.

Changing the software to match the process can be a complex task that involves designing new interface pages and extensive validation; however, other options can be explored either as a short-term fix or until a redesign is possible.

A temporary, short-term fix may be to follow the process as guided by a paper/electronic procedure, utilizing unused fields in the existing software for inputting new information required by the track-and-trend program, e.g. event categories.

There is also a possibility that the software package may be updated with minor changes by adding new fields onto existing interfaces and still using external procedures to drive the process. This approach adapts the software to enable the new track-and-trend process but requires less work and validation to achieve and so can be completed in less time.

Regardless of which approach is taken, it is important to remember that the intentions of the track-and-trend process must not be compromised just to make the process fit the software.

An important consideration when introducing a track-and-trend program is the installation and use of an appropriate data-handling package for pulling data out of the management software and analyzing that data as part of trending. This software must be able to interface directly with the deviation management package or with any format, e.g. a spreadsheet, which the management software uses to export data. The data-handling package must ideally be able to visualize the data (e.g. as graphs or control charts) as well as be versatile enough to look at the data from many views, e.g. by equipment, area, event category, root cause code, product, manufacturing area, etc.

A successful track-and-trend program is one in which the software used for management and trending complements the program. Any approach must be easily understandable by end-users and allow them to focus on the process and outcomes, rather than the picture being clouded by the nuances of the software being used.

4.0

Communication and training processes

The communication and training steps required to allow the risk-based DMS approach to be implemented are outlined below.

4.1 Communication

Timely communication with management to ensure understanding and buy-in, as well as the communication to global and local quality of:

- New workflows
- Rollout plans:
  - Timelines
  - Roles and responsibilities
  - Resources
  - Activities.

Site-wide communication, using different media/ methods to ensure those in key roles (e.g. operational team leaders, managers, daily triage team members) understand:

- What is required
- How to raise and get answers to their questions
- What needs to be done differently and what success looks like
- How they will be supported pre- and post-go-live.

Communication with Health Authority Inspectors to ensure an effective on-site briefing for their auditors on the new DMS.

4.2 Training

The types of training, target audiences for each, suggested content and delivery schedule are described below:

Overview training

- **When**: within one month of the go-live date
- **Target audience:** QA, investigators, event initiators, shop-floor management, senior management and human performance practitioners
- **How:** instructor-led, classroom-based
- **Duration:** 2 hours
- **Content:** new DMS workflow (the why, what, when, where, who and how), key principles, features and benefits, how it should work and make it operate effectively in practice.

Hands-on training

- **When:** in the run-up to go-live
- **Target audience:** QA, investigators and initiators
- **How:** instructor-led, classroom-based in small groups followed by on-the-job coaching as required
- **Duration:** 2–3 hours
- **Content:** new DMS workflow, information that must be captured at initiation to ensure it is right-first-time, worked examples of what should be track-and-trended and what should be investigated, and practical exercises using current events/observations. Also, daily triage process, understanding how trending will work in practice, changes planned to improve investigations and CAPAs, trending (including how repeats and reoccurrences will be treated)

Post-implementation training and review

- **When:** weekly/monthly for 3–6 months after the go-live date
- **Target audience:** QA, event initiators and investigators
- **How:** as self-directed learning teams, supported by the project team
- **Duration:** 1–2 hours
- **Content:** gathered data (top five track-and-trended, etc.) and feedback from QA, initiators and investigators, examples of best practice, examples of poor practice (and the action taken or planned to correct these), new learnings to be shared, results and key performance indicators (KPIs) for analysis, identification of any changes required and evaluation of all changes made.

Post-go-live support and training

- Provide ongoing one-to-one coaching and/or additional classroom training as required
- Publicize results, share successes site wide (boards, screens, intranet, site leadership team/management meetings and daily meetings).

An example milestone plan is shown in Appendix 1.

5.0

Improved investigation process

The main goal in creating a simplified, risk-based DMS process was to focus time and effort on a more in-depth investigation of medium- to high-risk deviations that have the potential to impact on product quality and batch release.

To improve the quality of investigation processes and ensure human factors are considered, the BioPhorum Human Performance Workstream established the DMS Workstream. Both teams worked very closely together and shared a common membership. The Human Performance Workstream created a Human Performance Investigations and Root Cause Analysis Best Practices sub-team, which reported the current state in 2016, best practices and recommendations for a better quality and more robust investigation process. *The investigation root cause analysis best practice report*, (see Appendix 5), identified 14 recommendations and 11 best practices. The report contains possible solutions to address opportunities for improvement in investigations and RCA, rather than an all-or-none mandate of required actions. It has been used by several member companies to improve the quality of investigator training. A critical trigger for improved investigations is the removal of 'human error' as an RCA category within the exception management process.

Properly addressing these opportunities will not only improve the velocity and effectiveness of adopting a strong human performance operating philosophy, but will ultimately result in enhancing continuous improvement (CI), organizational effectiveness and employee engagement.

Several BioPhorum member companies have shared the advanced investigator training that they created based on *The investigation root cause analysis best practice report*. Links to this training are given in Appendix 5.

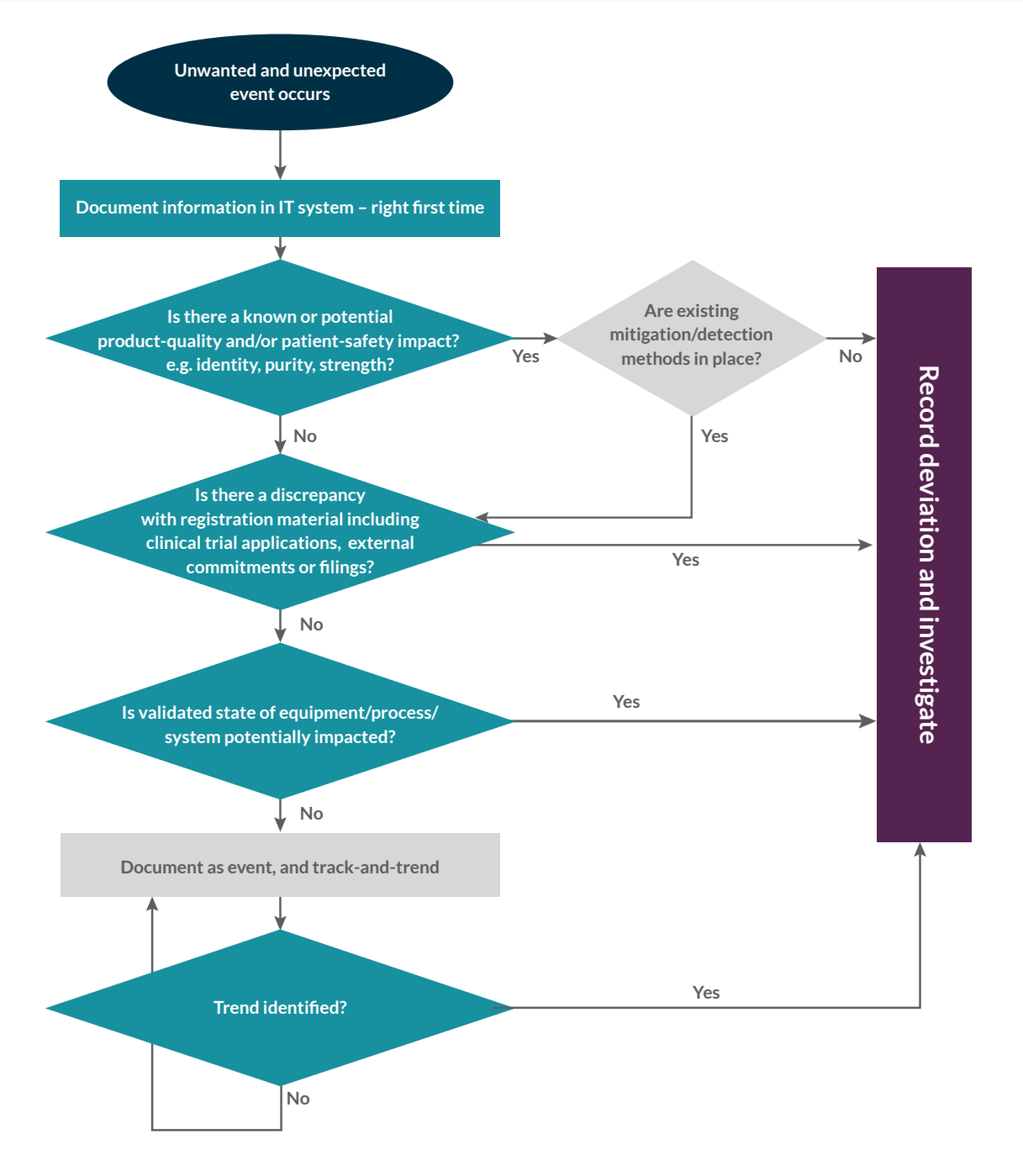
6.0

Risk classification and approvals process

The first step in the new risk-based approach to deviation management is an analysis of risk. This risk analysis considers the risk to product quality, to the registered process and the validation status.

An example of a risk classification process is shown in Figure 3 and discussed in the following sections. A version shared by a member company can also be seen in Appendix 4.

Figure 3: Event risk classification decision tree



6.1 Documenting the event

Following the occurrence of an event, a record should be created in the DMS (e.g. TrackWise) according to the company's SOP.

Event attributes should be documented within the record, such as associated department, document, equipment, lot/batch, etc.

Every event should be categorized based on a predetermined selection of categories that best describe the nature of the deviating issue, not the perceived root cause of the issue, i.e. categorize the 'problem statement'. Some company systems are configured to prompt users to select a root cause category. In these cases, a 'most probable cause' is suggested after some basic analysis of the event. The categories are to be used for trending purposes and may be tiered to narrow the selections.

Categories should be developed based on an analysis of a set of previous deviations, for example:

- Non-critical operating parameters out of range
- Incorrect/incomplete/illegible documentation
- Missing signature/date
- Calculation/rounding error
- Leak from a single-use container (e.g. buffer bag, tubing, etc.)
- Media/buffer solution out of range/discarded
- Use of a wrong version of a document
- Training missed/not performed/incomplete
- Process step misperformed
- Hard-coded document error
- Equipment setup issue:
  - Equipment malfunction
  - Personnel-/equipment-/material-flow violation.

6.2 Deciding to track-and-trend or investigate

The DMS decision tree, as shown in Figure 3, should be used to determine if the event will be documented as a track-and-trend event or as a deviation and investigated. This decision should take place at the time and place of discovery and be carried out on the floor as much as possible. The questions may be modified and/or combined to meet the company's business processes. However, the intent is a simple process with few decision points enabling any individual in the business to successfully categorize a deviation. Ideally, the decision process should be incorporated into the company's IT system to maintain a clear and accurate system of record that captures the decision points and rationale/justification. As a minimum, the DMS decision tree process should be detailed within the company's SOPs along with instructions for how and where to document the decision points.

Situations that always require an RCA investigation and assessment of impact include:

- When there is a potential product-quality and/or patient-safety impact
- When there is a discrepancy with registration material, including clinical trial applications (CTAs), external commitments or regulatory filings
- When the validated state of the equipment/process/system may be impacted.

6.3 Assess impact on product quality

The first question in the DMS decision tree is to determine any product-quality impact and ask, *Is there a known or potential product-quality and/or patient-safety impact, e.g. identity, purity, strength?* Ideally, a list of examples/scenarios that correspond with 'Yes' or 'No' answers should be provided (e.g. as a dropdown selection in the IT system or a list within the SOP) to guide the initiator. An example is shown in Table 3.

Table 3: Impact on product quality and/or patient safety

Is there a known or potential product-quality and/or patient-safety impact, e.g. identity, purity, strength?	
No	**Yes**
When it is immediately evident that there is no potential for product-quality and/or patient-safety impact, the decision tree should be followed to the next question.	In cases where it is determined that the event has a potential for product-quality and/or patient-safety impact, a subsequent question should be asked to determine if mitigation/detection methods are in place to prevent disposition/use of the potentially impacted batch. If mitigation/detection is not in place or not acceptable, the record should progress as an investigation.

If the first question is answered 'Yes', the corresponding question should be used to determine the mitigation/detection methods. Each company should predetermine acceptable mitigation/detection methods, applicable to their process, that provide enough assurance that the lot/batch is not at risk for disposition/use. If an acceptable mitigation/detection method is in place, specific details should be documented in the record to indicate how the controls in place mitigate or detect a potential impact that could occur as a result of the observation/event. The company may also want to state what mitigation/detection methods are not an acceptable means for justifying documentation of the situation as an observation/event. An example of acceptable and unacceptable mitigation/detection methods is shown in Table 4.

Table 4: Examples of acceptable/unacceptable mitigation/detection methods

Examples of acceptable mitigation/detection methods	Examples of unacceptable mitigation/detection methods
In-process controls	Final release testing
System suitability	Non-routine testing/additional testing
Microbial testing	Stability testing
Cell counts	Acceptance quality limit (AQL)

6.4 Assess regulatory impact

The second question in the DMS decision tree addresses the potential to impact on regulatory requirements. *Is there a discrepancy with registration material, including CTAs, external commitments or filings?* Ideally, a list of examples/scenarios that correspond with 'Yes' or 'No' answers should be provided (e.g. as a dropdown selection in the IT system or a list within the SOP) to guide the initiator. An example is shown in Table 5.

Each company should provide examples of situations that may result in a regulatory impact including:

- Reprocessing outside of approved production records
- Use of unapproved equipment in a commercial process
- Use of unapproved materials
- Missing or incorrect information on printed materials for commercial packaged goods
- Commercial process modification
- Alteration of solution components or formulations for commercial process.

Table 5: Impact on registration material

Is there a discrepancy with registration material, including CTAs, external commitments or filings?	
No	**Yes**
If it is determined that there is no potential impact on regulatory requirements, the decision tree should be followed to the next question.	If it is determined that there is a potential regulatory impact, the record should progress as an investigation.

6.5 Assess validated equipment/process/system impact

The third question in the DMS decision tree addresses *Is the validated state of equipment/process/system potentially impacted?* This is shown in Table 6.

Table 6: Impact on validated state of equipment/process/system

Is the validated state of equipment/process/system potentially impacted?	
No	**Yes**
If it is determined that the event does not impact on the validated state of the equipment, process or systems, the decision tree should be followed to the question.	If it is determined that there is a potential validation impact from the event, the record should be progressed as a deviation for investigation.

If all decision tree questions for the event are answered 'No', justification for the assessment should be documented in the record, which should be completed as a track-and-trend event. Best practice is to have dropdown selections in the IT system that explain how to document the rationale for saying 'No'.

6.6 Approvals process

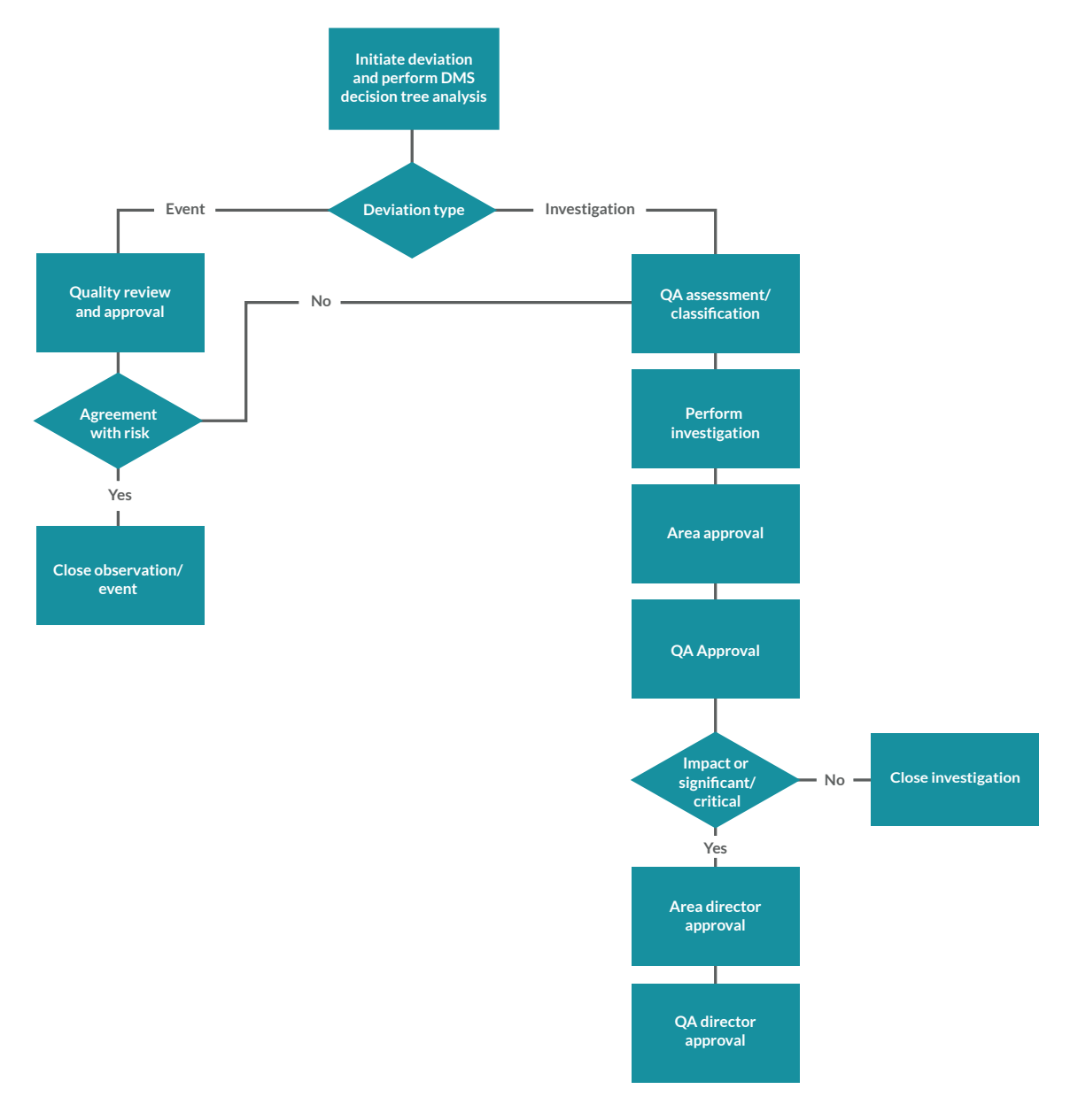
It is recommended by the DMS Workstream that there is some QA oversight of the classification of events, to either track-and-trend events or deviations for investigation, to identify misclassifications. An example of the QA approvals process is shown in Figure 4.

An overall process flow should be created to identify the levels of approvals required for closure of observations/events and investigations. As a minimum, observations/events should require a consensus agreement with the QA unit, which should review the record and consider these options:

- Close the record as an observation/event
- Cancel the record with appropriate justification and in line with company procedures
- Return the record to the initiator for additional information/clarification
- Escalate the record to an investigation.

Investigations may require different levels of approval based on criticality and/or impact.

Figure 4: Example approvals process flow from a member company



Due dates should be established for the closure of observations/events and investigations. Observations/events do not require RCA or an assessment of impact and, therefore, should be closed in a timely manner. Ideally, this should be driven by the company's IT system, but as a minimum should be specified in the company's SOPs.

6.7 The 'significant compliance issue' debate

The DMS Workstream debated long and hard whether to include the question *Is there a significant compliance issue?* in the DMS decision tree. In this debate, the team considered the practical experience of companies with the new DMS model in place, either as a pilot or running company wide. Consideration was also given to the results of one member company's internal workshops to address this specific question.

The conclusion and recommendation from the workstream debate were **not** to include this question for the following reasons:

- It is too open to interpretation, leading to too much discussion and inconsistent classification between sites/areas
- It leads to over-processing and lots of minor deviations/events classified as major deviations/ investigations because the deviation handler or QA unit evaluated the event as being a 'significant compliance issue', even though it was, in fact, a minor deviation/event
- When evaluating 'significant compliance issues', they could be placed in one or more of the following categories in the current decision tree:
  - Product quality/patient safety
  - Registration files
  - Validated state.

  For example, a data integrity issue should be classified as a major deviation/investigation if it has an impact on one of the above. If it has not, it will be classified as a minor deviation/event
- The model gives QA the final approval, so if there is some strange event that does not fit the decision tree, it makes sense to fully investigate. QA can always escalate with appropriate justification.

However, the DMS Workstream also recognizes and accepts that it is for each company to decide whether to include *Is there a significant compliance issue?* in its decision tree. Appendix 3 sets out guidance from companies who are addressing this question in their decision-making process.

6.8 Track-and-trend investigations

Each company must define its policy and SOP for identifying when a trend should be investigated and how investigations should be conducted. The DMS Workstream has produced guidance on track-and-trending that a company will find useful when developing its own approach.

Examples of situations that could be documented as a track-and-trend event include:

- Error in good documentation practice where all data supports acceptable results
- An incoming raw material failed some testing and was not used in the process (note: some companies may class this as a 'supplier corrective action required' and be managed in another system)
- A material, item or equipment is not used in a good manufacturing practice process (e.g. buffer discarded before use, equipment assembled incorrectly but fixed before use, etc.)
- Missed preventive maintenance
- Testing/sampling error where the final results were not impacted (e.g. execution of an additional test)
- Data loss that can be recovered
- Improper gowning.

Examples of situations that could be documented as an event with mitigation/detection methods in place include:

- Minor leak on closed/pressurized equipment
- Room pressure excursion
- Temperature excursion where validation data supports acceptability
- Non-critical parameter out of range.

Examples of situations that require an investigation include:

- Acceptable quality limit failure
- Commercial process modification
- Alteration of solution components or formulation for a commercial process
- Contamination (bacterial contamination or foreign material identified)
- Critical test out of specification
- Critical parameter out of specification
- Missing/incorrect information on printed material on commercially packaged goods
- Relabeling/repacking issue of a manufactured product
- Reprocess outside of approved production record
- Use of unapproved equipment in a commercial process
- Use of unapproved materials
- Regulatory impact.

7.0

Track-and-trending process

This section describes a process for the proactive trending of all events and those low-risk events that, while not investigated individually, must be monitored and analyzed effectively. The scope of this guide does not include recurrence trending as that is part of the established investigative process for deviations.

This guide represents the best practice recommendations of the DMS Workstream. It is, of course, for each company to determine its policy and prepare SOPs, work instructions and training materials to ensure their process is robust, well understood and followed consistently.

7.1 Principles

The track-and-trending process is based on the principle that many events are minor and pose little or no risk to patient safety, product quality or regulatory compliance and that they should be track-and-trended with actions taken when trends are identified. The significant resource this frees up should then be used to enhance quality for more effective, proactive and preventative work.

Incidents to be track-and-trended are generally symptoms of broader systemic process issues. Rather than conducting a comprehensive RCA on each low-risk event, these are more effectively addressed by trending for patterns and then utilizing CI methodologies to address the common causal issues that lead to the events. Therefore, a key principle is that the investigation of common causal issues will lead to a significant, sustainable reduction in deviations over time.

By evaluating trends at a global as well as a site level, a company can better ensure that potential company-wide and site-specific trends are identified and investigated with learning shared and applied more rapidly and effectively than before.

Lastly, it should be noted that a trend investigation or a trend action may be a CI activity (e.g. learning teams, kaizen events, kata, lean sigma, etc.) rather than a traditional deviation management investigation. The principle underpinning the process is to use the appropriate methods to learn from events and improve the process.

7.2 Track-and-trending objectives and critical success factors

The purpose of this trending program is to:

- Identify and address trends
- Identify trends that point to a deeper systematic issue that requires investigation
- Safeguard product quality and patient safety.

Key to the success of an effective trending program are:

- Ensuring there is an end-to-end process owner at a global level and a site level, who is driving CI and countering pressures to return to old, non-value-adding practices
- Ensuring its application consistently across the organization through proper management and quality oversight
- Using closed-record data over the use of initiated records, because this ensures the data analyzed for trends is unchanged
- Having managers and staff with expertise in QMSs and with the required understanding of their processes to accurately categorize events
- Having predefined criteria for categorizing events
- Avoiding ‘dilution’, i.e. having too many categories, sub-categories and unnecessary complexity to enable trends to be properly identified
- Allowing flexibility in determining if a trend warrants investigation or a CI activity.

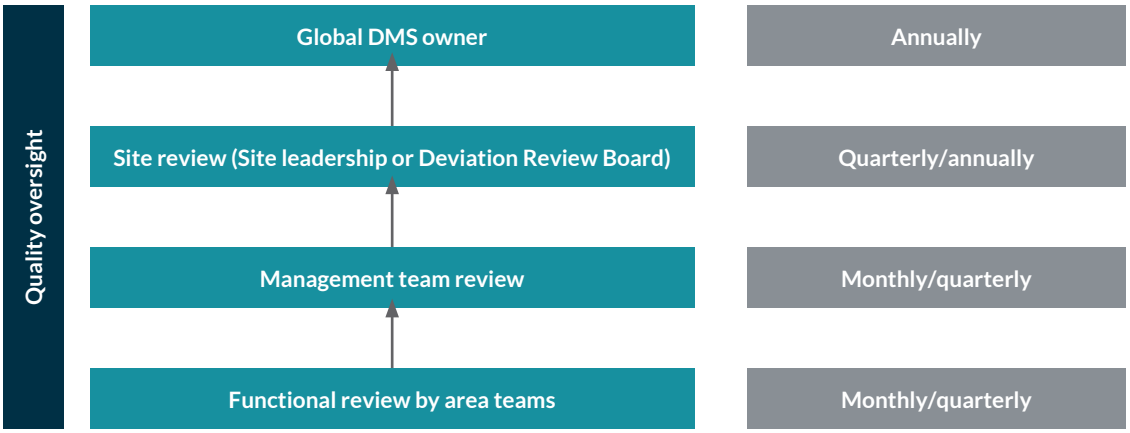
7.3 Data sources

The primary source of information for event trending is the company quality system, such as TrackWise or SAP, with data exported to other software tools for data analysis and reporting.

7.4 Event trending

Event trending is initiated by the function or area owning the event and on a predefined frequency. The review should be based on all events initiated within the predefined time. Data categorization is completed and, on identifying (or not) any trends or issues, the data is reported through the management structure in Figure 5.

Figure 5: Reporting relationship for trending program



The frequency of trending is process dependent. As a minimum, this should be quarterly by function. However, if the number of events is high, it may be relevant to conduct this monthly. This should be defined by each site as required.

A primary category and a sub-category from the list of defined events for each area should be assigned to all event records. Where applicable, assign additional sub-categories to provide extra granularity about the nature of a given event to allow for more actionable groupings of records and identification of trends (note: beware of dilution).

If there appears to be a significant increase in the overall total number of events, or within an event category or sub-category, further analysis should be undertaken to examine other attributes that may be contributing to the observed increase.

The rules and triggers for actions cannot be predefined as they depend on the frequency at which a process runs, how much past data is available to calculate statistically significant action limits and how the events were originally classified. In the experience of the team, the track-and-trend process should be an integral part of process monitoring with the operational teams using their professional judgment and experience, in addition to rules and statistical triggers.

An analysis of each sub-category should be made to determine if a trend can be identified.

Considerations for review include:

- Rate of event occurrence versus frequency of operation
- Recommendations and results of previous trend reports, including items previously identified as recurring issues.

The following actions could be proposed for each recurring issue:

- Create a new trend investigation
- Link the recurring issue to an existing trend investigation
- Link the recurring issue to an existing remedial action, such as a CAPA in progress
- Correct the issue
- Add to CI activity
- Continue to monitor a trend.

If a reference is made to an existing remedial action to mitigate a recurring issue, the need for an interim control should be considered. If the event is linked to a previous CAPA, an effectiveness review should be considered.

The analysis of positive trends should also happen to identify if control limits remain appropriate and if the positive change can be standardized across different areas.

The evaluation of trending should be completed by a multi-disciplinary team and include a review of data categorization, identified trends and proposed actions. The team should consist of the relevant technical staff (e.g. scientists and engineers), QA and production staff. The findings should be presented at management review.

Confirmed trends must be addressed and corrected, or justified as not requiring action. It is the area's responsibility to ensure trends are addressed in a timely manner.

Options include but are not limited to:

- Trend investigations:
  - Remedial action and effectiveness checks
- Corrections (caution: only to be completed where there is a clear and understood benefit in performing the correction):
  - Changes in working methods, including pre-job briefs and other human performance tools
  - Changes in roles and responsibilities
  - New work instructions
  - Training
  - SOP revision
- CI activities:
  - Lean sigma process improvement projects
  - Equipment and process error-proofing
  - Changes in equipment maintenance.

A trend report should be completed that outlines the high-level data analysis, all considered trends and proposed actions. This should be prepared and presented to the relevant management team. The trend report can be a formal report or a presentation.

The suggested content of a trend report includes:

- Scope – defines the period of data being reviewed
- Overview of data – a high-level review of the total number of events generated by month at department level, independent of subsequent categorization and analysis
- Executive summary – a snapshot of the evaluations and conclusions of the report, and the trends identified
- Trends (grouped and presented in tables) – trends recommended for new actions, previously identified trends with overdue actions and trends for which no additional actions are recommended. This should also include a review of any items identified as trends during the previous trend report, independent of whether the issue is part of the top 80% of a given category (found using Pareto analysis)
- For trends with no new action recommended, a notation should be provided referring to a subsequent justification given in the associated analysis section
- Analysis – summary of analyses performed for each primary category and applicable sub-category, including relevant charts and tables (these may be included in an appendix and referenced in the report text)
- Appendices – relevant lists of events assessed and categories assigned or a link to where source data is stored.

8.0

Governance of the process

The governance process used to manage the event classification varies across member companies, but the DMS Workstream makes the following recommendations for good practice.

A daily process should be used to manage events and deviations to ensure classification errors are corrected at source, and teams build learning in the classification process. Decisions should be made early to ensure that deviation investigations can start quickly while information is still retained by the staff involved, and events can be closed and moved to a track-and-trend action. If no daily process is used, errors may take some time to be identified, with the potential risk of deviations being misclassified as events.

8.1 Accountabilities and responsibilities

The DMS Workstream has defined specific responsibilities in the event-management process, which are outlined below.

Global DMS process owner – accountable for the end-to-end company deviation management process, i.e. event identification, classification, trending, investigation, reporting and the evaluation of CAPA effectiveness. They set and drive the CI of the process and related knowledge management.

Site DMS process owner – as above for the global DMS process owner but at a site level covering all functions. They also have responsibility for implementing the site trending program and ensuring site reviews are carried out.

Site review – a site-specific team should be identified (led by the site DMS process owner and/or operational excellence review staff) to discuss trending results. It should agree if any adverse trends exist across a site that need escalation to an investigation and to determine what the scope of that investigation should be. This could form part of a standing Deviation Review Board agenda or other site leadership meeting, where quality oversight is provided.

QA department – primarily responsible for oversight of the track-and-trending decision process, involvement and oversight at each stage of the trending program, approval of required reports and oversight of follow-through of actions agreed to improve quality. It is the responsibility of QA to ensure that this procedure is performed as described, that it is reviewed and updated as necessary, and that proper support documentation is maintained.

Function/department heads – responsible for ensuring that trending is happening within their areas of responsibility and for designating subject matter experts for their area to monitor and review any trends identified. The function or department head should:

- Concur that the identified trend is appropriate
- Approve the trending reports for their area
- Set action plans
- Address and manage any action plan from the time of the occurrence through to completion (this may be a CI project or a trend investigation)
- Share results at appropriate forums (up to site level or with a group of departments or sites).

8.2 Quality on the floor

In addition to the responsibilities outlined in Section 8.1, the DMS Workstream also strongly recommends having 'quality on the floor'. Members of the quality team being an integral part of the manufacturing flows allows discussions when problems arise. This will enable events to be classified correctly and provides the QA oversight of the deviations process in real-time. One of the biggest benefits for member companies that have implemented the risk-based approach is the ability to free QA staff from investigation processing and reassign them on the floor for CI and coaching activities.

8.3 Daily stand-up meetings

Many member companies have integrated the event-classification process into their daily stand-up meetings, as this gives a multi-disciplinary approach to event classification and resolution. This approach also improves the quality of the information collected as the event takes place, which is particularly helpful if an event is classed as a deviation. Daily conversations on events and deviations ensure that learning is shared by all team members and is not confined to those involved in the classification of the issue when it happened.

9.0

Being audit-ready

During the roll out of a risk-based DMS, member companies have experienced successful audits from these health authorities:

- Food and Drug Administration (USA)
- European Medicines Agency (European Union)
- Medicines and Healthcare Products Regulatory Agency (UK)
- Turkish Medicines and Medical Devices Agency
- Swiss Agency for Therapeutic Products
- Health Canada (Canada)
- Health Products Regulatory Authority (Ireland)
- Federal Services for Surveillance in Healthcare (Russian Federation).

In most inspections, no feedback was given by the health authority. It is helpful to disclose the new system upfront to inspectors and share a good process-flow diagram when describing the risk-based approach. Target dates for the completion of actions from track-and-trend or deviation investigations can be a focus area of discussions; these target dates need to be fully justified using a written rationale. Where feedback was given during inspections, it was to ensure that system issues are considered when investigating trends and to demonstrate that the track-and-trend process is in place and in use.

To be audit-ready, the DMS Workstream makes these recommendations:

- Make DMS part of self-inspection
- Use coaching opportunities to carry out spot checks
- Have site and global communities of practice to build experience and share real examples
- Frequently review the questions asked and use these to improve education
- Monitor metrics to ensure behaviors are correct
- Include subject matter experts in the DMS.

10.0

Benefits of a risk-based DMS – survey results

Seven member companies that have implemented the risk-based DMS completed a benefits survey and the results are summarized below (this is average data for all the companies):

- In manufacturing, the proportion of low-risk events ranged from 75–90% of all events
- Three companies adopted the advanced investigation methodology outlined in Appendix 5
- All seven companies applied the new process to biologicals manufacturing, with two also adopting the new process in finished product
- In finished product, 80–85% of all events were low risk
- Five companies observed a drop in deviations requiring investigation over the 24-month period since adoption. Four of these could attribute this to track-and-trending and the advanced investigation methodology
- Four companies saw a reduction in repeat deviations; one saw no change and two did not measure repeat deviations
- Four companies saw an improvement in CAPA effectiveness; one saw no drop and two did not measure CAPA effectiveness
- All companies had seen adverse event trends that had led to action being taken and issues being resolved
- One company reported a 48% drop in deviations over a 12-month period
- Behavioral benefits were reported:
  - More focus on CI activity
  - More time available to spend solving problems
  - Correction of root cause rather than the person
  - Professional judgment supported by data empowers teams to carry out investigations and resolve system issues
- Improved product delivery and lot release times
- One company reduced its QA team by 200. All were moved to CI work
- One team reduced its QA team from 20 to six at a single site
- An improvement in right-first-time figures.

Further data was shared by one member company (for 2017 and 2018):

- Number of overdue records dropped from 42% to 3%
- Closing minor events dropped from 35 days to 16 days
- Closing majors/critical deviations dropped from 73 days to 50 days
- Number of investigators dropped from 20 to six (redeployed as QA on the floor and in prevention projects)
- More time was available for improved investigator training
- Focus on product release instead of working deviations
- Customers saw improved right-first-time figures – fewer document review cycles
- Zero deviation/golden batches: zero in 2016, one in 2017, 13 in 2018
- FDA inspection recognized the BioPhorum model with no observations
- Fewer recurring deviations.

Several other companies shared case studies, which can be found in the members-only area in Appendix 6.

11.0

Suggested KPIs to sustain the new process and behaviors

The team advises the following KPIs are used to monitor the process:

- Right-second-time – this encourages collaboration with other groups when classifying events
- Toll-gate times – these tell if the process is being followed
- Investigator load/capacity – this shows if investigations are above expected levels, i.e. are there unofficial investigations of track-and-trend events?
- The % of deviations with extensions by department – this is a measure of how accurate your process is for setting closure dates
- Effectiveness checks initiated versus major deviations closed – this will monitor the quality of CAPA in your system. Advanced RCA tools should lead to more effective CAPA.

The team cautions against the use of '% minors versus majors' as this can become a target and influence behaviors. It is not helpful to share an expected value for this during training and roll out of the new process. This KPI should be monitored but should not have an expected value, as it is set by the process itself.

Acronyms and definitions

Acronyms

Term	Definition
CAPA	Corrective and preventative action
CI	Continuous improvement
CTA	Clinical trial application
DMS	Deviation management system
KPI	Key performance indicator
QA	Quality assurance
QMS	Quality management system
RCA	Root cause analysis
SQIPP	Product safety, quality, identity, potency or purity
SOP	Standard operating procedure

Definitions

These definitions are used throughout the guide for consistency and understanding. Many companies in the BioPhorum DMS Workstream have chosen alternative terminology to meet their own system and process needs.

Term	Definition
Deviation – new process	an excursion from the documented process that has been risk-assessed and found to potentially impact on product quality or batch release. This is then classed as a deviation and investigated. The closure date is based on the extent of the deviation and resulting CAPA.
Deviation – old process	an excursion from the documented process that is not risk assessed. Most events are classified as deviations and require an investigation. Many or all deviations lead to a CAPA, with a 30-day closure date.
Event category	predefined categories that best describe the nature of the event for trending purposes.
Event – new process	an excursion from the documented process. It must be recorded and risk assessed for impact on product quality.
Event – old process	an excursion from the documented process that is classified as a deviation and logged in the QMS (98% are then investigated).
Impact	adverse influence on product SQIPP, process or regulatory documents beyond established or expected requirements.
Investigation	a systematic inquiry to determine the root cause(s), evaluate potential impact, trends and identify CAPAs.
Track-and-trend event	an event with no risk to impact on SQIPP, process or regulatory filings. Or a situation with a low risk to impact on SQIPP with acceptable mitigation/detection methods in place. Events will be classified and track-and-trending put in place.
Trend	a statistical term referring to the direction or rate of increase or decrease in the magnitude of the individual data, or parameters of a time series of data, as a general movement over time. Trends may be positive or adverse and need to be evaluated.

Appendix 1

Example milestone plan

Milestone	Activity	Date from project start
1	Agree the implementation project plan (including goals, resources and organization) and secure leadership commitment to the project plan and change-management approach.	4 weeks
2	Define the process. Guidance is in place and training is designed and ready to deliver.	6 weeks
3	Complete the training of the site leadership team	8 weeks
4	Complete the training of all operators and quality staff critical to the success and visual management of the new process.	12 weeks
5	Complete the IT and process/procedural changes required to enable the new track-and-trend process.	12 weeks (in parallel with milestone 4)
6	Go-live.	13 weeks
7	Complete the advanced investigator training program and begin tracking improvements in CAPA effectiveness (target reduction in repeats and recurrences).	24 weeks
8	Complete the first major deep-dive trend investigation.	28 weeks
9	Complete the knowledge transfer to the next site/global implementation team.	30 weeks

Appendix 2

Example activity schedule

Milestone 1 – Agree the implementation project plan (including goals, resources and organization) and secure leadership commitment to the project plan and change-management approach	
a	Arrange meetings with key stakeholders to present the new model, its business case and the outline project plan, and gain authority to implement.
b	Mobilize the project team, clarify roles and time requirements, agree the detailed project plan (charter, activity schedule, risk management, etc.).
c	Build the communications plan.
d	Brief the team on the tools/guides provided by the BioPhorum DMS Workstream (e.g. decision trees, track-and-trending, communications and training plan).
e	Identify any gaps to be filled for company implementation (e.g. standard work, SOP and QMS changes, flowcharts and templates).
f	Complete initial assessment of IT system changes required and potential workarounds for go-live
g	Agree KPIs and report requirements.
Milestone 2 – Define the process. Guidance is in place and training is designed and ready to deliver	
a	Build a site-wide communications plan using different media/methods .
b	Communicate to key audiences – initiators, investigators, operations, triage team members, etc.
c	Prepare and organize overview training. Design, create materials and schedule the training.
d	Prepare and organize hands-on training.
Milestone 3 – Complete the training of the site leadership team	
a	Complete group and one-to-one training.
b	Ensure site leaders are brought into the change-management process and understand the role each can play to ensure success.
c	Resolve any issues raised by leadership teams.
Milestone 4 – Complete the training of all operators and quality staff critical to the success and visual management of the new process	
a	Complete hands-on training program for each target audience.
b	Define, agree and implement process triage and visual management plans (e.g. boards, daily meetings, etc.).
c	Agree project team reporting and evaluation process.

Example activity schedule (continued)

Milestone 5 – Complete the IT and process/procedural changes required to enable the new track-and-trend process	
a	Agree business and user requirements with IT.
b	Implement the agreed requirements.
c	Complete system testing in readiness for go-live.
Milestone 6 – Go-live	
a	Ensure project team is on the floor and available for support.
b	Begin project team evaluation program. Capture fixes, changes made and learnings.
c	Recognize and celebrate early successes.
Milestone 7 – Complete the advanced investigator training program and begin tracking improvements in CAPA effectiveness (target reduction in repeats and recurrences)	
a	Review historical deviation data to reclassify into track-and-trend events and deviations.
b	Review data for recurrences and repeats for both deviations and track-and-trend events by completing Pareto analysis. Identify target categories for further work.
Milestone 8 – Complete the first major deep-dive trend investigation	
a	From Pareto analysis of the track-and-trend data, identify the category for investigation.
b	Assemble a multi-disciplinary team to investigate the top Pareto category using the advanced investigation methodology.
c	Document the investigation findings and share with all stakeholders.
Milestone 9 – Complete the knowledge transfer to the next site/global implementation team	
a	Complete a thorough after-action review of all steps of the milestone plan, with a multi-disciplinary team.
b	Share the learnings with the transfer site/global team.

Appendix 3

Guidance for companies using *Is there a significant compliance issue?* in their decision-making process

If you have this question in your model, you may wish to include the following guidance on where this question should be answered as YES:

- There are issues arising from a design deficiency, significant execution errors or systemic execution errors within a quality system
- There is a failure to meet the commitments made to regulatory agencies as part of an inspection response
- There is a failure to meet the requirements contained within certain regulatory guidance documents
- A final drug substance/product batch has been released to an incorrect country
- There is a data/information fraud or critical data integrity issue
- There are incorrect data released from the quality control laboratories that were not identified by laboratory personnel
- A deviation was identified outside of routine processes (i.e. a surprise to the organization)
- A recurrence is unacceptable to the organization.

Appendix 4

Example of more detailed guidance from one company

A member company in the DMS Workstream has shared its own internal guidance. This is shown in a simplified form in Table 7 and in a more detailed form in Table 8. Note that Table 7 uses the term 'deviation' for all events that require classification. In this member company, if any of the questions in Tables 7 or 8 are answered 'Yes', an investigation is triggered. If the questions are answered 'No', a track-and-trend event is triggered. The company has provided some explanation below.

"In our company, we use the word 'deviation' to describe any unwanted event. All deviations must be reviewed to determine the likely cause of the deviation and the need for corrective and/or preventive actions and if we should track-and-trend or investigate. We anticipate that most deviations will be in the track-and-trend category.

Some deviations must undergo extensive investigations to determine the root cause. These deviations are identified by using a risk-based approach where you answer five classification questions. If you answer 'Yes' to one or more of the questions, the deviation will be classified as a major deviation and a root cause investigation must be made."

Table 7: Simple company example of the classification questions and when to answer 'Yes'

	Classification question	When to answer YES
1	**Is there a risk to product quality and/or patient safety?**	When we cannot rule out that the deviation impacts on the safety, quality, identity, potency or purity of a product or the performance of a device.
2	**Are we deviating from registration material, including clinical trial application (CTA)?**	When we do not comply with the contents of the documents that our company has submitted to regulatory authorities. Registration materials, including CTAs, are defined as the material we submit to regulatory authorities to obtain marketing authorization or approval to conduct a clinical trial .
3	**Are we deviating from the validation state of any equipment, process or system?**	When we do not follow the change-control process. When we use processes, equipment or systems that are not qualified/validated. When we operate outside of the validated range for critical parameters.
4	**Is further investigation needed to know why the deviation happened and/or to delimit the deviation?**	When we cannot determine what caused the deviation before we classify the deviation or when we cannot perform a final delimitation of the deviation before we classify it.
5	**Has the event happened before and now requires a more thorough investigation?**	When the deviation has happened before within the last 12 months and we suspect that the cause of the deviation previously identified is not correct and/or preventative actions are needed.

Example of more detailed guidance from one company (continued)

Table 8: Detailed company example of the classification questions

1	Is there a risk to product quality and/or patient safety?
a	Non-conforming products or material: components, raw materials, bulk, excipients, primary and secondary packaging materials and finished products that do not meet specification, unless: • The fault is only cosmetic (according to local procedures, to be specified by each company), and/or • The product or material has not or will not be used in production, and/or • There is a barrier in the process that prevents the release of affected items, for example: - A 100% routine inspection where items with faults are removed - Vision control ensuring the rejection of faulty items - Mechanical barriers preventing faulty components from being assembled/mounted on the line, for example: - A faulty device component cannot be assembled into a pen - A faulty aluminum cap cannot be mounted.
b	Mix-up of components, raw materials, bulk, excipients, primary and secondary packaging materials and finished products.
c	Contamination of components, raw materials, bulk, excipients, primary and secondary packaging materials and finished products.
d	Use of expired components, raw materials, bulk, excipients, primary and secondary packaging materials .
e	Use of components, raw materials, bulk, excipients, primary and secondary packaging materials that have no status assigned.
f	Problems with product stability and equivalency .
g	Lack of documentation for the product, if the lacking data cannot be found in other documentation.
h	Impact on data integrity, which may affect product quality and/or patient safety.
i	Lack of traceability in manufacturing, for example: • Used equipment • Used analytical method • Batch numbers • Item numbers.
j	Lack of execution of critical activities in production.
k	Quality control analysis faults that can result in a wrong conclusion on the quality of components, raw materials, bulk, excipients, primary and secondary packaging materials and finished products, for example: • Dilution errors • Analytical errors.
l	Potential impact on patient safety, for example: • Ask global safety and clinical units.
m	Potential impact on clinical trial conduct, for example: • Ask clinical unit.
n	The deviation results in a repetition of process steps or additional process steps, for example: • Disassembly • Sorting • Re-testing • Re-packaging. If the above has already been performed before the classification, the deviation must still be classified as a major deviation.

Example of more detailed guidance from one company (continued)

2	Are we deviating from registration material, including CTAs?
a	We are deviating from what we have stated in, for example: • Facility and equipment documents • Drug master files • Site master files • Product group instructions and process parameters registered with the authorities.
b	We are deviating from what we have stated in answers to inspection findings, e.g. that included in the change log of SOP documents.

3	Are we deviating from the validation state of any equipment, process or system?
a	Implementation of changes to equipment, processes or systems without following the change-control process and/or without adequate testing, qualification and/or validation.
b	Use of equipment, processes or systems before approval of qualification and/or validation.
c	Use of equipment outside of the qualified and/or validated range, e.g. A.V.

4	Is further investigation needed to know why the deviation happened and/or to delimit the deviation?
a	We are not sure what caused the deviation.
b	We know what caused the deviation, but we are not sure if the delimitation is correct.

5	Has the event happened before and now requires a more thorough investigation?
a	We doubt the cause we concluded in the previous deviation(s), e.g. because we have previously corrected a similar deviation and did not expect the same deviation to occur again.

Appendix 5

Investigation root cause analysis best practice report

The BioPhorum Human Performance Workstream identified the importance of effective investigations as they relate to furthering the maturity of a human performance operating philosophy and effective deviation management. In 2016, the Human Performance Investigations and Root Cause Analysis Best Practices sub-team delivered a report that included the current state, best practices and recommendations.

The report is available to members only and can be found here **https://bpog.imeetcentral.com/p/aQAAAAAEEdmR**

Advanced investigator training, designed by the Human Performance Workstream based on the recommendations of the Investigation root cause analysis best practice report, is available to members here **https://bpog.imeetcentral.com/p/ZgAAAAAAxzTF**

Appendix 6

Members-only area company case studies

Company	Case study presentation	Recording of presentation
Fujifilm	https://bpog.imeetcentral.com/p/aQAAAAAD0YsW	https://bpog.imeetcentral.com/p/aQAAAAAD0Ype
Regeneron	https://bpog.imeetcentral.com/p/aQAAAAADzOJV	https://bpog.imeetcentral.com/p/aQAAAAADzOMD
Biogen	https://bpog.imeetcentral.com/p/aQAAAAADzOIo	https://bpog.imeetcentral.com/p/aQAAAAAD_20t
Amgen	https://bpog.imeetcentral.com/p/aQAAAAADzOAz	https://bpog.imeetcentral.com/p/aQAAAAAD_20v
Sanofi	https://bpog.imeetcentral.com/p/aQAAAAADyHj9	https://bpog.imeetcentral.com/p/aQAAAAADyFYs
Merck & Co Inc., Kenilworth, NJ	https://bpog.imeetcentral.com/p/aQAAAAADw1KZ	https://bpog.imeetcentral.com/p/aQAAAAADw1Oa
Lonza	https://bpog.imeetcentral.com/p/aQAAAAADvRLI	https://bpog.imeetcentral.com/p/aQAAAAADvRNE

References

1 Chviruk B., Amherd E., Antonetti J.J, Verdon P. and Patnaud A., *Transforming Deviation Management*, BioProcess International, 15(8) 201, 7

https://doi.org/10.46220/2020DS001