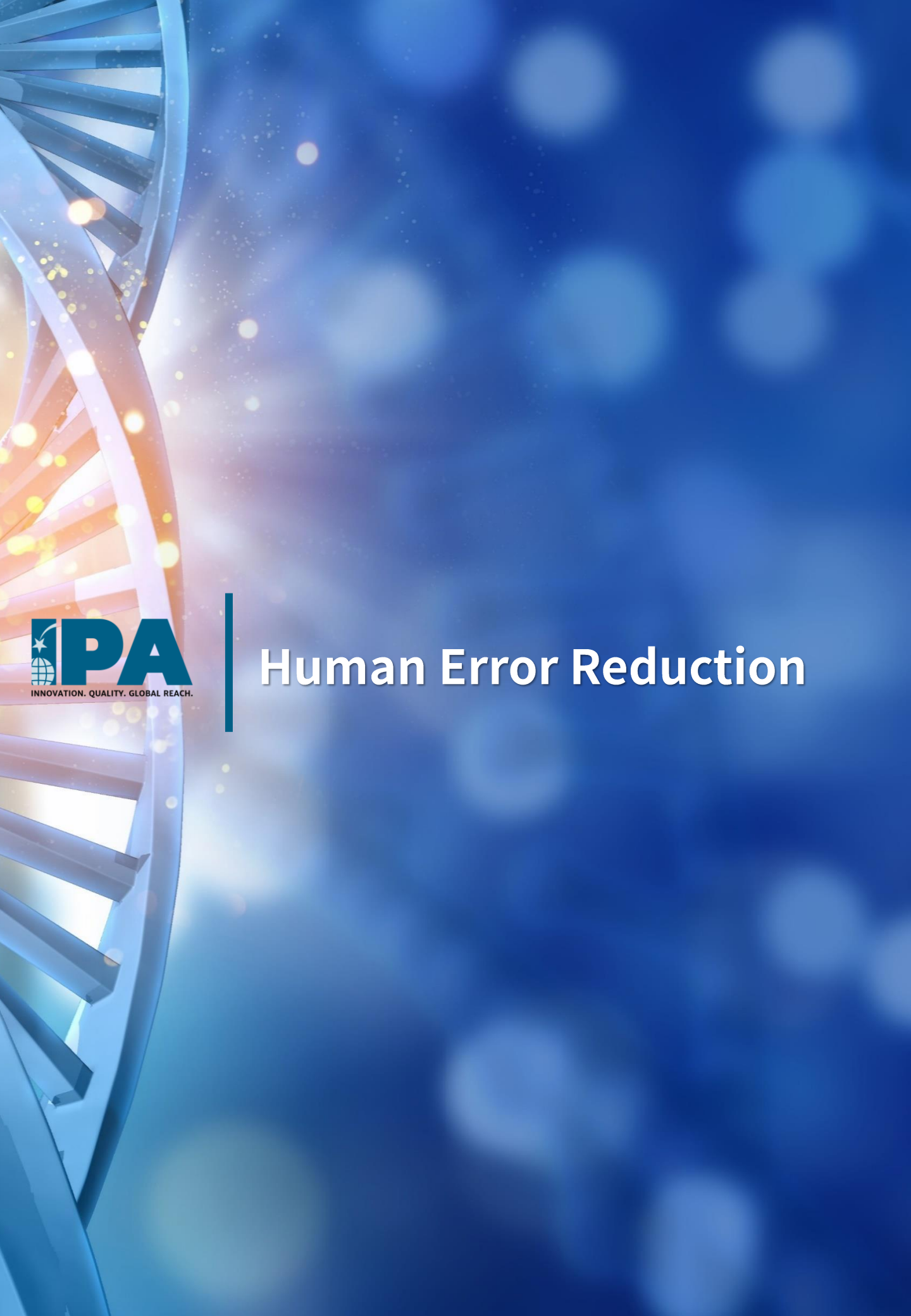
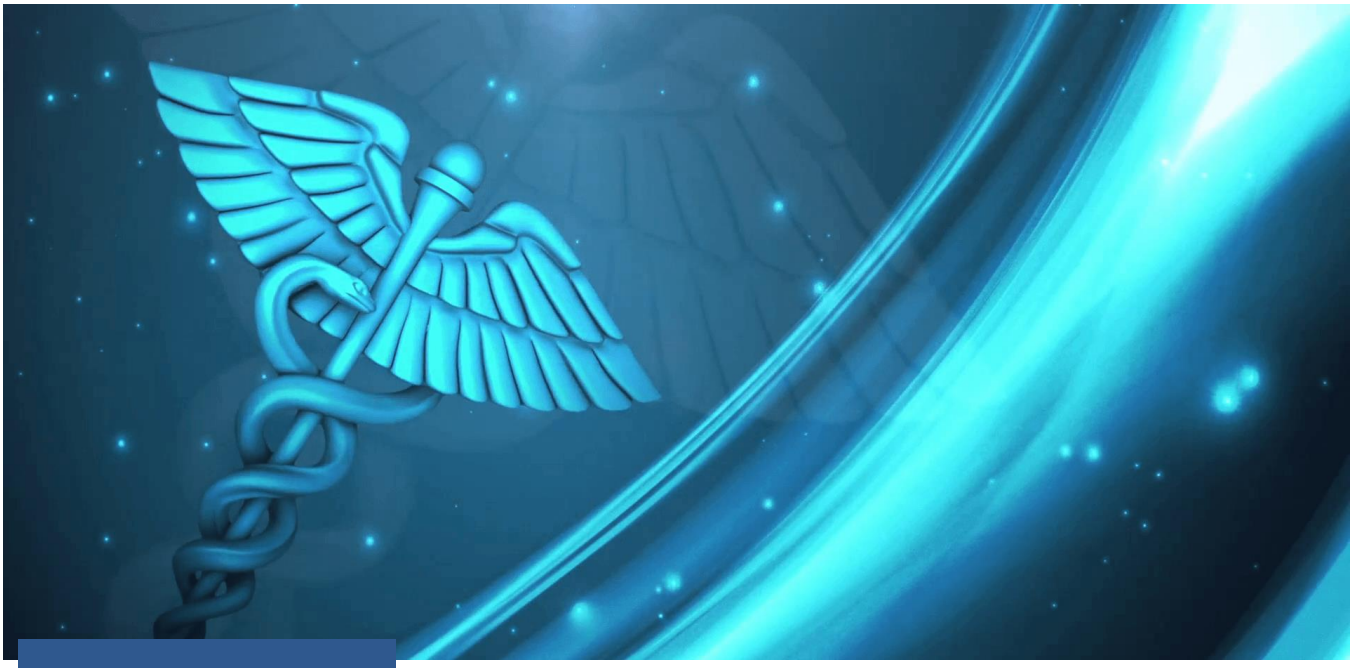

IPA
INNOVATION. QUALITY. GLOBAL REACH.
Human Error Reduction

CONTENTS



PREFACE

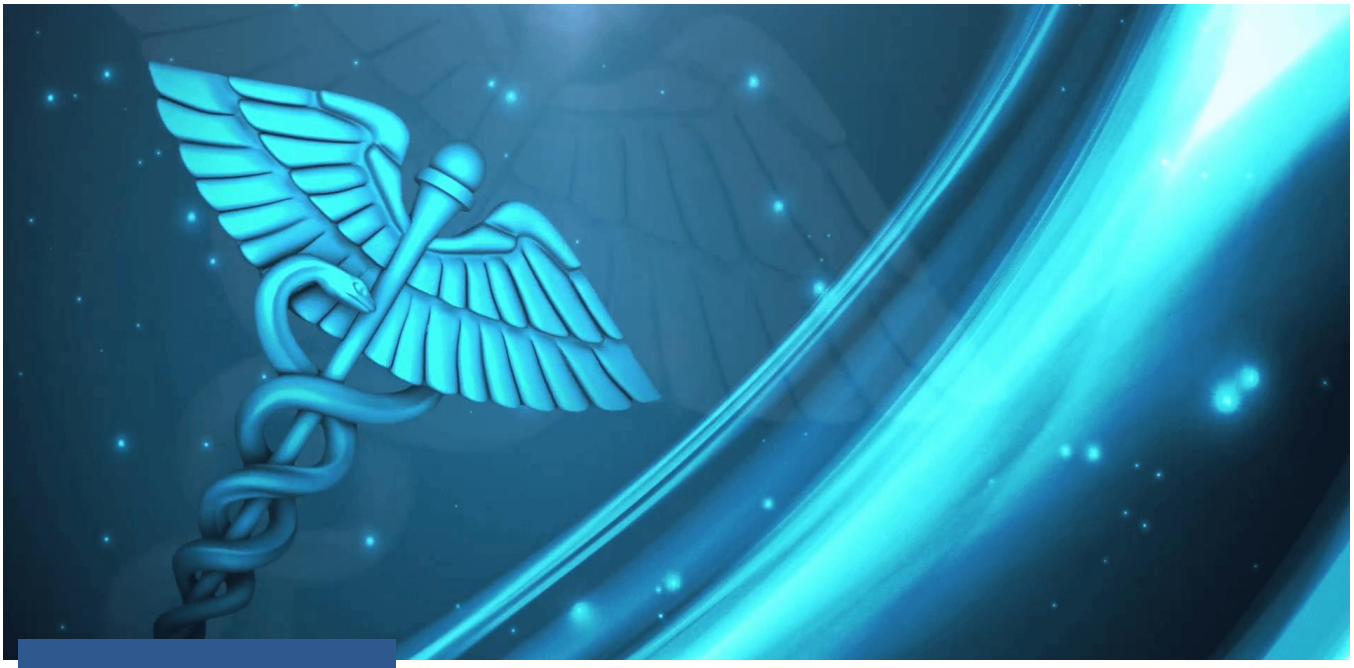
In April 2015, The IPA launched its Quality Forum (QF) to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of Best Practices Documents for several of these topics. In this document, we focus on best practices for Human Error Reduction. We had released a comprehensive set of Data Reliability Guideline in February 2017, Process Validation Guideline and Good Documentation Practice Guideline in February 2018, Investigation of non-conformities in February 2019 and Handling Market Complaints Best Practices in February 2020.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Sanjay Ghare (Cipla); Dr Ranjana Pathak (Dr Reddy's); Sneha Shree (Dr Reddy's); Yogita Bhanwaria (Dr Reddy's); Nilanjana Basu (Lupin); Narendra Deshpande (Lupin); Raju Tukra (Sun Pharma); Sweety Shah (Torrent); D B Sridhar (Zydus Lifesciences) and Manoj Kumar Gera (Zydus Lifesciences). The IPA wishes to acknowledge their concerted effort over the last 12 months. They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and other regulatory bodies such as UKMHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's 8th Global Pharmaceutical Quality Summit 2023, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.



PREAMBLE

In Feb 2019, IPA published a guideline on 'Investigations for Non-Conformities'. This has been a guiding document for handling all the investigations carried out in a pharmaceutical manufacturing facility. While the parent document elaborates on the procedures and various tools used in investigation, it only presents a bird's eye view when human error is regarded as a cause of non-conformance. Given the vast scope of the subject matter and its implication for the pharmaceutical industry, it is the need of the hour to have an illustrative guideline focusing entirely on human error investigation and its remediation. It is suggested that this guideline be read in conjunction with the mother guideline on investigation. Readers are assured of alignment between these two guidelines.

As technology advances, human error in manufacturing becomes more and more visible every day. Human error is responsible for more than 80 percent of process deviations in the pharmaceutical and related manufacturing environments. However, unlike other failures such as process or equipment failures, human failures are not commonly investigated in a similar detailed manner and, notwithstanding the root cause, the organization ends up in providing retraining to the concerned employee. On a similar note, USFDA draft guideline on Quality Metrics makes the following observation on retraining: "FDA has observed that less robust quality systems often rely on preventing recurrence solely through personnel re-training, i.e., the same training that has already been provided to the employee(s), while more robust quality systems consider re-design and re-development of the process." This re-design and redevelopment of process can only happen when there is a sound human error investigation process made available in the organization.

Time and again it has been realized that in order to prevent recurrence, the underlying cause of human error needs to be thoroughly understood in order to uproot the error from the system.

1 Purpose

This guideline intends to provide direction in human error investigations and describes various approaches and methodologies to carry out such investigations. This does not limit the application of individual experience and understanding in finding the true root cause. Rather these are expected to act in synergy when applied in conjunction with the described methodology. The guideline also defines the monitoring mechanism to be followed in an organization in order to sustain the application of this methodology in human error investigation.

2 Scope

This guideline is applicable to all the investigations carried out at manufacturing sites for non-conformities like batch failures, market complaints, system failures, equipment failures, out-of-specification results, out-of-trend results, deviations, out-of-calibration results, environmental monitoring failures, observation(s) outside acceptable range, any incident which occurs in QC, manufacturing facility, non-conformance with regulatory requirements, etc.

3 Responsibility

3.1 All employees and personnel involved in GMP functions, e.g., manufacturing, quality, engineering, IT, warehousing and distribution of pharmaceutical components, intermediates, drug substances or drug products, etc., are responsible for reporting any incident/non-conformity observed where the preliminary assessment indicates the possibility of human error.

3.2 The head of the respective department or the subject matter expert (hereinafter referred to as SME) from the department where the non-conformance has occurred shall lead the investigation.

3.3 The investigation leader shall be responsible for:

3.3.1 Planning the investigation to ensure that it is systematic and complete.

3.3.2 Forming the investigation team (involving SMEs from cross-functional teams as per the reported non-conformity).

3.3.3 Leading the team in developing, executing, and documenting the investigation plan, data collection including operator interactions, review and analysis, root cause determination, investigation conclusions, defining Corrective and Preventive Action (CAPA) along with CAPA effectiveness check plan.

3.3.4 Reviewing completed investigations with QA and obtaining approval of the investigations.

3.4 The composition of the investigation team shall be decided upon the evaluation of the problem statement and shall include SMEs from applicable departments, e.g., Engineering, Development, Quality Control (QC), Quality Assurance (QA), Production and other relevant departments as required, to assist in the investigation process.

3.5 Departmental/Functional heads shall ensure adequate resource allocation so that investigations can be concluded in a timely and effective manner.

3.6 Site QA head or his designee shall be responsible for review and approval of:

3.6.1 Experimental studies conducted to arrive at the root cause.

3.6.2 Investigation report.

3.6.3 Investigation extension, if required.

3.7 SMEs involved in the investigation shall be the signatories/reviewers in the investigation report.

3.8 Site QA head or designee shall communicate the findings of the human error investigations to the management periodically based on the Management Review SOP.

3.9 Site QA shall be responsible for sharing the applicable investigation details to with other sites in order to implement CAPA across respective sites in the organization.

4 Definitions

4.1 Human Factors: Any factor that influences behavior at work that can affect the output of the process where a human being is involved.

4.1.1 Human Failure

Any time a human activity deviates from accepted standards, rules, or procedures.

4.1.2 Human Reliability

The likelihood of successful human performance within specified timeframes and environmental conditions. It is critical to overall system reliability and is one factor that contributes to, or prevents, unwanted events occurrence.

4.1.3 Human Error

An act that may produce unintended results when a human being is involved. It is an action or decision that was not intended, that involved an involuntary deviation from an accepted standard, and that led to an undesirable outcome. For example, a laboratory technician, while performing two tests simultaneously, inadvertently swaps the samples.

4.1.4 Human Violation

A deliberate or intentional deviation from a rule or procedure. For example, a production operator fills out a cleaning record without actually performing the cleaning.

4.2 Investigation : A sequentially documented, logical, scientific review and/or analysis of data to discover facts and clues related to all quality events that lead to the identification of contributory root causes and associated corrective and preventive actions. It is a systematic approach to identify the assignable and most probable cause(s) of any reported non-conformance.

Various investigation techniques are summarized below. Further details on investigation techniques can also be referred from the earlier IPA guideline on 'Investigations for Non-Conformities'.

4.2.1 Drill Down Analysis

An interactive way to explore data points, review processes and view raw-level data in the grid without changing the underlying query.

4.2.2 Spaghetti Diagram

A visual representation using a continuous flow line tracing the path of an item or activity through a process.

4.2.3 Root Causes

The underlying reasons for the non-conformance which are confirmed by scientific evidence of a sequence of events and observations. Root cause analysis is a systematic method to understand the root cause(s) which contribute to the error, failure or non-conformity

4.2.4 Cause and Effect Diagrams (Ishikawa or Fish Bone)

A visual tool that is used to logically organize the potential causes of a desired result, or effect.

4.2.5 Why Analysis

The five whys technique constitutes a questioning process designed to drill down into the details of a problem and peel away the layers of symptoms. The technique was originally developed by Sakichi Toyoda who stated that "by repeating why five times, the nature of the problem as well as its solution becomes clear".

4.2.6 Gemba Walk

Gemba means "actual place". Gemba is a well-defined element of lean concepts and, as such, an accepted operational excellence tool in industries that have adopted lean concepts.

5 Procedure

5.1 INTRODUCTION

Human error has been considered a common cause of deviations, failures and/or variations in a process. In the manufacturing industry, human errors have been encountered under various labels (procedural disobedience, lack of attention, multitasking to name a few).

Errors are basically the symptoms of a cause or causes, which needs to be understood and addressed. Human error should be viewed as the effect, rather than the cause.

Introduction of technology viz., automation/artificial intelligence, etc., could prevent human error; however, such technologies are in the early stages of evolution in the pharma industry.

In the meantime, it is crucial to understand that the majority of the processes are still manual, i.e., these require human intervention and thus the occurrence of errors remain unpredictable to a large extent.

There are three primary elements that are potential triggers of human errors, viz. task complexity, behavioral characteristics, and error-prone situations.

In addition, there are multiple precursors to human error that contribute to the occurrence of errors.

Task Demands:

- Time pressure (in a hurry).
- High workload (memory requirements).
- Simultaneous, multiple tasks.
- Repetitive and monotonous actions.
- Incorrect interpretation (of instructions and situations).

Individual Capabilities:

- Unfamiliarity with task.
- Lack of knowledge/proficiency/experience.
- Lack of effective communication.
- Inadequate problem-solving skills.
- Lenient attitude for critical task.
- Illness and/or fatigue.

Work Environment:

- Distractions and interruptions.
- Changes or departures from routine.
- Confusing displays or controls.
- Culture of accepting workarounds.
- Unaddressed personality conflicts.

Human Nature:

- Stress (limits attention).
- Habit patterns.
- Assumptions (inaccurate mental picture).
- Complacency and overconfidence.
- Mindset ("tuned" to see).
- Inaccurate risk perception (Pollyanna Syndrome).
- Limited memory.

5.2 HUMAN ERROR CLASSIFICATION

When an operator does not execute a task properly, it is deemed as human error. However, when the failure event is investigated, multiple inherent process vulnerabilities may surface, viz. lack of clarity in work instructions, inadequate training, supervision, etc.

Despite the evolved understanding of human errors, the industry still adopts conventional approaches like retraining for remediation. However, training being a weak remediation, human errors are not eliminated completely and re-occur.

The classification of human error is given below:

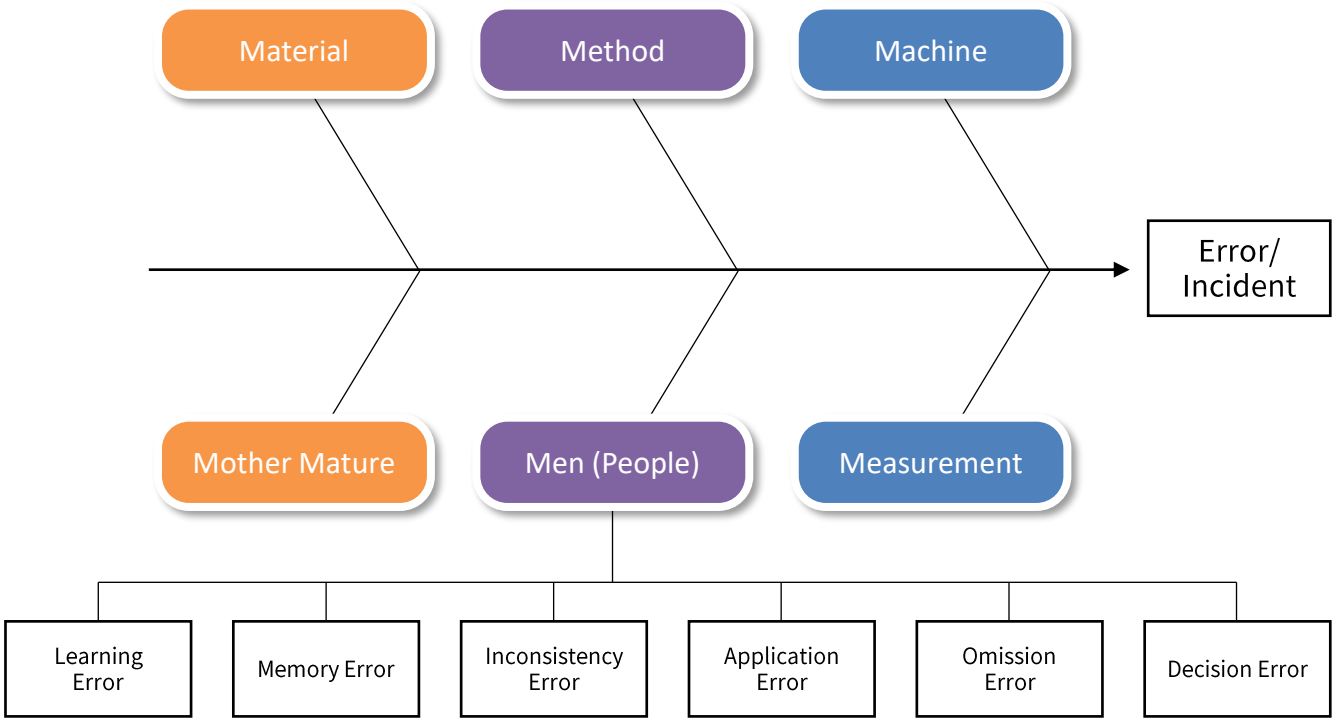
- Learning Gap
- Memory Gap
- Inconsistency
- Application
- Omission
- Decision Making

5.3 HUMAN ERROR INVESTIGATION

Errors, that take place at manufacturing shopfloor and laboratory, range from an error in entry to an error in quantity while batch charging. The risk impact of an error varies and the decision to go for a full-fledged human error investigation is best decided taking into account the risk impact.

5.3.1 Fishbone Analysis

The most common investigative tool used in various industries is the fishbone analysis wherein all the possible contributory factors are evaluated. When "Man" is identified as the most probable causative factor, further drilling down to the root cause can be done using sub-classification of various human factors as shown in the diagram below.



Along with the above methodology, the approaches mentioned below also can be employed for human error investigation.

5.3.2 Error Chain

In human error investigation, it is important to identify the 'error chain'. Behind any identified error (A) that leads to an untoward event (B), there is a sequence of factors that set up the conditions such that error A results in event B and without which event B would not have occurred. This is known as the 'error chain'.

The error chain consists of 'active failures' and 'latent conditions'.

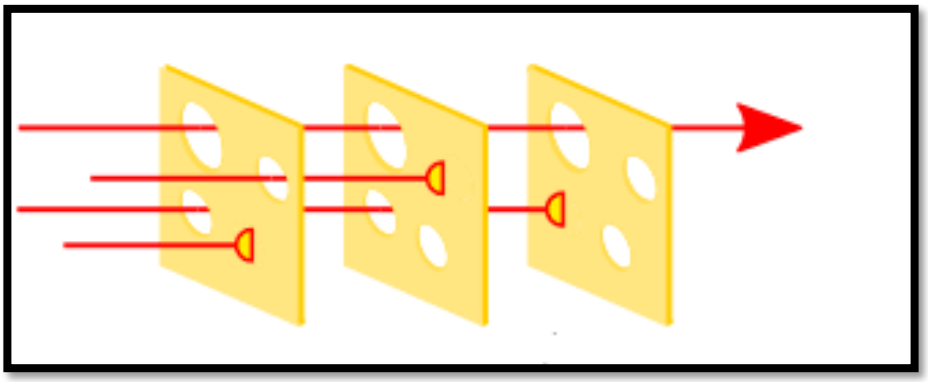
Active failures are acts committed by doers who are in direct relation with the system. These are in the form of slips, lapses, mistakes, and procedural violations. Active failures have a direct and usually short-term impact.

Latent conditions arise from decisions made by the author of the procedure and senior management. All such strategic decisions have the potential for introducing vulnerability into the system. Latent conditions have two types of adverse effects - they can be converted into 'Error Producing Conditions' within the local workplace (inadequate equipment or facility, procedure, under-staffing, etc.), and they can produce long-lasting gaps or weaknesses (design and construction deficiencies, unworkable procedures, etc.).

Latent conditions may remain dormant within the system for a long time before they combine with active failures and eventually create an opportunity for an incident to occur. Unlike active failures, that are often hard to predict. Latent conditions can be identified and resolved proactively. This is referred to as the identification of 'Error Producing Conditions' at the workplace.

5.3.3 Error Producing Condition (EPC)

Error Producing Condition (EPC) can be best explained using the 'Swiss Cheese Model'. Every system has various levels of controls (represented as slices of cheese as shown in the diagram below) and they keep on protecting the system to avoid a failure. These controls can be engineering controls, e.g., machine interlocks or alarms; administrative controls, e.g., procedures, visual aids/displays; and people control, e.g., training, briefing, etc. As per this model, even if one control fails, the other control(s) takes over to prevent a failure. However, on a rare occasion, when all these controls fail at the same time, there is an error producing condition. . The same is depicted below*:



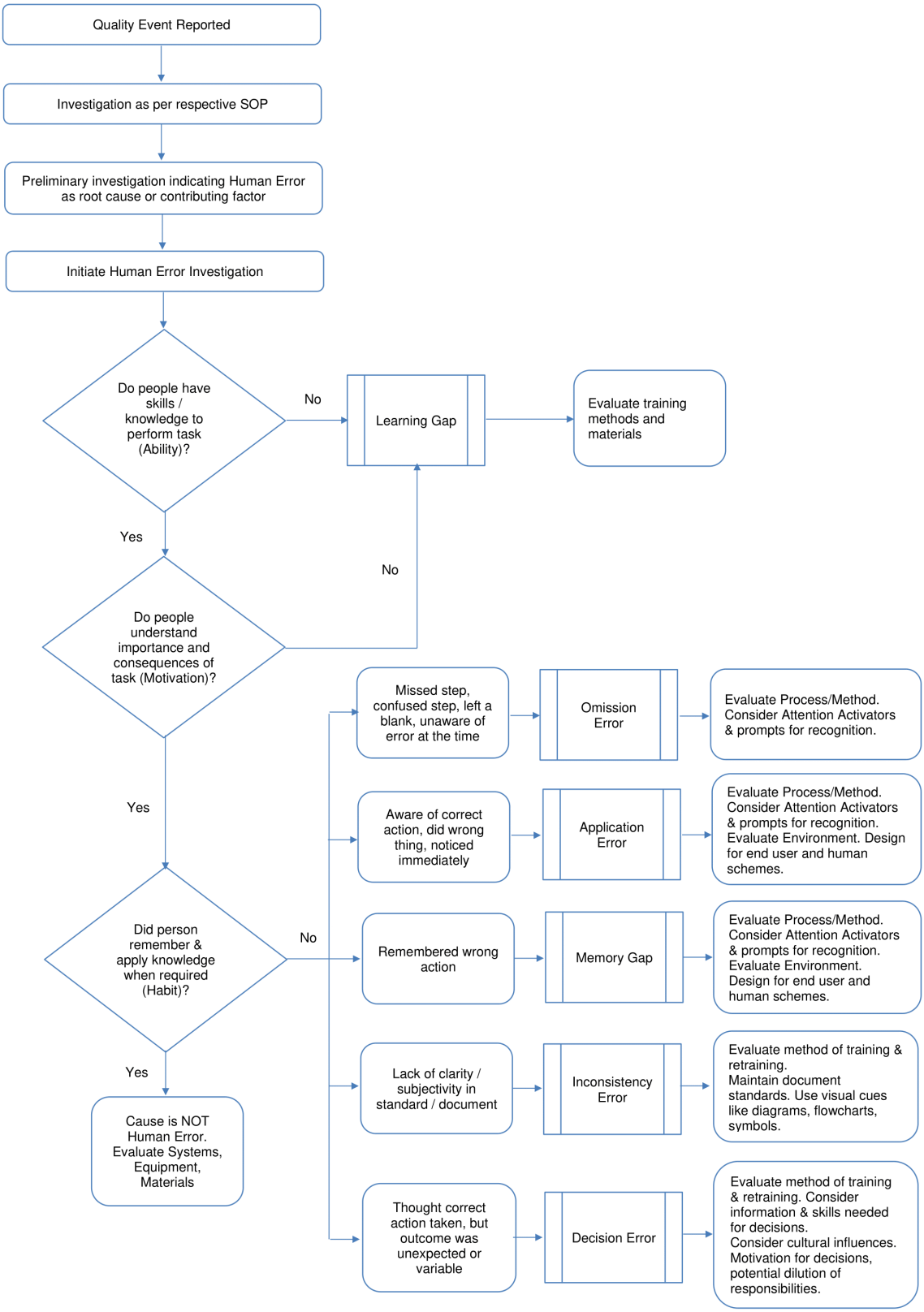
*https://en.wikipedia.org/wiki/Swiss_cheese_model

Measures like Gemba Walk have proved to be helpful as early warning of a potential failure.

5.4 ROOT CAUSE DETERMINATION

A: Flow chart

If the preliminary investigation indicates that the cause of failure is human error, the following path of investigation will help to drill it down further (www.pda.org).



B: Drill Down

Based on the initial investigation and arriving at the immediate cause using the previous guideline on Investigations for Non-Conformities, further drill down for the real cause of human error shall be done by:

- Observation of the analyst/operator by the investigator at their workstation/s.
- Interactive session with analyst/operator by the investigator to understand process and procedure adequacy and gap.
- Inviting and consolidating feedback from peers on the pain areas/possible causes around the event through a structured brainstorming process.
- If the cause of error is found to be related to people capability, it should be categorized accordingly. (Refer to 'Inadvertent error' under section 5.2)
- For system related shortcomings, the following evaluation checklist needs to be followed in order to understand whether the error has happened due to one or more of the factors listed below:
    - Absent or inadequate processes (Was there total clarity of instructions in the procedure?).
    - Training inadequacy (Was training adequate?).
    - Lack of experience (Was the relevant person experienced?).
    - Gaps in communication (Was supervision adequate?).
    - Deliberate error (Was there any sign of negligence?).
    - Timely availability of required resources (Was the infrastructural support for job delivery adequate?).
    - Stress conditions (physical and/or psychological) (Could fatigue play a role in this failure?).
- In addition, the overall governance structure and the identification of right metrics also plays a major role in sustenance of error-free situation.

Clarity of instructions in procedure

Sr. No.	Definition	Example
1	Is there an approved SOP in place for the task?	Absence of an approved procedure for layer separation in API manufacturing may lead to operator-to-operator variation and sometimes errors.
2	Does the existing SOPs provide all encompassing elaborations?	SOP says, "Wipe clean the entire surface using lint-free duster…," but does not mention ways to reach "hard to clean" surfaces.
3	Does the SOP mention handling deviations, if any, in the task/activity?	While adjusting pH of a solution, if it goes beyond the desired range, there is no instruction on how to handle such a situation, i.e., bring back the pH within range using acid/alkali or discard the solution and start afresh.
4	Approved procedure is available but not used often/always.	The SOP to clean a SS cartridge filter on steam line needs the filter to be boiled in dilute sulfuric acid followed by boiling in sodium carbonate solution and rinsing with potable water. The complexity may tempt people to skip or comply partially.

Sr. No.	Definition	Example
6	No startup checklist, for beginning of day/shift work. Reliance on memory (and not procedure) for identifying areas that need attention/check.	There is no checklist to ensure opening/closure of valves at the time of layer separation, transfer from reactor to centrifuge, etc.
6	No unambiguous visual indication of point reached in work sequence.	During a document review, a reviewer attends a phone call and on resumption does not remember the point in the document where it was left earlier.
7	Familiar tasks not performed recently or performed without checklist/prompt.	Assigning sample on the technique which was not practiced in near past.
8	Task, once familiar, but now used less often, performed without checking change in process details.	A major change in STP may go unnoticed to the analyst who returned to the particular STP after a considerable gap.

Was training adequate?

Sr. No.	Area of Evaluation	Example
1	Training does not cover all aspects of processes.	Selective training is given only on the activity supposed to be carried out by the person. For example, a new analyst is trained on how to create an HPLC sequence but not trained on amending sequence.
2	Training does not include recovery from upsets or unusual situations.	In API manufacturing, while performing vacuum distillation, if the vacuum is not achieved, the operator is not trained on all the points that need to be checked in order to achieve desired vacuum.
3	Training covers 'what,' but not 'how and why'.	Explaining 'why' part of the operation makes an operator/analyst think before acting. This also helps to take informed decision if required. For example, during sifting, operator is trained not to use any means to force the material through mesh without stating the reason or the consequence.
4	Every person performing task has not received full training and assessment (temporary staff/part-time/reassigned staff).	In case of shortage of manpower, a makeshift arrangement is made by providing just the required training of one particular section of operation and not the complete job role curriculum.
5	No formal training provided. Competence developed by working with more experienced person and by trial and error.	The absence of structured training.
6	No specific training for task, under assumption that it takes only common sense to perform the task.	An analyst is made/allowed to work on mobile phase preparation after reading the respective SOP but without explaining nuances of such preparation.

Was the relevant person experienced?

Sr. No.	Area of Evaluation	Example
1	Competence on one/some/most tasks assumed to extend to (all) others.	Irrespective of qualification of analysts on a particular technique, blanket assumption that employees of a department, e.g., Quality Control, know and can work on all the techniques.
2	Competence assumed to go with role/rank/qualification or experience.	Experienced employees are assumed to be competent.
3	Seldom-used processes not practiced or assessed regularly.	Processes which are not regularly used may not get practiced. For example, the air inlet chamber of an FBD/FBE positioned after the HEPA filter, is cleaned with a low frequency (say, once in a year). Due to this, compliance to the correct procedure may not be ensured.
4	Once familiar task, now used less often, performed without checking if the process details are unchanged.	The microbiologist who once used to handle autoclaving routinely was transferred to another section. During an exigency, when he was required to again operate the autoclave, he missed to execute the changed loading pattern.

Was supervision adequate?

Sr. No.	Area of Evaluation	Example
1	'Blind-eye' turned to 'custom and practice' violations of formal process.	Short cuts adopted by employees are ignored by supervisors in the interest of timely product dispatch.
2	To watch out for signs of complacency setting in e.g., in experienced people, routine process, low perceived risk, etc.	Warning signs dismissed as 'one-off cases', expressed concerns are dismissed, and possible consequences of error are downplayed/seen as manageable, thanks to a 'laissez-faire.' attitude.
3	Perception that the individuals and groups recognized as experts cannot be challenged, even if they do not comply with procedures.	Seniors in the group not challenged for not following procedure. For example, in the manufacturing shop floor, the concerned manager/senior does not adhere to required gowning practices.
4	Risk taking seen as necessary to achieve own objectives/expectations of others.	Identifying individuals/group of individuals that will do 'anything' to get the desired results.

Was there any sign of negligence?

Sr. No.	Area of Evaluation	Example
1	People working on 'autopilot' when the task is 'second nature.'	While filtration of mobile phase is going on, analyst is busy weighing reference standard without making sure that filtration is progressing as desired.

Was the infrastructural support for job delivery adequate, e.g., hardware design?

(This is important to consider in case there is any inherent problem with the machine that is responsible for the variant condition).

Sr. No.	Area of Evaluation	Example
1	Layout of the work area not matched to process requirements or natural sequence of activities.	Analyst/operator has to move a lot between two activities. This leads to fatigue. For example, position of valve on mother liquor line of a centrifuge placed in powder processing area is outside the area. Operator has to de-gown, move to area, close the valve, re-gown and resume.
2	Working surfaces overcrowded, where location is important; for example, various grades of items stacked in separate piles.	Typically, the glassware storage area, if not properly managed, can lead to picking of a 200ml volumetric flask instead of a 1,250ml one. Similar errors can happen with volumetric pipettes.
3	Several similar containers (bins, folders, etc.) used to keep different items that look alike.	Same as above, but for chemicals storage where similar containers with different chemicals are kept. If there is no discipline, an incorrect chemical can be picked up.
4	Background color of working surface provides poor contrast or competes with intended object of attention.	Any activity that needs visual judgement can be affected due to this. For example, while reading a meniscus, if the graduation line does not become clearly visible due to improper background, it can lead to dilution error. In another example, while performing layer separation in API manufacturing, when both the phases are clear solutions, there can be error of mixing the layer due to incorrect background color.
5	Screens, equipment displays, labels and documents etc., too far away to be seen easily.	Typically, displays/calibration labels may be misread if they are placed at an inconvenient height and expected to be read. Error may occur due to using an instrument/equipment which is out of validated calibration period.

Sr. No.	Area of Evaluation	Example
6	Things that need to be handled or adjusted are too far away to reach easily.	On a visual inspection conveyer belt if shorter employees are deployed, they may find it inconvenient to press the brake of conveyer belt on time.
7	Processes with differing requirements share same/nearby workspace.	Common area for mobile phase filtration and sonication creating noise and distraction.
8	Failure-critical task located where access is difficult.	Typically, in API manufacturing, valve operation to perform layer separation is located at a height. Without a proper platform, operator is likely to miss the separation leading to a mix-up.
9	Special clothing worn fit poorly, are uncomfortable or limit movement.	If some instruments, like a sonicator, are placed on a work bench, it becomes difficult for shorter analysts to observe proper sonication.
10	Special clothing worn fit poorly, are uncomfortable or limit movement.	Inappropriate gowning in areas where they are demanded can lead to discomfort in harsh environmental conditions. Another example is the use of inappropriate size of gloves that can reduce tactile sensitivity and lead to errors.
11	Lighting not appropriate for task, i.e., not bright enough, too much glare, wrong color, wrong angle, etc.	Inadequate lux level in the areas where visual activity is to be performed can pose challenge to sustained quality work. For example, in the document review area if lux level is low, there will be strain on the eyes of the reviewer which will be detrimental to a sustained high quality of review.
12	Overcrowding of visual field.	There is possibility of mix-up, if on a QC workbench, there is cluttering of glassware of current analysis as well as previous analysis; the latter have not been discarded due to pending review of documents or an OOS test result.
		In API manufacturing, valve mis-operation can occur when there is network of pipelines from which one has to select the appropriate valve.
13	Noisy, and activities which need silence located together.	Typically, the document reviewers, who need silence to focus, are made to sit in area where a lot of conversations happen, or a telephone is kept.
14	Some groups/individuals may not be able to fully comply.	Height of level indicator at such a level where a short person cannot reach. Machine set up is such that left handers cannot fully follow the procedure.

Could fatigue play a role in this failure?

Sr. No.	Area of Evaluation	Example
1	Person is working for long hours more frequently.	Especially in case of shortage of manpower or during peak of dispatch. Decay in vigilance and errors related to short-term memory lapse can occur.
2	Not enough breaks from work or no rotation of tasks.	For activities where physical exertion occurs, there can be reduced vigilance, e.g., visual inspection of secondary packing activity for prolonged time.
3	Shiftwork rotation.	If there are frequent changes in shifts (e.g., 2 days of night, two days of evening and 2 days of morning shifts), the circadian rhythm gets disturbed and leads to errors.
4	Staff shortage.	More work is divided among fewer people leading to adoption of short-cuts which in turn leads to errors.
5	People pressured to work when they are ill, or distressed by demands away from work.	People with illness are prone to make more mistakes. Similarly, if they are pre-occupied due to out-of-work pressure, they will be prone to mental fatigue.
6	Extremes of physical environment.	Extremes of temperature and/or humidity can tire operators quickly, resulting in decay in performance. This is quite likely in intermediate area of API manufacturing.

Based on the above analysis, one should list down possible contributing factors that led or could have led to the event under investigation.

While the above areas of evaluation will support the root cause analysis on case-specific investigations, if there is a trend of particular errors occurring at a particular section of manufacturing/testing, proactive measure(s) can be initiated to find out the root cause and stop the recurrence starting right from understanding the process (creation of a detailed process flow diagram), along with the identification of the error prone areas through the methodology described under section B (drill down) of Root Cause Determination. Subsequently, the right CAPA should be chosen and applied.

6 Human Error

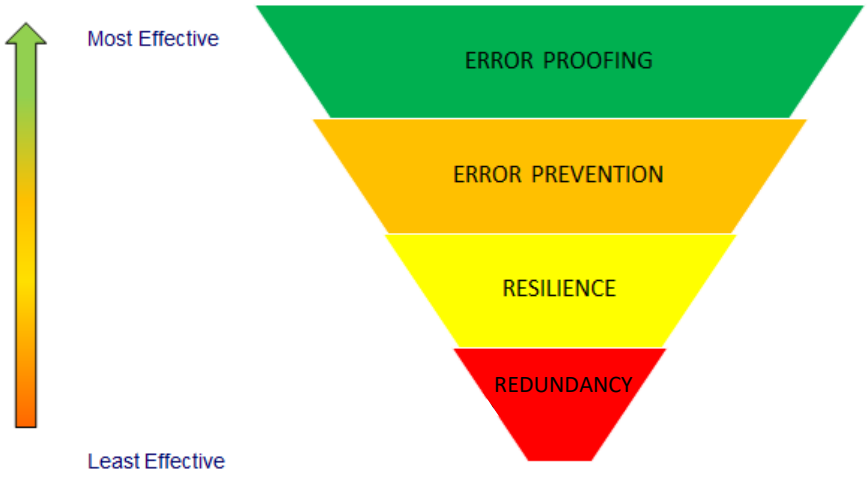
6.1 Error Handling Hierarchy and Hierarchy of Actions:

Organizations employ a wide range of error-reducing and error-containing techniques. These fall into one of four main error management strategies tabulated below, with examples:

Error Handling Model	Effectiveness	Description	Examples
Error Proofing (Mistake Proofing / Poka-yoke)	High	Design processes or systems in such a way that possibility of human errors is minimal.	❖ RMG cannot be operated if lid is open. ❖ Electronic data transmission tools such as bar code readers. ❖ Card reader checks to ensure training before admitting operator into specific area.

Error Prevention	High-Medium	Utilize attention activators within the documentation to prevent errors from occurring.	❖ Use of attention activators like
			  ❖ Sound.
			  ❖ Motion, change in pattern.
			  ❖ Change in colour.
			  ❖ Change in shape (e.g., use of boxes for text, symbols using different colour).
			  ❖ Change in text formats (bold, italic, size, etc.).
			❖ Use of colour in quality documents shall align with emotional associations (for example, green = go, red = stop). It is also easier to detect changes or omissions in patterns.

Resilience (Detect and Recover)	Medium-Low	Provide the option to “undo” the error, often utilizing additional attention activators or an undo or confirmation option when using electronic systems.	❖ In-process testing that allows adjustments like pH of a batch. ❖ Inclusion of a command (Yes/No) to recheck the record before finally submitting.
Redundancy	Low	Implementation of doer and checker principle / repetition of efforts.	❖ Double checking and observation of any activity by a second person. ❖ Retraining the same way as before (using same methodology/SOP/ learning assessment).



6.2 Derivation of Good Practices and Control Measures

For each vulnerable area, the corresponding 'good practice' is derived through brainstorming, Sometimes the good practice is easily defined, for example, for a low illumination area (e.g., 300 Lux), a good practice of improving the level of illumination (e.g., up to 700 Lux) can be quickly achieved. On the other hand, frequent transcription error can be addressed by applying a holistic approach (e.g., combination of good practices like sequencing of instructions, removing documentation redundancy, increasing font size in a document, improved ergonomics, reducing interruption/distractions, etc.).

One point to consider while proposing any good practice is that one must factor the associated fatigue/stress in its design. In such cases, good practices around availability of resources, clarity of instruction in the document, etc., should be made so robust that on 'bad days', the pre-designed cushion in the system will withstand the impact, thus preventing error.

6.3 Automation in Error Reduction

Automation is the use of technology to make a system, process or equipment run with least manual intervention. Automation, with correct set up, helps to reduce human error specifically in case of repetitive tasks. It does not necessarily remove the need for operators but it allows them to focus on other responsibilities.

The important goal of automation is to develop best possible tool for operators. This means that they should not just have access to data, but to data with context and meaning. For example, measuring the conductivity of purified water is of little value unless operators know its standard specification. The system should have provision to create charts and graphs that help operators to evaluate trends and understand target range.

Following are few examples of automations implementations at the shop floor.

Systems	Application
Electronic Logbooks	Electronic Logbook software is used to replace manual logbooks. This has reduced manual errors and also helped in real time entries.
Electronic Data Management	Electronic documentation systems have replaced the issuance of SOPs, forms and many other QMS documents. This system controls the issuance, storage, and archival through data-based system.
AHU ON/OFF Visual or Acoustic alarm	Audio Visual Display Alarms are installed in critical operation areas and connected with existing AHU systems in order to indicate AHU Stop/Trip status.
Online Temperature Monitoring	System-based temperature recording of quarantine rooms instead of manual recording. Online information of any excursion through alarm generation.
Online Recording of In-process Checks	Online recording and storage of in-process checks, instrument calibration results in software.
Digital Work Instructions (DWI)	DWI is used to digitalize manual checklists like cleaning checklist, visual inspection checklist, line clearance checklist, area cleaning checklist, preventive maintenance checklist, etc.
Cleaning Validation	Cleaning validation software is used for automatic calculation of surface residue limits, digitalize protocol and report templates.
Digital Display Board	Digital Display Boards can be used for general do's and don'ts practices.

7 Sustenance Of Human Reliability

Once an area attains an accepted level of human errors, multiple measures can be taken to sustain human reliability, as given below.

- Conducting periodic survey to gather information about perception of stakeholders on error reduction initiatives along with contemporary challenges. This will also throw light on emerging vulnerable areas.
- Periodic trending of data, i.e., before and after comparison of error reduction to see if the failure rates are reduced/maintained.
- Area-to-area comparison on error reduction initiatives/metrics in governance forum.

8 Case Studies

Following case studies provide a high-level insight on different categories of errors and recommendations for error controls using error handling hierarchy. However, an incident may involve multiple categories of errors. Identification of error category and further drill down analysis using specific checklists should be used along with correct perspective.

The error category should be read as a reference which may vary depending on the specific situation.

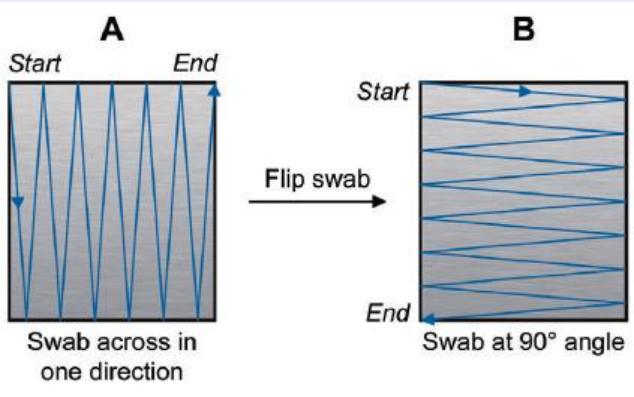
Error Description	Performing visual inspection of equipment surface cleanliness without inspector qualification.
Additional Information	Study results in biased outcome in terms of microbial proliferation, as ciprofloxacin itself exhibits inhibitory response to viable growth.
Error Category	Learning error
Recommendations	Campaign study protocol should be revised such that it should be ensured that the selected product does not have any known or unknown antimicrobial activity (Error Prevention Model).

Error Description	Swab samples for microbial and chemical examination collected from same location of equipment surface.
Error Category	Learning error
Recommendations	Revision of sampling plan of individual equipment to depict exact location for collection of microbial and chemical swab samples (Error Prevention Model).

Error Description	Performing visual inspection of equipment surface cleanliness without inspector qualification.
Additional Information	Learning gap (as the inspector was not qualified for inspection of equipment surface for its cleanliness) and procedural inconsistency for allowing personnel to inspect without prior qualification.
Error Category	Learning error
Recommendations	Inspector qualification procedure should be prepared, and cleaning SOP should be revised to incorporate a clause to perform inspector qualification, prior to deployment for visual inspection activity (Error Prevention Model).

Error Description	Operator forgets to check the environmental conditions of the manufacturing suite prior to commencement of the unit operation.
Error Category	Memory error
Recommendations	Usage of attention activator and a note added to SOP: “Record temperature and %RH prior to commencement of operation” (Error Prevention Model) OR Implementation of Environmental Monitoring System (EMS) for online data monitoring (Error Proofing Model).

Error Description	Wrong interpretation of chromatograms due to absence of reference chromatograms in STP.
Error Category	Inconsistency error
Recommendations	Reference chromatograms to be attached to the STPs and training to be imparted to analyst (Error Prevention Model).

Error Description	Inadequate swab sampling from equipment surface. Cleaning Validation (CV) protocol did not have the clause to perform zig-zag swabbing.
Error Category	Inconsistency error
Recommendations	Enhancement of CV protocol to include clause for zig-zag swab sampling in equipment surface along with pictorial depiction (Error Prevention Model). 

Error Description	OOS observed in assay test, i.e., obtained result as 194.6% against specification limit 90.0% to 110.0%.
Additional Information	Analyst did not make up the volume after addition of mobile phase.
Error Category	Omission error
Recommendations	Usage of pre-defined checklist (RDS) for execution of sample preparation (Error Prevention Model).

Error Description	Response ratio not achieved as per specified criteria, e.g., obtained similarity factor 0.97 against limit of 0.98 to 1.02.
Additional Information	Incident occurred because analyst had not dipped inlet filter in rinse bottle.
Error Category	Omission error
Recommendations	HPLC verification checklist to be appended to ensure that all the lines are dipped properly in the mobile phase/rinse line/fill wash with their respective solution, and pictorial representations of precautionary measures to be fixed in work benches as a job aid. (Error Prevention Model).

Error Description	"Verified By" sign missing in cleaning checklist of pressure vessel.
Additional Information	Operator who was supposed to verify the activity inadvertently missed signing in the "Verified By" column of cleaning checklist, as he was engaged in helping the other operator in cleaning activity.
Error Category	Omission error
Recommendations	Implementation of digital platform for cleaning execution (Error Proofing), OR Redesigning of checklist in HER (Human Error Reduction) format with gray background for non-executable instructions and white blanks for recording observations during execution (Error Prevention).

Error Description	Batch release prior to FG COA generation.
Error Category	Omission error
Recommendations	Enabling interlock in application used for batch release (like SAP) to ensure QC release w.r.t FG COA and subsequent QA review prior to batch release (Error Proofing Model).

Error Description	Analyst emptied contents of 19 capsule instead of 20 for assay test.
Additional Information	Analyst forgot to empty contents of 20th capsule and weighed 19 empty capsule shells along with 20th full capsule for assay test.
Error Category	Omission error
Recommendations	Incorporation of control limit component for average weight in LIMS (Error Proofing Model).

Error Description	During initial in-process check, thickness of tablets recorded out of BMR limit.
Additional Information	While calculating buffer weight for 5 litres of buffer, analyst mistakenly calculated for 6 litres and weighed more quantity of buffer than required for 5 litres.
Error Category	Application error
Recommendations	Incorporation of in-built buffer weight calculation in LIMS for the required quantity of mobile phase (Error Proofing Model).

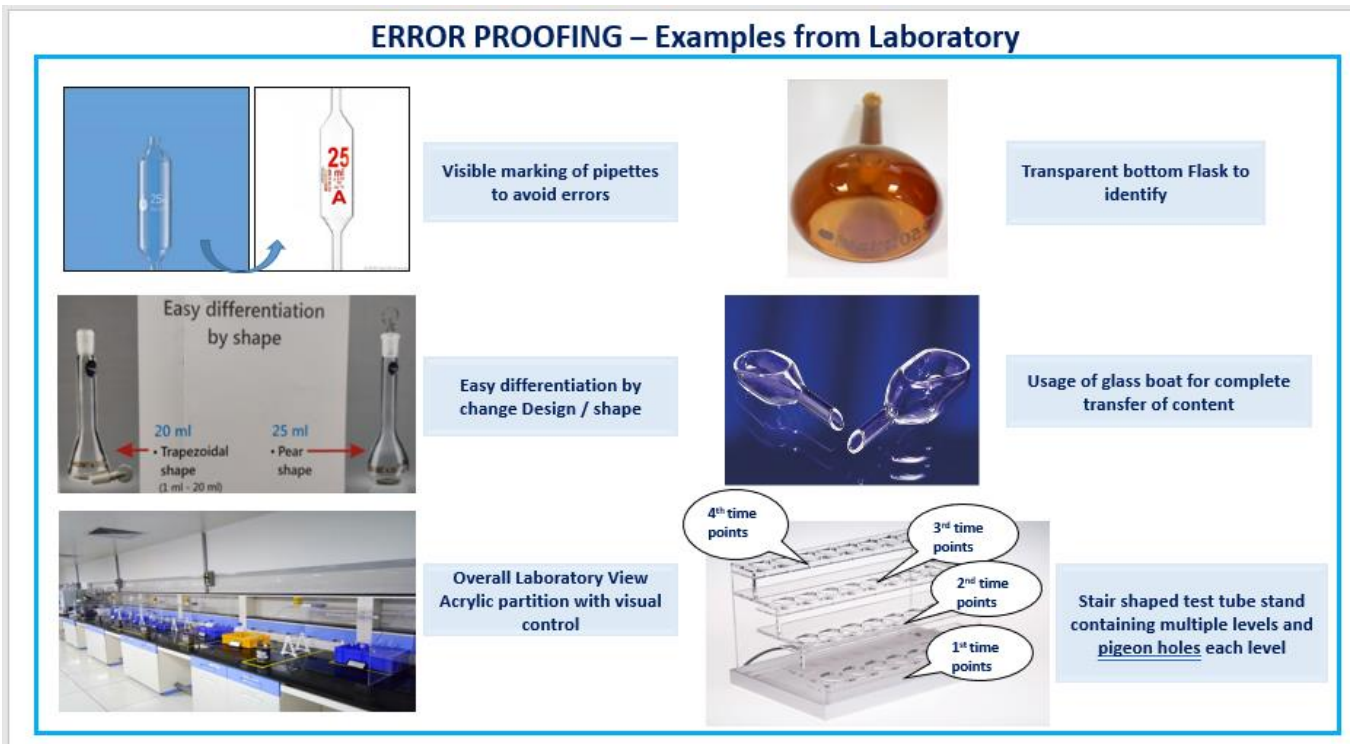
Error Description	Wrong sample weight taken by analyst.
Error Category	Application error
Recommendations	LIMS masters updation to include an alert mechanism when the sample weight to be taken is beyond specified limit (like 10%) of the target weight (Error Proofing Model).

Error Description	LOD of granules less than the target value of 1.0% w/w (0.5% w/w to 1.5% w/w) and high drying time (limit: 90 to 200 minutes; target: 150-180 minutes).
Additional Information	After LOD check at 60 minutes, process is continued till 150/180 minutes without verifying LOD intermittently. This leads to over-drying of granules, i.e., below target values.
Error Category	Decision error
Recommendations	Revision of BMR instruction to check intermittently at an interval of 15 minutes and abort the drying process once the target LOD is reached.

❖ **Mistake proofing in day-to-day analytical activities:**

Following actions can be implemented in QC laboratories to avoid human errors.

Action	Application
Usage of single row test tube stand.	To avoid solution interchange in profile dissolution test.
Different color rings inserted to the volumetric flask of different time point.	To avoid interchange of volumetric flasks in profile dissolution test.
Partition affixed on the desk of analyst.	To avoid interchange of glassware/solution.
Storage facility with segregation of cleaned glassware.	To avoid interchange of cleaned and dirty glassware or wrong selection of glassware.
Affixing printed labels on volumetric glass wares.	To improve label legibility & longevity.



9 Conclusion

Prof. James Reason, Professor Emeritus of Psychology at the University of Manchester, England, and architect of the Swiss Cheese Model, had famously written in 1990, that eliminating all human errors is close to impossible for the following reasons.

- Fallibility is part of the human condition.
- We cannot change the human condition.
- We can change the conditions under which people work.
- Human beings are prone to make errors.
- Naming, blaming, and shaming have no remedial value.

Hence, our efforts should address two areas:

- Reducing the probability of human error from the onset.
- When the unavoidable error occurs, implementing tools and processes to detect such human errors, and/or to minimize their impact on the quality of our processes.

The following table contains some key recommendations to follow when investigating and fixing human errors.

Do's	Don'ts
Investigate every human error up to its root cause(s).	Use human error as root cause.
Search for precursors of the human error (e.g., working from memory?).	Use retraining as the default corrective action for human failures.
Improve your work instructions and records by enhancing document formats.	
Improve your training system and measure the effectiveness of training efforts.	Assume that your employees are lazy and careless about their job.

To achieve continued success in reducing risk of human error, it is necessary to follow a well-designed strategy that includes the following types of processes, amongst others.

1. **Visibility:** Managers should have meaningful and comprehensive understanding of error risk and their potential consequence. To facilitate this, there needs to be a mechanism for highlighting the vulnerable areas to the attention of managers.

2. **Awareness:** The workforce needs to understands how to identify and address risk of error. To facilitate this, there needs to be periodic awareness sessions on error reduction.

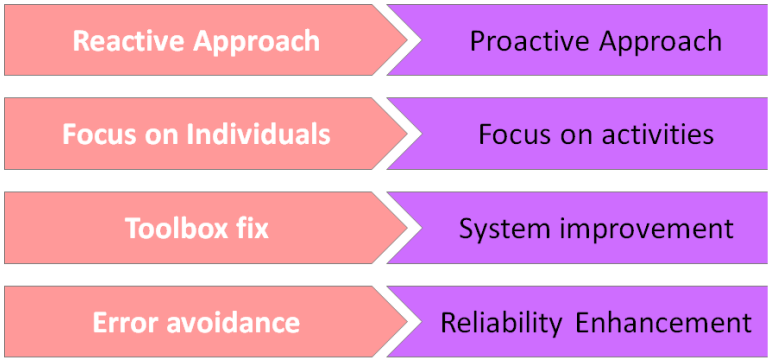
3. **Measurement:** Measurement of cause and consequences of error should be factored in driving new improvement projects throughout the organization.

4. **Handling:** Assessment on whether handling of failures help in long term error reduction should be done through review of identified metrics.

5. **Empowerment:** Provision should be made of time and resources needed to address error and empowerment of workforce to apply them.

6. **Deployment:** Knowledge-based development and proactive application of well-founded knowhow should be made wherever it has relevance.

As the above process is successfully applied in an organization, we may expect a transformational change happening leading to improved human reliability. The nature of transformation is indicated below.



The above approach gets validated in following statement of the renowned Quality Guru, Mr. Edward Deming, “85% of the reasons for failure to meet customer requirements are related to deficiencies in systems and processes rather than the employee. The role of management is to change the process rather than badgering individuals to do better.”

10 REFERENCES

- ASQ: American Society for Quality
- ICH: International Council For Harmonization
- IPA: Indian Pharmaceutical Alliance
- ISPE: International Society for Pharmaceutical Engineering
- PDA: Parenteral Drug Association
- Wikipedia: https://en.wikipedia.org/wiki/Swiss_cheese_model
- John M. Evans, Fellow of Chartered Quality Institute, UK.

The guidance document is prepared based on the long-standing experience of the team members on the subject matter and the information, data, definition and diagrams available in public domain. We sincerely acknowledge and appreciate all individuals who have contributed in this domain.

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