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Preliminary Hazard Analysis (PHA): Great approach to risk analysis in pharmaceutical industry

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Abstract

Preliminary Hazard Analysis (PHA) is a semi-quantitative evaluation executed to recognize, early within side the layout and definition level of a system, all potential hazards and hazardous events that can cause an accident, classify identified hazardous events according to their severity and identify the required hazard controls and their respective follow-up actions. It is a great tool for beginning to recognize the hazards of a system. In some cases, a PHA is all that is needed to analyse a simple system. It is also the first step in the hazard analysis of more complicated systems. This review illustrates PHA's use for analysing a maintenance process/procedure and discusses the injuries that can occur with poor design and recommend solutions.

Keywords: Preliminary Hazard Analysis; Accident; Recognise; Follow-up actions

1 Introduction

1.1 Terminologies [1]

1.1.1 Preliminary

Refers to coming before and usually forming a necessary prelude to something. (The PHA can be done in the design or pre-operation phase, or it can be the first (primary) analysis done on a mature system.)

1.1.2 Hazard

An activity or condition which poses risk of loss or harm.

1.1.3 Analysis

An examination of the elements of a system, separation of a whole into its component parts.

1.1.4 PHA

An early or initial system safety study of potential loss events. It is a list or inventory (PHL) of system hazards and includes qualitative, not quantitative, assessments of risk for the individual hazards.

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1.2 General Risk Management Methodology [as per ICH Q9 (R1)] [6,7]

- Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.
- Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on:-
  - For example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.
  - Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures).

2 Below is a non-exhaustive list of some of these tools

2.1 Basic risk management facilitation methods (flowcharts, check sheets etc.)

One of simple technique that is commonly used to structure risk management by organizing data and facilitating decision-making are through Flowcharts, Check Sheets, Process Mapping, Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

2.2 Failure Mode Effects Analysis (FMEA)

It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding (ex equipment and facilities)

2.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA).

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes.

2.4 Fault Tree Analysis (FTA)

The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes.

It is useful both for risk assessment and in developing monitoring programs.

2.5 Hazard Analysis and Critical Control Points (HACCP)

- HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety.
- HACCP consists of the following seven steps:
- Conduct a hazard analysis and identify preventive measures for each step of the process.
- Determine the critical control points.
- Establish critical limits.
- Establish a system to monitor the critical control points.
- Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control.
- Establish system to verify that the HACCP system is working effectively.
- Establish a record-keeping system.

2.6 Hazard Operability Analysis (HAZOP)

HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words".

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products.

2.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system.

The tool consists of:

- The identification of the possibilities that the risk event happens.
- The qualitative evaluation of the extent of possible injury or damage to health that could result.
- A relative ranking of the hazard using a combination of severity and likelihood of occurrence.
- The identification of possible remedial measures.

It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product.

2.8 Risk ranking and filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk.

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

2.9 Supporting statistical tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making.

A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

2.9.1 Control Charts

for example:

- Acceptance Control Charts
- Control Charts with Arithmetic Average and Warning Limits
- Cumulative Sum Charts
- Shewhart Control Charts
- Weighted Moving Average
    - Design of Experiments (DOE)
    - Histograms
    - Pareto Charts
    - Process Capability Analysis.

2.10 Concept of PHA[3,4]

- Preliminary Hazard Analysis (PHA) was introduced in 1966 after the Department of Defence of the United States of America requested safety studies to be performed at all stages of product development.
- The Department of Defence issued the guidelines that came into force in 1969 (Military Standard) (1969, 1999).
- Preliminary hazard analysis (PHA) is a semi-quantitative evaluation that is executed to

- Identify all potential hazards and accidental events that may lead to an accident.
- Rank the identified accidental events according to their severity.
- Identify required hazard controls and follow-up actions.

PHA can be used for

- As an initial risk study in an early stage of a project (e.g., of a new plant). Accidents are mainly caused by release of energy.
- The PHA identifies where energy may be released and which accidental events that may occur, and gives a rough estimate of the severity of each accidental event.
- The PHA results are used to
- Compare main concepts
- Focus on important risk issues
- Input to more detailed risk analyses.
- As an initial step of a detailed risk analysis of a system concept or an existing system. The purpose of the PHA is then to identify those accidental events that should be subject to a further, and more detailed risk analysis.
- As a complete risk analysis of a rather simple system. Whether or not a PHA will be a sufficient analysis depends both on the complexity of the system and the objectives of the analysis.

2.11 Scope [5,6]

The PHA shall consider:

- Hazardous components.
- Safety related interfaces between various system elements, including software.
- Environmental constraints including operating environments.
- Operating, test, maintenance, built-in-tests, diagnostics, and emergency procedures.
- Facilities, real property installed equipment, support equipment, and training.
- Safety related equipment, safeguards, and possible alternate approaches.
- Malfunctions to the system, subsystems, or software.

PHA is an inductive method whose goal is to make an identification of all phases in the life of a specific system/subsystem/sub-subsystem, the hazards, hazardous conditions and hazardous situations which could lead to an accident

The method identifies the possibility of accident and quantitatively evaluates the degree of the possible injuries or damage to health.

The goal of PHA is to identify areas which are critical to safety and to identify and evaluate hazards, as well as to identify design and operations requirements which are necessary for inclusion in the program concept phase.

The PHA provides consideration of the following for the identification and evaluation of hazards:

- Hazard sources (propellants, lasers, explosive, corrosives, pressure systems, and other energy sources).
- Safety-related interface considerations among various parts of elements of the analysed item, facilities and material capability, electromagnetic interference, fire or explosion initiation and propagation, etc.
- Environmental constraints, including drop, shock, vibration, noise, extreme temperature, electrostatic discharge, radiation, etc.
- Maintenance, test, and emergency procedures.
- Safety-related equipment, safeguards and possible alternative approaches (interlocks, monitoring, redundancies, fair protection, personal protective equipment, ventilation, etc.).
- Facilities, support equipment and training.

3 Procedure: Preliminary Hazard Analysis [10-16]

Hazard Identification process in General

3.1 Define the system

Define the physical and functional characteristics and understand and evaluate the people, procedures, facilities, equipment, and the environment.

3.2 Identify hazards

- Identify hazards and undesired events
- Determine the causes of hazards

3.3 Assess hazards

- Determine severity
- Determine probability
- Decide to accept risk or eliminate/control

3.4 Resolve hazards

- Assume risk or
- Implement corrective action
  - Eliminate
  - Control

3.5 Follow-up

- Monitor for effectiveness
- Monitor for unexpected hazards

3.6 PHA include four main steps: [1-5]

- PHA prerequisites
- Hazard identification
- Consequence and frequency estimation
- Risk ranking and follow-up actions

3.6.1 PHA prerequisites

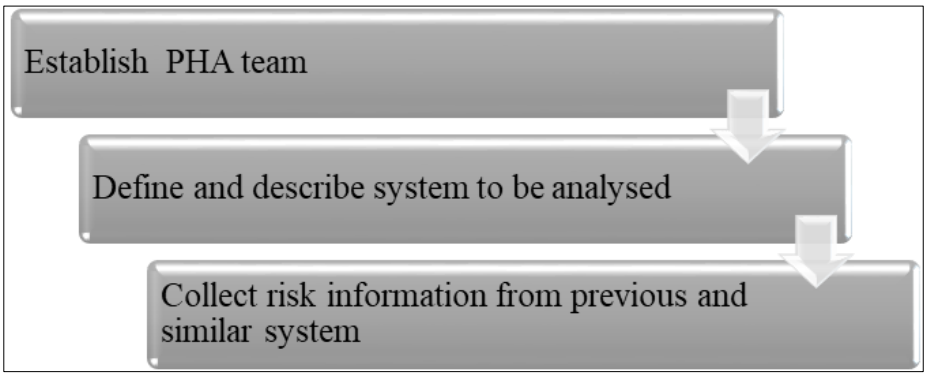

Figure 1 PHA Prerequisites Steps

Establish PHA Team

- A team leader (facilitator) with competence and experience in the method to be used.
- A secretary who will report the results.
- Team members (2-6 persons) who can provide necessary knowledge and experience on the system being analysed.
- How many team members who should participate will depend on the complexity of the system and also of the objectives of the analysis?

- Some team members may participate only in parts of the analysis.

System functions

As part of the system familiarization it is important to consider:

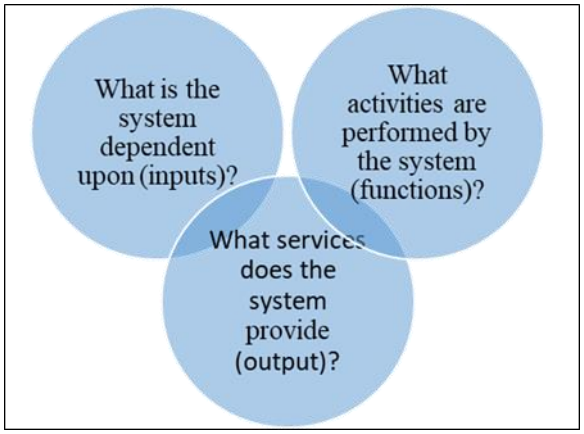

Figure 2 PHA System Functions

System breakdown

To be able to identify all hazards and events, it is often necessary to split the system into manageable parts, for example, into three categories

- System parts (e.g., process units)
- Activities
- Exposed to risk (who, what are exposed?)

The results of the PHA are usually reported by using a PHA worksheet (or, a computer program).

A typical PHA worksheet is shown below. Some analyses may require other columns, but these are the most common.

Example PrHA Worksheet

Area: _____ Meeting Date: _____

Drawing Number: _____ Team Members: _____

Hazard: Potential Accident	Cause	Major Effects	Accident Severity Category	Corrective/Preventive Measures Suggested

Figure 3 PHA worksheet

3.6.2 Hazard Identification

- All hazards and possible accidental events must be identified. It is important to consider all parts of the system, operational modes, maintenance operations, safety systems, and so on. All findings shall be recorded.
- No hazards are too insignificant to be recorded.

To get a complete survey of all possible hazards it may be beneficial to use a hazard checklist.

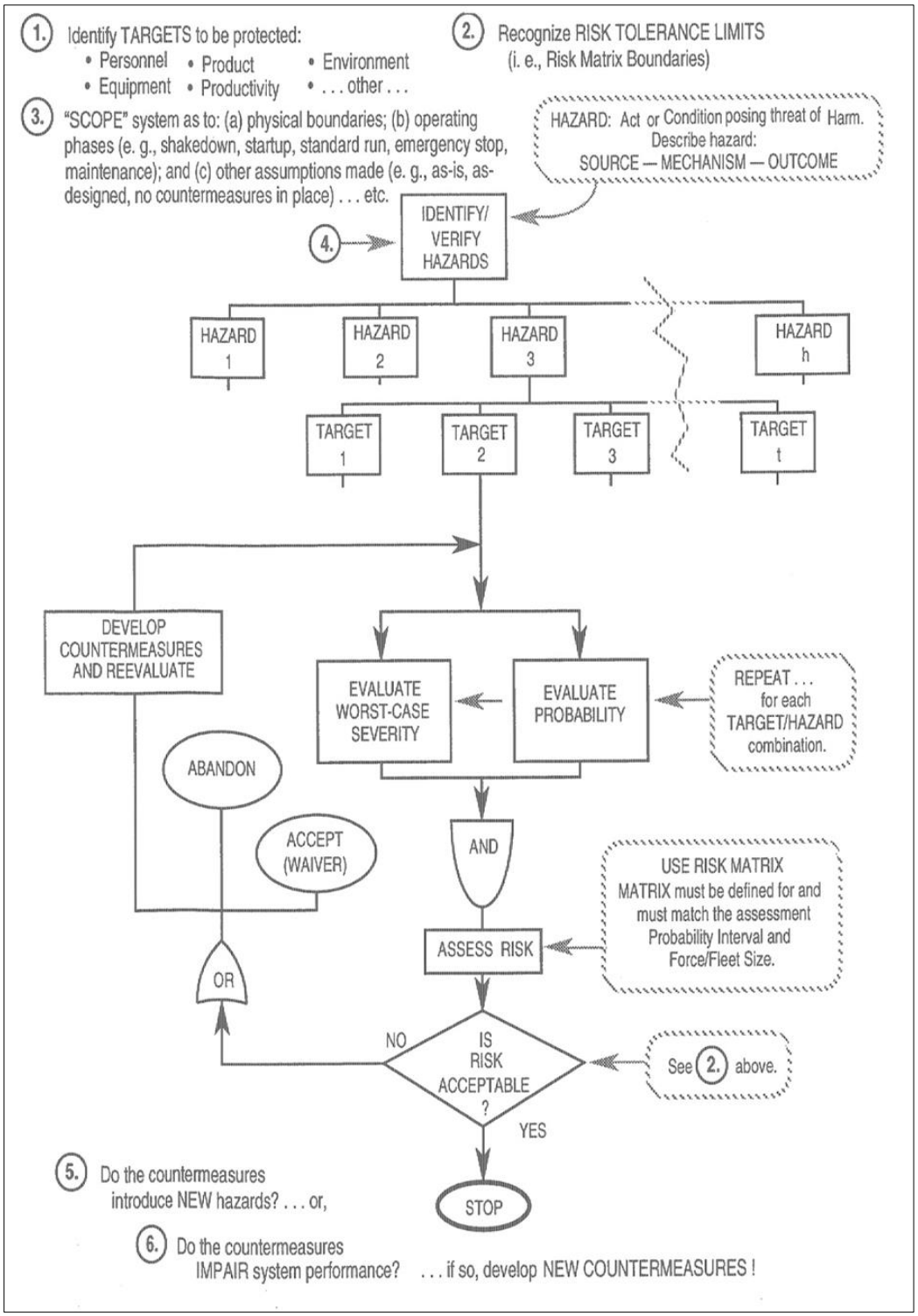

Figure 4 PHA Process

HAZARD IDENTIFICATION CHECKLIST
Facilities Areas

Surveyor Name:_____ Survey Date:_____

Work Unit:_____ Area/Room:_____

If "No" is selected, please correct the hazard and note the date.

		Yes	No	n/a	Date Corrected
	ADMINISTRATIVE				
1.	Current signage present and accurate? • Cal-OSHA 300A poster • UCI or UCIMC Emergency Procedure Flip Chart (all blue or multi-colored) • UC Irvine Injury & Medical Treatment (8/2009) • Hazardous Waste Guidelines (Ver. 3.0)				
2.	Staff knows how to report an incident/injury/safety concern?				
3.	Has staff reviewed the content of the UCI Emergency Procedures Flipchart?				
4.	Work unit emergency call list available?				
	RECORDKEEPING				
5.	Chemical/hazardous materials inventory?				
6.	MSDS's accessible?				
7.	Cal-OSHA Permits for Air & LPG ?				
8.	Tailgate meeting documentation?				
9.	Code of Safe Practices available?				
	FIRE/LIFE SAFETY				
10.	First Aid Kit accessible and stocked and evidence of regular inspection?				
11.	Emergency Action Plan/Fire Prevention Plan communicated?				
12.	Portable Extinguishers - Accessible, location marked, checked monthly, maintained annually?				
13.	Automatic fire sprinkler systems maintenance inspection quarterly?				
14.	Automatic sprinkler systems serviced every five years?				
15.	Standpipe systems serviced every five years?				
16.	Fire hoses and hose cabinets inspected?				
17.	Automatic system main drain flow test annually?				
18.	Smoke detectors and smoke activated door closures tested annually?				
19.	Fire hydrants inspected and serviced?				
20.	Evacuation drills held periodically?				
21.	Evacuation plans posted?				
	GENERAL WORK AREA				
22.	Work surfaces and walkways dry or slip resistant, no tripping hazards?				
23.	Exterior walkways in good condition?				

Last updated 10-14-11

Figure 5 Hazard Identification Checklist

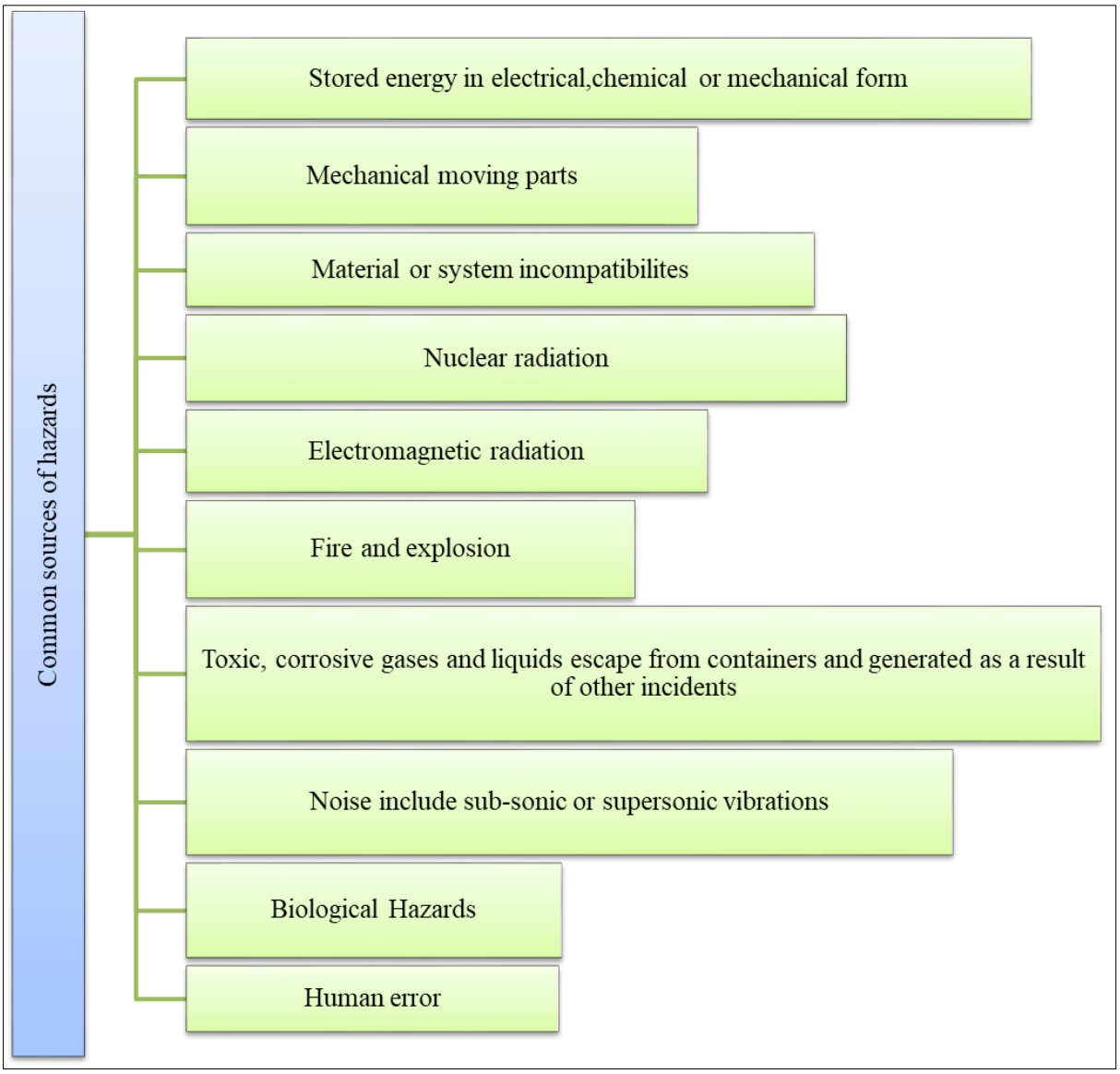

Figure 6 Sources of Hazards

3.7 Common sources of hazards included in preliminary analysis. [11,14]

3.7.1 Consequence and frequency estimation [15, 16]

The risk related to an accidental event is a function of the frequency of the event and the severity of its potential consequences.

To determine the risk, we have to estimate the frequency and the severity of each accidental event.

Which consequences should be considered?

An accidental event may lead to wide range of consequences, ranging from negligible to catastrophic. In some applications the severity of an average consequence of an accidental event is assessed. In other applications we consider several possible consequences, including the worst foreseeable consequence of the accidental event.

Severity classes

The severity of an event may be classified into four classes.

Table 1 Risk severity and Risk ranking

Rank	Severity class	Description
4	Catastrophic	Failure results in major injury or death of personnel.
3	Critical	Failure results in minor injury to personnel, personnel exposure to harmful chemicals or radiation, or fire or a release of chemical to the environment.
2	Major	Failure results in a low level of exposure to personnel, or activates facility alarm system.
1	Minor	Failure results in minor system damage but does not cause injury to personnel, allow any kind of exposure to operational or service personnel or allow any release of chemicals into the environment.

4 Classification of the possibility of occurrence of a hazard

Possibility of occurrence of hazard. Usually, it is divided into six possibilities.

Table 2 Types of Risk Occurrences

Explanation about Occurrence characteristics			**Hazard Grade**
Characteristic	**Element**	**Equipment**	
Frequent occurrence	Frequent occurrence	Commonly encounter	A
Easy occurrence	Occurs a few times in life cycle	Frequent appearance	B
Occasional occurrence	Likely to occur in life cycle	Occurs a few times in life cycle	C
Rare occurrence	Not necessarily occurs	Not really possible to occur	D
Not easy to occur	Probability is close to zero	Not necessarily occurs	E
Unable to occur	Not likely to occur	Not likely to occur	F

4.1 Frequency classes

The frequency of events may be classified into broad classes.

An example of such a classification is:

- Very unlikely Once per 1000 years or more seldom
- Remote Once per 100 years
- Occasional Once per 10 years
- Probable Once per year
- Frequent Once per month or more often

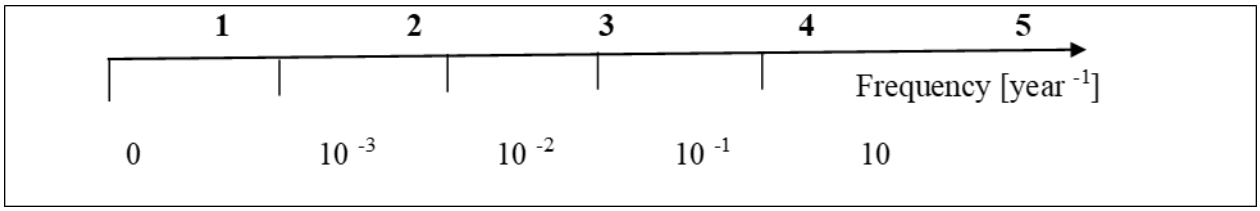

Figure 7 Logarithmic scale

4.1.1 Risk ranking and follow-up actions [13, 14]

Risk is stated as a combination of a given event/ consequence and severity of the same event/ consequence.

This Allows the events / consequences to be classified in a risk matrix

Table 3 Frequency of Risk

Frequency/ consequence	1 Very unlikely	2 Remote	3 occasional	4 probable	5 Frequent
Catastrophic	M	H	H	H	H
Critical	L	M	M	H	H
Major	L	L	M	M	H
Minor	L	L	L	M	M

Table 4 Colour Legend indicating types of risk

	Acceptable risk area
	Tolerable if ALARP (As low As Reasonably Practicable
	Unacceptable risk area

Therefore, As can be seen, we build a table where we locate each of the risks that we have detected based on frequency (columns) and severity (rows). From this colour and its level indicates as follows:

Table 5 Risk level and its description

Level	Name	Description
H	High	High risk, not acceptable. Further analysis should be performed to give a better estimate of the risk. If this analysis still shows unacceptable or medium risk redesign or other changes should be introduced to reduce the criticality.
M	Medium	The risk may be acceptable, but design or other changes should be considered if reasonably practical. Further analysis should be performed to give a better estimate of the risk. When assessing the need of remedial actions, the number of events of this risk level should be taken into account.
L	Low	The risk is low and further risk reducing measures are not required.

Table 6 Example of PHA Assessment for Pipeline Carrying Hazardous Material

Type of hazard	Causes	Consequences	L [a]	S[b]	R[c]	Mitigation	Recommendations	Action owner
Leak of Hazardous Material to atmosphere	Pipeline over pressurisation (e.g., closing isolation valve by mistake, scraper stuck in pipeline, and pressure	Pool fire	M[d]	L[e]	L	Pump ESD [f] System. Overpressure protection systems. Operating procedures (closing and opening isolation valves and	Consider installing redundant pressure protection systems (e.g., HIPPS [g] or relief valves) Ignition sources control around pipeline Design drainage system around pipeline to	Engineering department
		Flash fire		M	H[i]			
		Jet fire		M	M			
		Explosion		H	M			
		Toxic		H	H			

	control system malfunction)					scraping procedures) Pressure alarms and indicators on pipeline Control ignition sources Use PPE (fire resistance clothes—FRC—and Scott airbags for toxic impact) Emergency response planning (ERP) Spill control procedures	prevent the formation of large pools Install LDS [h] for early detection of leak Install toxic/flammable detectors around pipeline, where it passes by close proximity of public communities to initiate ERP	
	Corrosion	Pool fire	L	L	L	Corrosion management program (e.g., corrosion inhibitors, external coating, and cathodic protection systems) Scarping and in-line inspection (ILI) Proper material grade selection External inspection of pipeline	Maintain design velocity to avoid water accumulation in low points of pipeline (that can cause corrosion) Consider increasing corrosion allowance in pipeline material. Evaluate using corrosion resistance alloy (CRA) material to control corrosion.	Operations, inspection, and engineering departments
		Flash fire		M	L			
		Jet fire		M	L			
		Explosion		H	M			
		Toxic		H	M			
	External impact	Pool fire	H	L	M	Buried pipeline (if aboveground) External protection using concrete slabs (for buried segments of pipeline) and crash barriers (for aboveground pipeline segments)	Develop proper excavation procedures and work permit process to control third-party activities near the pipeline Establish designated pipeline corridor and protect it through fences and patrolling	Operations and security departments
		Flash fire		M	M			
		Jet fire		M	M			
		Explosion		H	H			
		Toxic		H	H			
	Operational errors (e.g., hot tapping by error)	Pool fire	M	L	L	Operating procedures	Establish and enforce hot work permit	Operations department
		Flash fire		M	H			
		Jet fire		M	M			
		Explosion		H	M			
		Toxic		H	H			
		Pool fire	L	L	L	Security procedures and patrol of pipeline corridor	Consider installing CCTV in areas close to public communities where impact can be high for continuous monitoring of pipeline (especially for aboveground segments)	Security department
		Flash fire		M	L			
		Jet fire		M	L			
		Explosion		H	M			
		Toxic		H	M			

- Likelihood (low, medium, or high).
- Severity (low, medium, or high).
- Risk (low, medium, or high).
- Medium level.
- Low level.
- Emergency shutdown systems.
- High-integrity pressure protection systems.
- Leak detection systems.
- High level.

Advantage: [4,5]

- Reduces injuries
- Reduces absenteeism
- Increases productivity
- Protects employees
- Assists in standard specific compliance (example: personnel protective equipment)
- Preliminary hazard analysis is one part of a participatory employee safety program.it gets workers active in the safety process.
- A PHA telegraphs management's interest in the safety of the individual worker.
- The Qualitative method is that it is easy to understand, apply and perform. It also saves time and cost.
- The Quantitative method is widely applicable, based on objective method and produce relatively accurate results.
- The comprehensive method is combination of subjective and objective methods and has high accuracy.

Disadvantages: [4,5]

- Preliminary Hazard Analysis (PHA) is more complex process.
- It sometimes difficult to implement.
- It requires high cost for predetermined process.
- It requires a considerable amount of preparation.
- Time consuming process.
- It does not provide an accurate risk reduction ranking. The PHA scale is limitation regarding frequency reduction as per category of risk.
- It needs high time commitment especially for larger systems.
- It considers technical and statistical aspects that every organisation may not afford it.
- It not gives exact surety about risk reduction but only assumes based on previous analysis of chemical process risks.

5 Conclusion

A PHA is a method of analysis to define hazards and hazardous situations that may lead to potential harms for a particular medical device in different use scenarios. It is particularly useful in the early phase of product development, where it can provide key inputs from the safety point of view. It can be linked to underlying risk analysis tools such as an FMEA, which are particularly useful for analyzing risk of device failures and implementing appropriate controls. When implemented in this way, a PHA helps to not only comply with the requirements of ISO 14971 but also provides an effective mechanism to analyze post-market information related to safety and take appropriate action.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors have no conflict of interest to declare.

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