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RISK MANAGEMENT PLAN FOR ADVERSE DRUG REACTIONS

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ABSTRACT

This procedure is designed, to achieve higher product quality with more flexible process design, to develop & implement a system of pharmacovigilance, for all modern medicines of the organization, as per stipulated rules & guidelines. The current climate in the pharmaceutical industry is influenced by the challenge of finding an appropriate balance between increased quality requirements, *compliance* with legal requirements, and cost pressure. The resources required for this are often very limited, which means that business processes must be organized more efficiently. If processes are reorganized at the expense of quality, the company may face damage to its reputation, for example, through product recalls. If savings are made in the area of compliance, recent examples clearly demonstrate that consequences of GMP breaches can incur costs in the region of hundreds of millions. The principle starting points for escaping from this dilemma lie in the targeted use of available resources and appropriate implementation of regulatory requirements. This begs the question: What is targeted and what is appropriate? This is where risk management can help. Terms such as *Quality Risk Management* (QRM), *Risk Based Approach* **(**RBA), *Risk Analysis* etc. have been familiar in the world of pharmaceuticals for some time. It should be made clear that these terms do not represent any fundamentally new developments. The new part of the concept is the actual approach of applying risk management systematically and across the board, and ensuring that the resulting advantages are fully utilized. The aim of risk management is to systematically evaluate processes and processing steps in terms of criticality and subsequently develop appropriate measures to control and minimise risks. Corrective measures can subsequently be prioritized, their success becomes measurable, and the quality of products and processes is improved. This may mean that critical processes require more attention than previously, but for uncritical processes, the current workload can be justifiably reduced. Experience has shown that this concept not only incorporates quality and compliance, but also covers efficiency, environment, health and safety, as well as additional security aspects such as access control.

KEYWORDS: QRM – Quality risk management, **RBA**- Risk based Approval, **CAPA** – Corrective and preventive action, **QMS** – Quality management system, **RPN** – Risk priority number, **ADR** – Adverse drugs reaction, **AE** – Adverse events.

INTRODUCTION

The aim of risk management is to systematically evaluate processes and processing steps in terms of criticality, and subsequently develop appropriate measures to control and minimize risks. Corrective measures can subsequently be prioritized, their success becomes measurable, and the quality of products and processes is improved. This may mean that critical processes require more attention than previously, but for uncritical processes, the current workload can be justifiably reduced. Experience has shown that this concept not only incorporates quality and compliance, but also covers efficiency, environment, health and safety.[18]

Advantages of risk management

- **Applicable across the board**: Risk management can be applied to all processes and products, and at all levels of a company.
- **Transparency:** A consistent risk management process provides concrete statements about critical points and enables you to derive measures for minimizing risk based on facts.
- **Integrated component of a QM system:** Systematic communication of the critical process points to the QM system enables specific optimization of the internal regulations. Elements of

risk management are integrated into the quality assurance process.

- **Preventive rather than** corrective: **Action, not reaction:** The systematic identification and evaluation of risk supports the prevention of prospective and retrospective activities (**CAPA** = *Corrective Action Preventive Action*).
- **Aggregation capability**: The communication process between management and the authorities is encouraged (also see the FDA's *risk based approach*).
- **Risk awareness in staff behavior:** The introduction of a sustainable risk management concept requires that all employees involved are aware of the risks.
- **Integration of existing risk management approaches:** It should be possible to integrate existing risk management approaches and activities into the overall system.
- **Standardized systematic approach to risk analysis:** A range of application-case-specific standards for recording and evaluating risks supports the comparability of similar processes and the utilization of synergies.
- **Regulatory environment[4,8]:** The current regulatory environment is influenced by two major initiatives
- **ICH Q9** *Quality risk management* (QRM), a global initiative providing a basis for the industry to evaluate processes and implement appropriate quality assurance measures.
- The FDA's *Risk Based Approach* (RBA), which primarily aims to optimize internal FDA procedures and inspection processes.

This considers these two developments. The following describes the actual contents and their significance, whereby many parallels can be drawn between the two initiatives.

- **EN ISO 14971:** Application of risk management to medical devices
- **FDA Guidance for Industry:** PAT-A F*ramework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance* (see chapter D.11 Guidance for Industry PAT -A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance)
- **FDA Guidance for Industry:** Quality Systems Approach to Pharmaceutical cGMP Regulations.

ICH Q9 Quality Risk Management: This document produced by the ICH (International Conference on Harmonization) is currently (November 2005) in step 4 of the ICH approval process (see chapter E.8 ICH Q9: Quality Risk Management). This is of great significance for the industry, since as an ICH document, it will be a worldwide standard and not only restricted to Europe or the USA.[4]

Interaction between ICH Q8, Q9 and Q10[4]

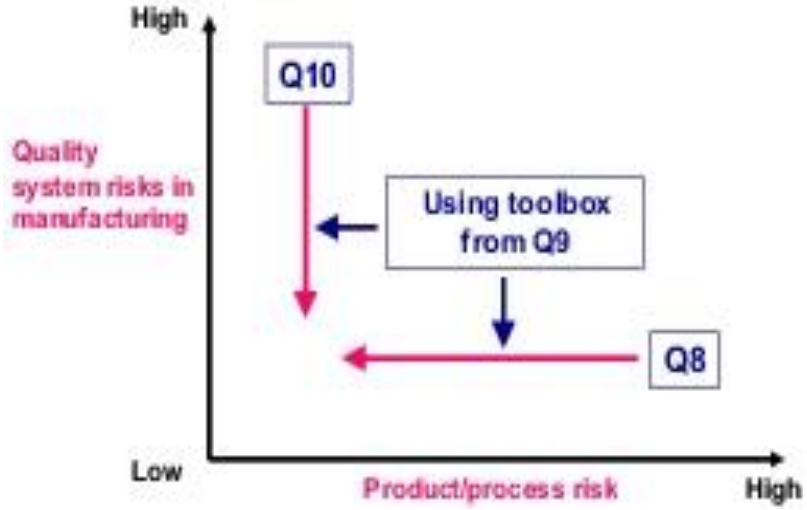

Figure-1: Interaction between ICH Q8, Q9 and Q10.

ICH Q9 does not contain any definitive new regulations. Instead it introduces a strategy, the basic principles, and a toolbox for evaluating processes in terms of risk, and standardizing and documenting this evaluation. In contrast to other ICH documents, it is therefore more of a "How-to" document, which does not specify a "what", but instead contains suggestions on "how". As described in the introduction to ICH Q9, it serves as a "foundation or resource document that is independent of, yet supports, other ICH quality documents".

In this context, "processes" includes all processes - manufacturing as well as quality management processes. For the latter, Annex II of ICH Q9 lists concrete starting points that can be individually customized and further expanded. ICH Q9 is not the only current ICH document that covers this subject area. It offers more of a

comprehensive approach, encompassing product development, manufacturing, and accompanying QM processes, which can be found in the three documents ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Quality Systems for Continuous Improvement. The interaction between these three documents is shown in above figure While ICH Q8 clearly focuses on the products and requires the relevant product-specific measures during development (design space), ICH Q10 provides specifications for a (product-independent) quality management system.

The FDA risk-based approach: The FDA also has a clear aim of returning from an approach that has in part become highly formalized, to a more science-based outlook (Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach). This stems from the realization that the current method inhibits innovation, and companies struggle to finance it in the long term. As a consequence, urgently required medicinal products may not become available on time. At the same time, the FDA itself also has limits in terms of capacity. For some time, it has not been unable to uphold the inspection intervals of two years as stipulated in specifications. This method also places emphasis on steering existing capacities towards the critical products, companies, methods, etc. This mainly affects cGMP inspections.

A good example of optimized cooperation between companies and authorities is provided by the FDA's considerations in the area of Change Control for manufacturing processes. Changes to complex products (e.g. proteins) manufactured in complicated processes are subject to a more intensive review by the authorities than previously. On the other hand, on a larger scale the FDA accepts a company's own change control system, if the quality system as such functions well, and the company can demonstrate a good understanding and monitoring of the relevant products and processes. As a result, well-monitored changes no longer need to be inspected or approved by the FDA. This enables capacities to be concentrated on critical products.

It is rapidly becoming clear that the industry and the authorities share many common aims and interests which can best be overcome in a joint approach. The table below provides a summary of the most important common interests, as well as some of the differences.

Table-1: Objectives of risk management for industry and the FDA.

Objectives of risk management for industry and the FDA		
	Quality risk management (industry)	Risk based approach (FDA)
Motivation	Increased requirements, cost and time pressure	Increase in the number of companies requiring inspection without additional inspector capacity
Aims	Greatest benefit at the lowest costs with the use of limited resources	
	Receive/create the opportunity to comply with own rules	
	Improvement of quality and compliance	Optimization of inspection behavior
Methodology	Structuring and prioritization of risks	
Risk model	Transparent, objective, systematic	

The area of *quality risk management* or *risk based approach* is a matter of great urgency and importance, both for the industry and for the authorities. The common goal is to provide patients with a sustainable, guaranteed supply of safe and effective medicinal products. In addition to the advantage of maximum transparency, the close cooperation between the authorities and industry enables a shared understanding and thus promotes effective implementation and mutual.

Science-based approach: The Science and Risk Based Approach initiated by the FDA has formulated the demand for a science-based and stable life cycle for pharmaceutical products. In accordance with the requirement to "know how it works", continuous quality should be guaranteed right from the development phase, and all critical aspects of the product and the manufacturing process should be analyzed (Quality by Design, ICH Q8).

Elements of risk management: The ICH Q9 Guide provides a systematic list of the steps that must be carried out in risk management. Here, less emphasis is placed on the requirement for each individual step in the process to be formally documented. Instead, it is necessary to establish how risks can be systematically identified, evaluated, and controlled in their causal relationships. The ICH Q9 Guide provides a very detailed description of the individual steps in risk management .The process itself follows a logical and systematic approach. Communication must be possible at all points in the process so that the affected functions accept the residual risk at an early stage, or so they can contribute new and important insights into an ongoing discussion. The risk management process is continual, each additional insight and experience should be rapidly incorporated in the process in order to contribute to the best possible and efficient solution.

Risk management and quality management system (QMS): Risk management acts as a very useful

supplement to any quality management system (QM system) in two respects. First, risk management can be used to specifically optimise an existing QM system through the application of suitable methods for evaluating the system and regulations, and deriving appropriate consequences. Second, a QM system is also an ideal vehicle for implementing a risk-based approach across the board (at least for QM processes).

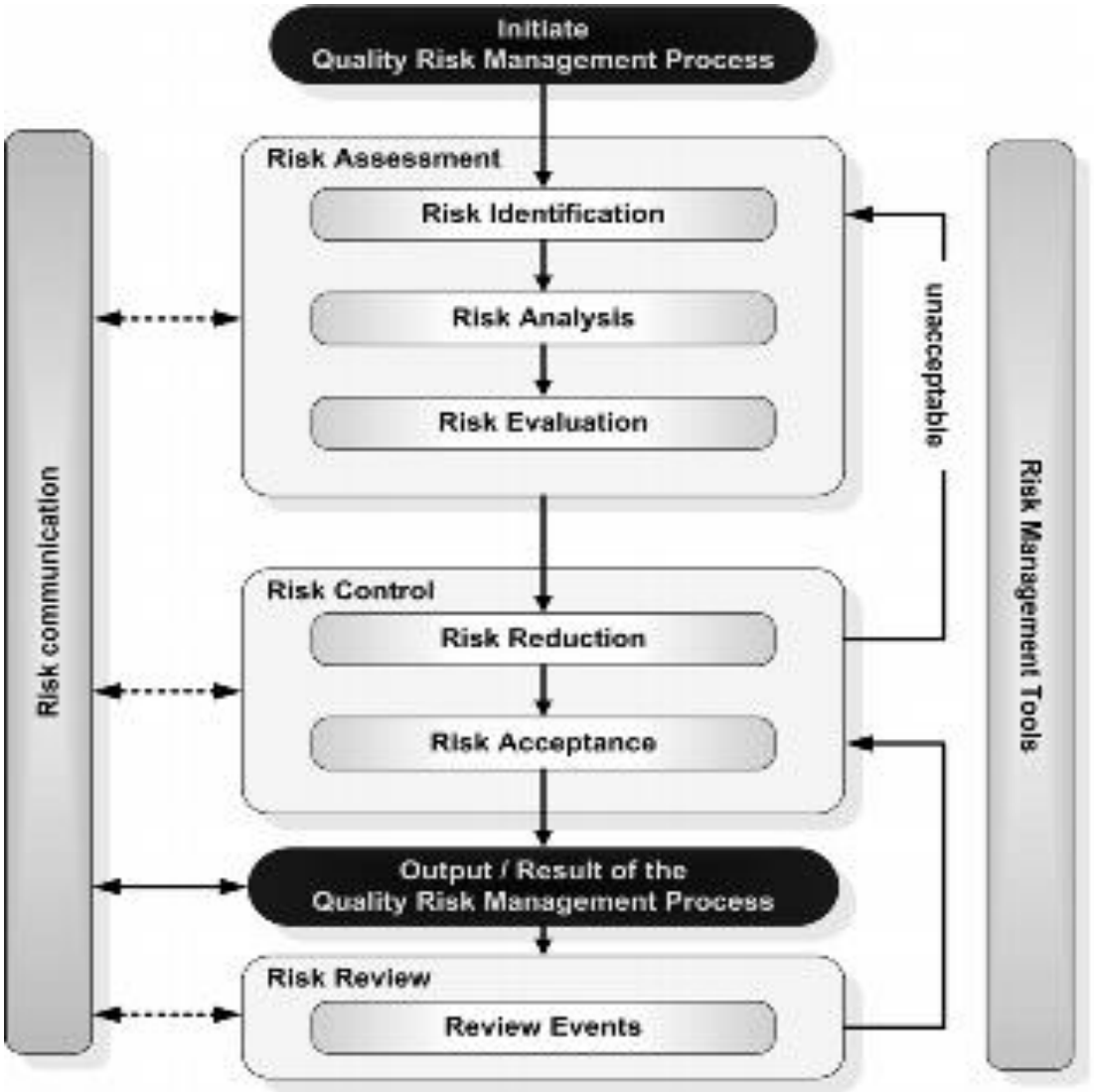

Figure-2: The quality risk management process according to ICH Q9.

Through the implementation of the risk-based approach in the QM system, it is possible to achieve considerable improvements in terms of

- Transparency of regulations and the relevant backgrounds.
- Acceptance of the system.
- Achievement of 100 % internal compliance by defining appropriate requirements in the regulations.
- Efficiency of the QM system through prioritization of the topics and reducing the scope of regulations to the necessary level.

Application to the QM system: A QM system consists of binding regulations that describe the internal implementation of external GMP requirements. In addition to formal compliance, the quality of products and processes is a clear objective. External specifications can frequently be interpreted to a greater or lower extent to allow for adaptation to suit the specific conditions within the company. Depending on the internal regulation, this interpretation can be handled in different ways - with the result that internal regulations can become highly specific or too detailed, while others are so general that no extra level of company-specific precision is achieved in comparison with the external regulations.

An initial general but well-documented risk evaluation of the individual blocks of a QM system (e.g. validation, documentation, deviations, etc.) can help to make the process more objective. The initial risk evaluation is performed on a general level in order to achieve a good overview of the whole system relatively quickly and with a reasonable initial expenditure. In a second step, a

detailed evaluation can then follow, which is subsequently reconciled with the general evaluation.

Risk Evaluation of a QM system[12]

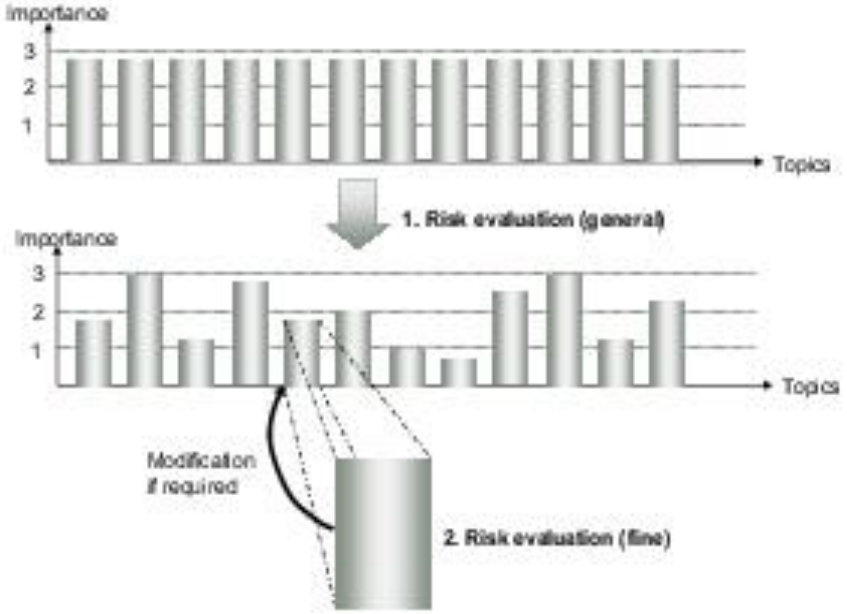

Figure-3: Risk Evaluation of a QM system.

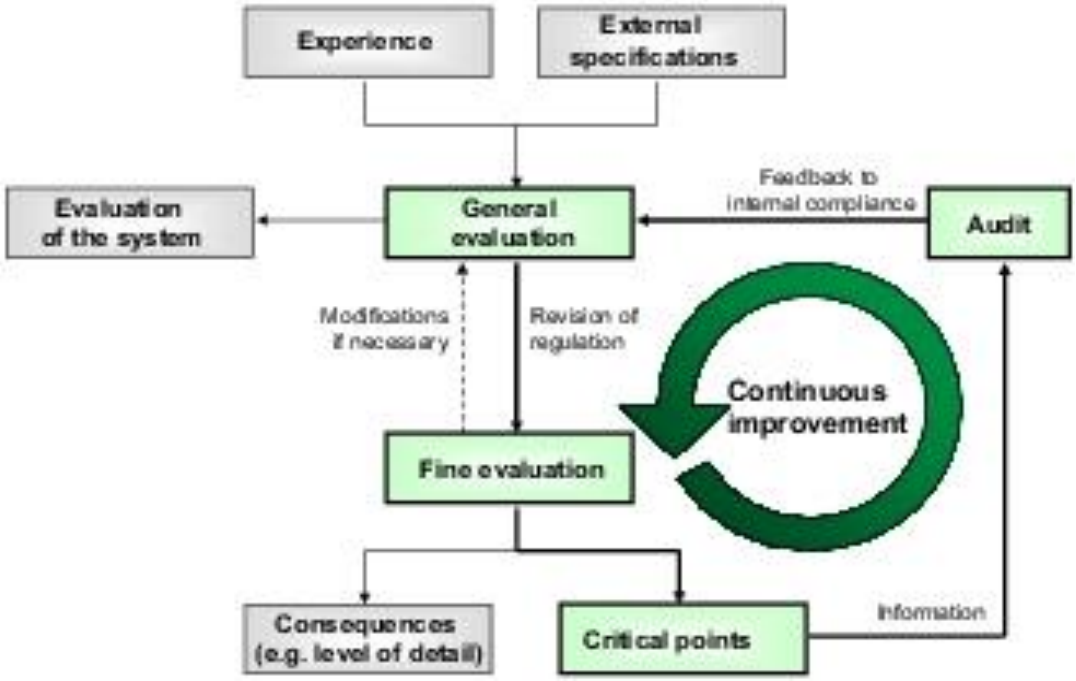

Figure-4: Closed loop for improving a QM system using risk management.[12]

Methods of risk management[11-13]

Methods of risk management acc. to ICH Q9, Annex 1

1. Basic risk management facilitation methods
2. Failure Mode Effects Analysis (FMEA)
3. Failure Mode Effects and Criticality Analysis (FMECA)
4. Fault Tree Analysis (FTA)
5. Hazard Analysis and Critical Control Points (HACCP)
6. Hazard Operability Analysis (HAZOP)
7. Preliminary Hazard Analysis (PHA)
8. Risk ranking and filtering
9. Supporting statistic tools

Table-2: Application examples of individual risk management methods.

Application examples of individual risk management methods				
Methods	**FTA**	**FMEA**	**HACCP**	**Statistical methods**
Risk identification	+	o	o	+
Risk analysis	o	+	o	+
Risk evaluation	-	+	o	+
Risk reduction	-	+	+	-
Risk acceptance	-	+	+	-
Risk review	o*			
Risk communication				
* In order to evaluate whether the planned measures have led to the expected success, additional instruments must be implemented that are suitable for the particular problem. This means that none of the methods mentioned here is suitable on its own. (+ = very suitable, o = limited suitability, - = not suitable)				

In the failure evaluation phase, as a general rule, only one line in the FMEA form is evaluated at a time. If the different causes of a failure are summarized in one line, the causes of the failure are evaluated together. In general, the following aspects of failures are evaluated:

- Probability of occurrence (O) of the cause of failure
- Severity (S) of the failure consequence
- Probability of detection (D) of the cause of failure

These three failure characteristics are assigned numerical values, which are used to calculate the risk priority number (RPN) by multiplying the three values together.

It is essential that the three evaluations are performed independently of each other. For example, evaluation of the severity of a failure must not also include its probability of occurrence or detection. If the consequences of a failure lead, for example, to a S = 8, this number should not be reduced only because the failure only occurs once a year.

Probability of occurrence (O) [Table-3]

Probability of occurrence (O)[11-13]

For a risk, it is of high importance to determine how often a failure occurs or can occur. The more frequently a failure occurs, the higher the risk. This means, for example, that O = 1 might stand for a rare occurrence and O = 10 a very frequent occurrence. The probability of occurrence is generally determined by the cause of failure.

Examples of evaluation guides for probability of occurrence

Evaluation guide for probability of occurrence		
Evaluation	**Classification**	**Explanation**
1	-	Failure frequency <0.01% or failure is not expected
2	Low	Expected failure frequency ≥0.01% and <0.05%
3	Low	Expected failure frequency ≥0.05% and <0.1%
4	Low	Expected failure frequency ≥0.1% and <0.2%
5	Medium	Expected failure frequency ≥0.2% and <0.5%
6	Medium	Expected failure frequency ≥0.5% and <1.0%
7	Medium	Expected failure frequency ≥1.0% and <2.0%
8	High	Expected failure frequency ≥2.0% and <5.0%
9	High	Expected failure frequency ≥5.0% and <10.0%
10	High	Expected failure frequency ≥10%

In this above, we can also directly see the problems that often occur when estimating probability of occurrence. In order to use this type of table, well-founded historical operating data must be available for a particular process or facility. If this historical operating data is not available, it can often be beneficial to reduce the level of detail by grouping together individual evaluation as follows.

Modified example of evaluation guide for probability of occurrence [Table-4]

Modified example of evaluation guide for probability of occurrence		
3	Low	It is very unlikely that the failure will occur.
6	Medium	It is assumed that the failure will occur occasionally.
10	High	It is assumed that the failure will occur frequently.

If it is also not possible to classify the probability of occurrence in this general evaluation, since no historical operating data regarding the probability of occurrence is available, this should initially be graded O = 10 (*worst case*). As new information becomes available, this figure can be reduced again.

Failure severity (S)[11-13]: The severity of a failure is an essential feature for this assessment. The severity of the failure is generally determined by the consequences of the failure. It should be clarified in advance whether the failure severity only affects the "end consumer" (patient), or whether the failure severity for the next "customer" should be considered.

Probability of detection (D)[11-13]: When determining risk, it is important to know whether a failure is detected or will be noticed from the customer or the pharmacist. The better the failure can be detected, the lower the risk. The numerical value thus decreases from 10 to 1, the higher the probability of detection is. This would mean that D = 1 is a value that, for example, can only be achieved if a fully automatic 100% test is integrated in the process or production process flow. D = 10 means that a failure is not detected. The probability of detection is generally determined by the cause of failure.

Definition of Terms[23,24]

Adverse Drug Reactions (ADRs): A response to a drug which is NOXIOUS and UNINTENDED, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of diseases, or for the modifications of physiological function.

Adverse Events (AE): Any untoward medical occurrence in a patient or clinical investigation subject upon administration of a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Pharmacovigilance: Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions/adverse events (ADRs/AE) or any other drug-related problem after they have been licensed for use.

Methods for application in any pharmaceutical industry[23,24]

1. In order to design, develop & implement a system of pharmacovigilance in the organization, a specialized Pharmacovigilance Committee (PVC) is formed having the following composition for the periodic review of the entire process (quarterly or more frequently, if required, but at least half-yearly).

1. In Charge, Research & Development
2. In Charge, Marketing & Sales Medical Advisor
3. In Charge, Quality Control
4. In Charge, Regulatory Affairs
5. In Charge, Factory
6. Marketing Manager
7. Corporate Advisor – Production (Technical)
8. In Charge, R&D serves as the Pharmacovigilance Coordinator of the Company, for necessary communication with regulatory authorities as well as amongst team members.

2. Apart from spontaneous reporting from various sources, through various channels, the Company develops and implements the following multimode approach & active surveillance strategies for data collection on ADR/AE of our products.

a) The Company designs & develops a dedicated "adverse event reporting" in web page where anybody and healthcare professionals (medical practitioners, dentists, nurses, pharmacists, physiotherapists, etc.) can voluntarily report drug-use related side effects, adverse experiences or untoward incidents in the format provided, named Medicinal Side Effects Reporting Form/P-Vig ICSR Form. It can be filled up & submitted online or can be downloaded, filled up & can be submitted via an ADR/AE specific email: Hard copies can also be handed over to Company representatives or mailed directly to the company address.

b) The Company envisages active solicitation & collection of ADR data in the format from medical practitioners & other healthcare professionals (nurses, physiotherapists, pharmacists, medicine wholesalers & retailers, etc.) through their marketing & sales field force, on a regular basis. In-charge, Marketing is responsible for this activity and sending the collected forms to the Pharmacovigilance Coordinator at periodic intervals (monthly, but at least quarterly). Serious AEs however, are to be intimated forthwith, as soon as it comes to his notice.

c) The Company carries out limited Post Marketing Observational Surveillance (PMOS) studies for selected products, from time to time as necessary.

Medicinal Side Effects Reporting Form (F1) / P-Vig ICSR Form [23,24]

REPORT DATE ☐☐ - ☐☐ - 20☐☐ Co. REF No. ☐☐☐☐☐☐☐☐☐☐

A. PATIENT: 1. Initials ☐☐☐☐ 2. Sex ☐ 3. Body Wt ☐☐☐ Kg 4. Residing at ☐☐☐☐

5. Date of Birth ☐☐ - ☐☐ - ☐☐☐☐ or Age at time of event ☐☐ Year / ☐☐ Months/ ☐☐ Days

B. SUSPECTED MEDICINE : (May tick >1 box wherever applicable. Use additional sheets if required.)

1. Brand		**2. Strength**	
3. Dosage Form	**Oral** ❑ Suspension ❑ Syrup ❑ Gel ❑ Tablet ❑ Capsule **Drops** ❑ Oral ❑ Eye ❑ Ear ❑ Nasal **Skin** ❑ Cream ❑ Gel ❑ Ointment **Injection** ❑ SC ❑ IM ❑ IV ❑ Infusion	**4. Composition** (Chemical / Compound / Molecular / Generic)	
5. Dose Amount / Quantity	❑ 1 ❑ 2 ❑ 3 ❑ 4 **Tablet** / **Capsule** / **TSF** (5 ml) Or, _____drops / puffs / ml / mg	**6. Dose Frequency & Duration**	❑ 1x ❑ 2x ❑ 3x ❑ 4x ❑ 5x ❑ 6x **daily** ❑ Stat ❑ SOS ❑ Weekly **FOR :** _____ days
		7.	
8. Start Date & Time		**9. STOP DATE ~** (last taken on)	
10. Reason for starting (Indication / Disease / Symptoms)		**11. Reason for stopping**	❑ Course / treatment complete ❑ Symptoms relieved / cured : by _____ % ❑ Oversight / negligence by patient / provider ❑ Appearance of side effects
12. Suggested * by (details)		**13. Prescriber / Doctor Name**	
14. Batch No.		**15. Expiry Date**	

[Table-5]

CONCLUSIONS

1. After collection of ADR reports from different sources, the Pharmacovigilance Coordinator puts them up for review & causality assessment by the Medical Advisor. After which, the Pharmacovigilance Coordinator compiles a comprehensive database.
2. A comprehensive review of the generated ADR/AE database is carried out by Pharmacovigilance Committee members, periodically as specified before. After which, a comprehensive action plan is formulated from time to time, to address important ADR/AE related issues, as & when required.
3. The data generated might also be used for submission of Periodic Safety Update Reports

(PSUR) to regulatory authorities, for newly approved drugs as applicable.

4. Suspected unexpected serious adverse event (SUSAR) due to drug, if any, obtained are to be communicated to regulatory authorities, within 15 days of collection of Adverse Events.

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