PHARMA DEVILS

PHARMACOVIGILANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Pharmacovigilance	**URS No.:**
Title: Signal Management	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1. OBJECTIVE:

This Standard Operating Procedure (SOP) provides general guidance on all topics and processes involved in preparation and maintenance of a Pharmacovigilance System Master File (PvMF).

2. SCOPE:

This SOP is applicable to ……

3. RESPONSIBILITY:

3.1. Pharmacovigilance Department:

Responsible to perform signal detection of ICSR's captured in PV database and for quantitative evaluation. Preparation, distribution, retrieval and destruction of this SOP.

3.2 Pharmacovigilance Officer In-charge(PvOI):

Responsible for clinical assessment, qualitative evaluation, signal validation and final conclusion of identified positive signals.

Review, training and effective implementation of this SOP.

4. ACCOUNTABILITY:

PvOI

5. PROCEDURES:

The Signal Management process shall comprise of Signal Detection, Validation, Prioritisation, Assessment and Recommendation for Action, Exchange of Information, Quality Requirements and Other Information.

5.1 SIGNAL DETECTION:

5.1.1. A Signal Detection Plan shall be prepared, reviewed and approved, and shall encompass, the potential sources, the frequency and method of data review as per format "Signal Detection Plan" as shown in Annexure I.

5.1.2. Sources of Signal Detection

- The potential sources for detecting signals are diverse for e.g. ICSRs, data from periodically reported safety reports, other department dataetc.
- The relevant sources that shall be searched for identifying signals shall be selected from the "Checklist of Potential Sources for Signal Detection" as shown in Annexure II.
- In the case a particular source of data is not applicable; a justification shall be documented on the Signal Management Plan.

5.1.3. Frequency of Data Review:

- The appropriate frequency of data review may be quarterly or as required and shall be specified with justification on the Signal Management Plan. It may also be specified in the PSUR and/or RMP, if applicable.
- The frequency of data review may be determined by considering the:
  - Risk inherent in a product,
  - Number of AE's/Adverse Drug Reactions received per year,
  - Potential public health impact of an adverse event e.g. patient exposure data,
  - Maturity of a product e.g. number of years on the market,
  - Safety profile of a product and whether there are events/interactions that are being actively monitored e.g. as part of a RMP. Even if a product has been on the market for many years, new safety concerns may be identified.

5.1.4. Method of Data Review:

- **A manual review of each of the following cases, from the potential sources, for a given period shall be done:**
  - Cases from HCP's and consumer reports
  - Serious and non-serious reports
  - Non-valid cases (containing details of at least an adverse reaction and a medicinal product)
  - Product quality complaints, if related to safety (e.g. lack of efficacy reports)
  - Special situation reports,
  - Lack of efficacy (a change in benefit may be as important as an increase in risk)
  - Medication errors
  - Off-label use
  - Overdose/misuse/abuse
  - Pregnancy/breastfeeding/lactation
  - Suspected transmission of infectious agents
  - Pediatric use
  - Compassionate/named-patient use
  - Reports received between submission and approval.

- **During the review of cases the following shall be considered:**
  - The number of cases (after exclusion of duplicates)
  - The patient's demographics (including age and gender)
  - The suspected medicinal product (including dose administered, formulation)
  - The suspected adverse reaction (including signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation (i.e. de-challenge / re-challenge information),and
  - An assessment of causality of a suspected association, that shall also consider, the presence of potential alternative causes including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship
- **Following shall also be taken care during data review process:**
  - Review of Summary Tabulation for period under review and since marketing authorization.
  - Review of the periodically prepared listings from the safety database containing all the adverse events reported during the respective period.

5.2. SIGNAL VALIDATION:

5.2.1. To validate a signal, its clinical relevance and previous awareness shall be reviewed.

- The clinical relevance of the signal shall be reviewed by assessing, for example:
  - The strength of evidence for a causal effect (e.g. number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders).
  - Seriousness and severity of the reaction and its outcome;
  - Novelty of the reaction (e.g. new and serious adverse reactions);
  - Drug-drug interactions;
  - Reactions occurring in special populations.
- **Previous awareness of the signal shall be reviewed by assessing, for example:**
  - The extent to which information is already included in the Sm PC/PL/PI/CCDS;
  - Whether the association has already been assessed in a PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

5.2.2. The new signal may be confirmed further through an in-depth review of other possible relevant sources of information which may provide a richer set of data on the same association, for example:

- Literature findings regarding similar cases;
- Experimental findings or biological mechanisms;
- Screening of databases with larger datasets (e.g. electronic safety database when the signal was sourced initially from ……...

5.2.3. Signals for which the validity is not confirmed shall be provided special attention in subsequent data review. The potential signal shall be monitored continuously until thereis enough evidence to confirm the signal.

For example, there may be an inadequate case documentation or a supporting evidence of a causal association only in some of the individual case reports. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases shall be reviewed at appropriate time intervals to ensure that all relevant cases are considered.

5.2.4. Outcome of the validation of signals as well as reasons why signals were not validated and information that can facilitate further retrieval of ICSR's and validation of signals shall be captured.

5.3 SIGNAL PRIORITISATION:

5.3.1 The validated signals with important public health impact or that which may significantly affect the benefit-risk profile of the medicinal product in treated patients shall be promptly identified. These signals shall be provided urgent attention and be prioritised for further management without delay.

5.3.2 The prioritisation process shall consider:

- The impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association;
- The consequences of treatment discontinuation on the disease and the availability of alternate therapeutic options;
- The strength and consistency of the evidence supporting an association, e.g., biological plausibility, a high number of cases reported in a short period of time, the measure of disproportionality of reporting and rapid increase of that measure over time and identification of the signal in different settings (e.g. general practice and hospital settings), data sources or countries;

- Clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions);
- The public health impact, including the extent of utilization of the product in the general population and in special populations (e.g. pregnant/ nursing women, children or the elderly) and the patterns of medicinal product utilization (e.g. off-label use or misuse).
- The public health impact may include an estimation of the number of patients that may be affected by an adverse reaction and this number could be considered in relation to the size of the general population, the population with the target disease and the treated population;
- Change in frequency or severity of a known adverse reaction;
- Novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product;
- If a marketing authorisation application for a new active substance is still under evaluation.

5.3.3 In some circumstances, priority may also be given to signals identified for products or events with potential high media and Pharmacovigilance stakeholder(s) interest in order to communicate the result to the public and healthcare professionals as early as possible.

5.3.4 Once a signal has been prioritised, a time frame for its management with the justification for the priority attributed shall be recommended approved, implemented and documented.

5.4. SIGNAL ASSESSMENT:

5.4.1. After a signal is prioritized, validated signal is further evaluated to identify the need for additional data collection or for any regulatory action by assessing available pharmacological, non-clinical, clinical data and information from other sources.

5.4.2. Sources of evidence shall include, for e.g.:

- The individual case safety report/s that triggered the signal.
- Other individual case safety report/s with similar event terms identified by using Standardized Med DRA Queries(SMQ's).
- Scientific literature
- Clinical trial and pre-clinical data
- Epidemiological data

5.4.3. SMQs, therapeutic or system organ class level shall be used to assess the signals at broader level.

The search for information to assess the significance of a signal if required and possible, shall be extended to other

products of the class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of a reaction (e.g. QT prolongation and Torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

5.5. RECOMMENDATION FOR ACTION:

5.5.1. Based on the extent of the information after the signal assessment, action should be recommended to each validated signal. Three possible actions; no further action for close signal, continuous monitoring or further action shall be recommended following signal assessment.

5.5.2. No further action:

A signal can be closed based on the available evidence and no further action shall be required. The decision and rationale for closing a signal shall be documented. However, if further evidence becomes available then the signal shall be re-assessed.

5.5.3. Continuous monitoring:

In some circumstances, for an open signal, a decision cannot be made until the evidence supporting the signal is strengthened. Except for situations of extreme risk, these signals shall be monitored until sufficient evidence becomes available to either confirm or refute the signal. The decision and rationale to justify monitoring a signal shall be documented.

5.5.4. Further Action:

- When there is a change in the benefit-risk profile as a result of a validated signal, further actions, shall be considered. The decision and rationale to take further action for a signal shall be documented.
- The recommended actions may include the following, fore. g.
  - Periodic review of the signals e.g. through PSUR's
  - Additional investigations or risk minimization activities
  - Update of the product information through regulatory procedure
  - Enhanced monitoring or follow-up technique
  - Conducting post-authorisation safety studies
  - Immediate measures including product recall or withdrawal marketing authorization
  - Follow recommendation by SRA at NCC-PvPI at IPC/CDSCO regulatory authority recommended committee, if any.

5.6. EXCHANGE OFINFORMATION:

5.6.1. The actions with the organisation, for a Validated signal:

- Notification to regulatory authorities by PvOI
- Escalation within the global safety function
- Discussion with relevant ……..
- Collation of a safety data package relating to the validated signal.

5.6.2. Post Signals confirmation:

- Emerging safety issues and signal assessment outcome should be exchanged with the competent authority.
- Provision of communicating safety information directly to Health Care Professionals/ patients or the public, for e.g. through letters or the …… website.
- Update of the Sm PC/PL/PI/ CCDS/ RMP (other product information documents etc.).

5.7. QUALITY REQUIREMENTS:

All validation, prioritization, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps shall be recorded tracked and documented systematically.

6. DISTRIBUTION:

Not Applicable

7. REFERENCES:

Not Applicable

8. ABBREVIATIONS:

AE	Adverse Event
ICSR	Individual Case Safety Report
MAH	Marketing Authorization Holders
NA	Not Applicable
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio

PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PvOI	Pharmacovigilance Officer In-charge
RMP	Risk Management Plan
SDR	Signal of Disproportionate Reporting
SMQ	Standardized Med DRA Query
SOP	Standard Operating Procedure

9. ANNEXURES:

S.No.	Title	Annexure No.	Format No.
1.	Signal detection plan	I	
2.	Checklist of potential sources	II	

10. REVISION HISTORY :

Revision No.	Effective Date	Reason for change	CC No.
00		New SOP	Nil

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ANNEXURE I
ADVERSE EVENT (AE) REPORT FORM

Report Type: Initial Follow-up Follow-up No:			
Date of AE Report:			
Please fill and return this form to …….within 24 hours of knowledge of adverse event within 24 hours of knowledge of adverse event			
1. Patient Information			
Initials/identifier:	Date of Birth (e.g. 01 Jan 1940)	Ethnic Origin: White Asian Black/African American Other, Please Specify	
Sex: Male Female	Height(cm):	Weight(kg):	
Pregnant: [ ]Yes[ ] No	Country of occurrence:	Tel. No:	
2. Adverse Event Information			
AE term(s):			
Course of event:			
Onset of AE or date and time when AE occurred:		Date:	Time:
Onset of AE or date and time when event became serious ,if applicable:		Date:	Time:
Present Status: Ongoing→ AE currently treated □Yes □No Resolved Please Specify Date:_____Time:_____			
Casedescription:Detaileddescriptionoftheevent(Includerelatedsigns/symptoms,course,outcome)			
Reason for seriousness:			
Resulted in death life-threatening required in patient hospitalization or prolongation of Existing hospitalization resulted in persistent or significant disability/incapability(as per reporter's opinion)/congenital anomaly/birth defect other medically important event(reporter's discretion)			
Intensity: Mild Moderate Severe			
Reporter's Causality: [ ] certainly[ ] probably[ ] possibly[ ] unlikely[ ] conditional[ ] un assessable [ ] not related			
Outcome of AE: Completely recovered/resolved Ongoing Fatal Lost to follow-up Unknown Recovered with sequel AE→ Specify:_____			
If outcome Is fatal: Cause of death:_____Date:_____Time:_____ Report of Autopsy available? □No □Yes (Please attach copy to this report) Further information:_____			
Lab test Details(with dates, results and normal range):_____			
3. Drug Details			
Name of the drug:_____Strength:_____Indication:_____			
Route of Admin:_____Dosage form:_____Dose:_____			
Frequency:_____Expiry date: DD/MM/YYYY			
Start date:(dd.mm.yyyy) Stop date:(dd.mm.yyyy) Ongoing:			

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	Action taken with suspect drug: None Dosage changed temporarily: Date:_____Dosage reduced Dosage increased Drugs top temporarily: Date:_____ Drug restarted: Date:_____ Drug withdrawn permanently Dosage not changed Unknown Not applicable		
	Additional suspect drug(if any) details as above:		
	Event abated after drug Stopped or dose reduced:	Event reappeared after Reintroduction of suspect drug:	If yes, did reaction recur?
	Yes No Not applicable	Yes No Not applicable	Yes No Not applicable

4. Patient's Relevant Medical History (Supplement attached Yes/No)

(E.g. Concomitant diseases, previous history of present condition, allergy, drug or alcohol abuse)

5. Concomitant Drugs

Drug Name (generic)	Dose/ Unit	Route	Frequency	Start date	Stop date	Ongoing	Causal relationship To event
							None Possible
	Indication:						
							None Possible
	Indication:						
							None Possible

6. Reporter Details

Name: Address: Country: Tel. No: Email:	Occupation:[ ]Physician[ ] Pharmacist[ ] Nurse[ ] Consumer[ ] Other, specify:…… Also reported to:[ ]Regulatory Authority [ ] Distributor[ ] None Date: DD/MM/YYYY, Signature:
7. Send this report to:	**8. To be filled by Manufacturer:**
…….	Date received by receiver: DD/MM/YYYY Name and sign of receiver: Safety Report ID:

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ANNEXURE II
CASE LOG

S.No.	Local tracking number	Country	Product	Source (Health authority, or Spontaneous reporter)	Information type (Single case, Safety finding from local literature review)