



STANDARD OPERATING PROCEDURE

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SOP No.

IPC/PvPI/SD/002

Revision No.

01

Section

SD Section

Effective Date

27/04/2016

Review Date

26/04/2019

Title: SOP for functioning of Signal Review Panel

1.0 OBJECTIVE

1.1 To lay down a procedure for identification, review and processing of new safety signals generated for drugs approved for use in India.

2.0 SCOPE

2.1 This SOP shall be limited to the safety data reported for the drugs including FDCs in PvPI database, published scientific reports, clinical trial registries, clinical reviews and PSURs submitted to the DCG(I). Safety reports of AYUSH and herbal drugs, medical devices, blood and blood products are out of purview of this SRP.

3.0 RESPONSIBILITY

- 3.1 All members of the quorum shall be responsible for the implementation of this SOP.
- 3.2 Signal Detection section shall be responsible for Coordination with Signal Review Panel.
- 3.3 Quality Manager/Technical Manager shall ensure overall implementation of this SOP.

4.0 ACCOUNTABILITY

4.1 Officer Incharge - Pharmacovigilance Programme of India

5.0 PROCEDURE

5.1 Resource materials used for the identification of Signal from

- PvPI database
- Scientific literature and case reports published in peer reviewed journals

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Reviewed by	Dr. [Signature]	SA	[Signature]	25/04/2016
Approved by	Dr. Kalai selvan	PSO	[Signature]	22/04/16

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- Clinical trial registries
- Clinical reviews
- PSURs
- Non interventional studies
- Information on other drugs in same class

5.1.1 If the potential signal(s) are identified from PvPI database, Member Secretary shall be responsible to place the detail information to the panel.

5.1.2 To obtain signal details from clinical trial registry based on recommendation of SRP, Secretary-cum-Scientific Director, IPC shall write to Secretary, Department of Health Research (DHR) with a copy of communication to DCG(I) for submission of the cases of interest to NCC-PvPI, IPC.

5.1.3 To obtain signal details from PSURs/PMS, Secretary-cum-Scientific Director, IPC shall write to DCG(I) for submission of the cases of interest to NCC-PvPI, IPC.

5.1.4 Information from published scientific literature can be shared by all members, after submitting them prior to Member Secretary.

5.2 Steps for potential signal detection

- *Signal Identification* usually involves a combination of statistical methods and review of individual case safety reports, as well as any relevant source of information (e.g. scientific literature).
- *Signal validation* in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis.

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- Signal analysis and prioritisation are performed by taking into account the potential impact of the signal on the benefit-risk profile of the involved medicine(s).
- Signal assessment is the scientific evaluation of all the evidence available, including additional data from AMC/MAHs, where applicable.
- Final decision shall be done after SRP meeting.

5.3 Identification of potential signal and its clinical review

5.3.1 According to SOP of SUSARs identification Unlisted ADRs/Uncommon ADRs are processed, Signal Detection team shall perform the *signal identification, signal validation and initial review of a signal*. The results of which shall be submitted by Member Secretary to the panel.

5.3.2 SRP shall evaluate the ICSRs against

- Quality and content of the data and completeness of ICSRs.
- A detailed clinical review of potential signal shall be done by SRP and if needed opinion of clinical experts shall be taken.
- If information is inadequate, SRP shall recommend NCC to furnish more information from the reporter within 15 working days.

5.4 Confirmation of causality

SRP shall establish causality of the report by

- Checking background rate of the event from UMC. Request for obtaining background rate from UMC shall be made by Member Secretary to panel member during the meeting.
- Consultation with relevant clinical experts. One member of SRP in concurrence with Chairperson shall identify a minimum of two clinical experts and Member Secretary would invite them as special invitee for the meeting.

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- Ensuring that therapeutic methods used were in compliance to standard treatment guidelines (Clinical experts might be consulted to confirm this)
- 5.5 **Assessment of strength of signal and its validation**
- 5.5.1 Minimum 3 reports shall be required to assess the strength of the signal. However the decision shall be taken on case to case basis depending on the nature of the drug, reaction, quality of the reports and available information.
- 5.5.2 Case reports with certain, probable, and possible causal association shall be used for the assessment. Unlikely case reports shall be considered after due consultation with the experts. Unclassified/unclassifiable reports shall be exempted from the review.
- 5.5.3 Following criteria besides majority vote of the SRP quorum shall have to satisfy at least two of the listed criteria to validate a signal.
- $IC_{0.25}$ value >0
 - $PRR \geq 2$ with lower bound of its 95% C.I. more than 1
 - A chi-square test value (with 1 degree of freedom) ≥ 4 and
 - Three or more cases to highlight potential signals
- 5.6 **Categorization of outcome of potential signal review**
- Not a clinically significant signal at present
 - To be reviewed to follow trend of signal strength
 - A clinically significant signal that requires some regulatory action
- 5.7 **Recommendation to the regulatory authority**
- 5.7.1 The SRP shall give its recommendation to the regulators in any of the following manner:
- Advisory note
 - Drug Alert
 - Change in Package inserts
 - Box warning

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- Withdrawal
- Suspension of Market registration
- Change in drug safety categories/drug schedules

5.8 Follow up actions

- 5.8.1 If SRP has concluded that a signal could not be confirmed, then it shall be deemed closed and would not require any further action.
- 5.8.2 If SRP has concluded that there is a signal then same shall be recommend by SRP for the preparation of a "draft signal report" for internal discussion and sharing with coordinators of AMCs of PvPI.

5.9 Data handling and record keeping

- 5.9.1 The outcomes of the SRP deliberation shall be tabulated containing at a minimum, the following information:
- Complete detail of the Drug
 - Number of Sources from which supporting ADR data was obtained
 - The severity of the signal
 - Classification of number of reports received from NCC, UMC and from any other regulatory agency/Pharmacovigilance authority.
- 5.9.2 The SRP shall maintain records of all its meetings, correspondence and other proceedings for a minimum period of five years in the Signal review cell at NCC.
- 5.9.3 Access to these records is permissible only for Member Secretary and Chairperson of the SRP. However, copies of original records can be shared by the Member Secretary with other members of the SRP.
- 5.10 Communication
- 5.10.1 First level of communication shall be from Chairperson/Member Secretary to all the members of the SRP.

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5.10.1.1 This information shall have Minutes of Meetings, certain key findings and scope for receiving suggestions.

5.10.1.2 The final version of all communications at this level shall be approved by the Chairperson.

5.10.1.3 This form of communication shall in electronic format.

5.10.2 Second level of Communication shall be from Chairperson to NCC. This level of communication shall be sent electronically but necessarily a signed hard copy shall also be sent. The categories of information in this section shall be:

5.10.2.1 Request for more data/Information from PvPI.

5.10.2.2 Request for more data/Information from other governmental/Private bodies.

5.10.2.3 Request for more data/Information from other International Pharmacovigilance Authority or from National Centres of the other countries.

5.10.3 Third level of communication shall be from member secretary-SRP to Officer Incharge of Pharmacovigilance.

5.10.3.1 This needs to be submitted in written and put on file.

5.10.3.2 The kind of Information sent in this manner can be minutes of the meeting of SRP along with key items for further work of SRP as and when required for which approval Officer Incharge of Pharmacovigilance is required.

5.10.4 The fourth level of communication shall be the most important and confidential communication.

5.10.4.1 The SRP shall recommend Secretary cum Scientific Director, IPC to communicate the outcome of the SRP meeting to CDSCO for appropriate regulatory action.

6.0 SAFETY AND PRECAUTIONS

6.1 Do not use any SOP if it is not signed and issued by QA Personnel's or the authorized signatories.

6.2 Do not use adhesive tape or whitener on SOP.

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6.3 Do not share the SOP information to outside the organization.

7.0 REFERENCES

7.1 SOP for operational functioning of Signal Review Panel

8.0 ABBREVIATIONS

IPC	:	Indian Pharmacopoeia Commission
CDSCO	:	Central Drugs Standard Control Organization
SOP	:	Standard Operating Procedure
PvPI	:	Pharmacovigilance Programme of India
SRP	:	Signal Review Panel
FDC	:	Fixed-Dose Combination
AMC	:	Adverse Drug Reaction Monitoring Centre
DCG(I)	:	Drugs Controller General of India
AYUSH	:	Ayurveda Yoga Unani, Sidha and Homeopathy
ICSR	:	Individual Case Safety Report
UMC	:	Uppsala Monitoring Centre
DHR	:	Department of Health Research
PSUR	:	Periodic Safety Update Report
PMS	:	Post Marketing Surveillance
NCC	:	National Coordination Centre
IC	:	Information Component
PRR	:	Proportional Reporting Ratio

9.0 ANNEXURE

Annexure-I : Glossary Format No. IPC/PvPI/SD/002-F01

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Annexure-I
Glossary

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Adverse drug reaction (ADR): A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Adverse Event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Clinical trial: A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety.

Information component (IC): The Information component (IC) measures the disproportionality in the reporting of a drug-ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected. The IC has also been implemented on electronic health records, to detect interesting temporal relationships between drug prescriptions and medical events.

Periodic Safety Update Report (PSUR): A systematic review of the global safety data in an internationally agreed format which became available to the manufacturer of a marketed drug during a specific time period.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

Post Marketing Surveillance: It refers to the monitoring of drugs once they reach the market after clinical trials. It evaluates drugs taken by individuals under a wide range of circumstances over an extended period of time. Such surveillance is much more likely to detect previously unrecognized positive or negative effects that may be associated with a drug.

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Proportional Reporting Ratio (PRR): For a given medicine, the PRR is the proportion of all reactions to a drug which are for a particular medical condition of interest, compared to the same proportion for all drugs in the database, in a 2 x 2 table.

Risk Management Plan (RMP): A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions.

Signal: Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.

Signal management team (SMT): Team responsible for the detection and management of new safety signals associated with the use of drugs.

VigiBase: The name of the WHO Global ICSR Database. It consists of reports of adverse reactions received from member countries since 1968.

VigiFlow: VigiFlow is a complete ICSR management system created and maintained by the UMC. It is web-based and built to adhere to the ICH-E2B standard. It can be used as the national database for countries in the WHO Programme as it incorporates tools for report analysis, and facilitates sending reports to VigiBase.

VigiMine: A statistical tool within VigiSearch with vast statistical material calculated for all Drug-ADR pairs (combinations) available in VigiBase. The main features include the disproportionality

VigiSearch: A search service for accessing ICSRs stored in the VigiBase database offered by the UMC to national pharmacovigilance centres and other third-party inquirers.

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