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I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for drug safety signal detection and management at PharmExpert LLC (Pharmex) for the Medicinal Products (MP) included in the Pharmacovigilance (PV) system in accordance with Good Pharmacovigilance Practices (GVP).

II. SCOPE

This procedure shall apply to signal detection and management process for the MPs for which Pharmex has responsibility in line with the agreement.

III. RESPONSIBILITIES

Role	Responsibility
Senior Pharmacovigilance Specialist (SPVS) **Head of Pharmacovigilance Department (HPVD)**	• Fully adhere to this SOP
Marketing Authorization Holder's Qualified Person responsible for Pharmacovigilance (MAH's QPPV)	• Review and approval of signal management process
Quality Assurance Manager (QAM)	• Compliance monitoring

IV. DEFINITIONS

Abbreviations used in the text are spelled out on its first mention.

Adverse event (AE) – any untoward medical occurrence in a patient to whom a MP is administered and which does not necessarily have a causal relationship with this treatment.

Adverse reaction (AR) – A response to a MP which is noxious and unintended. Response in this contest means that a causal relationship between a MP and an AE is at least a reasonable possibility.

Emerging safety issue – a safety issue considered by MAH to require urgent attention by the Regulatory Authority (RA) because of the potential major impact on the risk-benefit balance of the MP and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals (HCP).

Individual Case Safety Report (ICSR) – refers to the format and content for the submission of an individual report of suspected ARs in relation to a MP that occur in a single patient at a specific point of

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- Preventability, the consequences of discontinuing treatment and the availability of alternative therapeutic options
- The extent of use of the MP by the general population or in particular patient groups
- The complexity of the issue and the expected volume of data

b) Enter the outcome of the signal prioritization process in the section III (Prioritization & Assessment) of the «SAR Form» and in the «Signal Tracker».

c) Notify the MAH's QPPV about prioritization level of safety signals.

d) Set the timelines for the subsequent steps for the signal evaluation after the signal prioritization.

4. Signal Assessment-Evaluation of Risk

SPVS/HPVD:

a) Assess the signals with high priority within **7 business days**, the signals with normal priority within **14 business days**.

b) Review all the available pharmacological, non-clinical and clinical data and information from the following sources carefully considering the strengths and limitations of each source:

- The application dossier
- Literature articles
- Spontaneous reports
- Expert consultation
- Additional data held by MAHs and RAs

c) Assess the significance of a signal at a broader level, at the therapeutic or at the System Organ Class (SOC) level, or at the level of a Standardized MedDRA Query (SMQ) to obtain a potential link to a complex disease, to a prior stage or a reaction or to clinical complications of the AR of interest.

d) Enter the final assessment results in the «SAR Form» and «Signal Tracker».

5. Recommendation for Action

a) Following the signal management process, the decision may include the following conclusions:

- Signal open and assessment continues. Update an assessment status of the signal: high priority signals- every 7 days; normal priority signals- every 30 days
- Signal refuted: close the signal
- Signal is not assessed as an identified or potential risk

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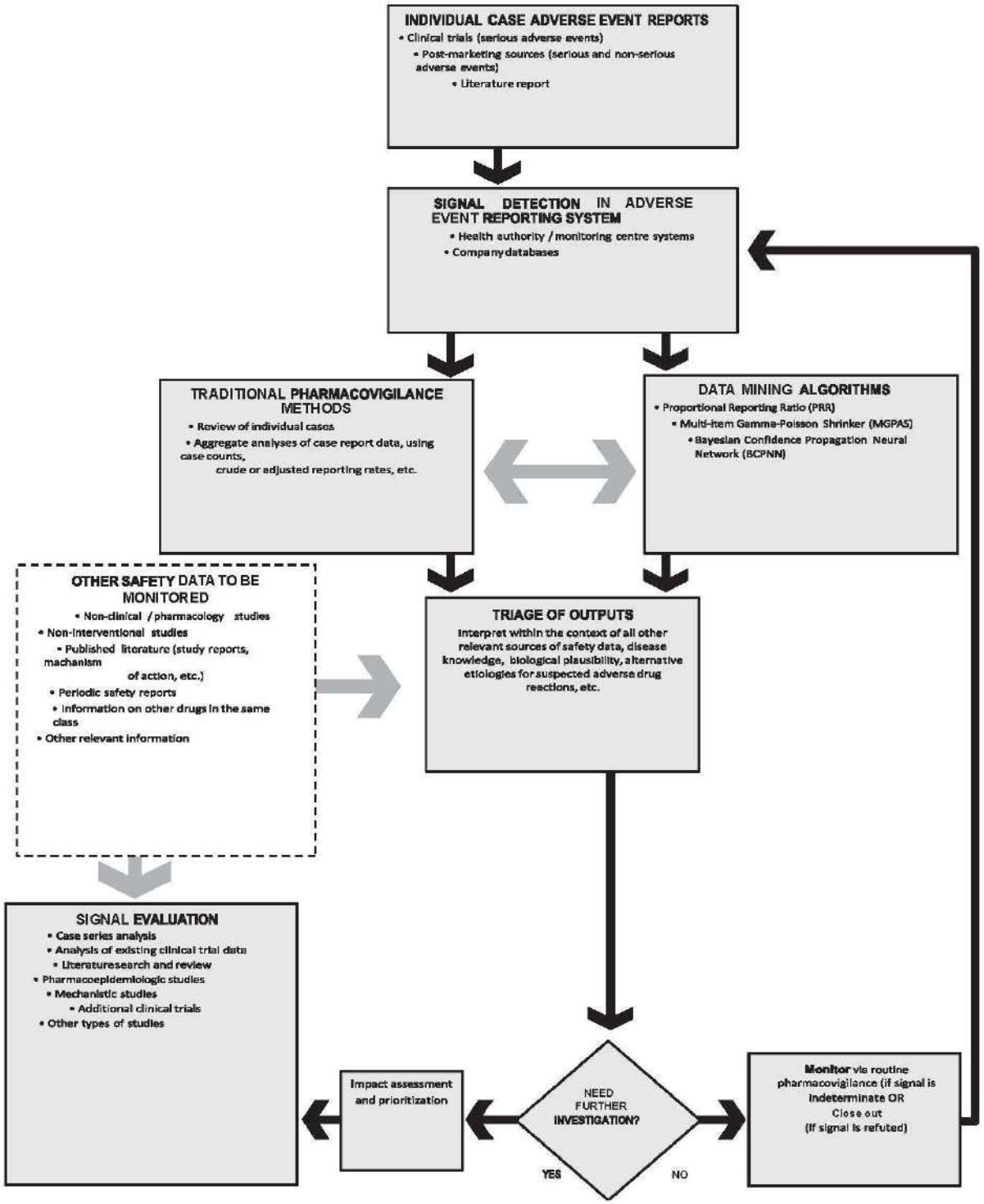
Signal Management process



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I. ADMINISTRATIVE INFORMATION	
MAH:	**No:**
Report date :	**Signal detection date:**
Pharmaceutical Form/Route of Administration/Strength:	**Relevant statistical measures:**
Suspect Drug (MP's Name/INN):	**Source of Signal:** ☐ Literature ☐ MAH database ☐ Clinical trials ☐ Other *[please specify below]*
II. SIGNAL VALIDATION AND EVALUATION	
Previous Awareness	
Listedness in SmPC	
Does the event reflect a new aspect of a known association?	
Has the association previously been addressed in a regulatory procedure?	
Consistency Of Evidence Across Cases And Various Data Sources	
Strengths Of Evidence	
Quality Of The Data	
Clinical Relevance	
Other Aspects To Be Considered	
Similar Cases (Literature Search)	
Similar Cases (Global Databases)	
Validation Status	☐ Yes ☐ No
III. **PRIORITIZATION & ASSESSMENT**	