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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

The process includes signal detection, validation, assessment, confirmation, prioritization, as well as any related recommendations, decisions, communications and tracking. Signal management process is described in the Table 1 (Annex I).

Signal detection is ongoing monitoring of AE reports comprises the retrieval of data from the global safety database at monthly intervals for all monitored products, and review of the data with the purpose of timely identification of (potential) new safety signals requiring further investigation. The monitoring also comprises data retrieval from the clinical databases for the analysis of non-serious AEs.
Retrieval strategies (case selection criteria, format, and periodicity of retrievals from the global safety database, for example) should be defined in advance on a per-product basis. Retrieval strategies and results of all ongoing monitoring activities must be documented.

2. Signal Sources

Pharmex may detect safety signals through the following sources, including but not limited to:

- consumers / patients;
- data obtained from non-interventional studies / trials;
- data from post-marketing studies, registers, observational programs;
- review of scientific and medical literature;
- data from the global safety database in the form of review of ICSRs/statistical analyses;
- preparation of aggregate reports;
- distributors;
- medical representatives;
- employees of MAH;
- employees of Pharmex;
- employees of Pharmex's vendors;
- information obtained from regulatory and health authorities;
- internet resources;
- mass media;
- pharmacy and medical institutions;
- HCPs including physicians, pharmacists, nurses and other HCPs;
- MAH's competitor.

3. Signal Detection Methodology

Following quantitative and qualitative methodologies are used in signal detection process, depending on the size of the database:

- Review of ICSRs
- Statistical analyses of large database
- Combination of both: ICSR review and statistical analyses

a) Review of ICSRs

For small databases, signal detection will involve mainly review of individual cases. Data from all appropriate sources should be considered. A single report of a serious or severe AR (for eg., one case of

- Number of cases supporting the association (after exclusion of duplicates and cases with no supporting temporal association)
- Number of cases appropriately documented with sufficient information about, e.g., suspect drug, event reported, demographics (age and gender), indication, outcome, concomitant medication
- Consistency of the evidence across cases (e.g. patterns)
- Route(s) of administration and product(s) formulation
- Cluster of reports, e.g., many reports from the same reporter, publication, etc.
- Cases fulfil the diagnostic criteria for the event

i) Strength of evidence

- Biological and pharmacological plausibility (possible mechanism)
- Dose relationship
- Number of cases with positive de-challenge
- Number of cases with positive re-challenge
- Low background incidence of the event
- Time to onset

j) Weaknesses

- Poor data quality of case reports
- High number of cases with confounding factors / alternative explanations
- Signs of stimulated reporting e.g. increased media attention
- Abnormal reporting pattern
- Presence of other risk factors for the event: underlying disease, co-morbidities, co-medications

Clinical relevance-seriousness and severity of AE (SOP-PV-001 «AE Processing»)

k) Clinical relevance

- Seriousness/severity of the event
- Reversibility of the event
- Event affecting special populations (e.g. pregnant women, children, elderly) or patients with pre-existing risk factors
- Events occurring in different patterns of use (e.g. off-label, overdose, misuse, medications errors)
- Association likely to apply to other active substances of the same class
- Potential for prevention

l) Other aspects to be considered

- Possible class effect
- Possible drug-drug interaction
- Possible medication error
- Possible quality issue