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I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for actively collecting, analyzing, validating, processing and reporting to Regulatory Authorities (RA) post-marketing Adverse Event (AE) reports and other safety related information received from any source in relation to Medicinal Products (MP) and/or Pharmacovigilance (PV) systems outsourced by Marketing Authorization Holders (MAH) to PharmExpert LLC (Pharmex) in line with the agreement.

II. SCOPE

This procedure shall apply to management of all post-marketing AE reports and other safety related information which may receive staff of Pharmex.

III. RESPONSIBILITIES

Role	Responsibility
All employees of Pharmex	• Daily monitoring of communication tools • Intake and registration of AE report and other safety related information • Transmitting of the reports to the PVS/SPVS/HPVD in a timely manner
Pharmacovigilance Specialist (PVS)	• Validation and follow-up • Entering case details in the «Case Register» • Storage of the documents in the Safety Database (SDB) • Submission of ICSR • Reconciliation of safety information
Senior Pharmacovigilance Specialist (SPVS)	• Validation and follow-up • Entering case details in the «Case Register» • Triage • Data Entry • Case Processing • Submission of ICSR • Storage of the documents in the SDB • Reconciliation of safety information • Regulatory Compliance
Head of Pharmacovigilance Department (HPVD)	• Quality Review

Medical Reviewer	• Narrative writing • Review and approval of the case assessment from a medical perspective
MAH's Qualified Person Responsible for Pharmacovigilance (QPPV)	• Review and approval of the Case processing
Quality Assurance Manager (QAM)	• Compliance monitoring

IV. DEFINITIONS

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

Abuse – this corresponds to the persistent or sporadic, intentional excessive use of a MP, which is accompanied by harmful physical or psychological effects.

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.

AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a MP, whether or not considered related to this MP.

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.

This includes ARs which arise from:

- The use of a MP within the terms of the marketing authorization;
- The use outside the terms of the marketing authorization, including Overdose, Off-label use, Misuse, Abuse and medication errors;
- The Occupational Exposure

Coding – In the context of AE coding, this is the process of matching the verbatim term from the case report form to a specific and unique MedDRA Preferred Term.

Day 0 (zero) – the clock for the submission of a valid ICSR starts as soon as the information containing the minimum criteria has been brought to the attention of the personnel of the MAH, including medical representatives and contractors. This date should be considered as day zero. It is the first day when the MAH gets knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. The timelines for submission are based on calendar days.

Important safety information – this reflecting changes in «risk-benefit» ratio should be considered for reporting to RA:

- Increase of expected serious ARs occurrence frequency that may affect drug risk-benefit ratio.

- Drug distribution limitations; drug withdrawal from the market; marketing authorization (MA) non-extension, cancellation or suspension on the territory of other countries due to drug safety and efficacy related reasons as well as those initiated by RA of the established countries or MAHs.
- Significant changes introduction to recommendations for medical use in other countries due to drug safety related reasons.
- Safety issues revealed during non-interventional post-marketing studies (PMS), clinical trials or pre-clinical studies.
- Safety information revealed as a result of signal detection activities and may affect risk-benefit ratio.
- Safety issues related to drug use not per summary of product characteristics (SmPC).
- Safety issues related to wrong information in SmPC, package leaflet and labeling.
- Lack of efficacy for drugs indicated to treat life-threatening pathologies as well as vaccines and contraceptives (or the absence of effect).
- Safety issues related to source materials for drug manufacturing and (or) its distribution.

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 time.

MedDRA – Medical Dictionary for Regulatory Activities. The dictionary is updated twice a year.

Medical Reviewer – employee of Pharmex or external consultant with appropriate education background.

Misuse – this refers to situations where the MP is intentionally and inappropriately used not in accordance with the authorized product information.

Occupational exposure – this refers to the exposure to a MP, as a result of one's professional or non-professional occupation.

Off-label use – this relates to situations where the MP is intentionally used for a medical purpose not in accordance with the authorized product information.

Overdose – this refers to the administration of a quantity of a MP given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.

Serious ICSR – a serious AR corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Solicited reports – a reports of suspected ARs are those derived from organized data collection systems, which include: clinical trials, non-interventional studies, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare professionals (HCP), compassionate use or name patient use, information gathering on efficacy or patient compliance.

Special Situations: