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I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for assessment of new safety data of medicinal products (MP) in accordance with Good Pharmacovigilance Practices (GVP).

II. SCOPE

This SOP applicable to Pharmacovigilance (PV) Specialists of PharmExpert LLC (Pharmex).

III. RESPONSIBILITIES

Role	Responsibility
Senior PV Specialist (SPVS) **Qualified Person responsible for PV (QPPV)**	• Fully adhere to this SOP
PV Specialist (PVS)	• Additional monitoring
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.

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.

Causality assessment – method used for estimating the strength of relationship between drug(s) exposure and occurrence of AR (s). It is the key factor for identification of new signals, measuring the strength of evidence, and in evaluating benefit risk profile of drugs.

Dechallenge – the clinical decision to withdraw or discontinue a drug to monitor the effect on an adverse event. Dechallenge (and rechallenge) play an important role in ascertaining a causal relationship. Dechallenge means that a drug that is suspected of causing the event is withdrawn. A dechallenge is positive when after removal of the drug the adverse event subsides or disappears. A dechallenge is negative when the event persists even after removal of the drug i.e. a causal relationship is unlikely.

Expected AR – nature or severity is consistent with that included in the appropriate reference safety information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Commentary: The concept of "expectedness" refers to events which may or may not have been previously observed and documented. It does not refer to what might have been anticipated (expected in a different sense) from the known pharmacological properties of the MP. Depending on the context, expected and unexpected can refer to labeled vs unlabeled (for official data sheets/package inserts for marketed products) or listed vs unlisted (for the Investigator's Brochure, Development Core Safety Information (DCSI), or Company Core Safety Information (CCSI)).

Listed or Unlisted (also, see Expected and Unexpected) (CIOMS VI) Any reaction which is not included in the Company Core Safety Information within a company's core data sheet for a marketed product is unlisted. If it is included, it is termed listed.

Preventable or avoidable AEs – a direct result of failure(s) to follow recognized, evidence-based best practices or guidelines at the individual and/or system level.

Rechallenge – the point at which a drug is given again to a patient after its previous withdrawal. In the instance you have a positive dechallenge (AE subsides or disappears after you remove the drug), reintroducing the drug represents a rechallenge. A positive rechallenge (i.e., the AE reappears when treatment is restarted), strongly suggests a causal relationship.

Risk – the combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk-benefit balance – an evaluation of the positive therapeutic effects of the MP in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the MP as regards patients' health or public health.

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.

Seriousness vs Severity – the term 'severe' must not be confused with 'serious'. In the English language, 'severe' is used to describe the intensity (severity) of a specific event (mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache).

Seriousness (not severity) is based on patient/event outcome or action criteria, and serves as a guide for defining regulatory reporting obligations.

Understanding the difference between seriousness and severity is critical to correctly reporting and evaluating AEs.

Severity – measure of the possible consequences of a hazard.

Special Situations:

- Lack of Therapeutic Efficacy
- Product quality complaints
- Exposure during pregnancy or parental exposure and exposure during lactation

- Accidental exposure / Occupational exposure
- Overdose
- Misuse, abuse or off-label use
- Medication error or risk of medication error
- Use of a MP in pediatric or elderly populations

Suspected AR – any AE for which there is a reasonable possibility that the drug caused the AE.

For terms and definitions refer to the SOP-QA-003 «Pharmacovigilance Glossary».

V. PROCEDURE

A. General Specification

Sources of New Safety Information

- Spontaneous/Voluntary Reports
- Clinical trials and Post marketing studies
- Regulatory reports
- License partner's reports
- Literature reports

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

All new safety data collected, identified and received by Pharmex is subject to assessment in accordance with this SOP. Assessment is made by QPPV or SPVS. Training of Assessor is performed in accordance with the «SOP-HR-002 Training».

B. Process