TABLE OF CONTENTS

I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for systematic monitoring of safety relevant information in locally and globally published scientific-medical literatures and other resources by PharmExpert LLC (Pharmex) for the medicinal products (MP) of Marketing Authorization Holders (MAH) in accordance with Good Pharmacovigilance Practices (GVP).

II. SCOPE

This procedure shall apply to Pharmex's personnel involved in Literature Search (LS) process.

III. RESPONSIBILITIES

Role	Responsibility
Head of Pharmacovigilance Department (HPVD)	• Preparing/renewal/revision of the LS resources list • Approval of to be reported findings before send to MAH/Third party
Senior Pharmacovigilance Specialist (SPVS) Pharmacovigilance Specialist (PVS)	• Fully adhere to this SOP
Local Person responsible for PV (LCPPV)	• Translation of LS keywords • Translation, verification and QC of identified information during LS
Quality Assurance Manager (QAM)	• Compliance monitoring
System Administrator (SA)	• Set up/reconfigure and ensure Monitoring system performance
PV Assistant	• Fully adhere to this SOP

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 context

means that a causal relationship between a MP and an adverse event is at least a reasonable possibility.

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.

Pharmex's personnel – staff of Pharmex and LCPPVs in the countries of responsibility.

Third party – the company partially/completely responsible for MAH's PV system or participate in the chain of functioning of PV system and directly/indirectly reports to MAH's QPPV (Qualified Person responsible for PV).

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

V. PROCEDURE

A. General Specification

1. MAH's Responsibility

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and the risk-benefit balance of MPs, particularly in relation to the detection of new safety signals or emerging safety issues including:

- suspected ARs originating from spontaneous reports and solicited reports in humans;
- special situations such as use of a MP during pregnancy or breastfeeding, use of a MP in a pediatric or elderly population, reports of off-label use, misuse, abuse, overdose, medication errors and occupational exposure with suspected adverse reactions;
- lack of therapeutic efficacy;
- suspected ARs related to quality defects or falsified MPs;
- suspected transmission via a MP of an infectious agent.

MAHs are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases that contain the largest reference of articles in relation to the MP properties no less frequently than once a week.

In addition, MAHs should have procedures in place to monitor scientific and medical publications in local journals in countries where MPs have a marketing authorization (MA).

2. Contracting out LS Services

The transfer of a PV task or function to conduct searches of the published scientific and medical literature should be detailed in a contract between the MAH and the service provider.

3. LS during MA Application

MAH has an obligation to review published scientific and medical literature to identify published articles that provide information that could impact on the risk-benefit assessment of the MP under evaluation in the period between the submission of the MA application and the granting of the MA.

For the purpose of the preparation of periodic safety update reports (PSUR) and the notification of emerging safety issues the requirement for LS is not dependent on a product being marketed. LS should be conducted for all products with a MA, irrespective of commercial status. It would therefore be expected that LS would start on submission of a MA application and continue while the authorisation is active.

4. Recommended Resources

Recommended resources of safety information for the drug safety monitoring:

At local level:

- Periodical medical publications
- Materials of a local scientific conferences and symposiums
- Other sources of information available on the territory (social networks, non-core Internet portals, patient support sites, etc.)

At global level:

- Health-related databases: Medline (PubMed), Cochrane Collaboration Library, Wiley Online Library, Excerpta, Medica or Embase
- Official websites of manufacturers of original drugs
- International specialized Internet portals
- Materials of international conferences and symposiums
- Other resources can be used including social networks, web sites, web pages, blogs, internet forums, chat rooms, health portals if there is evidence to suppose that drug names have been mentioned by patients

5. ICSR Identified During Literature Screening

Day zero for LS is the date on which an organisation becomes aware of a publication containing the minimum information for an ICSR to be reportable. It is sometimes possible to identify the date on which a record was available on a database, although with weekly literature searching, day zero for a reportable AR present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available. Organisations should take appropriate measures to obtain articles promptly in order to confirm the validity of a case.

If multiple MPs are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected AR should be considered by the concerned MAH(s).

One case should be created for each single patient identifiable. Relevant medical information should be provided and the publication author(s) should be considered as the primary source(s).