I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for swift response to identified/received Emerging Safety Issue (ESI) and Significant Safety Issue (SSI) at Pharmexpert LLC (Pharmex).

II. SCOPE

This procedure shall apply to Pharmex's staff involved in Pharmacovigilance (PV) processes.

III. RESPONSIBILITIES

Role	Responsibility
PV Specialists	• Swift response to identified/received ESI/SSI • Safety communication to MAH's QPPV/RA
Marketing Authorization Holder's Qualified Person responsible for PV (MAH's QPPV)	• Initiation/ review and approval of USR procedure • Providing necessary documents • Implementation of RA decision
Quality Assurance Manager (QAM)	• Compliance monitoring

IV. DEFINITIONS

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

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

Examples include:

- major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contra-indication, a restriction of use of the MP or its withdrawal from the market;
- major safety-related regulatory actions outside the EU, e.g. a restriction of the use of the MP or its suspension.

Urgent safety restriction (USR) – means an interim change in terms of marketing authorisation due to new information having a bearing on the safe use of the MP.

Risk-benefit balance – an evaluation of the positive therapeutic effects of the MP in relation to the risks,

4. USR initiation by MAH

a) Upon receiving from MAH's QPPV request on initiation of USR, PV specialists within 24 hours submit or request LCPPV for submission of necessary documents to the RA.

b) PV specialist on approval of MAH's QPPV initiates USR in other drug authorization countries (where applicable).

5. Necessary Documents

a) The MAH/Pharmex is advised to submit draft proposals for the following information, if available/appropriate.

- Summary of Product Characteristic (SmPC) amendments
- Package Leaflet (PL) amendments
- Contents and the proposed receiver of the DHPC (Direct Healthcare Professional Communication)
- Any draft communication texts e.g. public statements, Q&A documents etc.
- Timetable for start and finish of the 24-hour USR
- Timing for release of public communication
- Proposals for actions relating to recall and distribution of new packaging information and distribution of DHPC together with corresponding

b) Urgent safety restriction and variation shall be implemented within a time frame agreed by the MAH and the RA.

6. Archiving

a) Storage folders for documents related to USR are clarified in the relevant SOPs.

b) Archiving process is performed according to the SOP-QA-001 «GDocP».

VI. ANNEXURE

None.

VII. INTERNAL REFERENCES

SOP-PV-003 «Case Assessment»

SOP-PV-017 «Handling of RA Requests»

SOP-QA-001 «GDocP»

SOP-QA-003 «Pharmacovigilance Glossary»

VIII. REVISION HISTORY, APPROVALS