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I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure of the preparation, review, approval and submission of Development Safety Update Report (DSUR) by PharmExpert LLC (Pharmex) to Regulatory Authorities (RA) of the respective countries in accordance with Good Pharmacovigilance Practices (GVP).

II. SCOPE

This procedure shall apply to Pharmex's employees involved in the processes of determining the submission timeline, preparation, review, approval and submission of Marketing Authorization Holder's (MAH)/Sponsor's DSUR to whom Pharmex offer the service in line with the agreement.

III. RESPONSIBILITIES

Role	Responsibility
Senior Pharmacovigilance Specialist (SPVS)	• Preparation and tracking of «PSUR/DSUR Submission Plan» • Preparation and submission of DSUR
Head of Pharmacovigilance Department (HPVD)	• Approval of «PSUR/DSUR Submission Plan» • Review and approval of draft of DSUR
MAH/Sponsor	• Review and approval of final DSUR
Quality Assurance Manager (QAM)	• Compliance monitoring

IV. DEFINITIONS

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

Investigational medicinal product (IMP) − a MP which is being tested or used as a reference, including as a placebo, in a CT, including products already with a MA but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Data lock point (DLP) − the date (month and day) designated as the cut-off for data to be included in a DSUR. It is based on the Development International Birth Date (DIBD).

Development International Birth Date (DIBD) − date of first approval (or authorisation) for conducting an interventional Clinical Trial (CT) in any country.

Sponsor − an individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a CT.

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

V. PROCEDURE

A. General specification

A DSUR is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study).

1. Objective

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

- examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;
- describing new safety issues that could have an impact on the protection of CT subjects;
- summarising the current understanding and management of identified and potential risks;
- providing an update on the status of the clinical investigation/development program and study results.

2. Scope of the DSUR

The DSUR should provide safety information from all ongoing CTs and other studies that the Sponsor is conducting or has completed during the review period including:

- CTs using an investigational drug (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials [Phase I – III]);
- CTs conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase IV));
- therapeutic use of an investigational drug (e.g., expanded access programs, compassionate use programs, particular patient use, single patient IMP, and treatment IMPs);
- CTs conducted to support changes in the manufacturing process of MPs.

The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from:

- observational or epidemiological studies;
- non-clinical studies (toxicological and in vitro studies);
- related DSURs, if applicable to the investigational drug
- manufacturing or microbiological changes;
- studies recently published in the literature;
- CTs with results indicating lack of efficacy that could have a direct impact on subject safety (e.g., worsening of the underlying condition if the indication is serious or life-threatening);
- any other source of relevant safety findings for products in the same therapeutic class; and
- CTs conducted by a co-development partner, if permitted by the contractual agreement.

3. DSUR's structure

DEVELOPMENT SAFETY UPDATE REPORT UPDATE REPORT

ACTIVE SUBSTANCE(S): <INN>

ATC CODE(S): <Code(s)>

MEDICINAL PRODUCTS COVERED:

[Pharmaceutical form, dosage, Marketing authorization holder//Sponsor of clinical trial]

DEVELOPMENT INTERNATIONAL BIRTH DATE (DIBD): <Date>

INTERVAL COVERED BY THIS REPORT

From <date> to <date (i.e. data lock point)>

DATE OF THIS REPORT:

<Date>

OTHER INFORMATION:
<Other identifying or clarifying information if necessary>
SPONSOR OF CLINICAL TRIAL:
<Name>
<Address>
<E-mail address> (contact person for the DSUR procedure)
NAME AND CONTACT DETAILS OF THE QPPV:
<Name>
<Address>
<Telephone number>
<Fax number>
<E-mail address>
SIGNATURE (QPPV or designated person):

<Country>, YYYY

TO REGULATORY AUTHORITIES

This document is a confidential communication of <MAH Name>. The information contained within may not be reproduced or otherwise disseminated without the approval of <MAH Name>. (YYYY)

The following information is presented in the “Introduction”:

- **international approval date of the investigated drug, international birth date, reporting period, report number;**
- **name of the investigated drug, pharmacotherapeutic class, mechanism of action, indications for use, release form, dosage, route of administration;**
- **brief description of investigated populations;**
- **brief description of the kind and timing of the clinical trials included in the report.**

No	Finding	Checklist-Section 1	Comments
1	CR	Submitted by DIBD or IBD (if applicable)	
2	CR	Reporting period specified	
3	CR	The serial number of DSUR is indicated	
4	CR	Provides more complete information on the mechanism of action (if applicable)	
5	CR	Pharmacotherapeutic class indicated	
6	CR	Contains indications for use	
7	CR	Contains an indication of the route of administration	
8	CR	Contains an indication of the dosage regimen	
9	CR	Contains an indication of all developed dosage forms	