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1. General

Control of medication use requires collecting field data about adverse events (AEs) resulting from medication therapy.

Regulation 7(B)(2) of Pharmacists Regulations (Medical Products) 1986 (hereafter: the Regulations) requires any Marketing Authorization Holder (MAH) to immediately notify the Administration of any new information related to the product registered by him via the Appointed Pharmacist.

Update No. 1 of this SOP, dated August, 2012, specifies the types of information requiring reporting by the MAH and enables the MAH to appoint a pharmacist, who should serve as a **Qualified Person responsible for Pharmacovigilance (QPPV)** in matters related to the reports included in this SOP, according to the standard worldwide practice.

The aim of Update No.2 of February 2013 is:

1. To clarify the work processes related to reporting AEs and new safety information
2. To update the definitions of the SOP
3. To update the types of information requiring reporting by the MAH as detailed in section 3.1 of this SOP.
4. To update the address for transfer of AE and safety information reports:

   ADR@MOH.HEALTH.GOV.IL

5. The update is effective from May 1, 2013.

The aim of update No. 3 of this SOP is to adjust the SOP to the Pharmacists Regulations (Medical Products) (Revision) -2013. The update is effective from December 1, 2013, except for sections 3.1 and 3.2.2.10, which come into effect along with the Regulations of Pharmacovigilance and sections 3.2.2.1 and 3.2.2.2, for which the timeline for reporting will change when the Regulations of Pharmacovigilance become effective.

2. Definitions

"**The Regulations**" - Pharmacists Regulations (Medical Products) (Revision) -2013

"Qualified Person responsible for Pharmacovigilance (QPPV)" – A pharmacist or a physician, holder of an Israeli license, with practical experience of 2 years in his profession, appointed by the MAH to serve as a QPPV according to this SOP. For a product which is a medical gas, adequately qualified practical engineer may be appointed, as defined in the Act of Technicians and Practical Engineers – 2012. If such a pharmacist or a practical engineer has been appointed, he should consult a physician regarding new clinical issues related to his duty as required.

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A person who is not a pharmacist, but is actually involved in pharmacovigilance in MAH's company at the time of issue of this SOP, may serve as a QPPV provided that he holds a B.Sc. diploma in Life Sciences or Natural Sciences, and has 3 years of practical experience in pharmacovigilance.

"**Marketing Authorization Holder (MAH)**" - as defined in the Regulations.

"Signal" - as defined by the World Health Organization (WHO) and Uppsala Monitoring Centre

"New safety information" - Any safety information potentially affecting product safety according to section 3.2.2 of this SOP.

"Appointed Pharmacist" - as defined in the Regulations.

"Adverse Event (AE)" - Any undesirable and unintended event resulting from the use of the product.

"Serious Adverse Event (SAE)"– A reversible or an irreversible event for which any of the following is true:

Caused death; life threatening; resulted in persistent or significant disability or incapacity or severe or prolonged morbidity; required hospitalization or prolonged the current hospitalization;

Caused a congenital defect or harmed pregnancy as a result of treatment with the product during pregnancy;

Or other medically/clinically significant events, which may endanger the patient or require medical intervention to prevent the situations listed above.

"AE of abnormal incidence" – An AE where the incidence has increased beyond the known incidence (according to Physician's Leaflet or according to the pharmacovigilance data of the company) or beyond the incidence reported in the literature.

"Product" as defined in the Pharmacists Ordinance [New Version],- 1981.

3. SOP contents:

3.1 Qualified Person Responsible For Pharmacovigilance (QPPV) appointment

The MAH should complete the details of the QPPV in Appendix 2 of this SOP and transfer them together with the CV and contact details of the QPPV to the Administration by mail (ADR@MOH.health.gov.il);

The Administration will approve the appointment using Appendix 3 of this SOP.

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3.2 Pharmacovigilance and reporting by the MAH:

3.2.1 The MAH should operate a pharmacovigilance system to monitor AEs and new safety information for the product registered by him.

3.2.2 The MAH, via the QPPV (or the Appointed Pharmacist until the Regulations come into effect), should report to the Risk Management and Drug Information Department at the Ministry of Health in the following cases:

3.2.2.1 Prohibition, restriction or alert related to a safety problem (either existing or potential) determined by a health authority of a recognized country regarding the product, its marketing or use; immediately and no later than 3 working days from the day of the Israeli MAH notification. This section will come into effect along with the Regulations, and until then, reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification.

3.2.2.2 Notice to the healthcare professionals or to the public issued by the manufacturer, MAH or a health authority of a recognized country regarding the product, its marketing or use, which is related to an AE, except for product leaflet update; immediately and no later than 3 working days from the day of the Israeli MAH notification. This section will come into effect along with the Regulations, and until then, reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification.

3.2.2.3 Any SAE observed in Israel. Reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification.

3.2.2.4 An AE or lack of efficacy observed during the first 12 months of marketing a new product formulation in Israel; for this matter, formulation changes are defined as type II formulation changes according to the European Directive definitions. In addition, a cluster of 5 or more non-serious AEs for a product following a non-type II formulation change should be reported; reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification.

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3.2.2.5 AEs observed outside of Israel, which are considered as AEs affecting product safety and requiring attention (signal); reporting every 30 days.

3.2.2.6 New information published in the professional literature regarding product safety; reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification.

3.2.2.7 New information published in the professional literature as valid case reports (according to the criteria specified in section 3.2.5.2) affecting product safety; reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification;

3.2.2.8 An AE of abnormal incidence relative to the AE incidence indicated in the Physician's Leaflet approved in Israel, or to the AE incidence based on the pharmacovigilance data of the company, or to the AE incidence reported in the literature.

Evaluation of abnormal AE incidence in Israel should be carried out by the MAH once every three months with respect to AEs reported in Israel, unless the MAH receives information about abnormal incidence via signals from the MAH or the manufacturer overseas.

Reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification

For products with MAH /manufacturer overseas, sections 3.2.2.5-3.2.2.8 may be reported by signals as received or identified by the MAH /manufacturer overseas after they have been evaluated by the company and determined to be possibly related to the medication. (Please indicate the criteria on which the evaluation was based).

3.2.2.9 DSUR for registered medications investigated in post-marketing studies in Israel; once a year.

3.2.2.10 Reports on non-serious AEs (known and unknown) observed in Israel. Within 90 days from the day of the Israeli MAH notification. This section will come into effect along with the Regulations.

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3.2.2.11 Product PSUR or PBRER; according to the timelines determined by the European Union GVP and published on the European Union website (EURD List), as updated from time to time. If required, the special report with the signed declaration may be transferred within 7 working days from the date of the periodic report submission according to the European timelines.

If the product is not listed in the European Union GVP timelines or in case of a generic product for which no reporting is required according to the European Union GVP, the Risk Management and Drug Information Department should be contacted to receive exemption from submission or to receive timelines and instructions for submission.

If required, the Risk Management and Drug Information Department may ask the MAH to submit an unscheduled PSUR.

3.2.2.12 Any information received by the Israeli MAH potentially affecting product safety, which is not included in sections 3.2.2.1-3.2.2.11; reporting should be carried out immediately, and no later than 15 calendar days from the day of the Israeli MAH notification

To dispel any doubt, the reports in sections 3.2.2.1-3.2.2.12 also refer to product used not according to the instructions for use or the safety guidelines (warnings/contraindications) or the Physician's Leaflet/ Patient's Leaflet, as well as to off label use.

For veterinary products, exceptions are made for sections 3.2.2.4-3.2.210 and section 3.2.2.12.

Despite the aforementioned, the Risk Management and Drug Information Department may change the timeline for reporting of any of the above sections, if required.

3.2.3 **Manner of reporting:**

(a) A report as specified in sections 3.2.2.3 and 3.2.2.4, 3.2.2.10 should be transferred by the online form available on the MOH website, after the QPPV has verified that the report is valid and contains the data required according to the European Union GVP principles.

(b) Reporting as specified in sections 3.2.2.1, 3.2.2.2, 3.2.2.5-3.2.2.9, 3.2.2.11 and 3.2.2.12 should be carried out by email to ADR@moh.health.gov.il

(c) Despite the statement in section b, case reports (3.2.2.7) should be transferred as individual reports by online form, if possible.

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d) MAH reporting for sections 3.2.2.5-3.2.2.8 by signals should transfer them to ADR@moh.health.gov.il for each product separately every month, if received.

(e) In addition to the statements in sections b and d, in case of reporting about abnormal incidence (section 3.2.2.8), in addition to sending the notice by email to ADR@moh.health.gov.il , individual reports should be transferred by the online form, if possible.

3.2.4 Periodic safety reports (PSUR or PBRER):

3.2.4.1 The MAH, via the QPPV, should transfer to the Risk Management and Drug Information Department the complete PSUR or PBRER of the product according to the timelines established by the European Union GVP. Transfer of the report to the Risk Management and Drug Information Department should be carried out according to the GVP guidelines or according to Department's request.

If the product is not listed in the European Union GVP timelines or in case of a generic product for which no reporting is required according to the European Union GVP, the Risk Management and Drug Information Department should be contacted to receive exemption from submission or to receive timelines and instructions for submission.

3.2.4.2 The QPPV should review the periodic safety report and submit a special report including all the sections specified below, with an executive summary enclosed, and submit a complete and signed declaration according to Appendix 1.

If required, the special report (Appendix 1) with the signed declaration may be transferred within 7 working days from the date of the periodic report submission according to the European timelines.

The declaration refers to the following PSUR sections

- Actions Taken in the Reporting Interval for Safety Reasons
- Changes to Reference Safety Information
- Data in Summary Tabulations
- Overall Safety Evaluation

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Or to the following section in the PBRER and new PSUR

- Actions Taken in the Reporting Interval for Safety Reasons
- Changes to Reference Safety Information
- Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
- Cumulative and Interval Summary Tabulations from Post marketing Data Sources
- Long-term Follow-up
- Overview of Signals: New, Ongoing, or Closed
- Signal and Risk Evaluation
- Integrated Benefit-risk Analysis for Approved Indications
- Conclusions and Actions

3.2.4.3 Information affecting product safety appearing in the executive summary, as well as additional information present in sections required for reading and absent from the PSUR or PBRER executive summary, should be transferred to the Risk Management and Drug Information Department together with the declaration.

3.2.4.4 If measures have been taken during the reporting period, or if measures are planned to be taken, based on the report conclusions, to change the conditions of product marketing due to safety reasons by the manufacturer or authorities such as EMA, FDA or any other authority as mentioned in the report, the measures taken or to be taken should be indicated, with the reason for those measures, and annnotation whether the MAH has submitted or intends to submit an application to update the information leaflets in Israel accordingly.

3.2.5 Postmarketing Spontaneous reporting of individual case safety report (ICSRs)

3.2.5.1 ICSRs are of great importance for drug safety follow up.

3.2.5.2 There are 4 **minimal** criteria for valid report:

1. Identifying details of the patient - at least one of the following details: age, gender, initials or name, etc.

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2. Identifying details of the reporting entity (reporting company, or a healthcare professional, or the patient by self reporting) - to enable contact with the reporting entity in order to obtain additional details
3. Name of the suspected medication / product
4. AE

3.2.5.3 The MAH is responsible for submitting an AE Report (using the online form available on the MOH website) with complete information, as much as can be obtained from the reporter and in accordance with the guidelines of the Risk Management and Drug Information Department. It should be clarified that complete information does not mean identifying details of the patient, but rather information required according to the report form.

3.2.5.4 The MAH, via the QPPV, must make every effort to obtain the details required for investigation of the AE, as indicated in the form available on the MOH website, and document his efforts to obtain these details. These efforts should be presented to the MOH, upon request.

3.2.5.4 The MAH should guide his employees responsible for obtaining the information to receive as much information as possible and to request the reporter's consent for follow up, if required (especially in case of an SAE). If the MAH received the information from a patient, the MAH should try to receive attending physician's details and patient's consent for obtaining additional information from the physician if necessary.

3.2.6 Follow up reports.

3.2.6.1 Follow up reports should be submitted for all the SAEs reported in general, as well as for additional reports, if the MAH is requested to do so by the Risk Management and Drug Information Department, by updating the online form of the original report.

If this is impossible, Follow up reports may be submitted by email to ADR@moh.health.gov.il. The title of the email should contain the words "Follow-up" and the reference No. of the original report. It is advisable to complete as much data as possible without compromising patient's privacy to avoid duplicate reporting in the system.

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3.2.6.2 Follow up reports for SAEs should be submitted within 15 calendar days from the day of receiving new information or in accordance with the request of the Risk Management and Drug Information Department.

3.2.6.3 If no new information can be obtained within two months from the day of the original report submission to the MOH, the MAH should document and store his unsuccessful attempts to obtain additional information. This documentation of the unsuccessful attempts should be presented to the Risk Management and Drug Information Department, upon request.

3.2.7 The QPPV should concentrate all the reports about AEs and safety information collected by him and present or transfer them to the Risk Management and Drug Information Department, upon request.

3.2.8 The QPPV should make his records available for review by the Administration at any time he is requested to do so.

4. Responsibility for implementation:

Product Marketing Authorization Holders
Pharmaceutical Administration, Ministry of Health

5. Applicable documents:

Pharmacists Ordinance [New Version]- 1981.
Pharmacists Regulations (Medical Products) - 1986.
Pharmacists Regulations (Good Manufacturing Practice for Medical Products) - 2008.
SOP of Notification of Defect or Product Recall (SOP 3),
SOP of Product Related Information Transfer and Crisis Management (SOP 84)
Guideline on good pharmacovigilance practices (GVP)

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6. **Circulation**:

CEO
Deputy CEO
Head of Medical Administration
Head of Administration for Medical Technologies and Infrastructures
Head of Public Health Services
Pharmaceutical Administration
District Pharmacists - Jerusalem, Tel Aviv, Haifa, Center, North, South
Institute for Standardization and Control of Pharmaceuticals
Legal Counselor's Bureau
Manufacturers/ Importers - Medical product MAHs
Medication distributors
Israel Manufacturers Association - Pharmaceutical Branch
Association of Chambers of Commerce - Pharmaceutical Branch
Pharma Israel
Pharmacists Association - The New Union
Israel Organization of Pharmacists
Union of Pharmacists - Branch of Pharmacies
Pharma chains
Pharmaceutical services at hospitals
Pharmaceutical services at HMOs
Circulation of Medical Administration circular

Authors of the SOP update:
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Mgr. Einat Gorelik
Person approving the SOP:
Dr. Eyal Schwartzberg

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Appendix 1

Declaration for periodic safety report - PSUR or PBRER

Attn: Pharmaceutical Administration - Risk Management and Drug Information Department

Product Registration No. ____/_____/_____/____

I, the QPPV (or the Appointed Pharmacist until the Regulations come into effect) of the MAH _____ submit to you the periodic safety report, its executive summary and conclusions regarding the product_____
Report No. _____ for the period of _____ until:_____

After I have read the executive summary and conclusions of the report and the following sections in the PSUR :

Actions Taken in the Reporting Interval for Safety Reasons
Changes to Reference Safety Information
Data in Summary Tabulations
Overall Safety Evaluation
Or the following sections in the new PBRER or PSUR :
Actions Taken in the Reporting Interval for Safety Reasons
Changes to Reference Safety Information
Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
Cumulative and Interval Summary Tabulations from Post-marketing Data Sources
Long-term Follow-up
Overview of Signals: New, Ongoing, or Closed
Signal and Risk Evaluation
Integrated Benefit-risk Analysis for Approved Indications
Conclusions and Actions

I, the QPPV submit a copy of this Appendix to the Appointed Pharmacist for his information.

☐ According to the executive summary and conclusions and/or the sections read there were/ there were no events affecting product safety. If there were- Please specify briefly, including reference to the appropriate chapter (or copy the relevant information)

_____
_____

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☐ In the reporting period, measures have been/ have not been taken to change the conditions of product marketing due to safety reasons by the manufacturer or authorities such as EMA, FDA or any other authority as mentioned in the report (including updates of Company Core Data Sheet (CCDS) for the product)

☐ If measures have been taken as mentioned in the previous section - please briefly specify the measures taken, the safety information which has led to taking these measures and accordingly, what has been done/ will be done in Israel in view of these measures.

_____
_____
_____
_____

Signature and stamp:_____ Date: _____

_____

State of Israel - Ministry of Health

Pharmacovigilance and Drug Information Department
P.O.B 1176 Jerusalem 9101002
ADR@moh.health.gov.il
Tel: 972-2-5080269 Fax: 972-2-6474858

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Appendix 2

Application for approval of a Qualified Person Responsible For Pharmacovigilance (QPPV) appointment

Date:

Attn:

Director of Risk Management and Drug Information Department,
Pharmaceutical Administration, Ministry of Health

RE: Application for approval of a Qualified Person Responsible For Pharmacovigilance (QPPV) appointment

I hereby request your approval to appoint _____ ID No. : _____ _____ _____ __as a Qualified Person Responsible For Pharmacovigilance (QPPV) of (name of the company/ institution):_____,
to perform the actions required according to this SOP and SOPs published by the Ministry of Health from time to time.

I know that the Qualified Person Responsible For Pharmacovigilance (QPPV) is the professional authority responsible for pharmacovigilance on behalf of the MAH - according to the SOP of Reporting AEs and New Safety Information, and according to the Pharmacists Regulations (Medical Products) (Revision) -2013. I undertake to provide the Qualified Person Responsible For Pharmacovigilance (QPPV) with all the information relevant to his work to enable him to perform it as described above.

Hereby attached ☐ CV (including contact details and details of professional experience, including professional training courses)

Sincerely,

Name of the appointing person _____His duty _____Signature_____

(for the use of Pharmaceutical Administration)

Approval of the appointment of the above QPPV has been granted - copy of the approval is enclosed

_____ _____

Director of Risk Management and Drug Information Department

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Date

Appendix 3

Approval of a Qualified Person Responsible For Pharmacovigilance (QPPV) appointment

Name: ___ _____

ID No.:

Has been approved as a Qualified Person Responsible For Pharmacovigilance (QPPV) for the company

_____

Address: _____

The Qualified Person Responsible For Pharmacovigilance (QPPV) is the professional authority responsible for pharmacovigilance on behalf of the MAH according to the SOP of Reporting AEs and New Safety Information.

The approval is effective from: _____

_____

Director of Risk Management and Drug Information Department

CC: Appointing person

Director of Pharmaceutical Administration

State of Israel - Ministry of Health
Pharmacovigilance and Drug Information Department
P.O.B 1176 Jerusalem 9101002
ADR@moh.health.gov.il
Tel: 972-2-5080269 Fax: 972-2-6474858