SCOPE Work Package 7
Quality Management Systems

Pharmacovigilance Quality Manual Template

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SCOPE

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Contents

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Acknowledgments

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This paper was developed and approved by all WP7 active partners (BG, ES, HU, IT, PT and UK).

WP7 would like to thanks colleagues from Lareb (NL) and Halmed (HR) for permission to include their quality manual and quality manual table of contents as examples in the annexes to this quality manual template.

Purpose of the document

The purpose of this document is to introduce a template which can be used by Pharmacovigilance (PV) Departments to set up or improve their own Quality Manuals (QMs).

The Commission Implementing Regulation (IR) (EU) No 520/2012 requires that "All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records." (Art 8.4).

According to the 'Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems': "a procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. The quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two."

Several National Competent Authorities (NCAs) consider the QM as the most appropriate document to provide a high-level description of the management quality system of the pharmacovigilance (PV) system and its performance. It may also be an instrument to connect to the general aims and objectives of Agencies.

Therefore a QM could provide added value to overview own PV system and its interconnections and relevance of specific processes (as defined by the relevant standard operating procedures (SOPs). It is a tool to address the principles of GVP and to describe in general the policy, the strategy and the processes of the PV system. The QM could also include Key Performance Indicators (KPIs) to monitor the overall performance of the system.

Finally, it could also be used as reference document to introduce the QMS to new staff and auditors.

This QM template is aimed to support agencies while they draft their first QM or while they would like to implement the existing one, it covers many specific pharmacovigilance processes and provides text examples that can be included in an Agency's QM. The template is supported by Lareb's (NL) QM and HALMED's (HR) PV QM index.

Sections described in this paper may not cover all relevant activities performed in a PV Department and may not be suitable for every NCA. Each NCA is free to tailor the practices presented in this document relevant to local practice.

Definitions and abbreviations

Terminology	Description
EMA	European Medicines Agency
EU	European Union/Europe
GVP	Guideline on Good Pharmacovigilance Practices
HALMED	Agency for Medicinal Products and Medical Devices of Croatia
ISO	International Organisation for Standardisation
IT	Information Technology
LAREB	Landelijke Registratie Evaluatie Bijwerkingen
MAH	Marketing Authorisation Holder
KPI	Key Performance Indicator
MS	Member State
NCA	National Competent Authority
PV	Pharmacovigilance
QMS	Quality Management System
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SOP	Standard Operating Procedure
WI	Work Instruction
WP	Work Package

1. Introductory section

1.1 Scope of the quality manual

Please provide a short introduction of the Quality Manual (QM) and its application.

Please indicate whether the QM has any relationship with any International standard/s:

Examples

- "This QM of Pharmacovigilance has been drafted with the aim defining the quality pharmacovigilance system in (name of the organisation) and includes a summary of structures, quality system procedures and processes, to achieve the objectives described in Art. 15 of the Commission Implementing Regulation (EC) No 520/2012…"
- "This document provides a high-level description of the pharmacovigilance system of the Agency and includes a description of the quality system for the performance of pharmacovigilance activities. It is compatible with the guidelines on Good Pharmacovigilance Practices (GVP), Module 1: pharmacovigilance systems and their quality systems (and the Agency quality manual)."
- "The QM describes the Quality Pharmacovigilance System which is featured to satisfy the interested internal parties and stakeholders…"
- "This QM is consistent with the general principles of the ISO 9000 Standards on good quality management practices, specifically the ISO xxxx Standards on QMS, issued by the International Organization for Standardization (ISO)…"
- "The QM is applied to all activities that are included in the Pharmacovigilance System and that are foreseen by Directive 2001/83/EC and by Regulation 726/2004 and amended versions…"

  ---Insert Agency aims and objectives---

  ---Insert Agency PV aims and objectives---

1.2 General summary

Brief overview of the Organisation of the Agency/PV Office (a more detailed description should be included in section 5 (Organisation).

A short historical background to and milestones of the Office/National PV could help introduce the office.

If the office performs its activities within a national PV network, outline the role of the office in this context.

Please introduce the quality system and mention the main objectives and activities of the office.

2. Normative references

You may either list the relevant legislation in this paragraph or eventually include a reference to an existing internal dedicated document collecting all PV legislation.

Example

- "Legislation concerning PV activities is collected in the document "Pharmacovigilance Normative" archived in the Pharmacovigilance Office (and/or in the intranet)…"

Or list in this section the main legislation, guidelines (GVP, ICH etc.) national and international, relevant to the performance of the activities of the PV System in place.

3. Definitions and acronyms

3.1 Definitions

Some definitions are listed below, further relevant definitions should be added.

Examples

Pharmacovigilance

- "Pharmacovigilance is the set of activities designed to collect, in a systematic and on an ongoing basis, the best possible information on drug safety in order to ensure, (and also through the adoption of specific regulatory measures), that the medicinal drugs available on the market have a favourable risk-benefit balance for the population…"

Pharmacovigilance System

- "A pharmacovigilance system is used to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC, as amended by Directive 2010/84/EU, as well as by Directive 2012/26/EU of the European Parliament and of Council, moreover a pharmacovigilance system is mainly used to monitor the safety of authorised medicinal identifying any change in the profile of benefit/risk…"

Good Pharmacovigilance Practices (GVP) for the European Union

- "A set of guidelines for the conduct of pharmacovigilance in the EU, drawn up based on Article 108a of Directive 2001/83/EC, by the European Medicines Agency in cooperation with competent authorities in Member States and interested parties, and applying to marketing authorisation holders in the EU, the Agency and competent authorities in Member States…"

Inspection

- "Activities of verification of marketing authorisation holders, as well as of those in charge to carry out on their behalf pharmacovigilance activities, compliance structures, documentation, personnel and processes of pharmacovigilance to legal provisions and GVP…"

Audit

- "In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes…"

Adverse Drug Reaction (ADR)

- "A response to a medicinal product which is noxious and unintended (DIR 2001/83/EC Art 1(11))1. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure (DIR 2001/83/EC Art 101(1)). Conditions of use outside the marketing authorisation include off-label use, overdose, mis-use, abuse and medication errors…"

3.2 Acronyms

Provide a list of all the acronyms used in the Quality Manual. The English acronyms (e.g. ADR, CAPA, EMA) should also be provided in local language if used in the Office.

Below the most commonly used acronyms in regulatory documentation and some other acronyms proposed for this Pharmacovigilance Quality Manual template. The Office is encouraged to refer to its own acronyms (as used in local procedures).

Examples

- "In this Quality Manual the following acronyms are used:

ADR	Adverse Drug Reaction – (local language translation)
CAPAs	Corrective actions/Preventive actions – (local language translation)
CMDh	Coordination group for Mutual recognition and Decentralised procedures – Human – (local language translation)
DHPC	Direct Healthcare Professional Communication – (local language translation)
DIR PV Office	Director of Pharmacovigilance Office (in case of separate Offices for assessment and inspection it may be helpful to define the two)
EMA	European Medicines Agency – (local language translation)
GVP	Good Pharmacovigilance Practices – (local language translation)
ICH	International Conference on Harmonisation
LTT	Lines To Take – (local language translation)
MAH	Marketing Authorisation Holder – (local language translation)
NUI	Non Urgent Information – (local language translation)
PV	Pharmacovigilance
PV Office	Pharmacovigilance Office (includes both assessors and inspectors)

PRAC	Pharmacovigilance Risk Assessment Committee – (local language translation)
PSMF	Pharmacovigilance System Master file
PSUR	Periodic Safety Update Report – (local language translation)
QM	Quality Manual
QMS	Quality Management System
QP	Quality Policy
QS	Quality System
RAS	Rapid Alert System – (local language translation)
RQA	Responsible Quality Assurance – (local language translation)
RMP	Risk Management Plan – (local language translation)
RT	Responsible for the Training
SOP	Standard Operating Procedure – (local language translation)
SOP/M	Management Standard Operating Procedure
USR	Urgent Safety Restriction – (local language translation)
WHO	World Health Organisation – (local language translation)
WI	Working Instruction – (local language translation)
WP	Working Party – (local language translation)

4. Pharmacovigilance quality system

4.1 Scope of the Quality Management System

Please describe the scope of the Quality Management System (QMS). The description included in GVP I – I.B.2. can be quoted in this paragraph:

Example

- "The Quality System (QS) is part of the PV system and consists of its own structures and processes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management (IR Art 8(2))…"

Please describes the main tasks of your QMS.

Example

- "A QMS:
  - Identifies and describes the operative processes…
  - Sets the steps and interactions for each process…
  - Identifies effective performance indicators for each process…
  - Identifies inputs, outputs, activities, responsibilities and documents for each process…
  - Identifies the check point for each process…
  - Sets a system to collect data and verify the performance indicators to pursue corporate objectives and continuous improvement…"

Please also add how the QMS guides the PV activities.

Example

- "The PV Office relies on the QMS which is managed according to the contents of this Quality Manual PV, Management Standard Operating Procedures (SOPs/M) and Standard Operating Procedures (SOPs). This approach ensures transparency, reproducibility and harmonisation of various decisions taken as a whole in the entire system…"

4.2 Quality objectives for the pharmacovigilance system

Please mention the quality goals of the PV system. The quality objectives described in the GVP I (I.B.4. Overall quality objectives for pharmacovigilance) may be of inspiration in drafting this paragraph. Along with the overall quality objectives please consider the specific objectives of the Office.

Please include what is done to achieve them (detailed description of the activities should be provided in section 7 (Compliance management).

4.3 Quality requirements for pharmacovigilance activities

The PV Office should define the requirements for the activities to perform. The GVP I.B.2 paragraph may help drafting this paragraph.

Example

- "The PV Office pre-defines quality requirements in accordance with the quality objectives…"

4.4 Review of the quality requirements for pharmacovigilance activities

Please mention how the Office reviews process requirements before initiating any procedure, especially any new procedure.

Confirm the Office meets the requirements set in legislation and in the guidelines.

Examples

- "The PV Office regularly scans the current legislation, guidelines and templates to be up-to-date and compliant in delivering the activities both nationally and internationally…"
- "The PV Office regularly scans the current legislation, guidelines and templates to verify the MAHs are inspected and compliant with their legal responsibilities…"
- "The PV Office has systems in place to assure compliance with current requirements…"

4.5 Changes to requirements for PV activities

Please briefly mention how the Office manages changes to the requirements.

4.6 Design and development of PV activities

Please briefly describe how the Office designs and elaborates on new activities.

4.7 Management review

Briefly explain the management of the review of the PV QMS with the involvement of the Director of Pharmacovigilance Office (DIR PV) /upper management.

Mention here the SOP where the Management review is detailed, if applicable.

Cross-reference with section 13.4 (Quality improvements) may be included if applicable.

Examples

- "The PV DIR participates in the management review meetings for the QMS of PV, convened (periodicity) by the RQA to evaluate the suitability, adequacy and effectiveness of the QMS of Pharmacovigilance using as a reference the findings of the audits…"
- "Re-examinations can be carried out more frequently if organisational needs, significant amendments or other special situations will arise…"
- "The modalities of the management review and adoption of improvement actions are detailed in the SOP…"

Please also list inputs analysed to review the QMS.

Examples

- "The documentation prepared by the (RQA or RQA of the PV Office) consists of:
  - The outcome of the internal audits…
  - Any complaints or suggestions by the stakeholders…
  - The performance of the processes…
  - The corrective and preventive actions started, in progress or completed…
  - The actions taken as a result of previous reviews…
  - Proposals for continuous improvement…
  - Changes to the Organisation, processes and everything that can affect the QS of PV…
  - Indicators and indexes identified to monitor the achievement of the objectives for the quality…"
- "Based on these documents, the RQA draws the agenda for a review meeting with those who are responsible for the Quality Assurance of the PV Office…"

5. Organisation

5.1 Structure

Please include a short description of the NCA.

Examples

- "The (Name of the National Competent Authority) is the National competent agency entitled to the regulatory activity of the human (and/or veterinary medicinal products and/or medical devices) in (name of the country)…"
- "The (Name of the National Competent Authority) cooperates with the Ministry of Health and Stakeholders…"

Please describe the organisational structure of the body responsible for PV activities (PV Dept., PV Office, PV Inspector Dept., etc.).

A diagram may help to represent the Organisation.

5.2 Responsibilities within the Quality System

Please detail the responsibilities of the managerial staff in relation to the PV System. The following responsibilities derived from the GVP I can be mentioned in the paragraph. Include any other peculiarity of the personnel with management responsibilities related to the PV Office activities.

Director of the Pharmacovigilance Office

Please define here the role of the DIR PV Office and his/her main responsibilities and task related to PV system and its QS.

Examples

- "The DIR PV Office is responsible for the (supervision) of the assessments and inspections activities performed in the Office…"
- "He/she establishes the annual inspection program, identifying for each inspection, the inspection team and identifying its lead inspector…"
- "He/she contributes to the quality cycle for pharmacovigilance activities…"
- "The manager helps to identify and assess the needs of theoretical and practical training of the personnel of the PV Office…"

- "He/she manages, promotes, coordinates, the human resources and he/she is responsible for management of financial and material resources and results service…"
- "He/she draws up the contents of the Quality Manual of Pharmacovigilance…"
- "The DIR PV Office helps define the policy and goals for the QS; He/she attends meetings of the management review of the quality system, coordinates the work, verifies the effectiveness of the processes in place and any preventive action, corrective or improvement…"
- "The DIR PV Office also establishes relationships with stakeholders in order to promote the PV system to protect public health…"

Director of the Quality Assurance

Please briefly describe the role and responsibilities of the Responsible (Director) of Quality Assurance (RQA) and its relationship with the PV QS.

Examples

- "The RQA assures compliance with legislation, the QM (QMs), the SOPs…"
- "The RQA guarantees the issues of procedures and monitors their updates…"
- "The RQA plans and carries out internal audits to the Quality Management System…"
- "The RQA elaborates the Corrective and Preventive Actions…"
- "The RQA prepares and presents to the management the report on the performance of the QMS during the meeting/s…"
- "The RQA coordinates and ensures the smooth participation of all the personnel of the NCA during the external audits…"
- "With reference to the audit of the system of Pharmacovigilance follows the provisions of the "Guideline on good pharmacovigilance practices (GVP) – Module IV – Pharmacovigilance audits."…"
- "The RQA is responsible for the quality planning, quality adherence, quality control and assurance, and quality improvements of the NCA quality system…"

Responsible for the Quality Assurance of the PV Office

Please briefly describe the role and responsibilities of the Responsible for the Quality Assurance of the PV Office.

Examples

- "The RQA appointed by the Director of the PV Office…"
- "The RQA of PV Office updates the procedures of the PV Office as needed…"
- "The RQA prepares the Office to the audits of the system of Pharmacovigilance…"
- "The RQA attends the meetings of the management review…"
- "The RQA manages and monitors any finding and the Opportunities for Improvement suggested…"
- "The RQA of the PV Office is responsible for the quality planning, quality adherence, quality control and assurance, and quality improvements of the PV Office QS…"

Responsible for Training of the PV Office

Please briefly describe the role and responsibilities of the Responsible for the Training (RT) of the PV Office.

Examples

- "The DIR PV Office is also the responsible for the training of the Office…", or
- "The Responsible for the training is appointed by the Director of the PV Office…"
- "The RT keeps training plans and records for documenting, maintaining and developing the competences of personnel…"
- "The RT is responsible for the internal training of the assessors/inspectors of PV…"
- "The RT oversees the participation in training courses…"
- "The RT is informed of all activities of in-house and out-of-house training…"
- "The RT cooperates in the activities related to the training in the PV System…"
- "The RT is part of the evaluation group for the evaluation of the training level of the personnel…"
- "The RT coordinates with the training manager of the NCA to update the documentation of staff training…"

Safety Assessor

Please briefly describe the role and responsibilities of the Responsible for the assessor. Recall seniority levels if applicable.

Examples

- "The assessor performs safety evaluation on the benefit/risks of the medicinal products…"
- "The assessor (according with the SOP number …) has the following functions…"
- "On the base of the experience and training is classified in…"

PV Inspector

Please briefly describe the role and responsibilities of the Responsible for inspections. Recall seniority levels is possible.

Examples

- "The inspector performs the PV inspections with the aim of ensuring the MAH fulfils its duties and responsibilities in accordance with legal provisions…"
- "The inspector (according with the SOP number …) has the following functions…"
- "On the basis of the experience and training is classified in…"

PV Committee/s

Mention here the main committees within the NCA that manage safety issues and their main role and responsibilities. Quality committees should also be mentioned here.

5.3 Infrastructure

First of all, it is advisable to determine the infrastructure that the PV processes require in order to support process operations. Then, briefly describe the infrastructures.

Example

- "The infrastructure is owned by the Organisation, which is responsible for its maintenance. In case of any malfunctions or structural problems, the DIR PV or other staff involved, promptly inform the deputed Office (state name of the Office responsible for maintenance of the appropriate action)…"

5.4 Environment for the operation of processes

If applicable, include any reference to national legislation related to protection of the environment in workplaces and to related internal procedures/guidelines.

Example

- "The Organisation fulfils the provision of the Law (…) hence is committed to the protection of health and safety in the workplace for its staff. The details of the arrangements made by the (Name of the NCA) to obtain and preserve an appropriate work environment are drawn in the (number/name of SOP) or (name of Documentation)…"

6. Policy

6.1 Planning

Please describe here what the top management puts in place to ensure the quality planning: mention the annual plan of the Organisation and/or Office.

Describe the process for the finalisation of the Quality Policy (QP) and the role of the parties involved.

Please specify who has responsibility and authority to establish, implement and maintain the Quality System.

6.2 Review of the policy

Please mention how the Office reviews the policy planning.

7. Compliance management

7.1 Introduction

Introduce briefly what is ensured by the procedures and processes in the quality system of the Office.

Example

- "To comply with regulatory requirements and achieving the objectives of quality (see. Par. 6.2 "Quality objectives for pharmacovigilance") the PV Office operates the following quality system procedures and processes:
  - Collect/evaluate ADRs
  - Signal management
  - Risk communication
  - Inspection…"

7.2 Core processes

Please list here the Standard Operating Procedures (SOPs) in place in the PV Office. It is advisable to group the SOPs in cluster of PV activities and it is recommended to quote the number and the name of the related SOP.

Cross-referencing with other sections of the QM is suggested.

Also provide a short description of the Working Instructions (WI) and agreement(s) with other offices in place in your office to perform the PV activities.

Examples

- "The processes identified for the PV activities are the following:
  - ADR activities: management, monitoring, analysis, evaluation of ADRs and subsequent follow-up
  - Signal management
  - Management and assessment of PSUR, PSMF, RMP, educational material, Referral
  - Management of exchange safety information internal and external, national and international (Rapid Alert, NUI, USR, Issue, etc.)
  - Management of safety communication (DHPC, LTT, EMA communication, etc.)
  - Training for personnel (assessor/inspector) (and stakeholders)
  - Safety emergencies management
  - Preparation/conduction/conclusion of an inspection
  - Planning the annual inspections
  - Interaction between the assessors and the inspectors (trigger an inspection)."

7.2.1 External parties

Describe tasks performed by subcontractors, if applicable.

8. Management of human resources

8.1 Personnel

Please include a general statement and possibly comment on the personnel needed to operate and control the processes.

Also clarify how the personnel is informed of the QMS and carries out work in accordance to it.

Example

- "The DIR PV Office identifies the skills needed to carry out the activities of Pharmacovigilance. The Upper Management of the Organisation, also according to the general staffing plan, provides the appropriate human resources…"

8.1.1 Competence

Please illustrate the competence and skills required for running the PV Office in compliance with the QMS.

Examples

- "The definition of training originates from a prior definition of the skills required…"
- "The staff of the PV Office works on the basis of instructions and training received, as well as on the basis of experience in the field of PV…"
- "In this sense, all the technical and administrative personnel is in possession of the qualifications and requirements prescribed by the current legislation…"
- "The new staff are provided with initial training on:
  - Arrangements for the performance of activities required by legislation and internal regulations…;
  - The quality management system and the relevance and importance of personal activities as a contribution to the achievement of objectives for the quality…;
  - The training system and how to record them…"
  - "Staff are required to participate in training related to the QMS and they are invited to attend training sessions offered both in–house and out-of-house…"
  - "The operating procedures for management of internal staff training are set out in specific procedures (mention the name/number of the SOP/s)…"

8.2 Training

Please outline how the training is planned and realised, the main factors and processes involved.

Please include a general statement on the commitment of the Responsible of the PV Office to the management of personnel.

Examples

- "Every year an annual planning of the training is discussed by…"
- "The DIR PV Office ensures that staff are properly trained and that they receive continuing education…"

8.2.1 Training on business continuity

Please indicate how the Office and/or the Organisation provides appropriate instructions on the processes to be used in case of urgency, including business continuity. Cross reference to section 7.2 (Core processes) may be performed.

9. Communication

9.1 Internal communication

Please describe processes which require communication and collaboration of the PV Office with others offices.

Below are some examples. This section should be highly personalised according to existing Departments and Offices and to existing relations among them within the Organisation.

Examples

- "In carrying out its activities the PV Office/s collaborate/s with the offices listed below:
  - Registration Office
  - Quality System Office
  - Quality of Medicinal Products Office
  - Communication Office
  - Legal office
  - Information Technology support Office…"

9.2 External communication

Please mention here the PV Office communication policy established with respect to external parties.

Examples

- "All activities carried out by the PV Office are planned and implemented also in compliance with the expectations of stakeholders…"
- "Top management shall ensure that stakeholders are considered…"

10. Record management

10.1 Record handling and control

Please introduce in general terms how records are managed and stored, and describe the system in place for validation and back up.

Examples

- "Quality System of the PV Office is documented by:
  - The Organisation chart with the structure and staff assignments
  - Training plans and records…
  - Operating procedures…
  - Instructions for compliance management processes…
  - Appropriate instructions on how to proceed in case of urgency, in particular to ensure the business continuity…
  - Performance indicators to continuously monitor the good performance of the activities of pharmacovigilance activities…
  - Audit reports and follow-up of quality system…"
- "The management of documentation regarding each process is detailed in specific SOPs describing the steps of registration, updating, storage and traceability…"
- "In order to ensure access to the documentation of critical processes a (common intranet folder/validated work-sharing database/validated repository) is available…"
- "These documents are backed up by an automated system…"
- "The description of archiving in this space is detailed in the SOP (quote number and name)…"

11. Audit

11.1 Introduction

Please describe how the audits are planned, prepared, conducted and the outcome of the audit process. GVP Module IV should help draft this paragraph.

Examples

- "The RAQ programs the internal audits (quote the periodicity of the audit/s) and informs the PV Office personnel (Director) about the subject and the data in advance (n days/months before)…"
- "The audits are conducted by appropriately qualified personnel…"
- "The RAQ (Upper Management/Director General/advisory board) may evaluate the possibility of using some external staff to comprise the audit team…"
- "The audits are conducted by RAQ/other Dept./etc. according to the following procedure:
  - Initial meeting
  - Check process
  - Logging and transmission of the audit report…"
- "Operating procedures for planning, conducting and reporting of audits are described in the SOP (number and name)…"
- "The people involved in the audit shall be trained…"
- "If some findings are detected, the RAQ should define appropriate corrective actions to eliminate the findings and, subsequently, the RAQ or the person designated will verify the implementation and effectiveness of the actions defined…"
- "In the event that a specified requirement is not satisfied…"
- "The outcome of the audits is always analysed in the Management Review…"

11.2 Internal audit

Please describe the scope and outcome of internal audits.

Examples

- "With the aim to check periodically if the activities are carried out in the PV Office in accordance with SOPs and legal requirements, internal audits are performed, (state the number of the SOP that describes the internal audits)…"
- "The following documents are drafted:
  - The plan of the internal audits
  - The report of the audit
  - The list of findings
  - The list of improvement opportunities
  - The description of the corrective actions and improvement proposals…"
- The implementation of the corrective actions are tracked in… (describe the way the corrective actions are tracked).
- "The results of the audits are transmitted to the European Commission every two years. In the transmission of the results of the Internal Audit Commission, the team of auditors follow the procedures set by the "Guideline on good pharmacovigilance practices (GVP) – Module IV – Pharmacovigilance audits"…"

11.3 External audit

Please describe how the external audits are planned, conducted, recorded etc.

11.4 Control of externally provided processes

In case some PV activities are subcontracted (Ref. Par. 7.2.1 External parties) please explain how these activities/services are audited. Describe planning, roles, responsibilities and records.

Examples

- "The following activities (processes) are delegated to other parties (Ministry of Health, national Institute, University, public/private company…)…"
- "These services are audited every year by…"

11.5 Corrective actions

If the Office or the Organisation is provided with a procedure to manage the findings, reference to the SOP can be made.

In any, please specify how the Office intends to manage the findings.

Example

- "Findings need to be addressed by the definition of corrective actions. The process of investigation of findings and criteria used to identify the relevant corrective actions and possible preventive actions are described in the SOP (quote number and name of the SOP)."

12. Performing evaluation

12.1 Performance indicators

Please mention here how the Office plans arrangements to verify the processes. This paragraph should contain the main Key Performance Indicators used to monitor the PV activities.

Example

- "The Office has set KPIs for each procedure (reference is made in each SOP) appropriate stages to verify the activity and the output of that activity…"

12.1.1 Monitoring and measuring resources

Please briefly describe how the resources are monitored and measured in the PV Office, if applicable.

13. Improvement

13.1 Introduction

Please introduce the overall commitment of the Office towards opportunities for improvements in the PV QS.

Examples

- "The PV Office considers ways to enhance the output of the processes and to support innovation in the PV activities."
- "The management review or any findings are triggers to consider opportunities to make incremental changes, to transform the operations and to take corrective actions with the aim to improve the activities."

13.2 Continual improvement

Please inform about the main activities the Office has in place for continuous improvement. Cross-referencing with Section 4, Pharmacovigilance quality system may be applicable. Also, reference to the policy of the Organisation/Office is suggested if applicable.

Examples

- "The QP of the QMS is based on the review meetings activities, on the ongoing process of verification of its business and on the identification of the areas where improvements should be introduced."
- "All staff can suggest improvements or suggestions by (reference the main steps of the procedure used to communicate/operate/monitor the improvements with mention to the responsibilities)…"

13.3 Control of non-conformities

Please briefly describe the management of non-conformities identified during the PV activities.

Examples

- "All staff can report non-compliant situations by… (communicating to the DIR PV / using the module / writing an anonymous complaint / sending an email to the Quality staff / etc.…"
- "The DIR PV (the responsible of the quality of the PV Office) (the responsible of the quality of the Organisation) identifies the person responsible of the proposed corrective action that must be approved by…"
- "The DIR PV monitors (the responsible of the quality of the PV Office) (the responsible of the quality of the Organisation) the implementation and effectiveness of the corrective action and closes the non-conformities or requires additional corrective actions…"

13.4 Quality improvements

Please describe how the Office corrects and improves the structures and processes.

Below is some standard documentation which may help to set the improvements.

Cross-referencing with Section 4.7 (Management review) may be applicable.

Examples

- "The following decisions are taken in order to improve the quality system:
  - Definition of the objectives for the new plan…
  - Implementation of corrective actions…
  - Identification of Preventive Actions and/or Opportunities for Improvement…
  - Prioritisation…
  - Resource planning…
  - Improving the effectiveness of the QMS and of the activities…
  - Identification of the future needs of the Organisation for strategic planning…"
- "The findings of the meeting are recorded in the minutes of the Review (include reference of SOP if available) prepared by the RAQ and forwarded to the DIR PV (and to all the participants in the meeting)…"

Annex 1. Table of Contents of the HALMED's PV Quality Manual

8. **Requirements for management system**
   - 8.1 General
     - 8.1.1 Quality policy statement
     - 8.1.2 The principles of good pharmacovigilance practices
     - 8.1.3 Quality objectives
     - 8.1.4 Responsibility for the pharmacovigilance quality system
   - 8.2 Change management
   - 8.3 Document management
   - 8.4 Record management
   - 8.5 Compliance management
   - 8.6 Crisis management in pharmacovigilance
   - 8.7 Management review
   - 8.8 Internal audits
   - 8.9 Nonconformity and corrective actions
   - 8.10 Preventive actions
   - 8.11 Improvements
   - 8.12 Complaints

Appendices

PV Quality Manual is updated at least once every three years by staff from Quality Assurance Office and PV department together.

There are no specific criteria for prioritisation in updating the PV Quality Manual.

Annex 2. Lareb's Quality Manual

1. General

2. Policy
   - 2.1 Planning
   - 2.2 Quality policy
   - 2.3 Implementation
   - 2.4 Evaluation
   - 2.5 Evaluation policy

3. Organisation
   - 3.1 Matrix Structure
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4. Primary Processes
   - 4.1 Setting procedures
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5. Results
   - 5.1 Customer satisfaction
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6. People
   - 6.1 Recruitment
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7. Resources
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Appendix 1 Summary of Procedures

Note: the corresponding procedures are listed in brackets and in italics below certain sections in this quality manual

1. General

Since 1985 the Netherlands Pharmacovigilance Centre Lareb (Nederlands Bijwerkingen Centrum Lareb) has drawn attention to side effects of medicinal products, initially only through regional reporting centres. Since 1995 it has been designated as a national reporting centre for side effects of medicinal products. The pharmacovigilance centre has since developed into a widely recognised reporting and knowledge centre in the field of adverse drug reactions and safer use of medicinal products during pregnancy and lactation.

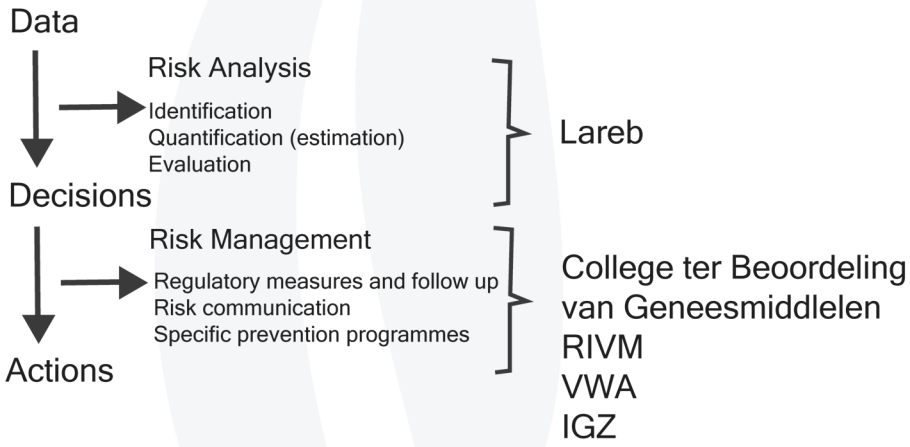
In 1991 Lareb was set up as an umbrella organisation for regional initiatives to register and analyse adverse reactions to medicinal products. The core task of Lareb is: registering, assessing and analysing side effects of medicines and vaccines. Lareb performs this work under the Dutch Medicinal Products Act and therefore the Pharmacovigilance Centre is also funded by the government. Lareb works in close collaboration with the Medicines Evaluation Board.

In 2011 two tasks were added. Lareb also now monitors the safety of vaccines administered as part of the national immunisation programme. In addition, the Teratology Information Service is also run by Lareb. This is the centre for knowledge in the field of the use of drugs during pregnancy and lactation.

Lareb also informs interested parties through publications and training

The Dutch Healthcare Inspectorate (Inspectie voor de Gezondheidszorg (IGZ) has a regulatory role and a monitoring function in respect of unregistered medicines. The role of the Medicines Evaluation Board (MEB) regulatory authorities) is to coordinate pharmacovigilance in the Netherlands.

The following chart shows the division of tasks. The Dutch Institute for Public Health and Environment (RIVM) is responsible for implementing the national immunisation programme.



2. Policy

2.1 Planning

Every five years Lareb draws up a policy plan in consultation with collaborating parties.

Prior to the final plan both internal and external parties are involved via a step-by-step plan. After a brainstorming session with staff, there follows a consultation of the Scientific Advisory Board (Wetenschappelijke Advies Raad (WAR), the Board and external parties, always including the Ministry of Health, Welfare and Sport (VWS) and MEB. Policy issues are further worked out based on criteria such as importance, feasibility, results, planning and investment. Then, the initial policy is drafted after discussion with the Board and finally adopted by the Board. Because all employees and various external parties are involved, there is broad support.

The policy plan contains policy for the coming period. Once established, employees and working partners are informed.

The policy plan also elaborates the tasks undertaken by Lareb under the Medicinal Products Act and the tasks assigned since 2011, the Vaccine Safety and Teratology Information Service (TIS).

Overall, this concerns:

1. encouraging the reporting of adverse reactions by doctors, pharmacists and patients;
2. receiving, processing, recording and evaluating Dutch reports of suspected adverse drug reactions from doctors, pharmacists and other persons working in healthcare, and patients;
3. retrieving from Eudravigilance and evaluating Dutch reports of serious adverse reactions submitted by marketing authorisation holders;
4. forwarding reports of serious adverse reactions to various authorities, including the European Medicines Agency (EMA), World Health Organisation (WHO), and marketing authorisation holders;
5. performing signal detection using, among other the Lareb database, the EudraVigilance database and WHO database;
6. keeping automated systems up-to-date;
7. structured consultations between Lareb and cooperating parties;
8. since 1 January 2011 the registration and assessment of adverse reactions to vaccines used in the national vaccination programme (Rijksvaccinatie programma (RVP); this task has been taken over from the Dutch Institute for Public Health and Environment (RIVM);
9. work of the Teratology Information Service (TIS): counselling by healthcare providers via a telephone service and monitoring of exposed pregnancies;
10. disseminating knowledge on adverse reactions.

These activities are carried out in accordance with current legislation as laid down in European legislation and Dutch legislation:

- Directive 2001/83/EC Article 101, 102; 2012/26/EU Regulation (EC) 726/2004 and 1027/2012/EU
- EMA Guidelines on Good Pharmacovigilance Practice (GVP)
- Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No. 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council
- Medicinal Products Act
- Regulation 1235/2010
- Directive 2010/84/EC Decision by the Ministry of Health, Welfare and Sport to bring TIS under the aegis of Lareb (letter GMT/FBBI-2972441 dated 3 February 2010)
- Decision of the Ministry of Health, Welfare and Sport to bring registration, evaluation and reporting on suspected adverse reactions to vaccines used in the national vaccination programme under the aegis of Lareb (letter PG/CI-2.981.236).

The Board is responsible for monitoring changes and/or additions to the terms of the relevant legislation and regulations. If necessary, it will take actions to ensure that the work complies with these. Also if new processes are added or existing processes are changed, it will check whether the laws and regulations are still being complied with.

Based on the policy plan, each year an annual plan is drawn up setting out the objectives for the coming year. This looks at the policy proposals that have already been achieved and the policy proposals that require further attention. The results of this analysis are incorporated when formulating the new plan and the new policy proposals formulated therein.

This plan is discussed with the staff in December on a Lareb day and then finalised. During the current year employees are informed of additional policy matters during Lareb afternoons as well as by reports on the intranet.

The policy plan is translated into concrete plans for employees. These plans give direction to the activities of the pharmacovigilance centre.

On the basis of the action plan and the associated annual plans, the Board determines what resources are necessary to carry out this work. To carry out its work, however, the pharmacovigilance centre is dependent on the grant that they receive through the Ministry of Health, Welfare and Sport. Lareb applies for the necessary subsidy based on the necessary resources. Based on the subsidy awarded, the resources can be assembled. These resources relate mainly to employees and automation.

The plans are periodically evaluated. The period is different for different kinds of plan, as well as the evaluation.

Procedure for drawing up departmental and individual annual plans for staff

Plan	Evaluation	Reporting
Policy plan	In the year for new action plan	Evaluation report
Annual plan	Periodically in Steering Group Annually	Minutes of Steering Group Management review
Personal annual plan	In periodic discussions Performance appraisal	Appraisal report

2.2 Quality policy

Quality management is an important tool for monitoring and continuing to develop the quality of the primary process. The potential for this is naturally linked to the available expertise and a good internal organisation. For the internal anchoring of the processes, an (electronic) manual has been developed setting out the internal arrangements. This manual is regularly reviewed and maintained.

Quality targets

Reliability and high quality output are highly valued at Lareb. This is demonstrated, for example, by the 'Manual' which sets out all procedures and work instructions within Lareb. The aim is to strive for optimum quality and to make the administrative workload secondary to this.

Area of application

The quality policy covers all activities carried out by Lareb and listed above in 10 points. Activities take place at its headquarters in 's-Hertogenbosch. In addition, activities are carried out by an employee at the UMCG in Groningen, mainly relating to education.

By obtaining the ISO 9001 certificate for the tasks, Lareb is aiming for external recognition of the efforts they put into this. Certification is also an opportunity to show external parties that Lareb is actually a high-quality organisation.

Lareb excludes the following clauses:

- Certiked clause Primary Processes2/ISO paragraph 7.5.5 'Preservation of product '
- Certiked Primary Processes 1/ISO paragraph 7.5.4 'Customer property'

2.3 Implementation

The pharmacovigilance centre is a professional organisation. To achieve optimal results requires a high degree of professional freedom. The frameworks for the activities are outlined by the Steering Group through the annual plans which include input, corrections and adjustments by employees. Employees are responsible for their material output. However, in the initial period for new employees a material check also takes place. There is focused on effort and, if possible, on final result.

The Steering Group has a role in overseeing task coordination and, where necessary, setting priorities. Coordinating the work of each employee takes place via the matrix. Efficiency in work is monitored by working systematically and evaluating this. At employee level the annual plan, agenda, key figures and time-keeping can be helpful in this.

2.4 Evaluation

Ongoing attention to quality and improvement is embedded organisation-wide through evaluations by the Steering Group with those responsible within the core processes and projects run by Lareb, in which implementation of the Lareb policy is discussed and, if necessary, updated. Lareb afternoons also form a sounding board, looking at coordination of work and agreement on decision making. In this way, all employees are involved in the implementation of the policy.

Examples of meetings are listed in the table below.

Meeting	Frequency	Minutes
Steering Group	1 / 2 weeks	x
Consultation with software provider / office automation	Periodically	x
Consultation with Lareb Intensive Monitoring (LIM)	1 / 6-8 weeks	x

Preventive measures

As regards preventive measures in its primary tasks, the pharmacovigilance centre has so-called control points built in to minimise risks to the delivered product. From here, if necessary, a targeted adjustment can take place. Examples of this are:

- Triage of reports to be evaluated into categories according to degree of complexity
- Possible additional control especially of 15 day (“serious”) reports, before distribution to various external bodies takes place
- Assessment of new signals of side effects in the quarterly report for the CBG by the members of the Scientific Advisory Board
- Assessment of scientific articles prior to submission for publication by the Steering Group. Where relevant, the marketing authorisation holder of the product in question is offered an opportunity to comment on the draft publication

- Potential press releases are checked for content by experts
- Important national and international external presentations are held internally first
- Incorporating quality checks into automated processes
- Periodical review of privacy policy

As indicated earlier the electronic manual plays an important role in the quality management system, especially in the control of the primary process. In addition to keeping the manual updated, automation, continuing education, keeping an eye open for new developments and exploiting partnerships also play an important role in the quality management.

The signals which are recognised by this are analysed by the relevant responsible officials and proposals drawn up for improvements. During the annual management review, or earlier if the analysis makes this necessary, the Steering Group determines which proposed improvements are actually developed into areas of improvement. These improvements are further developed and implemented within the entire organisation.

2.5 Evaluation policy

The (quality) targets and policies are periodically assessed. Based on the results, if necessary, additional measures are taken in the subsequent period and are assessed for effectiveness.

Once a year the Steering Group reviews the quality policy as a whole in a so-called management review. The electronic manual indicates how the management review is carried out exactly and who is responsible for providing the necessary data and where this data comes from.

The following information is used to carry out the management review:

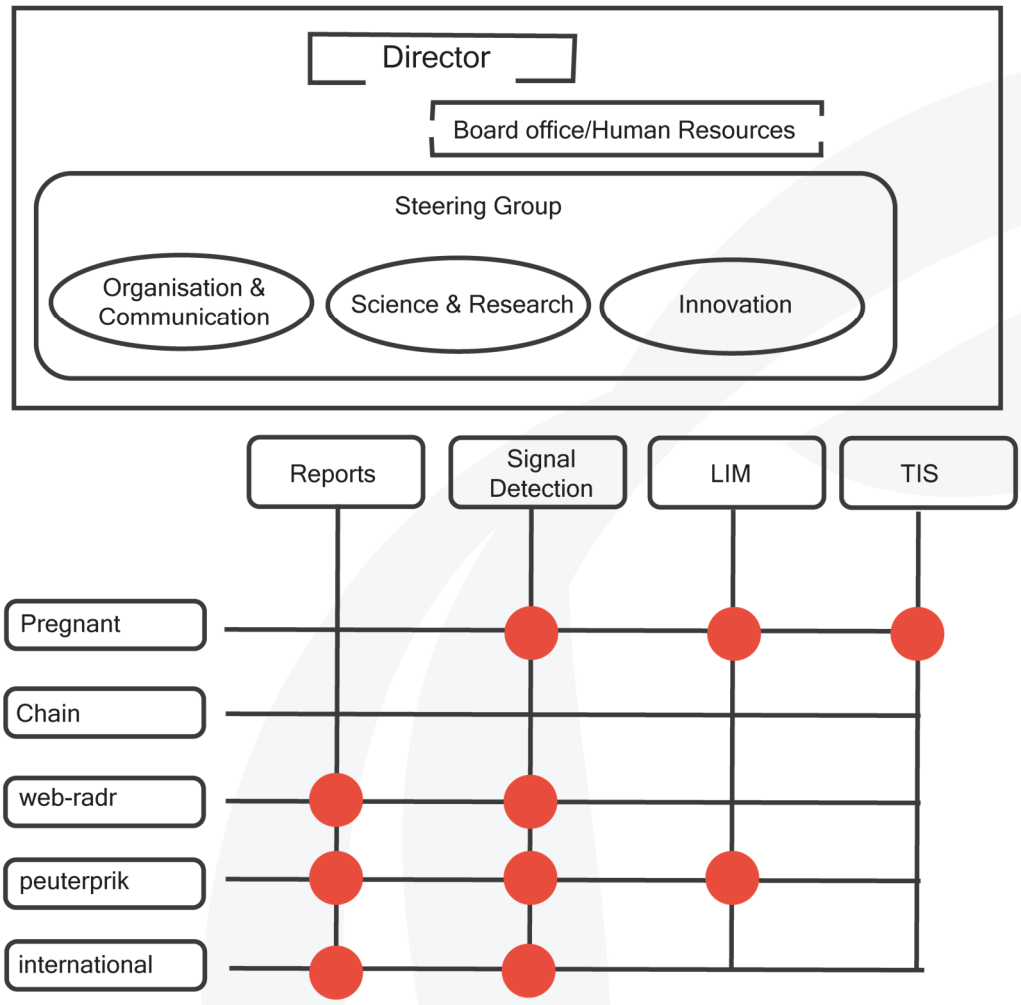
- Report from the previous Management Review
- Recommendations for improvements
- Results (process performance, performance indicators)
- Results from external evaluations, including feedback from customers
- Results from internal evaluations
- Results from the audits (internal and, where applicable, external)
- Status of preventive and corrective measures already identified
- Performance by suppliers (resources)
- Staff (including job satisfaction)
- Developments (internal/external) which may impact on the quality management system

The management review leads to decisions and measures relating to:

- improving the effectiveness of the quality management system and associated processes
- improving the product/services
- resource requirements, including both equipment and number/training of staff.

(Procedure Management Review)

3. Organisation



3.1 Matrix Structure

The pharmacovigilance centre Lareb is based in 's-Hertogenbosch and has an office in the university hospital in Groningen. It employs a total of around 40 staff, of which most are doctors and pharmacists with great knowledge of side effects of medicines. The tasks and responsibilities of the employees are set out in job descriptions.

The matrix structure was introduced in 2015. Responsibilities are delegated to coordinators and project leaders and the connecting criteria are the nature of the activities (the core processes) and activities with a specific purpose (the projects).

The **Director's office**, consisting of the Director and Deputy Director, is assisted by the executive secretary. She is also charged with the management of personnel matters.

General management is the responsibility of the Steering Group headed by the Director. There are also activities that apply to the organisation as a whole, namely organisation and communication, science and research, and innovation. These are the responsibility of the Steering Group.

Organisation & Communication

The primary process of Lareb is focused on the core task: registering, assessing and analysing adverse reactions of medicines and vaccines. Supporting processes, such as secretarial tasks, finance, automation, accommodation and communication are facilitating to this core task. The head of organisation & communication monitors the quality of these supporting processes.

Science & Research

The scientific quality transcends the matrix. This should be monitored in the different core processes and projects. Various scientific personnel work within Lareb, each with specific tasks on different projects. In the Steering Group consultations, research and project proposals are discussed together with the person responsible from the organisation. In signal management consultation the scientific quality and progress of the work of Lareb is monitored. This concerns selecting and writing signals, but also publications and research reports that are written at Lareb. The head of science and research ensures the quality of the scientific output of Lareb, partly determines the direction of the scientific policy, is project leader of a number of studies and supervises PhD students.

Innovation

For a knowledge-based organisation, it is important to continue to innovate in order to best monitor the safety of medicines. This requires creativity by the staff. By maintaining the dialogue and learning from each other, cross links and synergy can occur which can lead to new innovations. The new organisational structure, a brainstorm, setting up working groups and also the accommodation are designed to promote this creativity. That also applies to an open culture in which processes can easily be held up to the light and proposals for improvements are easily generated. Good ideas are picked up and implemented expeditiously.

A prerequisite for this is that the employees of Lareb realise the usefulness of innovation, and receive the tools to be able to think up and implement innovations. This requires a climate in which people dare to think critically about the current situation, are able to come up with new solutions and are driven enough so that it does not remain an idea but leads to innovation. The staff should especially be involved in product and process innovations.

Core processes

Reports

Since 2011, in addition to focusing on medicinal products, the core process reports has also involved reports on vaccines. The emphasis with the latter is on reports of adverse reactions of vaccines administrated via the National Immunisation Programme, as well as reports on travel and influenza vaccines. Each year summary reports of these are prepared for external parties.

Tasks include:

1. Encouraging reports through presentations, education and PR
2. Evaluating reports from doctors, pharmacists and patients
3. In addition specific questions from caregivers about side effects are answered

A (content) coordinator for Vaccines and a coordinator for medicinal products monitor the core process reports. Furthermore, this work primarily involves report assessors, divided into senior and junior assessors. There is also an assessor working in Groningen who primarily also undertakes the (coordination) of presentations and education. Finally, there are a number of staff charged with inputting adverse reaction reports.

(Various procedures: Department Reports: Medicines and Vaccines)

Signal detection

For the core process signal detection the following areas can be distinguished:

1. Signal detection for medicinal products and vaccines
2. Research and development
3. Quality control

4. Education and training
5. Dissemination of information

Scientific staff work within signal detection, each with specific tasks in the above areas.

(Various procedures: Analysis/Signal detection)

LIM

Lareb is involved in several innovative projects which are in line with the primary process. In the field of monitoring systems several years ago Lareb started to develop the Lareb Intensive Monitoring System (LIM) as a modern web-based version of the Prescription Event Monitoring (PEM) system in the UK. LIM is a survey which asks users of drugs or vaccines about their experience(s) with a drug or vaccine. These may concern a specific drug or vaccine but also medicines or vaccines within patient groups. With the knowledge gained through this research there is more information available about the occurrence of adverse reactions, the nature, course, risk factors, well-being and consequences for health.

With the information obtained from LIM practical treatment advice can be given and can ultimately promote medicine adherence.

Currently LIM is being developed for other target groups than pharmacists, working with project groups, which shape the projects from start to completion and evaluation.

(Various procedures LIM)

TIS

The core process TIS gives doctors, midwives and pharmacists information about possible harmful effects of exposures, such as: drugs, diseases, radiation and occupation, before or during pregnancy and lactation. If questioners indicate that exposure to a drug has occurred in pregnancy, in these cases once born the child is monitored for congenital abnormalities. (Various procedures TIS)

Cooperating parties

The Steering Group directs Lareb. The Board consists of physicians and pharmacists from the circles of the major doctors' and pharmacists' organisations. Patient organisations are also represented on the Board. The Scientific Advisory Board monitors the scientific level of the work and results.

The primary process involves stimulating reports, processing and storing them, and finally distribution to third parties. This is broadly a task of the core process Reports. The secondary process supports the primary process. Secondary processes mainly include tasks such as automation, training and publications.

Both patients and healthcare professionals, mostly doctors and pharmacists, report adverse reactions to drugs and vaccines to Lareb. These are recorded and evaluated. Assessment mainly involves determining the relationship between the drug and the adverse reaction. After this, the reporter has the option of receiving feedback on the report.

(Various procedures: Reports)

Each quarter the Medicines Evaluation Board receives an overview of signals of adverse reactions found by Lareb. If an acute serious adverse reaction/problem occurs an interim report may be sent. In addition, it is possible for the MEB itself to make a content request to Lareb to find out more about certain associations between medicines and adverse reactions.

If a signal applies to their area of responsibility it is also passed on to the RIVM and the Healthcare Inspectorate.

(Procedure: Quarterly report, procedure safety concerns and procedure requests MEB)

In addition to this so-called quarterly report, the pharmacovigilance centre also publishes regularly in scientific journals for the benefit of the medical and pharmaceutical profession as well as the users of medicines. Whenever requested and/or required public information is also given in the media on signals and/or side effects.

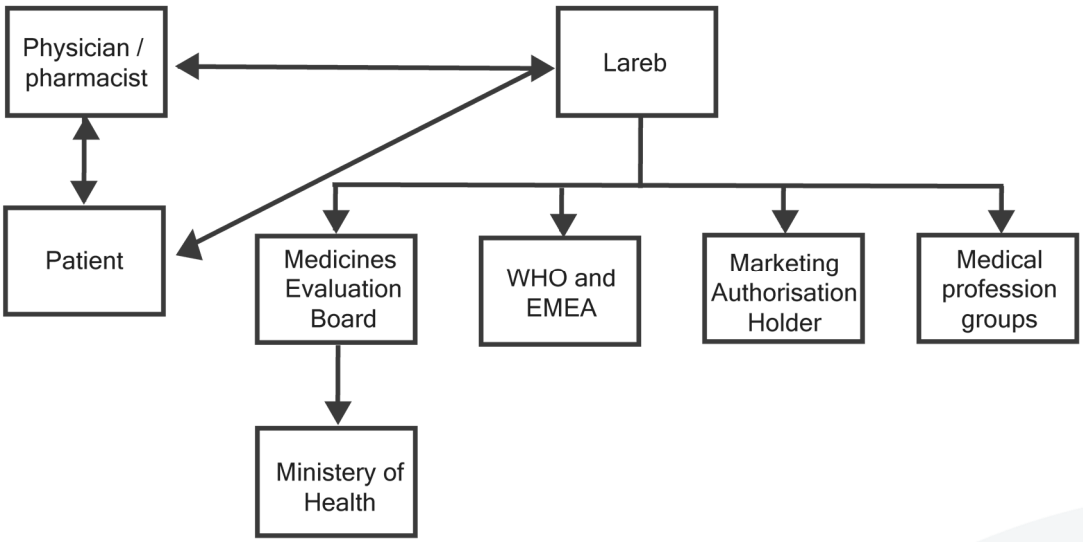
(Procedure: Publications, procedure media contacts)

Reports of serious adverse reactions are also passed to the relevant pharmaceutical industry within two weeks. Also Lareb publications are submitted for comments to the marketing authorisation holder.

(Procedure: Contacts with marketing authorisation holders, answering questions from marketing authorisation holders)

Data from Lareb also goes to the European Medicines Agency (EMA), the European registration authority and the Uppsala Monitoring Centre of the World Health Organisation (WHO) which collates adverse drug reactions worldwide.

(Procedure: Sending adverse event reports to other bodies, procedure for making corrections)



3.2 Organisation quality policy

The director has overall responsibility for the design and implementation of the entire quality management system.

Lareb also has appointed a quality officer who is responsible for all operational matters relating to the quality system. Think about planning internal audits and management review. The management review takes place annually at the beginning of a calendar year. Members of the Steering Group and the quality manager take part in this. The quality manager oversees the process of preparation of the MR and the reporting thereof. The management office currently carries out the collation of the information that is required for the MR and takes the minutes.

For the implementation of internal audits, the quality officer is assisted by two officials who perform other tasks within Lareb. In this way Lareb ensures that employees do not audit their own work. The process owners and/or specifically designated officials are responsible for drafting improvements that are needed in response to the audit. Think of corrective and preventive action in response to internal audits. The quality officer is responsible for monitoring progress in this.

Furthermore, the responsibility of the quality policy is of course the responsibility of all employees.

3.3 Establishing processes

The quality manual provides an overview of the establishment of the quality management system at Lareb. An important part of this is the (electronic) manual setting out all processes and work instructions regarding the primary process. In all regular consultation the desire to adapt the work methods may emerge. Also, it may be desirable to modify a process in response to the results of an audit. Lareb has appointed a manual coordinator to manage the process of amendment, version control, communication and archiving of procedures and work instructions. For the exact work method see the process descriptions “establishing and implementing a procedure” and “establishing and implementing a work instruction” from the manual. The mandatory ISO procedures are contained in the manual. (See Appendix 1)

3.4 Conducting internal audits

There are three internal auditors appointed who have been trained in “internal auditing”. The auditors work in different processes or projects within Lareb to ensure the independence of the auditors for an audit topic. Each year, the quality manager draws up an audit plan in consultation with the Steering Group. This audit plan ultimately ensures that every three years, all subjects from the Certiked model are audited. The focus remains on the primary process.

The auditors establish the audit findings and feed them back to the auditees and, if they agree with the findings, to the Steering Group. If needed, measures for improvement are also decided. The follow-up is monitored by the process owners or a delegated person.

The exact way in which internal audits are carried out is included in the electronic manual.

(Procedure: Internal Audits)

4. Primary Processes

4.1 Setting procedures

Every five years Lareb draws up a policy in cooperation with stakeholders and institutions with which Lareb closely cooperates. This policy forms the basis for further activities at Lareb. Based on the policy plan, Lareb draws up an action plan setting out the actions for the coming year.

Regular consultations take place between Lareb and the MEB. Based on these, adjustments can be made in the cooperation. If this is the case, then this is recorded in the minutes of the meeting.

Lareb has a number of other activities and projects which are not covered by the subsidies provided by the government. Arrangements and accountability for the tasks, performance and goals to be achieved are made separately with relevant funding bodies and external parties. This is stipulated in contracts and on relevant project applications and, where applicable, determined by the terms of the funding body.

4.2 Implementing tasks

The policy plan is drawn up in collaboration with all employees. This feeds into annual plans for individual employees. Periodically the results obtained are sent out.

The electronic manual outlines the implementation of all processes. In addition to the outline at top level, there are work instructions for various tasks.

The implementation especially of the primary processes is regularly discussed in the (weekly) meeting. If the implementation does not match the description the reason for this is traced. Then the necessary corrective measures are defined and implemented.

In the execution of the primary process Lareb is strongly dependent on automated support for efficient and reliable handling. The automated system ensures uniform recording and processing of reports.

Reports reach Lareb electronically or in hard copy. Electronic reports come directly into the system (database) and are hereby immediately anonymised. They are assigned a unique serial number so the reports can be traced at all times. Only employees have access to the data from the original reporter.

No-one else has access to this data. Hard copy reports are entered into the database which also generates a unique serial number. In these reports too, details of the original reporter are accessible only to employees of Lareb. The hard copy report is scanned, whereby the PDF is given the same unique serial number as the database, and the PDF is placed in the appropriate folder on the server. The original hard copy reports are initially filed for a number of years at head office. After this period they are destroyed.

There is an internal monitoring system to ensure that contracts and collaborative agreements for other projects and activities are evaluated in due time and whether or not extended and/or modified.

Learning from experience

Knowledge-sharing is often thought of as internal knowledge-sharing, i.e. the sharing of knowledge within the organisation.

Lareb goes a step further. The aim is for all the knowledge available to be accessible to everyone and thus function as a knowledge centre in the field of adverse reactions.

Examples of external knowledge are the website for both professionals and patients, newsletters, e-learning courses, the Adverse Reaction Day, presentations and participation in education and publications. New signals of adverse reactions are also disseminated nationally and internationally.

The processes are highly automated. This applies to both the receipt and input of the reports, and to the assessment process and database management and analysis. There is also a knowledge management system. There is also a knowledge system for TIS. This system makes all knowledge data within Lareb accessible to all employees. Employees therefore do not duplicate their work and can make optimum use of all previously collected information.

Employees can select which training courses they want to take. Not all employees in a particular function take the same course. Internal meetings are typically used to share the knowledge gained. At the meeting, employees can also present interesting reports to each other. Specific medical or pharmaceutical topics are discussed with each other at the next scheduled two weekly meetings (so-called. “Knowledge lunch”). Regular in-service training by an external speaker also takes place at these meetings.

(Procedure: Knowledge Management, TIS incoming telephone service and Scientific consultation)

Working groups are set up to investigate and evaluate existing processes and methods, and to come up with suggestions for improvement and/or new proposals for work methods, organisation and processes. Examples of groups are: stimulating reports, report form, clinical quality, causality model, feedback, screening sector reports, signal detection.

(see *Overview of working groups in the annual plan*)

5. Results

Lareb periodically measures the results of its service. This mainly involves quantitative data. Within Lareb mainly qualitative aspects are of great importance. But these qualitative aspects are difficult to measure precisely. An additional difficulty is that Lareb is heavily dependent for the quality of its service, both quantitatively and qualitatively, on the reports received from third parties.

It is therefore very difficult to make the quality of the service SMART. The ways in which this happens are shown in this chapter.

It is worth noting that Lareb tries to encourage reporting of adverse reactions in quantitative and qualitative terms by giving presentations and education to various target groups. Also by other PR communications, including mailings, Lareb tries to focus attention on reporting of adverse events.

5.1 Customer satisfaction

Every quarter there is coordination between Lareb and MEB and Lareb and RIVM. Here the latest situation regarding the activities is discussed. Satisfaction with the services is also discussed. The results of the meeting are recorded in the minutes and, where necessary, adjustment takes place.

Periodically, there is consultation with all partners in the pharmacovigilance chain: Ministry of Health, Welfare and Sport, MEB, RIVM, Dutch Healthcare Inspectorate, CCMO[1] and CIBG[2]. The ongoing focus here is on satisfaction with cooperation in the chain.

A good relationship is maintained with various professional groups and patient organisations. Regular consultations with them take place, where new initiatives may emerge that can contribute to improving the reporting process or knowledge-sharing. By review or consultation with professional groups it is possible to respond in the correct manner when distributing information to relevant parties following a report. Relevant reactions, questions or comments from individual doctors or pharmacists are regularly discussed, for example at the meeting at the beginning of the week. Complaints or suggestions from both patients and care-providers are systematically recorded by staff and discussed between the management and organisation & communication and in the Steering Group. In addition, a survey of customer needs is launched in order to better meet the wishes of various care-providers and patients. This survey can be repeated regularly for various target groups.

(Procedure: Handling complaints)

5.2 Staff satisfaction

Lareb is a small organisation with an open structure. Structurally there is no separate staff satisfaction survey site. Satisfaction is subject to discussion during the performance appraisal interviews, but also this can be addressed at meetings during the year. Attention is also paid to the professional development of its employees. See also ‘Employees – Professionalisation’.

Yearly staff meetings are organised where small groups of employees discuss various matters with the director. Outcomes here have, among other things, led to changes in the organisation or HR policy and possibly to staff regulations.

5.3 Measuring performance

Within various processes performance indicators have been set to give an indication of quality. These performance indicators are also included in the policy and plans of individual employees.

Think about the number of reports that are processed, the number of publications and the number of courses to be enjoyed and/or delivered.

The performance indicators are regularly measured and discussed with line managers. If necessary, adjustment takes place. It should be noted that the employees are not able to influence all of the data themselves. Thus, without any good reports, no thorough analysis can take place. Reporting takes place in the minutes of Steering Group meetings or various other meetings. The generic key figures are reported in the annual accounts of the subsidies.

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[1] Central Committee on Research Involving Human Subjects

[2] Central Healthcare Professionals Information Point

6. People

6.1 Recruitment

Lareb periodically determines whether an expansion of the workforce is necessary and, if so, what kind of employees. Those directly involved, in consultation with the director, determine which job is relevant for the new employee. A job description is already present for the replacement or expansion of an existing post.

Then, a new employee is recruited in accordance with a fixed roadmap. For employees who are mainly engaged in the primary process of Lareb, professional knowledge is paramount.

6.2 Professionalisation

New employees receive a thorough introduction programme. Attention is also paid to the importance of Lareb's commitment to quality and the processes described in the manual. The coordinator in question sets up the introduction programme for the new employee.

Subject to requirements set out in the job descriptions Lareb has no standard measurement in the sense of requirements for training before employees can perform certain tasks. After the introduction programme a new employee is supervised for a prolonged period by a designated person or persons who closely monitor the quality of the work to be performed.

Within Lareb there is no official career ladder, but employees may have specialised tasks in accordance with their level of education, work experience and interest.

Within Lareb employees, in consultation with the director, determine which courses they would like to follow. Courses also include training and seminars. Based on this the management, in consultation with the Steering Group, then determines who actually takes what course. This is recorded in the individual year plans. If applicable, the director may also ask an employee to take a course that is in the interests of Lareb. Afterwards the employee completes an evaluation of the course. Every year a complete overview is drawn up of the courses taken per employee.

At the end of the course, if relevant, feedback is given to employees who were not on the course. Depending on the type of course determines the manner in which the feedback is best given. Examples include the Lareb afternoons or knowledge lunches. Sharing the knowledge limits the cost of training.

6.3 Evaluation

There is a yearly assessment cycle within Lareb. At the beginning of the year, based on the multi-year policy plan and the annual plan derived from it, the objectives for each employee are indicated in the individual annual plans. During the year, if necessary, consultation and assessment takes place over the situation with regard to achieving the objectives. At the end of the year, appraisal interviews and a formal assessment take place. The assessment is based on the existing job description and the objectives drawn up at the beginning of the year, with space given to new tasks that have emerged in the course of the year.

During the appraisal interviews staff satisfaction over the past year is also discussed as well as recording wishes for the coming year.

When employees leave Lareb, an exit interview takes place with an external human resources consultant who feeds back the findings to the director. It is possible that improvements emerge for staff retention at Lareb. Lareb has a small staff and the turnover is low. A thorough analysis of the exit interviews in order to identify structural improvements is not possible/expedient.

(HRM entry and staff regulations)

7. Resources

The resources that are used, primarily relate to (office) automation and the parties responsible for external presentation. Think of the designer and printer who handles all the printing. Its quality is directly linked to the image of the pharmacovigilance centre. (Office) automation allows effective and efficient handling of the primary process.

7.1 Procurement

The evaluation of suppliers in a small organisation is ongoing. In concrete terms this means examining whether cooperation is working satisfactorily during a job. If it is satisfactory, this outsourcing will be continued in the next project/programme.

Procurement mainly takes place in the field of automation and design/printing. The primary process consists of registering and analysing reports. The collating and registration of adverse reactions is largely automated, using a system specially developed for Lareb. A third party is called on for this. Any adjustments are carried out by this party. The Service Level Agreement (SLA) sets out details of the commitment. Lareb can inspect the status of work and evaluates through monthly project reports.

A second external party is used for the daily management and for office automation. There is ongoing coordination and Lareb itself can inspect the status of breakdowns. The exact details are set out in an SLA. In addition, an overall evaluation is regularly included. If necessary, corrective measures are taken.

(Procedure: Automation, Fallback)

There is also a long-term relationship with the current designer and printers. The performances of these suppliers are evaluated during a project or the year. If necessary measures are also taken here to arrive at as good and efficient a result as possible. As long as no corrective measures are necessary, no separate reporting of supplier audits takes place.

The pharmacovigilance centre organises meetings on a regular basis as part of in-service training or seminars in the field of adverse reactions. Lareb is supported by various parties for administrative work (registration, certificates) and organisational work (venue rental, catering). Afterwards evaluation takes place between the various parties and arrangements are made for a next activity.

7.2 Cooperation

When it comes to the safety of medicines, cooperation is important. Sharing of expertise and information to detect signals as soon as possible are paramount.

The cooperation described here applies specially to submitting and processing reports and relaying the results to the MEB and RIVM. However, this is more a kind of customer/supplier relationship than the cooperation intended in the Certiked model. Cooperation in that sense does not occur at Lareb.

7.3 Management

The management of resources relates only to the management of the automation system. This is attended to by the automation coordinator. The system is backed up both daily and monthly. Details are described in the procedure “Back-up”.

(Procedure: Back-up)

Appendix 1: Summary of Procedures

1	**General**
	Establishing a procedure
	Establishing a work instruction
2	**Quality**
	Registrations
	Dealing with complaints
	Internal audits
	Management review
	Drafting individual annual plans for employees
3	**Steering group**
	Steering group
	Media contacts
4	**Signal detection**
	Scientific consultation
	Periodic screening of database
	Knowledge management
	Quarterly report
	Publication
	MEB requests
	Safety concerns
	Recoding non-current MedDRA
	Informing reporters
	Storing source data
5	**Science and Research**
	Research

6	**Reports**
	Dealing with questions from marketing authorisation holders about Lareb reports
	Receiving hard copy adverse event reports
	Screening of adverse event reports
	Inputting adverse event reports
	Triage
	Assessing adverse event reports
	Feedback on adverse event reports
	Review consultation on drugs and vaccines
	Information Document on Adverse Effects
	Annual reports on vaccines
	Deaths (or other serious report) after administering vaccine
	Reporting and information on safety monitoring of influenza vaccines
	Electronic sector reports
7	**TIS**
	Follow-up registration
	Forwarding follow-up results to L2010
	Storing literature_RefMan
	Telephone service_incoming
8	**Stimulating reports and Education**
	Acquisition, preparation, delivering and archiving of presentations
9	**LIM**
	LIM, coding via CMS
	LIM, implementation in daily practice
	LIM, starting and stopping GMO

10	**IT**
	Automation
	Back-up
	Fallback
	Sending adverse event reports to other bodies
	Implementing corrections after checking acknowledgment files EMA
	Monitoring import of adverse event reports
11	**Organisation and communication**
	Manual Support
	Financial administration
	Website
	Clarification