Guideline on Good Pharmacovigilance Practices

Module IV-Pharmacovigilance Quality System

TURKISH MEDICINES AND MEDICAL DEVICES AGENCY

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SECTION I

Structures and Processes

1.1.Introduction

This module is prepared to provide a guideline to Marketing Authorization Holder in order to establish and maintain the quality assurance systems with respect to pharmacovigilance. Marketing Authorization Holders should establish and use suitable and effective quality systems to perform pharmacovigilance activities. Quality system application should be performed according to the whole quality targets provided in section 1.5 and instructive principles provided in section 1.6 and it should be taken into account that the application of quality system and provision of quality targets for each drug in the quality system is very important to meet the pharmacovigilance-related tasks.

1.2. *Pharmacovigilance system*

Pharmacovigilance system is described as a system which is used to perform tasks and responsibilities in "The Regulation on Safety of Drugs" established by Marketing Authorization Holders and Applicants and Relevant Institutions and Other Organizations and which is designed to determine any changes in benefit/risk balance by monitoring safety of drugs.

Like other systems, pharmacovigilance system is also defined by structure, process and results. Including the necessary structures, there is a specific module in Good Pharmacovigilance Practices (GVP) for each specific pharmacovigilance process.

1.3. *Quality, quality objectives, quality requirements and quality system*

The quality of a pharmacovigilance system can be defined as all the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.

In general, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under 1.5.

Specific quality objectives and quality requirements for the specific structures and processes of the pharmacovigilance systems are provided in each Module of GVP as appropriate.

The quality system is part of the pharmacovigilance 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

1.4. *Quality cycle*

The quality system shall be based on all of the following activities:

• quality planning: establishing structures and planning integrated and consistent processes;

• quality adherence: carrying out tasks and responsibilities in accordance with quality requirements ;

• quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and

• quality improvements: correcting and improving the structures and processes where necessary

1.5. *Overall quality objectives for pharmacovigilance*

The overall quality objectives of a pharmacovigilance system are:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
- contributing to the protection of patients' and public health.

1.6. *Principles for good pharmacovigilance practices*

With the aim of fulfilling the overall quality objectives in Act 1.5. The following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met.
- Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
- All personnel of the marketing authorisation holder should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organisation should engage in continuous quality improvement following the quality cycle in 1.4.
- Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
- Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions.

1.7. *Responsibilities for the quality system within an organisation*

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities. Their responsibility should include adherence to the principles defined in 1.6.

In accordance with the quality cycle (see 1.4.), managerial staff with management responsibilities in any organisation should be responsible for:

- ensuring that the organisation documents the quality system as described in 1.12.;
- ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- ensuring that adequate resources are available and that training is provided (see 1.8.);
- ensuring that suitable and sufficient premises, facilities and equipment are available (see 1.9.);
- ensuring adequate compliance management (see 1.10);
- ensuring adequate record management (see 1.11.);
- reviewing the pharmacovigilance system including its quality system at regular intervals in risk- based manner to verify its effectiveness (see 1.13.) and introducing corrective and preventive measures where necessary;
- ensuring that mechanisms exist for timely and effective communication,
- identifying and investigating concerns arising within an organisation regarding suspected non- adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- ensuring that audits are performed (see 1.13.).

In relation to the management responsibilities described above, upper management within an organisation should provide leadership through:

- motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organisation; and
- assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

1.8. *Training of personnel for pharmacovigilance*

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel (see 1.7.).

All personnel involved in the performance of pharmacovigilance activities shall receive

initial and continued training.This training shall relate to the roles and responsibilities of the personnel [Regulation on Safety of Drugs Act 5 (5), Act 26)].

The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel [Regulation on Safety of Drugs Act 26 (3)]. Training plans should be based on training needs assessment and should be subject to monitoring.

The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organisation should receive and be able to seek information about what to do if they become aware of a safety concern.

There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of urgency, including business continuity (see 1.12.2.), shall be provided by the organisation to their personnel.

1.9. *Facilities and equipment for pharmacovigilance*

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see 1.5.). Facilities and equipment which are critical for the conduct of pharmacovigilance (see 1.12.2.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies in their valid versions and to keep the IT systems up-to-date accordingly.

1.10. Compliance management by marketing authorisation holders

For the purpose of compliance management, marketing authorisation holders shall have specific quality system procedures and processes in place in order to ensure the following:

- the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder
- the scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorisation or associated with occupational exposure
- the submission of accurate and verifiable data on serious and non-serious adverse reactions to Turkey Pharmacovigilance Center (TUFAM) within the legally required time-limits.
- the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals.
- effective communication by the marketing authorisation holder with authority, including communication on new or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisations measures, periodic safety update reports, corrective and preventive actions and post-authorisation safety studies;
- the update of product information by the marketing authorisation holder in the light of scientific knowledge;
- appropriate communication of relevant safety information to healthcare professionals and patients.

1.11. *Record management*

The organisation shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information.

A record management system shall be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate
safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

The record management system should support:

- the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- timely access to all records;

- effective internal and external communication; and
- the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

In addition, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process. As part of a record management system, specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.

There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

The record management system should be described in a record management policy.

1.12. *Documentation of the quality system*

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.

A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. 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. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

In order to have a systematic approach, the organisation should define in advance:

- quality objectives specific to their organisations in accordance with the overall quality objectives provided under 1.5. and the structure- and process-specific quality objectives in accordance with each Module of GVP.
- methods for monitoring the effectiveness of the pharmacovigilance system (see 1.13.).

The quality system shall be documented by:

- documents on organisational structures and assignments of tasks to personnel (see 1.12.1);
- training plans and records (see 1.8.);
- instructions for the compliance management processes (see 1.10.);
- appropriate instructions on the processes to be used in case of urgency, including business continuity (see 1.12.2);
- performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities;
- reports of quality audits and follow-up audits, including their dates and results.

Training plans and records shall be kept and made available for audit and inspection.

It is recommended that the documentation of the quality system also includes:

- the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
- a record management policy;
- records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
- records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
- records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

1.12.1. Additional quality system documentation by marketing authorisation holders

In addition to the quality system documentation in accordance with 1.12., marketing authorisation holders shall document:

- their human resource management in the pharmacovigilance system master file (PSMF);
- job descriptions defining the duties of the managerial and supervisory staff;
- an organisational chart defining the hierarchical relationships of managerial and supervisory staff;
- instructions on critical processes (see 1.12.2.) in the pharmacovigilance system master file (PSMF);

- their record management system in the pharmacovigilance system master file.

It is recommended that the documentation of the quality system additionally includes the

organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

For the requirements of documenting the quality system in the pharmacovigilance system master file or its annexes.

1.12.2. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

- continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;
- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between marketing authorisation holders and competent authorities, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk- benefit balance of products for the aim of safe and effective use of medicinal products;
- keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable competent authority;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

Business continuity plans should be established in a risk-based manner and should include:

- provisions for events that could severely impact on the organisation’s staff and

infrastructure in general or on the structures and processes for pharmacovigilance in particular; and

- back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders and competent authorities.

1.13. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

Processes to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include:

- reviews of the systems by those responsible for management;
- audits;
- compliance monitoring;
- inspections;
- evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients.

The organisation may use performance indicators to continuously monitor the good performance of pharmacovigilance activities in relation to the quality requirements. The quality requirements for each pharmacovigilance process are provided in each Module of GVP as appropriate.

The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system (see 1.12.) at regular intervals, with the frequency and the extent of the reviews to be determined in a risk-based manner. Pre-defined programmes for the review of the system should therefore be in place. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness. Audits of the quality system should include audit of the pharmacovigilance system which is the subject of the quality system. The methods and processes for the audits are described in Module IV. In relation to the pharmacovigilance system of a marketing authorisation holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited. The report should include the results of audits of organisations or persons the marketing authorisation

holder has delegated tasks to, as these are part of the marketing authorisation holder‘s pharmacovigilance system. For competent authorities, the audit report shall be sent to the management responsible for the matters audited.

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. Additionally, Authority should have in place arrangements for monitoring the compliance of marketing authorisations holders with legally required pharmacovigilance tasks and responsibilities.

1.14. *Preparedness planning for pharmacovigilance in public health emergencies*

Any pharmacovigilance system should be adaptable to public health emergencies and preparedness plans should be developed as appropriate.

SECTION II
General Responsibilities

2.1. *Overall pharmacovigilance responsibilities of the marketing authorisation holder*

The marketing authorisation holder shall operate a pharmacovigilance system and shall establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities .

There may be circumstances where a marketing authorisation holder may establish more than one pharmacovigilance system, (e.g. vaccines, products available without medical prescription).

A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorisation in the format of a pharmacovigilance system master file and be maintained by the marketing authorisation holder for all authorised medicinal products The applicant or the marketing authorisation holder is also responsible for developing and maintaining product- specific risk management systems.

Guidance on the structures and processes on how the marketing authorisation holder should conduct the pharmacovigilance tasks and responsibilities is provided in the respective GVP Modules.

2.1.1. Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance

As a part of pharmacovigilance system, the qualified person responsible for pharmacovigilance and deputy of the qualified person responsible for pharmacovigilance who has suitable features and is responsible in pharmacovigilance in Turkey should always and consistently be authorized.

A common the qualified person responsible for pharmacovigilance and deputy may be assigned

if different marketing authorization holders operating acts under the partnership roof conduct a common pharmacovigilance system. However, these persons could not conduct any other tasks than being the qualified person responsible for pharmacovigilance.

If Marketing Authorization Holder conducts all pharmacovigilance-related tasks via a contracted pharmacovigilance service corporation, Marketing Authorization Holder may not employ the qualified person responsible for pharmacovigilance. However, some of the pharmacovigilance-related tasks are conducted via a contracted pharmacovigilance service corporation; Marketing Authorization Holder should employ the qualified person responsible for pharmacovigilance continuously [Regulation on Safety of Drugs Act (5), (6)].

The duties of the qualified person responsible for pharmacovigilance shall be defined in a job description. The hierarchical relationship of the qualified person responsible for pharmacovigilance shall be defined in an organisational chart together with those of other managerial and supervisory staff. Information relating to the qualified person responsible for pharmacovigilance shall be included in the pharmacovigilance systems master file.

Marketing Authorization Holder should provide pharmacovigilance officer to get sufficient authority that would affect quality system and pharmacovigilance activities. Marketing Authorization Holder should provide that required structure and processes are in force for the qualified person responsible for pharmacovigilance to exactly perform responsibilities listed in section 2.1.12. To accomplish this, Marketing Aurhorization Holder should provide the qualified person responsible for pharmacovigilance to have access to all relevant information especially relating with the followings:

- emerging safety concerns and any other information relating to the benefit/risk evaluation of the medicinal products covered by the pharmacovigilance system;
- ongoing or completed clinical trials and other studies the marketing authorisation holder is aware of and which may be relevant to the safety of the medicinal products;
- information from sources other than from the marketing authorisation holder,
- the procedures relevant to pharmacovigilance which the marketing authorisation holder has in place at every level in order to ensure consistency and compliance across the organisation.

Regular inspection results and criteria used with relation to the quality system established in section 1.7 and 1.13 should be shared with the qualified person responsible for pharmacovigilance by managers.

Compliance information should be periodically given to the qualified person responsible for pharmacovigilance.

In particular with regard to its adverse reaction database (or other systems to collate adverse reaction reports), the marketing authorisation holder should implement a procedure to ensure that the qualified person responsible for pharmacovigilance is able to obtain information from the database, for example, to respond to urgent requests for information from the competent authorities or the Agency, at any time. If this procedure requires the involvement of other

personnel, for example database specialists, then this should be taken into account in the arrangements made by the marketing authorisation holder for supporting the qualified person responsible for pharmacovigilance outside of normal working hours.

When a marketing authorisation holder intends to expand its product portfolio, (for example, by acquisition of another company or by purchasing individual products from another marketing authorisation holder), the qualified person responsible for pharmacovigilance should be notified as early as possible in the due diligence process in order that the potential impact on the pharmacovigilance system can be assessed and the system be adapted accordingly. The qualified person responsible for pharmacovigilance may also have a role in determining what pharmacovigilance data should be requested from the other company, either pre- or post-acquisition. In this situation, the qualified person responsible for pharmacovigilance should be made aware of the sections of the contractual arrangements that relate to responsibilities for pharmacovigilance activities and safety data exchange and have the authority to request amendments.

When a marketing authorisation holder intends to establish a partnership with another marketing authorisation holder, organisation or person that has a direct or indirect impact on the pharmacovigilance system, the qualified person responsible for pharmacovigilance should be informed early enough and be involved in the preparation of the corresponding contractual arrangements (see 2.1.3.) so that all necessary provisions relevant to the pharmacovigilance system are included.

2.1.1.1 Qualifications of the qualified person responsible for pharmacovigilance

Marketing authorization holder must make sure that the qualified person responsible for pharmacovigilance and deputy of the qualified person responsible for pharmacovigilance must have adequate theoretical and practical information in order to carry on pharmacovigilance operations.

The applicant or marketing authorisation holder should provide the qualified person responsible for pharmacovigilance with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the qualified person responsible for pharmacovigilance taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the qualified person responsible for pharmacovigilance in the medicinal products covered by the pharmacovigilance system.

2.1.1.2. Role of the qualified person responsible for pharmacovigilance

The qualified person responsible for pharmacovigilance shall be responsible for the establishment and maintenance of the marketing authorisation holder's pharmacovigilance system. Thus, the qualified person responsible for pharmacovigilance must have authority on performance of the quality system and authority to influence carrying out farmacovigilance operations and to comply legal requirements, to maintain and to improve them. For this reason, the qualified person responsible for pharmacovigilance must have access to farmavigilance system main dossier. The qualified person responsible for pharmacovigilance must have an position which gives him/her authority over information present in pharmacovigilance system master file, of which the responsibility for it to contain true and up to date information belongs to the qualified person responsible for pharmacovigilance.

In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the qualified person responsible for pharmacovigilance should include:

- having awareness of medicinal product safety profiles and any emerging safety concerns;
- To have information about all circumstances and obligations related to safety and safe usage of drugs.
- having awareness of risk minimisation measures.
- being aware of and having sufficient authority over the content of risk management plans.
- to participate in evaluation and end of procedure protocols of post approval safety studies according to risk management plans
- having awareness of post-authorisation safety studies requested by a Authority including the results of studies
- ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP.
- ensuring the necessary quality, including especially the correctness and completeness, of documents submitted to the Authority.
- ensuring a full and prompt response to any request from the Authority for the provision of additional information necessary for the benefit- risk evaluation of a medicinal product
- providing any other information relevant to the benefit-risk evaluation to the Authorities.
- providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals)

This responsibility for the pharmacovigilance system means that the qualified person responsible for pharmacovigilance has oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and

training of personnel in relation to pharmacovigilance). Specifically for the adverse reaction database, if applicable, the qualified person responsible for pharmacovigilance

should be aware of the validation status of the database, including any failures that occurred during validation and the corrective actions that have been taken to address the failures. The qualified person responsible for pharmacovigilance should also be informed of significant changes that are made to the database (e.g. changes that could have an impact on pharmacovigilance activities).

2.1.2. Specific quality system processes of the marketing authorisation holder

In applying the requirements set out in 1.10, the marketing authorisation holder shall put in place the following additional specific quality system processes for ensuring:

Monitoring usage of MedDRA terminology cited in Regulation Article 5 (3) about Regulaton on Drug Safety for clasification, presentation, accesability, determination and evaluation of benefit/risk, electronic data exchange and communications of pharmacovigilance and drug information , using systematic or regular random examinations.

- the retention of minimum elements of the pharmacovigilance system master file as long as the system described in the pharmacovigilance system master file exists and for at least further 5 years after it has been formally terminated by the marketing authorisation holder
- the retention of pharmacovigilance data and documents relating to medicinal products as long as the marketing authorisation exists and for at least further 10 years after the marketing authorisation has ceased to exist.

To keep the product information up to date by manufacturing authorization holder in the light of scientific knowledge by continuous monitoring of publications released about drug safety.

During the retention period, retrievability of the documents should be ensured. Documents can be retained in electronic format, provided that the electronic system has been appropriately validated and appropriate arrangements exist for system security, access and back-up of data. If documents in paper format are transferred into an electronic format, the transfer process should ensure that all of the information present in the original format is retained in a legible manner and that the media used for storage will remain readable over time.

Documents transferred in situations where the business of the marketing authorisation holder is taken over by another organisation should be complete.

2.1.3. Quality system requirements for pharmacovigilance tasks subcontracted by the

marketing authorisation holder

Marketing authorization holder outsource certain aspects of pharmacovigilance system to a Contracted Pharmacovigilance Service Institution (CPSI) or to a service provider on contract basis.

The marketing authorisation holder shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorisation holder.

When the manufacturing authorization holder assigns some or all of pharmacovigilance duties to a contractor, manufacturing authorization holder will still has the responsibility of application of effective quality system of these duties. All the conditions explained in the GVP applies to contract holders as well. In addition, contractor is subject to inspections by the Authority.

When tasks are given to a CPSI, manufacturing authorization holder must prepare the contracts, to detail and upgrade them. The contract defining the authorizations and responsibilities stating the authorities and responsibilities of each party, the MA holder and the contractor should be clearly documented. A definition of operations and/or services defined by the contract should be added to pharmacovigilance system master file and a list of contracts of related product(s) should be enclosed to pharmacovigilance system master file.

Agreements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. . Manufacturing authorization holder must add the tasks it outsourced, the possible interactions with the contractor, the detailed data interchange with time lines to the contract.

Agreement should also contain clear information on the practical management of pharmacovigilance as well as related processes, including those for the maintenance of pharmacovigilance databases. Further, they should indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended.