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AZPIL Marketing Company Quality Manual

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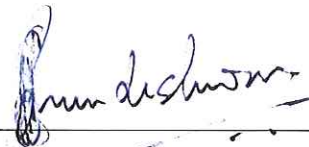
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Purpose

AstraZeneca India Pharma India Ltd (AZPIL) is committed to the development, manufacture and supply of high quality of medicines in compliance with Company standards, International codes, standards and regulations and local regulatory requirements.

The AstraZeneca Code of Conduct, Global Policies and International Procedures describe the expectations and processes with which all AstraZeneca employees must comply in order to meet the high ethical standards expected of everyone. The Global Policy on Quality and Regulatory Compliance sets out the minimum standards for Quality and Compliance across the product development, manufacture and distribution value chain, including relevant marketing company activities.

The purpose of this document is to describe the key aspects of the Quality Management system to be established in the AstraZeneca India Pharma India Ltd marketing companies.

Scope

This standard specifies the QMS for AZ MCs in relation to:

- Good Clinical Practice (GCP) for Non-interventional studies involving primary data collection
- Good Pharmacovigilance Practice (GVP)
- Good Regulatory Practice (GRP)
- Good Manufacturing Practice (GMP)
- Good Distribution Practice (GDP).

Procedure

1. Quality Policy

AZPIL is committed to the delivery of high quality services and solutions to our customers and stakeholders. This is achieved through our commitment to quality, our patient and customer focus and the dedication of all employees. The Marketing Company President of AZPIL is accountable for and committed to the development of a culture of Quality Assurance and for compliance with appropriate external and internal codes of practice in the GxP regulated environment and shall appoint a GxP Co-ordinator.

General requirements:

The Country President must ensure that there is an appropriate GxP quality system in place to cover the relevant activities.

The quality system must provide the following as a minimum:

- The appointment of a person who ensures that relevant GxP procedures are in place.
- The person responsible within the MC must make sure that all GXP activities, if they are not adequately described in global Standard Operating Procedures (SOPs), are defined in local SOPs. These SOPs must be set up to assure compliance with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), AstraZeneca Quality and Compliance Manual (QCM), Good Regulatory Practice (GRP) or any global procedure laid down for GCP or GMP as appropriate. The SOPs must also document which of the above are applicable.
- All personnel employed in GxP activities are suitably qualified and trained, with evidence of training. There is a system of regular self-inspection with timely completion of corrective actions.

There is a regular review of the quality system in place with the aim of continuous improvement.

GxP applicable to AZPIL MC:

AstraZeneca MC in India performs following activities, which may require adherence to GMP, GCP, the AstraZeneca QCM, GRP, Global Clinical Procedural Documents and other functional global procedures as appropriate.

- Maintenance of product licences, clinical trial authorisations, manufacturing authorisations and distribution licences
- Health Authority interactions
- Management of Regulatory Knowledge
- Clinical Trial applications
- License maintenance including Pharmacovigilance, Chemistry Manufacturing and Controls (CMC) variations and post approval commitments to regulatory authority
- Secure archiving of records and information (paper and electronic)
- Handling of complaints, adverse event reporting, handling of Regulatory Authority interfaced recalls and issue management
- Creation and approval of market specific labelling, and life cycle management of labels
- Handling of Registration samples
- Handling of clinical supplies and physicians' samples

- Coordination, control and monitoring of clinical trials initiated and managed by the MC
- Self-inspections
- Control of registered specifications and regulatory compliance
- Reporting on Quality & Compliance to Management

2. Scope of the AZPIL Commercial Quality System

2.1. Good Clinical Practice (GCP)

GCP activities associated with clinical studies initiated and/or managed by AZPIL (typically non- interventional studies) are the responsibility of the AZPIL Medical Division and therefore fall within scope of the AZPIL Quality System. Support for GCP activities related to such studies will be provided by the local Regulatory affairs team. Clinical trial activities conducted by or on behalf of the MC must be in accordance with ICH GCP, national laws and local or regional regulatory requirements. The MC must ensure that Global Clinical Development Procedural Documents are applied consistently as appropriate. The MC must document which activities are covered by GCP.

2.2 Good Manufacturing Practices (GMP/GMP)

GMP activities in the MC must meet local laws as appropriate. For example, the GMP and GCP requirements as per the Drugs and Cosmetics Act 1945 and Rules thereunder. The MC must ensure that the AstraZeneca QCM Procedures and Guidelines are applied consistently as appropriate. The MC must document which activities are covered by GMP and which regulations apply

2.3 Good Pharmacovigilance Practice (GVP)

The Medical Communications and Patient Safety Department within the AZPIL Regulatory Division is responsible for all local pharmacovigilance activities associated with clinical and marketed products. All local GVP activities therefore fall within the scope of the AZPIL Commercial Quality management System. Local operating procedures or working guidelines will be established where necessary to provide local context in order to ensure compliance with the expectations set out in the international procedure.

2.4. Good Regulatory Practice (GRP)

The primary roles of the Regulatory Affairs Departments within AZPIL are to register new medicines and maintain the licences of existing medicines, throughout the life of a product, as per the local requirement. All local GRP activities therefore fall within the scope of the AZPIL QMS.

AZ GRP requirements are described in AZ International Procedure IP 1-P56-cv-X "Good Regulatory Practice in AstraZeneca'. This procedure defines the key GRP process areas and sets out the roles and responsibilities for each of the process areas. Local operating procedures and working instructions will be established to provide local context and

ensure compliance with the expectations set out in the international procedure.

- The MC must describe the GRP quality management system.
- The MC is committed to have adequately resourced, skilled and trained personnel to perform GRP activities to meet key license to operate regulatory activities.
- The Country President and senior MC management should receive recorded training on their obligations to quality and license to operate.

1. GRP Quality Statement

- To maintain effective quality management system to comply with AstraZeneca GRP requirements.
- To ensure compliance with as per the applicable law
- To comply with all regulatory commitments.
- To improve our services to meet the changing needs and expectations of our external stake holders

2. GRP Quality System

The GRP Quality System shall include:

a. SOP Control Framework

- SOPs are designed to identify what activities are critical for achievement of license to operate GRP activities.
- SOPs should describe stepwise activities for the key processes.
- Local SOPs must align with Global procedures such as Global Regulatory Affairs (GRA) SOPs, QCM and International Procedures (IP).

b. Training Programme

- The management and documentation of training within AZPIL will be undertaken in line with the expectations set out in International Procedure IP 2-P11-cv-M "Management and Documentation of Training and Job Descriptions."
- All staff, including contractors and outsourced partners, will receive training to enable them to conduct key tasks within their roles and to understand the importance of compliance and consequences of non-compliance with expected standards.

- For each GxP role a training matrix against key global and local procedural documents will be established and regularly reviewed.
- An induction training plan for each role will be established for each role, describing key procedural training requirements to be completed during the initial period of employment
- Each member of staff will have a training record in which they will be expected to provide evidence of their training against their role requirements.
- Staff undertaking GxP roles will be expected to maintain an up to date CV as part of their training record. Local Working Instructions which govern the management of training within the different GxP areas will be established

c. Self-Monitoring System to Verify the Quality System is Robust

Monitoring of compliance with the expectations of the GRP Quality System will be achieved by annual reviews of compliance with the documented requirements of the core regulatory processes. A self-audit programme will be established at the end of each year. Audit findings and resultant actions will be documented and tracked to completion. A local procedure will be established to define the roles, responsibilities, processes and reporting requirements for the self-audit programme.

The local procedure on training records also mandates an annual review of staff training records. This activity is a key component of the self-monitoring programme. In addition indicators of the overall robustness of the quality system are provided by consideration of key metrics during the formal management review processes.

d. Corrective and Preventive Action Management

Where a self-monitoring system identifies noncompliance or weakness in the GRP license to operate requirements, there must be system of reporting and correcting errors. This should include an investigation to identify the root cause of the failure, agreed and recorded action steps to correct failures, and an action plan to improve the system to prevent it happening again

e. Change Management System

Change management is an integral component of many activities within AstraZeneca. Changes affecting AZ products are managed using the global R&D and Operations change management processes and are outside of the scope of the C-QMS for AZPIL. Change management within AZPIL is focused on understanding the impact of internally or externally driven changes (proposed or actual) to the business operating model or environment and Quality Systems. Formal change management system shall be in place.

This must include risk assessment of impact to processes, compliance and GRP activities, of particular importance are external legislative changes.

f. Management and Control of Documents and Records

GRP/GMP

The control of regulatory documents in AZPIL is described in a local SOP on the management of Regulatory Knowledge. For global AstraZeneca products this local procedure mandates the use of the Global Electronic Library (ANGEL) as the sole repository for Regulatory Knowledge. AstraZeneca India also markets a range of products solely for the local market (so called Products of Local Opportunity - POLO). These products are excluded from the scope of the global ANGEL system. Accordingly the local procedure describes the processes for storage of all regulatory knowledge pertaining to this range of products.

Local procedures are in place describing the processes associated with the storage and archiving of hard copy documentation in compliance with the AstraZeneca record policies and Records Archiving and Destruction (RAD) schedule.

SOPs and other procedural documents accessed by AZPIL staff are controlled by the relevant global and local document management systems.

Metrics associated with the performance of the Regulatory Affairs India QMS are held electronically in a GRP compliance folder within the Regulatory Affairs shared drive

Patient Safety documents are managed in accordance with the Local Law

AZPIL adverse event case specific source documents including letters, faxes, emails and medical records, are retained electronically in the local Pharmacovigilance database indefinitely. Hard copy source records are stamp dated and retained in their original receipt form in secure fire-proof cabinets in AstraZeneca archival (AZA). The Patient Safety Outsourcing Partner does not retain these documents. Archived records are managed by the AZA Information Management Partner.

Management Review

AZPIL will establish a management review system to ensure continuous suitability, adequacy and effectiveness of the quality system as detailed in the procedure 1-P54-cv-M Quality and Compliance Management Reviews. The details of the management oversight of the C-QMS are described below.

Monthly

GRP/GVP/GMP/GDP

GRP and GMP compliance will be a standing agenda item on the monthly Regulatory Affairs Departmental meetings. The status of ongoing issues (Quality Investigations), tracking of actions arising from previous investigations, and new compliance related matters will be reviewed. Actions and progress against previously agreed actions will be captured in the Regulatory Quality Tracking Tool (RQTT).

GVP

With regard to adverse event reporting, there are two key compliance figures:

- Compliance with local regulations (including local Health Authority, Head of the Institution and Ethics Committees);
- Compliance with Global Patient Safety Standards.

Monthly compliance will be measured for adverse event reports received and submitted by the Patient Safety Outsourcing Partner. This includes reports to the AZ Global Data Entry Site, the Indian Regulatory Authority, Licence Partners, and cases received from external vendors involved in adverse event reporting including Adverse Event Web-form users.

Monthly reconciliation activities will be conducted for product quality complaints, with associated adverse events included in the global Patient Safety and Complaints Management databases. Adverse event reports received by the Patient Safety Outsourcing Partner from Licence Partners and vendors including AE web-form users, in addition to adverse event reports submitted to the global Patient Safety database by the Patient Safety Outsourcing Partner will be reconciled regularly.

Monthly line listing reports of adverse event reports received are to be forwarded to the Head regulatory affairs for review and acknowledgement.

All Patient Safety quality management activities will be documented including data collected, data reviewed, any findings or discrepancies and corrective actions implemented. This includes key pharmacovigilance activities such as case handling, safety agreements, organised data collection, published literature, and document-archive and out of hours procedures.

Quarterly

Senior management oversight and governance of the operation of the AZPIL C-QMS will be standing agenda items as part of the quarterly Local Compliance Committee (LCC). In line with the expectations of IP-1-P6-cv-X "The Quality Management System in the AstraZeneca Commercial Organization" quarterly management review will

include the following aspects:-

- Setting and monitoring the objectives for the C-QMS.
- Review of any escalated GXP issues or risks.
- Review of performance indicators used to monitor the effectiveness of key processes.
- Review of performance of outsourced activities.
- Review of outputs of self-monitoring into the effectiveness of the C-QMS.
- Review of outputs from external assessments (regulatory inspections and customer audits)
- Follow up of actions from previous management reviews.

C-QMS performance indicators to be considered during quarterly reviews will be;-

- Complaints
- Ongoing Quality Investigations
- CAPA activities arising from Quality Investigations
- Change Management activities arising from changes in the AZPIL operating environment (internal or external)
- Outcomes from internal (local or global) self-assessment activities
- Findings from external inspections

Management reviews and outcomes should be documented concurrently and typically within 15 calendar days from the time of the review.

Annually

Performance and status of the overall C-QMS will be reported to the AstraZeneca SMT in accordance with documented requirements for reporting of business compliance status.

In addition, an annual Pharmacovigilance checklist is to be completed and submitted to Global Patient Safety for review. Key activities include adverse event management, quality and compliance management, risk management plans and activities, periodic safety

reporting, safety agreements, resource management and business continuity.

Annual adverse event training is to be undertaken by all AZPIL employees.

Reference: 1-S6-CV-X: STANDARD FOR THE ASTRAZENECA MARKETING COMPANY QUALITY MANAGEMENT SYSTEM

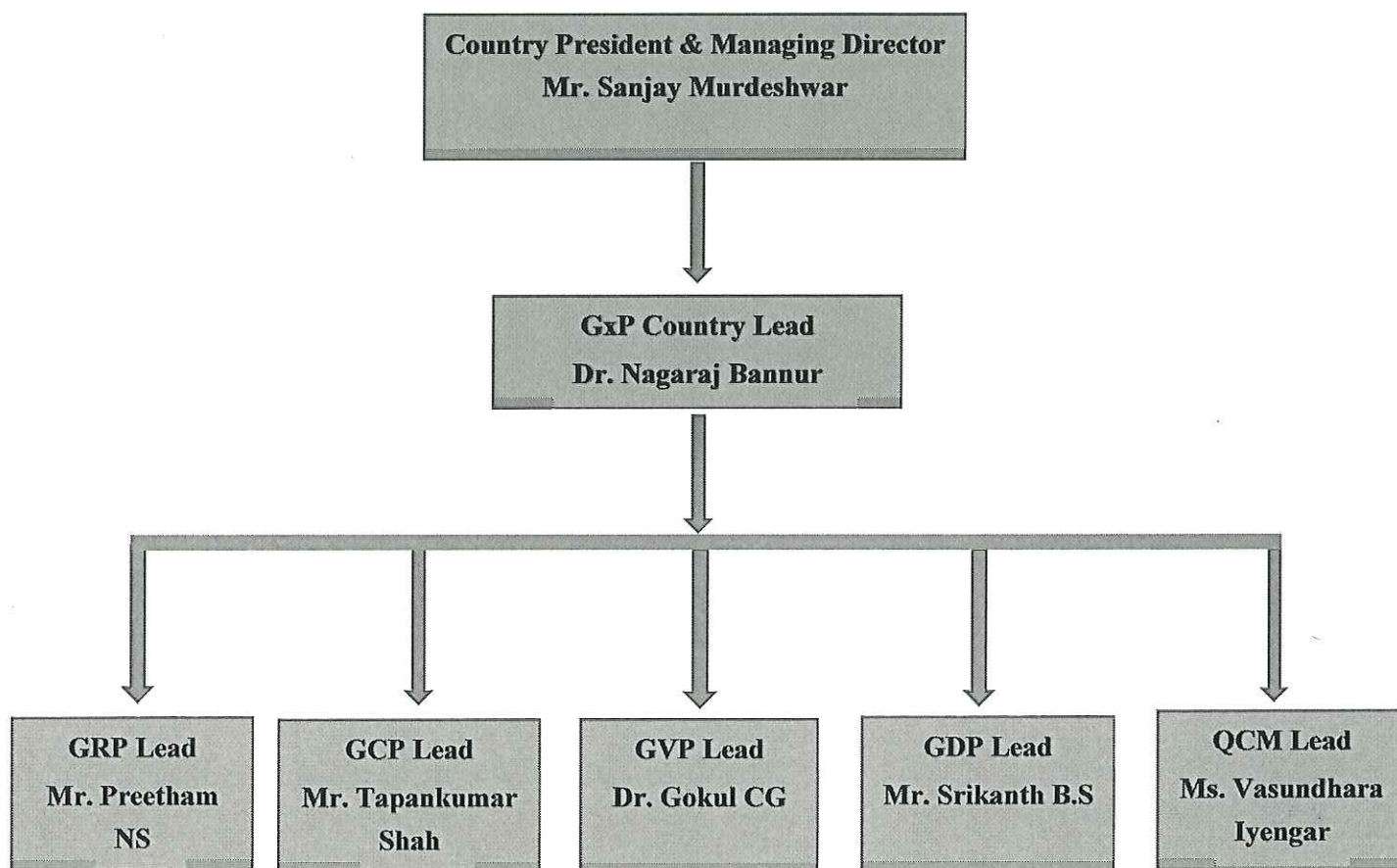
REVISION HISTORY

Version	Description of change
2.0	New standard based on 1-S6-CV-X: STANDARD FOR THE ASTRAZENECA MARKETING COMPANY QUALITY MANAGEMENT SYSTEM V 1.0. Further clarifies accountabilities and responsibilities for the Marketing Company QMS

Annexure 1:

1. GxP organogram
2. Management review format

Annexure 1: GxP Organogram



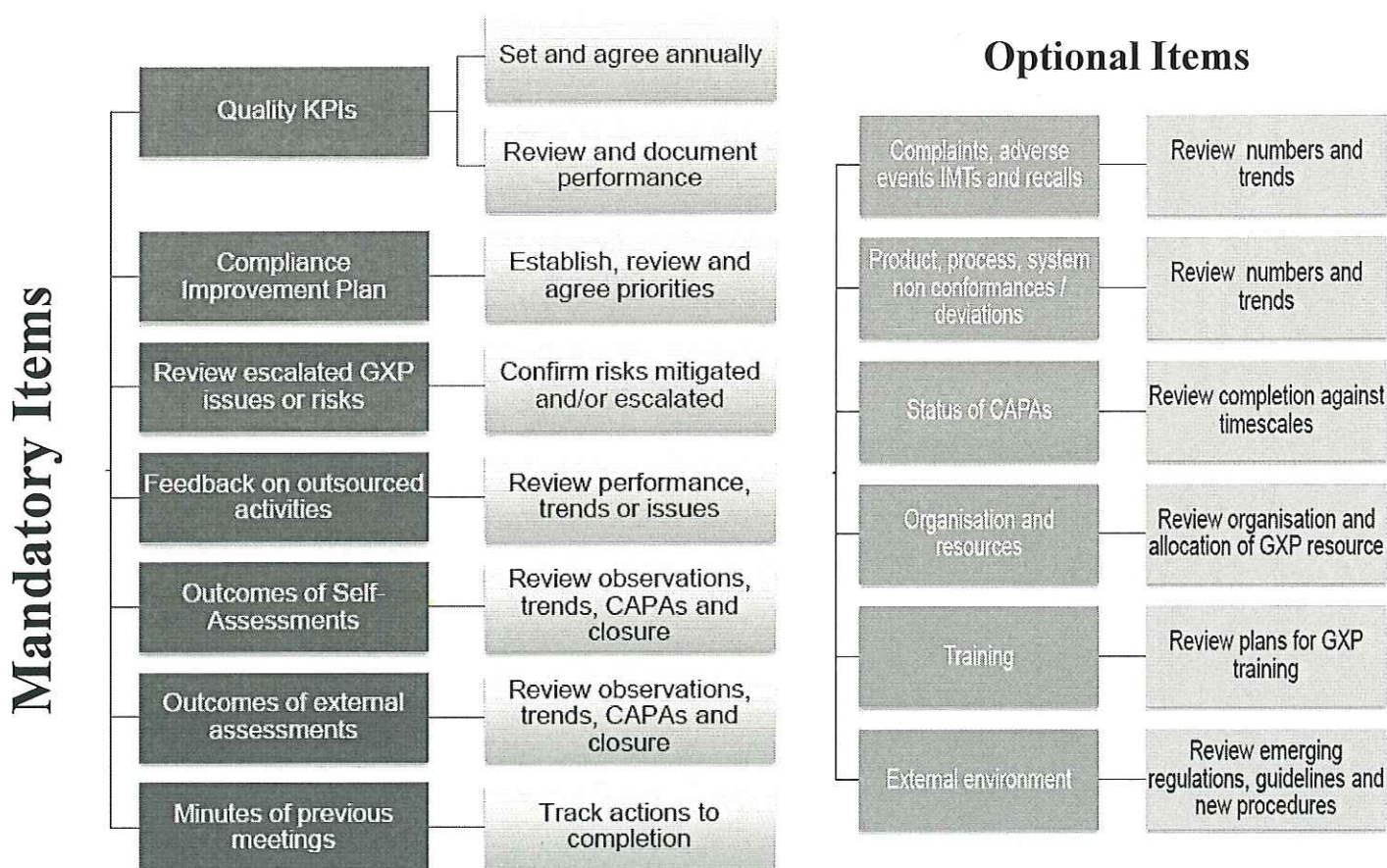
AstraZeneca Pharma India Limited
Block N1, 12th Floor
Manyata Embassy Business Park
Rachenahalli, Outer Ring Road
Bangalore - 560 045

Annexure 2: Management review System format

1. Management Review System:

- **Purpose:** Ensures that Senior Management has effective oversight of the status of GxP compliance in-country
- **Frequency:** At least quarterly
- **Required Attendees:** CP, GxP Country Quality Lead and GxP Quality Leads
- **Requirements:** Meeting minutes, tracking of actions to close
- **Performance Indicators for Review:**
 - Complaints
 - Ongoing Quality Investigations
 - CAPA activities arising from Quality Investigations
 - Change Management activities arising from changes (internal or external)
 - Outcomes from internal (local or global) self-assessment activities
 - Findings from external inspections

2. Management Review Agenda



GxP Quality Incidents:

GXP Area	Description of the Event	Date Identified	Status	Comments
GDP				
GMP				
GVP				
GCP				
GRP				

GxP Issues and Risks/Outsourced Activities:

Key Issues and Risks				
GXP Area	Description of the Issue/Risk	Key Action	Status	Comments
GDP				
GMP				
GVP				
GCP				
GRP				

Out Sourced activities				
GXP Area	Description of outsourced activity	GxP Activity	Status	Comments
GDP				
GMP				
GVP				
GCP				
GRP				

Assessments, Audits, KPIs and CIPs:

Assessments and Audits				
GXP Area	Type of Assessment/Audit	Date	Status	Summary of Findings and Actions
GDP				
GMP				
GVP				
GCP				
GRP				

Overall Status of Country Quality KPIs and Compliance Improvement Plans

Overall Status of Country Quality KPIs and Compliance Improvement Plans					
	Number of KPIs/Activities	Number completed	Number on Track	Current Issues	Overall status
Country quality KPIs					
Compliance Improvement plans					