Guidance on the interpretation and implementation of European Good Distribution Practice

Chapter 1 – Quality Management

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Preface

It is of key importance that medicinal products are not only made to a high quality in accordance with Good Manufacturing Practice, but that the quality and integrity of these products are maintained through the entire supply chain to the patient. This is where Good Distribution Practice (GDP) comes into play.

The distribution network for medicinal products is often complex, involving many different parties. In addition to the challenges associated with this complexity, there is also a growing threat from criminal activities seeking to introduce falsified medicines into the legal supply chain. The European regulators recognised several years ago that there was a need to update the content of the 1994 GDP guideline to take into account advancements in practices and changes in legislation since it was issued. A consultation draft was issued in mid 2011 and, following the receipt of many comments from interested parties, a final revised version was issued in March 2013 with an effective date of 8 September 2013.

The new guideline has a much stronger focus on the quality system with clear responsibilities and processes and the application of risk management principles. More detailed guidance is given on most elements. New chapters relating to transportation and specific provisions for brokers have been added.

The Pharmaceutical Quality Group issued a monograph on Pharmaceutical Distribution in 1997 and initiated planning to revise this in line with the new regulatory guideline. Whilst undertaking this planning it was identified that the European Compliance Academy were also planning to produce some guidance in response to requests from members. The two organisations therefore decided to join forces and set up a joint steering committee led by Afshin Hosseiny with Philip Butson, Ashley McCraight and Oliver Schmidt.

An early decision was that we would initially target key chapters and issue each as it became available rather than wait until a complete guide had been prepared. This has enabled us to shorten the time to the provision of some guidance and also provides an opportunity for us to collect feedback and enhance the material before issuing a complete guide. The first versions of the chapters will have different formats and styles due to the different volunteer teams involved in their preparation which we have chosen not to edit into a common format for the time being. We would appreciate feedback on what works best for you, the user.

In this document, text from the EMA guideline is given in italic Calibri font, followed by guidance from the team in normal Times New Roman font.

Please provide any feedback and suggestions for improvement using the email address monographs@pqg.org or info@gmp-compliance.org.

For this particular chapter on Quality Management, we would like to thank the hard work of the authoring team Ursula Greene, Shashi Patel, Milena Samban and Neil Wayman. Additional material was provided by Afshin Hosseiny and editing was undertaken by Philip Butson, Afshin Hosseiny and Ashley McCraight.
1.1. Principle

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities (2). All distribution activities should be clearly defined and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and where relevant validated. The quality system is the responsibility of the organisation’s management and requires their leadership and active participation and should be supported by staff commitment.

(2) Article 80(h) of Directive 2001/83/EC

- What is the rationale for the point in the guidance

This purpose of this guidance is to ensure that the principles of Quality Management are understood and put into effect by pharmaceutical distributors. It is important that activities relating to the distribution of pharmaceuticals are detailed within appropriate, approved procedures that set out clear responsibilities for personnel and management. The importance of quality risk management approaches to the design of quality systems is also discussed in this section of the guide.

- What are the risks and benefits associated with that piece of the guidance

A structured approach to managing quality through a QMS involves definition of critical processes and the identification of the critical aspects of those processes. Knowledge of the processes enables management to define responsibility and assign adequate resources for each activity. A QMS is a management tool which when used correctly, will increase the efficiency of a company, saving costs by reducing waste. This guidance requires Wholesale distributors to design and implement quality systems with risk management principals at their core. This shall provide for the secure distribution of pharmaceutical products, helping to ensure that only legitimate pharmaceuticals enter the supply chain and reach the end user, having been shipped and stored under conditions that ensure they remain within the legal supply chain; thus ensuring their integrity and quality.

- How might this be implemented/ what does it mean

A pharmaceutical distributor should develop process maps of their critical activities, define the critical control points and describe the areas of responsibilities. Procedures should be developed and verified by systematic reviews to ensure that they appropriately control processes to ensure consistency and address potential risks. The implementation of the Quality Management System shall be led by the organisation’s management and its importance to all personnel include in training and regular reminders to ensure awareness leading to compliance and continual improvement.

- Additional text

Process mapping can be basic, displaying the process in a single dimension with the flow of activities and their order. Process maps can also be more detailed and include responsibilities for each of the process steps along with the references to other procedures etc. When creating your process map first identify the start and end of your process. Create a list of the steps within your process and then place these in the sequence of events. Use appropriate symbols.
in your map to identify inputs to the process, the process steps themselves, process outputs, controls and feedback/communication pathways.

Further information relating to Quality Management Systems can be found in ISO 9004, Eudralex Volume 4, Part III/ICH Q9 Quality Risk Management
1.2 Quality Management

The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product delivered maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation.

- **What is the rationale for the point in the guidance**

A defined process for managing the QMS will provide appropriate tools for the company to manage their quality related activities to ensure and secure a supply of products to their customers. The Quality Management System shall ensure through appropriate procedures, processes, organisational structures and resources that products delivered and ultimately administered to patients will still retain their quality attributes. The Quality Management System shall also ensure that the product, at all times is handled, stored and transported within the legal supply chain.

- **What are the risks and benefits associated with that piece of the guidance**

Without a defined QMS, the company runs the risk of wasting resources, losing control of operations and potentially impacting the product quality and supply to customers. If a company’s Quality Management System is not suitable for purpose, this may increase the risk of infiltration of falsified medicine into the legitimate supply chain.

- **How might this be implemented/ what does it mean**

The company should have an organisation chart that details the organisational structure; this should detail where all personnel fit in the organisation and it should be included in the quality manual; it should be version controlled. Key personnel (e.g., Quality Manager, Warehouse Manager, Responsible Person) should have appropriate training, experience and competence and their roles and responsibilities should be defined. The company should have clearly documented processes and approved procedures (SOPs) that detail how activities are to be performed. Sufficient resources (personnel, equipment, premises etc) shall be available within the company to ensure that procedures can be complied with.

1.2 Quality Management

The quality system should be fully documented and its effectiveness monitored. All quality system-related activities should be defined and documented. A quality manual or equivalent documentation approach should be established.

- **What is the rationale for the point in the guidance**

A quality manual draws together the elements of the quality system into a controlled document enabling ready access by all personnel to the same management approved information. Since the purpose of the quality system is to ensure effective delivery of operational activities, it is important that this effectiveness is monitored and actions taken to
improve it as appropriate.

- **What are the risks and benefits associated with that piece of the guidance**

  The Quality Manual benefits both the customer and the supplier; by outlining adequate quality systems in place, a business can ensure that it routinely delivers the expected service to the customer, reducing the time and resource required to investigate and rectify errors and maintain customer satisfaction levels.

- **How might this be implemented/ what does it mean**

  This should be implemented through the preparation and establishment of an approved Quality Manual that is controlled under the Documentation Management system. Appropriate KPIs should be defined in the Quality Manual for critical activities and for performance of the QMS itself. Requirements for monitoring KPIs should also be defined in the Quality Manual and reflected in individual SOPs.

A Quality Manual normally contains the description of the quality system, including:
(a) The quality policy (see Section 2);
(b) The scope of the quality system;
(c) Identification of the quality system processes, as well as their sequences, linkages and interdependencies.
(d) Process maps and flow charts can be useful tools to facilitate depicting quality system processes in a visual manner;
(e) Management responsibilities within the quality system (see Section 2).

Guidance on preparation of the Quality Manual and of general quality systems can be found in ISO 9004.

1.2 Quality Management

A responsible person should be appointed by the management who should have clearly specified authority and responsibility for ensuring that a quality system is implemented and
What is the rationale for the point in the guidance

It is important that one person be identified to take responsibility for ensuring that the quality system is implemented and kept up to date and reflective of current practice, best practice and regulatory and legislative expectations.

What are the risks and benefits associated with that piece of the guidance

The benefits to the company will include ensuring continued compliance with the regulations and best practice standards and maintenance of the quality system. There are also benefits to the patient in that the Responsible Person (RP) has responsibility to ensure that procedures, processes, organisational structures and resources are implemented and maintained such that the quality of products delivered and ultimately administered to patients retain their quality attributes.

How might this be implemented/ what does it mean

An appropriately qualified individual as described in section 2.2 of the guidance and local legislation should be recruited to the position of Responsible Person; it is desirable that this person hold a degree in pharmacy. It is also imperative that this person be given adequate support from senior management to ensure that they have the necessary authority to match their responsibility for implementation and maintenance of the quality system. The role and responsibilities of the RP should be documented under the QMS. The RP should have a job description that reflects their role, responsibilities and authority; it should be signed and dated by both the RP and a management representative. The job description should be reviewed at least annually and updated as required to ensure its continued currency.

1.2 Quality Management

The size, structure and complexity of distributor’s activities should be taken into consideration when developing or modifying the quality system.

What is the rationale for the point in the guidance

If a company is relatively small in size and handles low volumes of products locally, it would not be expected that the QMS for this company would be comparable to a company that for example, is buying and selling products in many geographical locations.

Whenever the company expands either the size or complexity of its operations, the management should review the QMS to ensure that it is still capable of controlling the expanded operations. If a potential risk is identified, then, the QMS should be modified to minimise the impact of the identified risk.

What are the risks and benefits associated with that piece of the guidance

Without a defined QMS that is commensurate with the complexity of the company’s activities, the company runs the risk of wasting resources, losing control of operations and
potentially impacting product quality and supply to customers.

The company can benefit from accurately identifying resource requirements and applying appropriate resources to these areas.

### How might this be implemented/ what does it mean

A company should map their process, and then using this mapped process, they should take a risk based approach to designing the QMS. This should ensure that the QMS is reflective of the complexity of the company’s activities and size of the company.
1.2 Quality Management
A change control system should be in place. This system should incorporate quality risk management principles, and be proportionate and effective.

- **What is the rationale for the point in the guidance**

A structured system for documenting and assessing change should form part of the QMS. The purpose of this is to ensure that when changes are suggested, they are assessed for appropriateness using quality risk management principles and approved before being implemented. The change control system should ensure that all relevant personnel are made aware of the changes in advance of the change and that the change is subject to a post implementation review to ensure its satisfactory implementation and absence of unintended consequences.

- **What are the risks and benefits associated with that piece of the guidance**

The benefits of change control include assurance that changes made to the systems, facilities or equipment will not produce in negative effects that may result in the occurrence of costly mistakes or a loss of process or product quality. It can also expedite the implementation of change in a safe and effective way. A good change control system will improve efficiency and reduce waste. Good documentation of changes facilitates later review.

- **How might this be implemented/ what does it mean**

A change control system should be in operation which ensures all changes are submitted for approval of their appropriateness. Normally they should be considered by a multi-disciplinary team of appropriate composition reflecting the nature of the change. Details of the change, the rationale behind the change and an assessment of the risks and potential impacts of the change should be documented.

A quality risk management (ICHQ9) approach should be taken to evaluate proposed changes. The change should be considered in relation to the potential impacts on regulatory requirements, customer Quality Agreements, validation status, and personnel training requirements. The change should then be approved or rejected. Critical changes should be evaluated after implementation to confirm the change objectives were achieved and that there was no deleterious impact on quality. An example might be a change in a temperature monitoring process where you would expect that training of all users in the changed system would be performed before implementation.

Note: Many low risk changes require no special action, for example a change that is made to a spelling in a procedure.
The change control system should cover planned changes to:

- Processes
- Materials e.g. ice packs/ packaging materials
- Equipment, facilities, utilities e.g. Semi-automated picking systems, cold rooms, strong room etc.
- Computer systems and software e.g. ERP systems.
- Temporary or emergency changes for example arising from a temporary disruption in
supply
- Master records e.g. SOPs, test and statistical methods, work instructions, specifications, Quality Manual, quality policy

● References

Most regulatory guidance regarding change management is currently found within texts relating to validation. However, the principles from these texts are more widely applicable to change management as part of the quality management system.

- EU GMP guidelines, Part I annex 15
- ICH Q7 or EU GMP Part II chapter 13
- PIC/S Recommendations PI 006-3
- ICH Q9
- ICH Q10

1.2 Quality Management
The quality system should ensure that:
(i) medicinal products are procured, held, supplied or exported in a way that is compliant with the requirements of GDP;
(ii) management responsibilities are clearly specified;
(iii) products are delivered to the right recipients within a satisfactory time period;
(iv) records are made contemporaneously;
(v) deviations from established procedures are documented and investigated;
(vi) appropriate corrective and preventive actions (commonly known as CAPA) are taken to correct deviations and prevent them in line with the principles of quality risk management

● What is the rationale for the point in the guidance

The processes and procedures defined in the Quality Management System need to ensure that patients receive correct products at correct condition in a timely manner. To achieve this, responsibilities need to be clear and appropriate records need to be made in a timely manner and retained. If there have been any deviations, they need to have been appropriately handled. A good CAPA system not only addresses correction of issues identified as having occurred, but, using quality risk management principles, actively seeks to anticipate risks and mitigate them through appropriate preventive actions. It minimises risk of counterfeit product entering the supply chain and maintained product quality by ensuring the specified conditions for storage and transportation of the product are respected.

● What are the risks and benefits associated with that piece of the guidance

The key benefit of a detailed QMS is protection of products, minimising patient safety risks, and reducing the risk of product contamination or damage in the supply chain.
How might this be implemented/ what does it mean

i. In order that this can be achieved, the company must reflect on the requirement when designing processes and procedures including the QMS; ensuring that they meet the requirements of the current guidelines.

ii. The responsibilities for key personnel including management must be specified; usually in a written job description. This Job Description is a document that outlines the duties and tasks assigned to an individual and is signed by both the employee and the manager to demonstrate agreement.

iii. Written procedures should be available where needed and followed to ensure that orders are processed, picked, packed and delivered without error and within a reasonable timeframe. Where validated, automation can be used to support these processes.

iv. A key requirement of a QMS is that all records are made at the time actions are completed and never retrospectively to ensure accuracy. This is a fundamental requirement of a GDP QMS. Personnel should be trained on the importance of this requirement.

v. The impact of a departure from a defined and approved process should be considered; this is usually done through a deviation system. Deviations must be documented in real time and investigated promptly. This investigation should include a root cause analysis, whether the problem has occurred previously (recurrence analysis) and a risk assessment. Immediate actions should be taken as appropriate to contain the impact of the problem; consideration should be given to appropriate corrective and preventive actions (CAPA).

vi. A CAPA system should complement the deviations management system. Its purpose is to ensure that in the event of a deviation, appropriate actions are taken to:

   a. Implement corrective action(s) – this is an action to eliminate the cause of a detected nonconformity or other undesirable situation. There can be more than one cause for nonconformity. Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent recurrence.

   b. Implement preventive actions where necessary to eliminate the cause of a potential nonconformity or other undesirable potential situation. There can be more than one cause for a potential nonconformity. Preventive action is taken to prevent occurrence whereas corrective action is to prevent recurrence.

   c. Correction is an action to eliminate a detected nonconformity.

These CAPAs should be documented and approved by the quality team and a log should be maintained to ensure that they are implemented within a reasonable time frame. The management team should review the progression on CAPA actions and trends, and take action if appropriate.

Risk management principles should be used to ensure that actions taken are focussed on the safety of the patient and commensurate with risk.
1.3. Management of outsourced activities

The quality system should extend to the control and review of any outsourced activities related to the procurement, holding, supply or export of medicinal products. These processes should incorporate quality risk management and include:

(i) assessing the suitability and competence of the Contract Acceptor to carry out the activity and checking authorisation status, if required;
(ii) defining the responsibilities and communication processes for the quality-related activities of the parties involved;
(iii) Monitoring and review of the performance of the Contract Acceptor, and the identification and implementation of any required improvements on a regular basis.

What is the rationale for the point in the guidance

When an activity is outsourced it remains the responsibility of the contract giver to ensure it is carried out correctly, but it is outside of their direct operational control. Management of outsourced activities is therefore necessary to provide assurance that these activities will be conducted as required and should therefore be part of the quality system. It is essential that the contract acceptor is both technically competent and legally able to undertake the required activities. To avoid any misunderstanding or uncertainty regarding requirements and responsibilities, there needs to be a written agreement between the parties and on-going communication processes. The contract acceptor needs to exercise appropriate oversight to ensure the ongoing suitability of the contractor’s performance and act to address matters if this is not the case.

What are the risks and benefits associated with that piece of the guidance

The risks to the contract giver are that the contract acceptor is not technically or legally able to undertake the activities required of them and that these are therefore not carried out appropriately. This could ultimately create a risk for patients at the end of the supply chain. The contract acceptor is also at risk if arrangements between the two parties are not clear. Through an initial and ongoing process of contractor assessment, coupled with clear written contracts and on-going communication, these risks can be substantially mitigated for both parties. The identification of any issues and the timely implementation of improvements is of benefit to both parties.

How might this be implemented/what does it mean

The company QMS should include a procedure describing the selection, assessment and appointment of potential service providers. The procedure should define the details of contract, ensuring that the quality and technical aspects of the contracted task (outsourced
task) is clearly defined. The roles and responsibilities of each party should also be defined in the contract. The contract should be reviewed periodically to ensure it remains up to date. The contract should also include details of communication processes, including ‘out of hours’ contacts, and notification of quality issues.

An agreed set of metrics (Key Performance Indicators) for monitoring performance can be beneficial to both parties, ensuring compliance and aiding improvement.

There should also be regular communication between the parties, with frequency dependent on the volume and criticality of operations. The aim being to develop a partnership between the parties which is beneficial to both.

1.4. Management review and monitoring

The management should have a formal process for reviewing the quality system on a periodic basis. The review should include:

- i. measurement of the achievement of quality system objectives;
- ii. assessment of performance indicators that can be used to monitor the effectiveness of processes within the quality system, such as complaints, deviations, CAPA, changes to processes; feedback on outsourced activities; self-assessment processes including risk assessments and audits; and external assessments such as inspections, findings and customer audits;
- iii. emerging regulations, guidance and quality issues that can impact the Quality Management System;
- iv. innovations that might enhance the quality system;
- v. Changes in business environment and objectives.

The outcome of each management review of the quality system should be documented in a timely manner and effectively communicated internally.

- What is the rationale for the point in the guidance

The Management Review aims to ensure that senior management are given regular feedback of the performance of the Quality Management System and are made aware of risks so that they can identify and allocate adequate resources to ensure that quality objectives can be achieved and that the QMS remains aligned with the business needs and the regulatory expectations.

- What are the risks and benefits associated with that piece of the guidance

The benefits of implementing Management Review and a monitoring process include:

- i. Continuous identification of improvements to the QMS that are required to ensure sustainability of quality and compliance
- ii. Continuous identification of improvements to the operational processes and procedures in place
- iii. Ensuring the appropriate resources are in place, that possibilities for innovation can be discussed and resources planned as appropriate and that resources and support are made available to ensure the continued compliance with the regulations.
iv. Ensuring the Quality Management System is in line with the business environment and objectives on an on-going basis
v. Minimising risk to the business and customer
vi. Improving efficiency by reducing waste

This benefits both the patient and the organisation by ensuring the safety and sustainability of the operations. The risk is that without such reviews emerging issues may not be identified and flagged to management in a timely manner to enable appropriate resources to be directed to deal with them.

**How might this be implemented/ what does it mean**

This can be implemented by putting in place a structured and formalised process for conducting the review. The most appropriate means to achieve this will depend on the size of the organisation and the scale of its activities. There should be regular scheduled meetings (typically at least quarterly) of defined management with the objective of reviewing the status of the QMS. Certain metrics may be reported more frequently and additional meetings arranged if required to address emerging trends.

On a regular basis (typically every 3 months), the outputs from the QMS are discussed; these outputs would include but are not limited to trends of:

- Complaints
- Deviations
- Self inspection findings
- External audit inspection findings including regulatory authority inspections
- Change control
- CAPA
- Risk Assessments

A procedure should define the data to be reviewed together with the schedule and format of reporting. The process should include formal review meetings attended by defined members of management which will typically have a standard agenda to ensure coverage of all elements, including the follow up of actions from previous meetings. Documented reports and minutes from formal review meetings should be appropriately retained. Minutes should be taken during the meeting including the points discussed, the decisions taken or actions to be taken, timelines and responsibilities; these should be shared with all relevant the stakeholders. Ideally, actions should be managed under the CAPA system.

It is normally useful to define within the procedure for conducting Management Review:

- The management team by title e.g. Responsible Person, QA Manager, Operations Manager.
- The required attendees – by title e.g. Executive Manager, Chief Executive Officer
- The required resources to ensure the review meeting runs efficiently – KPIs, Audit reports, previous agenda items and follow up activities and timeline details.

**References**

- ISO 9001 and 9004
1.5. Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products. It can be applied both proactively and retrospectively.

Quality risk management should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. The level of effort, formality and documentation of the process should be commensurate with the level of risk. Examples of the processes and applications of quality risk management can be found in guideline Q9 of the International Conference on Harmonisation (ICH).

• What is the rationale for the point in the guidance

It has not been standard practice in the past for distributors to formally evaluate quality risks to their business operations. QRM introduces the opportunity to understand those risks and to put into place measures to reduce the risks and/or to control risks that cannot be removed. This structured approach will enable distributors to minimise the potential for adverse quality impacts relating to their business operations which can be cost and time efficient.

• What are the risks and benefits associated with that piece of the guidance

Benefits:
Identifies areas of potential problems which may otherwise not have been considered, allowing preventive actions to avoid the costs associated with failure.
Allows considering if adequate controls are in place or required to be implemented i.e. identifies the vulnerabilities in a distribution operation.
• Can potentially improve the process e.g. numerous checks may be in place but may not be effective; these can be replaced by checks that are directly associate with the quality risks to the business
• Can streamline processes thereby achieving time and cost savings
• Make processes more efficient

Risks:
• The QRM process may seem tedious, and deadlines may become difficult to achieve if the risk assessment process is not optimal.
• Could result in wasted resources as the focus may not be diverted to the high risk areas of the business

• How might this be implemented/ what does it mean

Companies will need to write a procedure (SOP) that covers the four elements of QRM, namely assessment, control, communication and review of risks to the quality of medicinal products. Risk assessment is a part of the QRM process. Selected personnel should be formally trained in risk assessment methodologies and these personnel should facilitate the conduct of risk assessments by groups of personnel, selected to reflect the nature and scope of each risk assessment to be performed. Dedicate time to develop and define the QRM process; systematically work through the various elements of your distribution operations and risk rank those operations. Perform prospective risk assessments on all critical areas of distribution operations; document the outcomes; identify actions required to remove or to control those risks and communicate the risks and the control measures to the stakeholders. Ensure that your Contract Acceptors are included in the process to an appropriate degree.