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GMP Series

The Road to a Pharmaceutical Quality System

Excerpt from the GMP Compliance Adviser

Contents

1 Pharmaceutical quality system (PQS)

Here you will find answers to the following questions:
- What is the objective of the PQS?
- What are the key elements of the PQS?
- What roles do quality policy and quality planning play?
- What are the responsibilities of management?
- How are the regulatory requirements implemented in practice?

1.1 The aims and basic principles of the PQS

Every patient who is ill and takes a medicinal product hopes it is effective and heals the illness or at least alleviates the symptoms. However, the scandal in the USA in 1937 involving the preparation Elixir Sulfanilamide and causing the deaths of 107 patients, and the Thalidomide disaster at the beginning of the 60s in Germany made it obvious that one thing is more important: medicinal products must be safe. This is why the primary objective of the pharmaceutical quality system (PQS) is **patient safety**. Chapter 1 of the EU GMP Guidelines stipulates that all holders of a Manufacturing Authorisation must ensure that the manufactured medicinal products
- are fit for their intended use,
- comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation and
- do not place patients at risk due to inadequate safety, quality or efficacy.

The final bullet point shows how important patient safety is for the authorities: safety always comes first, followed by the quality and efficacy of the medicinal product.

A number of stakeholders with different tasks work together to achieve this objective: the pharmaceutical company, the drug regulatory authorities and supervisory authorities (see figure 1). During the development of the medicinal product, the pharmaceutical company ensures that it meets the quality requirements before applying to the relevant authority for a marketing authorisation. The regulatory authority reviews the application before making a decision. If it is successful, the marketing authorisation defines the framework for all further activities. As far as the authorities are concerned, the safety of the patient is guaranteed (only) when the medicinal product is manufactured and tested in accordance with the requirements of the marketing authorisation. Only products that meet this requirement may be placed on the market. The authorities must be notified if changes are made that affect the marketing authorisation and, if necessary, the changes must be approved. The supervisory authorities are the third party involved. They carry out regular inspections of the medicinal product manufacturer to check their compliance with the requirements of the marketing authorisation and GMP/GDP.

The medicinal product manufacturer is obliged to implement, maintain and continuously improve a **PQS** in order to manufacture medicinal products that meet the above-mentioned requirements at all times. The PQS must be comprehensively documented using instructions and records and include all aspects that individually or jointly affect the quality (and safety and efficacy also) of the medicinal product specified in the marketing authorisation. The PQS covers the entire life cycle of the medicinal product from pharmaceutical development through technology transfer to commercial production until the product is discontinued. It also includes the development and monitoring of the internal and external quality-related processes. It expressly covers all of the processes that are outsourced to contract manufacturers, contract laboratories and other service providers, including all of the interfaces with suppliers, contract givers and customers.

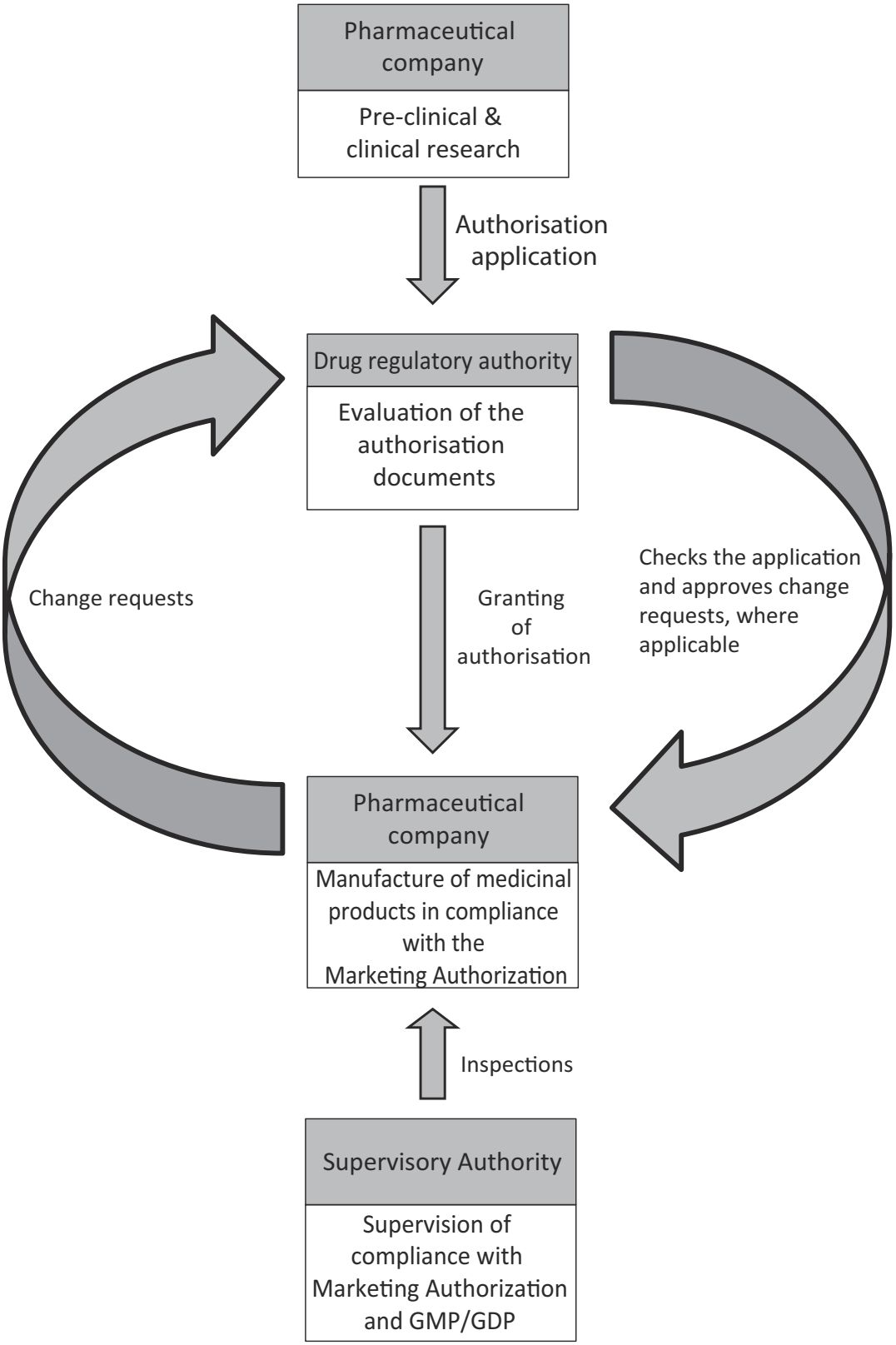

Figure 1 *Patient safety: Interaction between the pharmaceutical company and the drug regulatory authority and supervisory authority*

Depending on the size of the company and the number of branches and subsidiaries, the **PQS** can apply to a single operation or across the group as a whole. Hybrid forms are also common in corporate groups: policies that apply across the group regulate the corporate principles of the quality system and are supplemented by local documents for the individual sites. These implement the global requirements of the company in local instructions.

The most important PQS-related **regulatory requirements** can be found in Chapter 1 of the EU GMP Guidelines (Pharmaceutical Quality System). The requirements in Chapter 1 of the Guidelines are complemented by ICH Q10 (*Pharmaceutical Quality System*). ICH Q10 has been incorporated into Part III of the EU GMP Guidelines and includes three important **quality objectives**:

- *Product Realisation:*
  The PQS should allow the manufacture of products with quality attributes that meet the needs of patients, health care professionals and the regulatory authorities.
- *State of Control:*
  The manufacturer should establish effective monitoring and control systems in order to provide assurance of continued suitability and capability of the processes.
- *Continual Improvement:*
  Because "stagnation means regression", the manufacturer is obliged to identify and implement areas for improvement with regard to company products, processes and systems using current sources of knowledge.

In order to achieve these objectives, the following **elements** of the PQS are of central importance (see also figure 2):

- quality policy and quality planning (see chapter 1.3 *Quality policy, quality planning and quality objectives*)
- documentation (see chapter 2 *The documentation of the pharmaceutical quality system (PQS)*)
- a large selection of tools (see chapter 1.4 *PQS tools*)
- suitable and adequate resources, i.e. premises, facilities, equipment and personnel (see chapter 1.2 *Resources*).

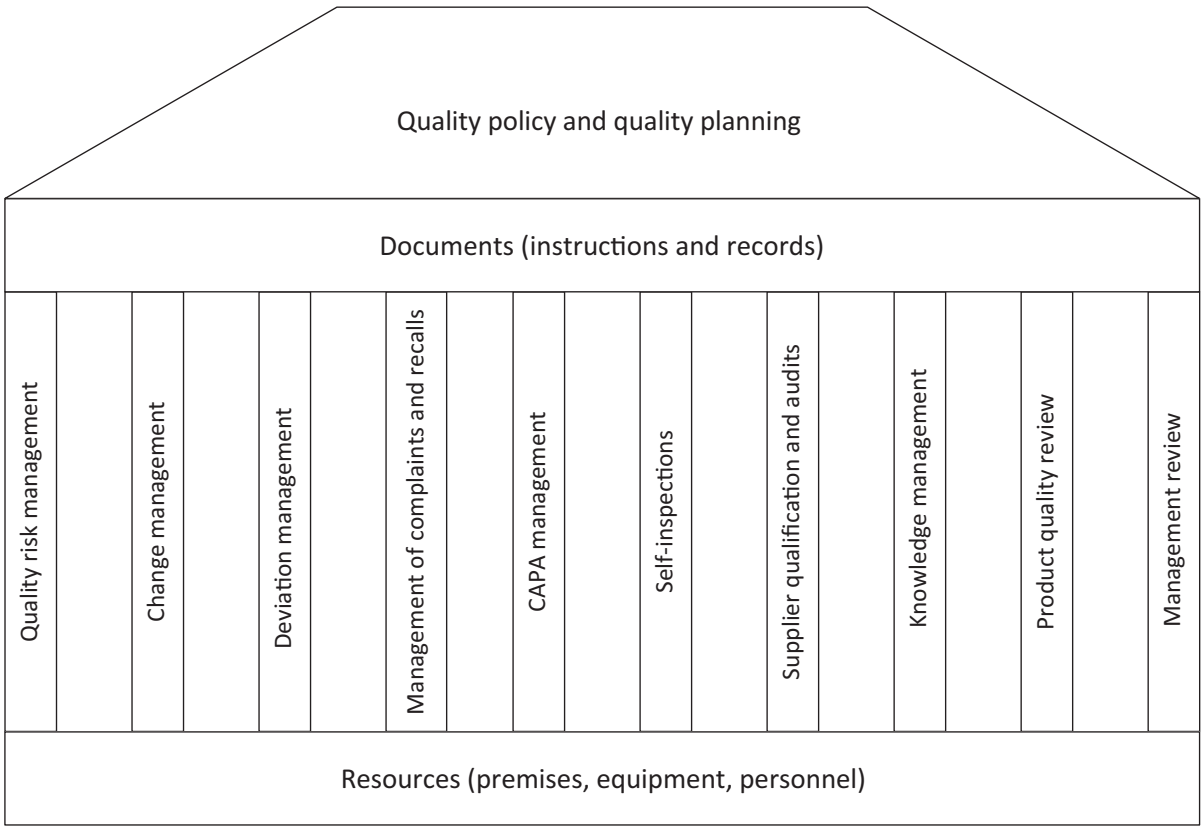

Figure 2 The PQS and its individual elements

The significance of the individual elements for the PQS are examined in detail below.

2 The documentation of the pharmaceutical quality system (PQS)

Here you will find answers to the following questions:
- What is the significance of documentation for the PQS?
- What are the different types of documentation?
- What general requirements apply to documentation?
- Is a PQS documentation hierarchy necessary (documentation pyramid)?
- What GMP documentation does a pharmaceutical company need?
- What is a quality manual and how is it created?

Give more paper – this ironic phrase is often used to explain the abbreviation *GMP*. Funnily enough, it expresses the fact that documentation is of central importance to a pharmaceutical quality system (PQS), which is described in chapter 1 *Pharmaceutical quality system (PQS)*. If it's not written down, then it didn't happen! Without documentation – everything is nothing...

In principle, all quality management systems differentiate between two types of documentation: instructions and records. Records can also be subdivided into raw data or original records and their evaluation (see chapter 2.2.2 *(Original) records and reports*). This means that all activities within the scope of the PQS always follow the sequence below:
- *Planning:* Each activity is planned in advance and its implementation is described in an approved instruction.
- *Implementation:* Each activity is carried out on the basis of an approved and valid instruction.
- *Documentation:* Each implemented activity is immediately documented.
- *Evaluation:* All documented activities are evaluated once or on a regular basis, e.g. in reports or in the context of the PQR, management review (see chapter 3 *Management review*) or self-inspections. The knowledge gained from these evaluations is used as a basis for future planning. This applies to the revision of existing processes or the implementation of new processes and thus to the revision of existing documents as well as the creation of new documents. This completes the circle (see figure 9).

Figure 9 *The cycle of PQS activities*

Input for a management review in accordance with ISO 9001:2008
Output for a management review in accordance with ISO 9001:2008
• Improved effectiveness of the quality management system and its processes
• Improved product with regard to customer requirements
• Resource requirements

Figure 11 Management review in accordance with ISO 9001 (cont.)

Input for a management review in accordance with ICH Q10
• Inspection and audit results

• Periodical quality reviews that may contain the following:
  • Measurement of customer satisfaction (complaints, recalls)
  • Conclusions from process performance monitoring and product quality monitoring
  • The effectiveness of changes affecting the process or product including changes that result from CAPA measures

• Follow-up measures from previous management reviews
• Measurement results with regard to the realisation of defined quality targets

• Measurement results of key performance indicators which are used to monitor the effectiveness of the PQS processes, e.g.:
  • Complaints, deviations, CAPA, change management
  • Feedback on outsourced processes
  • Self-evaluation processes including risk evaluations, trending and audits
  • External evaluations (results of inspections and audits)

Potential management monitoring tools in accordance with ICH Q10
• Developing regulations that have an impact on the existing quality management system
• Innovations that may improve the existing PQS
• Changes in the business environment and business objectives
• Changes in product ownership rights
Output of the management review and monitoring in accordance with ICH Q10
• Improved manufacturing processes and products
• Improved PQS and related processes
• Revision of the quality policy or quality objectives
• Provision and (re)organisation of resources, training
• Gaining and sharing knowledge
• Documentation and immediate and effective communication of the management review results including escalation to senior management

Figure 12 Management review in accordance with ICH Q10

rised and evaluated during the management review. This reduces the cost of the management review considerably. The management review itself can be a good indicator for the effectiveness of the PQS tools: if the compilation of data for the management review is complicated and time-consuming, this is a reliable indication of incomplete or inefficient monitoring of the PQS performance. To ensure continuous improvement, the management review should define measures to improve the corresponding PQS tools whenever this type of problem occurs.

3.3 Management review output

During the next step, the key performance indicator data compiled for the management review input is compared with the current quality objectives and the corresponding data from the previous year. In this way, a check is carried out to see whether the company has met its quality objectives and whether there have been improvements compared to the previous year. The results of this comparison are summarised in the management review output which focuses on answering the following questions:

- Have the current quality objectives been achieved?
- Is the company in compliance with the contents of the quality policy?
- Is the PQS a suitable system for ensuring compliance with the GMP requirements at all times?
- What improvements have been made compared to the previous year?
- What needs to be improved in the year ahead?

In a best case scenario, the answer to the first three questions is an unconditional "Yes". The following tasks must then be completed at the end of the management review:

- Definition of new quality objectives or new specifications for existing quality objectives. An improvement over the previous year should always be aimed for in line with the continuous improvement process.
- Definition of improvement measures, if required. These are used to increase the efficiency of the PQS and meet the quality objectives.
- Assignment or restructuring of resources (depending on the defined objectives and measures: staff, rooms, equipment, etc.). Adequate resources must be provided to ensure that the quality objectives can be achieved and the improvement measures implemented. For this reason, resource planning is an integral part of any management review.

If the answer to all or some of the first three questions is "No", a thorough **root cause analysis** is essential:

- Why have the defined objectives not been met?
- Why was it not possible to implement the quality policy?
- Why are there GMP compliance issues?

Based on the root cause analysis, the company defines suitable corrective actions to remove the causes that prevented the objectives being met.

The contents of the management review, i.e. both input and output (new quality objectives, defined improvement and corrective actions, decisions about the resources) are summarised in a **report**. It must be ensured that the data used for the management review input is traceable and the relevant monitoring files are clearly identified. This report is signed by the management levels involved in the management review. These usually include the management, heads of department as well as the heads of Production, QC and QA (see also chapter 3.4 *Implementation of the management review*).

Afterwards, the results of the management review and the new quality objectives are communicated throughout the company. Staff members can only actively commit themselves to achieving these objectives if they know and understand them.

For example, management can present the quality targets and (selected) results during staff meetings. Alternatively or additionally, they can be discussed during the annual performance review of the employees and – if this has been implemented in the company – they can be broken down into appropriate individual objectives and included in the target agreements for the individual employees.

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cirQum is a service provider in the area of pharmaceutical quality management (GMP, GCP, GLP, GCLP, GDP, GACP) with a focus on outsourced audits, quality management consulting and training. The company's focus is primarily on the GMP audits of contract manufacturers and contract laboratories, including manufacturers of active ingredients, excipients and packaging materials. Furthermore, cirQum carries out GACP audits of the growers and suppliers of vegetable raw materials for manufacturers of herbal medicinal products. The company also specialises in GDP audits of hauliers, warehouses and wholesalers, and GCP, GCLP and GLP audits of test centres, laboratories and testing facilities. It offers training courses and seminars on GXP issues as well as pharmaceutical quality management consultancy.

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