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Part I
Chapter 1 Quality Management

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Principle

The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Qualified Person(s).

The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

Quality Assurance

1.1 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

(i) medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;

(ii) production and control operations are clearly specified and Good Manufacturing Practice adopted;

(iii) managerial responsibilities are clearly specified;

(iv) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

(v) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;

(vi) the finished product is correctly processed and checked, according to the defined procedures;

(vii) medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;

(viii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

(ix) there is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.

Good Manufacturing Practice for Medicinal Products (GMP)

1.2 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

(i) all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

(ii) critical steps of manufacturing processes and significant changes to the process are validated;

(iii) all necessary facilities for GMP are provided including:

- appropriately qualified and trained personnel;
- adequate premises and space;
- suitable equipment and services;
- correct materials, containers and labels;
- approved procedures and instructions;
- suitable storage and transport;

(iv) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

(v) operators are trained to carry out procedures correctly;

(vi) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

(vii) records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(viii) the distribution (wholesaling) of the products minimises any risk to their quality;

(ix) a system is available to recall any batch of product, from sale or supply;

(x) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

1.3 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

(i) adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

(ii) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;

(iii) test methods are validated;

(iv) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

(v) the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

(vi) records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

(vii) no batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations;

(viii) sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product Quality Review

1.4 Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

(i) A review of starting materials including packaging materials used in the product, especially those from new sources.

(ii) A review of critical in-process controls and finished product results.

(iii) A review of all batches that failed to meet established specification(s) and their investigation.

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

(v) A review of all changes carried out to the processes or analytical methods.

(vi) A review of Marketing Authorisation variations submitted/granted/refused, including those for third country (export only) dossiers.

(vii) A review of the results of the stability monitoring programme and any adverse trends.

(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

(ix) A review of adequacy of any other previous product process or equipment corrective actions.

(x) For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.

(xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

(xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

The manufacturer and marketing authorisation holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The Qualified Person responsible for final batch certification together with the marketing authorisation holder should ensure that the quality review is performed in a timely manner and is accurate.

Quality Risk Management

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

1.6 The quality risk management system 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 quality risk management process is commensurate with the level of risk

Examples of the processes and applications of quality risk management can be found inter alia in Annex 20.