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GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS PART I

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TABLE OF CONTENT

CHAPTER 1

PHARMACEUTICAL QUALITY SYSTEM

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 or Clinical Trial Authorisation, as appropriate, 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 its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Pharmaceutical Quality 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 Authorised Person(s).

The basic concepts of Quality Management, Good Manufacturing Practice (GMP) 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.

PHARMACEUTICAL QUALITY SYSTEM [1]

1.1 Quality Management 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 Management therefore incorporates Good Manufacturing Practice.

1.2 GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing through to product discontinuation. However the Pharmaceutical Quality System can extend to the pharmaceutical development lifecycle stage as described in ICH Q10, which while optional, should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

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[1] National requirements require manufacturers to establish and implement an effective pharmaceutical quality assurance system. The term Pharmaceutical Quality System is used in this chapter in the interests of consistency with ICH Q10 terminology. For the purposes of this chapter these terms can be considered interchangeable.

1.3 The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. The design of the system should incorporate appropriate risk management principles including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.

1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

(i) Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

(ii) Product and process knowledge is managed throughout all lifecycle stages;

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

(iv) Production and control operations are clearly specified and Good Manufacturing Practice adopted;

(v) Managerial responsibilities are clearly specified;

(vi) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;

(vii) Processes are in place to assure the management of outsourced activities;

(viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;

(ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future;

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

(xi) Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;

(xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

(xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;

(xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems.

This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles;

(xv) Medicinal products are not sold or supplied before an Authorised 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;

(xvi) 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;

(xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.

1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.

1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.

1.7 The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

1.8 Good Manufacturing Practice is that part of Quality Management 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, Clinical Trial 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, in accordance with the Pharmaceutical Quality System;
- 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) Procedures are carried out correctly and operators are trained to do so;

(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;

(vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;

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

(ix) The distribution of the products minimises any risk to their quality and takes account of good distribution practice;

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

(xi) Complaints about 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

1.9 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 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 approved personnel and methods;

(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 or Clinical Trial 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 an Authorised Person that it is in accordance with the requirements of the relevant authorisations;

(viii) Sufficient reference samples of starting materials and products are retained in accordance with Annex 19 to permit future examination of the product if necessary and that the sample is retained in the final pack.

PRODUCT QUALITY REVIEW

1.10 Regular periodic or rolling quality reviews of all authorised 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 and in particular the review of supply chain traceability of active substances;

(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 preventive 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 or 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.

1.11 The manufacturer and, where different, Marketing Authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. 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 product quality review. The Authorised 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

1.12 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.

1.13 The principles of Quality Risk Management are that:

(i) 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;

(ii) 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 or ICHQ9.

CHAPTER 2

PERSONNEL

PRINCIPLE

The correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

GENERAL

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Pharmaceutical Quality System and continually improve its effectiveness. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organisation chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit referred to in point 2.5 and the position of the Authorised Person(s) are clearly shown in the managerial hierarchy.

2.3 People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

2.4 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place to achieve the *quality objectives,* and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the Pharmaceutical Quality System and GMP compliance through participation in management review.

KEY PERSONNEL

2.5 Senior Management should appoint Key Management Personnel including the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the Authorised Person(s) designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.7, 2.8 and 2.9. Additionally, depending on the size and organisational structure of the company, a separate Head of Quality Assurance or Head of the Quality Unit may be appointed. Where such a function exists usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and senior management should therefore take care that roles, responsibilities, and authorities are defined.

2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows:

a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation;

b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities;

c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s).

2.7 The head of Production generally has the following responsibilities:

(i) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

(ii) To approve the instructions relating to production operations and to ensure their strict implementation;

(iii) To ensure that the production records are evaluated and signed by an authorised person;

(iv) To ensure the qualification and maintenance of his department, premises and equipment;

(v) To ensure that the appropriate validations are done;

(vi) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.8 The head of Quality Control generally has the following responsibilities:

(i) To approve or reject, as he/she sees fit, starting materials, packaging materials, intermediate, bulk and finished products;

(ii) To ensure that all necessary testing is carried out and the associated records evaluated;

(iii) To approve specifications, sampling instructions, test methods and other Quality Control procedures;

(iv) To approve and monitor any contract analysts;

(v) To ensure the qualification and maintenance of his/her department, premises and equipment;

(vi) To ensure that the appropriate validations are done;

(vii) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of Quality Control are summarised in Chapter 6.

2.9 The heads of Production, Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality including in particular the design, effective implementation, monitoring and maintenance of the Pharmaceutical Quality System. These may include, subject to any national regulations:

(i) The authorisation of written procedures and other documents, including amendments;

(ii) The monitoring and control of the manufacturing environment;

(iii) Plant hygiene;

(iv) Process validation;

(v) Training;

(vi) The approval and monitoring of suppliers of materials;

(vii) The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;

(viii) The designation and monitoring of storage conditions for materials and products;

(ix) The retention of records;

(x) The monitoring of compliance with the requirements of Good Manufacturing Practice;

(xi) The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;

(xii) Participation in management reviews of process performance, product quality and of the Pharmaceutical Quality System and advocating continual improvement;

(xiii) Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

TRAINING

2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.11 Besides the basic training on the theory and practice of the Pharmaceutical Quality System and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.12 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.

2.13 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.14 The Pharmaceutical Quality System and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

PERSONNEL HYGIENE

2.15 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

2.16 All personnel should receive medical examination upon recruitment. It must be the manufacturer’s responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the

manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.17 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.19 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

2.20 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.21 Personnel should be instructed to use the hand-washing facilities.

2.22 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the annexes.

CONSULTANTS

2.23 Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

CHAPTER 3

PREMISES AND EQUIPMENT

PRINCIPLE

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

PREMISES

General

3.1. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5. Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production Areas

3.6 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks.

Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

i. the risk cannot be adequately controlled by operational and/ or technical measures,

ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta-lactams) or

iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

Further guidance can be found in Chapter 5 and in Annexes 2, 3, 4, 5 & 6.

3.7. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.9. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11. Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12. Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for such use.

3.14. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

3.15. Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

3.17. In-process controls may be carried out within the production area provided they do not carry any risk to production.

Storage Areas

3.18. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.19. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.22. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.24. Highly active materials or products should be stored in safe and secure areas.

3.25. Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

3.26. Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

3.27. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.29. Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

3.30. Rest and refreshment rooms should be separate from other areas.

3.31. Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.32. Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.33. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

EQUIPMENT

3.34. Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.35. Repair and maintenance operations should not present any hazard to the quality of the products.

3.36. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.37. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38. Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39. Production equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40. Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43. Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.44. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

CHAPTER 4

DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document.

Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term ‘written’ means recorded, or documented on media from which data may be rendered in a human readable form.

REQUIRED GMP DOCUMENTATION (BY TYPE)

Site Master File: A document describing the GMP related activities of the manufacturer.

Instructions (directions, or requirements) type:

Specifications: Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing, Packaging and Testing Instructions: Provide detail all the starting materials, equipment and computerised systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.

Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.

Protocols: Give instructions for performing and recording certain discreet operations.

Technical Agreements: Are agreed between contract givers and acceptors for outsourced activities.

Record/Report type:

Records: Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.

Certificates of Analysis: Provide a summary of testing results on samples of products or materials[2] together with the evaluation for compliance to a stated specification.

Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

GENERATION AND CONTROL OF DOCUMENTATION

4.1 All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

4.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.

4.3 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.

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[2] Alternatively the certification may be based, in-whole or in-part, on the assessment of real time data (summaries and exception reports) from batch related process analytical technology (PAT), parameters or metrics as per the approved Marketing Authorisation dossier.

4.4 Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.

4.5 Documents within the Quality Management System should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.6 Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

GOOD DOCUMENTATION PRACTICES

4.7 Handwritten entries should be made in clear, legible, indelible way.

4.8 Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.

4.9 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

RETENTION OF DOCUMENTS

4.10 It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Authorised Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents.

4.12 For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorisation remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for

retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

The following section gives some examples of required documents. The quality management system should describe all documents required to ensure product quality and patient safety.

SPECIFICATIONS

4.13 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.

Specifications for starting and packaging materials

4.14 Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

a) A description of the materials, including:
   - The designated name and the internal code reference;
   - The reference, if any, to a pharmacopoeial monograph;
   - The approved suppliers and, if reasonable, the original producer of the material;
   - A specimen of printed materials;

b) Directions for sampling and testing;

c) Qualitative and quantitative requirements with acceptance limits;

d) Storage conditions and precautions;

e) The maximum period of storage before re-examination.

Specifications for intermediate and bulk products

4.15 Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

4.16 Specifications for finished products should include or provide reference to:

a) The designated name of the product and the code reference where applicable;

b) The formula;

c) A description of the pharmaceutical form and package details;

d) Directions for sampling and testing;

e) The qualitative and quantitative requirements, with the acceptance limits;

f) The storage conditions and any special handling precautions, where applicable;

g) The shelf-life.

MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

4.17 The Manufacturing Formula should include:

a) The name of the product, with a product reference code relating to its specification;

b) A description of the pharmaceutical form, strength of the product and batch size;

c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;

d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.18 The Processing Instructions should include:

a) A statement of the processing location and the principal equipment to be used;

b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);

c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;

d) Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)];

e) The instructions for any in-process controls with their limits;

f) Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;

g) Any special precautions to be observed.

Packaging Instructions

4.19 Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

a) Name of the product; including the batch number of bulk and finished product;

b) Description of its pharmaceutical form, and strength where applicable;

c) The pack size expressed in terms of the number, weight or volume of the product in the final container;

d) A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;

f) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use;

g) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

h) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

i) Details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Record

4.20 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

a) The name and batch number of the product;

b) Dates and times of commencement, of significant intermediate stages and of completion of production;

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

e) Any relevant processing operation or event and major equipment used;

f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

g) The product yield obtained at different and pertinent stages of manufacture;

h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;

i) Approval by the person responsible for the processing operations.

Note: Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception / out-of-specification (OOS) data reports.

Batch Packaging Record

4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

The batch packaging record should contain the following information:

a) The name and batch number of the product;

b) The date(s) and times of the packaging operations;

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;

e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;

f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;

h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information;

i) Approval by the person responsible for the packaging operations.

PROCEDURES AND RECORDS

Receipt

4.22 There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.

4.23 The records of the receipts should include:

a) The name of the material on the delivery note and the containers;

b) The "in-house" name and/or code of material (if different from a);

c) Date of receipt;

d) Supplier’s name and manufacturer’s name;

e) Manufacturer’s batch or reference number;

f) Total quantity and number of containers received;

g) The batch number assigned after receipt;

h) Any relevant comment.

4.24 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

4.25 There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Testing

4.26 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

Other

4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data.

4.28 Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

- Validation and qualification of processes, equipment and systems;
- Equipment assembly and calibration;
- Technology transfer;
- Maintenance, cleaning and sanitation;
- Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training;
- Environmental monitoring;
- Pest control;
- Complaints;
- Recalls;
- Returns;
- Change control;
- Investigations into deviations and non-conformances;
- Internal quality/GMP compliance audits;
- Summaries of records where appropriate (e.g. product quality review);
- Supplier audits.

4.30 Clear operating procedures should be available for major items of manufacturing and test equipment.

4.31 Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

4.32 An inventory of documents within the Quality Management System should be maintained.

CHAPTER 5

PRODUCTION

PRINCIPLE

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

GENERAL

5.1. Production should be performed and supervised by competent people.

5.2. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3. All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed information.

5.4. Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6. Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8. Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10. At every stage of processing, materials and products should be protected from microbial and other contamination.

5.11. When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly hazardous, including highly sensitising materials.

5.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13. Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean).

5.14. Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of materials and products from one area to another are connected in a correct manner.

5.15. Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control department when appropriate.

5.16. Access to production premises should be restricted to authorised personnel.

PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

5.17. Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below and in Chapter 3 can be applied. The production and/or storage of technical poisons, such as pesticides (except where these are used for manufacture of medicinal products) and herbicides, should not be allowed in areas used for the manufacture and / or storage of medicinal products.

5.18. Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other materials (starting or in-process), and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.

5.19. Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational

measures, including effective and reproducible cleaning processes to control risk of cross-contamination.

5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multiproduct facility, where justified.

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:

Technical Measures

i. Dedicated manufacturing facility (premises and equipment);

ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;

iii. Design of manufacturing process, premises and equipment to minimize risk for cross-contamination during processing, maintenance and cleaning;

iv. Use of “closed systems” for processing and material/product transfer between equipment;

v. Use of physical barrier systems, including isolators, as containment measures;

vi. Controlled removal of dust close to source of the contaminant e.g. through localised extraction;

vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;

viii. Use of single use disposable technologies;

ix. Use of equipment designed for ease of cleaning;

x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;

xi. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

xii. Use of automatic clean in place systems of validated effectiveness;

xiii. For common general wash areas, separation of equipment washing, drying and storage areas.

Organisational Measures

i. Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;

ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;

iv. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;

v. Specific measures for waste handling, contaminated rinsing water and soiled gowning;

vi. Recording of spills, accidental events or deviations from procedures;

vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;

viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

ix. Use of common general wash areas on a campaign basis;

x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

5.22 Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.

VALIDATION

5.23 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.24 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.25 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

5.26 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

STARTING MATERIALS

5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.

5.28 The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification.

5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required:

Active substances

Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the manufacturer of the medicinal product.

Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall verify such compliance either by himself/herself or through an entity acting on his/her behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.

Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross- contamination from other materials on site. The report should fully reflect

what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.

Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.

Excipients

Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the PIC/S Guideline PI 045-1 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'.

5.30 For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels and approved manufacturer and supplier information maintained by the medicinal product manufacturer. The receiving checks on each delivery should be documented.

5.31 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.32 Starting materials in the storage area should be appropriately labelled (see section 13). Labels should bear at least the following information:

i. The designated name of the product and the internal code reference where applicable;

ii. A batch number given at receipt;

iii. Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);

iv. Where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.33 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6).

5.34 Only starting materials which have been released by the Quality Control department and which are within their retest date should be used.

5.35 Manufacturers of finished products are responsible for any testing of starting materials[3] as described in the marketing authorisation dossier. They can utilise

[3] A similar approach should apply to packaging materials as stated in section 5.45.

partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing[4] of each batch according to Annex 8.

5.36 The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:

i. Special attention should be paid to the distribution controls (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material;

ii. The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier;

iii. The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person with appropriate qualifications and experience. The signature assures that each batch has been checked for compliance with the agreed product specification unless this assurance is provided separately;

iv. The medicinal product manufacturer should have appropriate experience in dealing with the starting material manufacturer (including experience via a supplier) including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered;

v. The medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer's or supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.

5.37 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.38 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.39 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

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[4] Identity testing of starting materials should be performed according to the methods and the specifications of the relevant marketing authorisation dossier.

PROCESSING OPERATIONS: INTERMEDIATE AND BULK PRODUCTS

5.40 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.41 Intermediate and bulk products should be kept under appropriate conditions.

5.42 Critical processes should be validated (see "Validation" in this Chapter).

5.43 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.44 Any significant deviation from the expected yield should be recorded and investigated.

PACKAGING MATERIALS

5.45 The selection, qualification, approval and maintenance of suppliers of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.46 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.47 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.48 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

PACKAGING OPERATIONS

5.49 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.50 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

5.51 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.52 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.53 Containers for filling should be clean before filling. Attention should be given to avoid and remove any contaminants such as glass fragments and metal particles.

5.54 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.55 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.56 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.57 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.58 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.59 On-line control of the product during packaging should include at least checking the following:

i. General appearance of the packages;

ii. Whether the packages are complete;

iii. Whether the correct products and packaging materials are used;

iv. Whether any over-printing is correct;

v. Correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.60 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

5.61 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.62 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.

FINISHED PRODUCTS

5.63 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.64 The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 6 (Quality Control).

5.65 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

REJECTED, RECOVERED AND RETURNED MATERIALS

5.66 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

5.67 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.68 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.69 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.70 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

PRODUCT SHORTAGE DUE TO MANUFACTURING CONSTRAINTS

5.71 The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations.

CHAPTER 6

QUALITY CONTROL

PRINCIPLE

This chapter should be read in conjunction with all relevant sections of the GMP guide.

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

GENERAL

6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarised in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, oversee the control of the reference and/or retention samples of materials and products when applicable, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

GOOD QUALITY CONTROL LABORATORY PRATCTICE

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Outsourced Activities, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

(i) Specifications;

(ii) Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;

(iii) Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;

(iv) A procedure for the investigation of Out of Specification and Out of Trend results;

(v) Testing reports and/or certificates of analysis;

(vi) Data from environmental (air, water and other utilities) monitoring, where required;

(vii) Validation records of test methods, where applicable.

6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in Chapter 4 on retention of batch documentation.

6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any Out of Trend or Out of Specification data should be addressed and subject to investigation.

6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available.

Sampling

6.11 The sample taking should be done and recorded in accordance with approved written procedures that describe:

(i) The method of sampling;

(ii) The equipment to be used;

(iii) The amount of the sample to be taken;

(iv) Instructions for any required sub-division of the sample;

(v) The type and condition of the sample container to be used;

(vi) The identification of containers sampled;

(vii) Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;

(viii) The storage conditions;

(ix) Instructions for the cleaning and storage of sampling equipment.

6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.

6.14 Further guidance on reference and retention samples is given in Annex 19.

Testing

6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods.

6.16 The results obtained should be recorded. Results of parameters identified as critical quality attributes should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data:

(i) Name of the material or product and, where applicable, dosage form;

(ii) Batch number and, where appropriate, the manufacturer and/or supplier;

(iii) References to the relevant specifications and testing procedures;

(iv) Test results, including observations and calculations, and reference to any certificates of analysis;

(v) Dates of testing;

(vi) Initials of the persons who performed the testing;

(vii) Initials of the persons who verified the testing and the calculations, where appropriate;

(viii) A clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person;

(ix) Reference to the equipment used.

6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.19 Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures. The level of controls should be commensurate to their use and to the available stability data.

6.20 Reference standards should be established as suitable for their intended use. Their qualification and certification, as such, should be clearly stated and documented. Whenever compendial reference standards from an officially recognised source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented). These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorised by the National Competent Authority.

6.21 Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. The expiry date of reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

6.22 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.23 Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.

6.24 Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.

6.25 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

On-going stability programme

6.26 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

6.27 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

6.28 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

6.29 The ongoing stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the ongoing stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and Annex 15.

6.30 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

(i) Number of batch(es) per strength and different batch sizes, if applicable;

(ii) Relevant physical, chemical, microbiological and biological test methods;

(iii) Acceptance criteria;

(iv) Reference to test methods;

(v) Description of the container closure system(s);

(vi) Testing intervals (time points);

(vii) Description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);

(viii) Other applicable parameters specific to the medicinal product.

6.31 The protocol for the on-going stability programme can be different from that of the initial long term stability study as submitted in the Marketing Authorisation dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH/VICH recommendations).

6.32 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.33 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

6.34 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.

6.36 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Technical transfer of testing methods

6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.

6.38 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.

6.39 The transfer protocol should include, but not be limited to, the following parameters:

(i) Identification of the testing to be performed and the relevant test method(s) undergoing transfer;

(ii) Identification of the additional training requirements;

(iii) Identification of standards and samples to be tested;

(iv) Identification of any special transport and storage conditions of test items;

(v) The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements.

6.40 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.

6.41 Where appropriate, specific requirements described in other guidelines should be addressed for the transfer of particular testing methods (e.g. Near Infrared Spectroscopy).

CHAPTER 7

OUTSOURCED ACTIVITIES

PRINCIPLE

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the roles and responsibilities of each party. The Pharmaceutical Quality System of the Contract Giver must clearly state the way that the Authorised Person certifying each batch of product for release exercises his/her full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Regulatory Authorities with respect to the granting of marketing and manufacturing authorisations. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of national law.

GENERAL

7.1 There should be a written contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.

7.3 Where the Marketing Authorisation holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

THE CONTRACT GIVER

7.4 The Pharmaceutical Quality System of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:

7.4.1 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract

Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed;

7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his/her premises, equipment, personnel, other materials or other products;

7.4.3 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.5 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He/she should also ensure, either by himself/herself, or based on the confirmation of the Contract Acceptor's Authorised Person, that all products and materials delivered to him/her by the Contract Acceptor have been processed in accordance with GMP and the Marketing Authorisation.

THE CONTRACT ACCEPTOR

7.6 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

7.7 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him/her are suitable for their intended purpose.

7.8 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him/her under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should not make unauthorised changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.

7.10 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

THE CONTRACT

7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.

7.12 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).

7.13 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.14 The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or their mutually agreed subcontractors.

CHAPTER 8

COMPLAINTS AND PRODUCT RECALL

PRINCIPLE

In order to protect public and animal health, a system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions. Guidance in relation to these principles is provided in Chapter 1.

All concerned Competent Authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply. In situations where product on the market is found to be non-compliant with the marketing authorisation, there may be a requirement to notify concerned Competent Authorities. Reference should be made to relevant legislative requirements.

In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.

PERSONNEL AND ORGANISATION

8.1 Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. These persons should be independent of the sales and marketing organisation, unless otherwise justified. If these persons do not include the Authorised Person involved in the certification for release of the concerned batch or batches, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.

8.2 Sufficient trained personnel and resources should be made available for the handling, assessment, investigation and review of complaints and quality defects

and for implementing any risk-reducing actions. Sufficient trained personnel and resources should also be available for the management of interactions with Competent Authorities.

8.3 The use of inter-disciplinary teams should be considered, including appropriately trained Quality Management personnel.

8.4 In situations in which complaint and quality defect handling is managed centrally within an organisation, the relative roles and responsibilities of the concerned parties should be documented. Central management should not, however, result in delays in the investigation and management of the issue.

PROCEDURES FOR HANDLING AND INVESTIGATING COMPLAINTS INCLUDING POSSIBLE QUALITY DEFECTS

8.5 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.

8.6 Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.

8.7 As not all complaints received by a company may represent actual quality defects, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.

8.8 There should be procedures in place to facilitate a request to investigate the quality of a batch of a medicinal product in order to support an investigation into a reported suspected adverse event.

8.9 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

i. The description of the reported quality defect.

ii. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature-sensitive products) should be performed.

iii. The need to request a sample, or the return, of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out.

iv. The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.

v. The decision-making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.

vi. The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.

vii. The internal and external communications that should be made in relation to a quality defect and its investigation.

viii. The identification of the potential root cause(s) of the quality defect.

ix. The need for appropriate Corrective and Preventive Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.

INVESTIGATION AND DECISION-MAKING

8.10 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.

8.11 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.

8.12 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.

8.13 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/product specification file or GMP. Such decisions should be timely to ensure that patient and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.

8.14 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.

8.15 Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities

in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.

ROOT CAUSE ANALYSIS AND CORRECTIVE AND PREVENTATIVE ACTIONS

8.16 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

8.17 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

8.18 Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.

8.19 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

PRODUCT RECALLS AND OTHER POTENTIAL RISK-REDUCING ACTIONS

8.20 There should be established written procedures, regularly reviewed and updated when necessary, in order to undertake any recall activity or implement any other risk-reducing actions.

8.21 After a product has been placed on the market, any retrieval of it from the distribution network as a result of a quality defect should be regarded and managed as a recall. (This provision does not apply to the retrieval (or return) of samples of the product from the distribution network to facilitate an investigation into a quality defect issue/report.)

8.22 Recall operations should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect public or animal health prior to establishing the root cause(s) and full extent of the quality defect

8.23 The batch/product distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.24 In the case of investigational medicinal products, all trial sites should be identified and the countries of destination should be indicated. In the case of an investigational medicinal product for which a marketing authorisation has been

issued, the manufacturer of the investigational medicinal product should, in cooperation with the sponsor, inform the marketing authorisation holder of any quality defect that could be related to the authorised medicinal product. The sponsor should implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall. The sponsor should ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

8.25 Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authorities should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products.)

8.26 All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled. For very serious issues (i.e. those with the potential to seriously impact upon patient or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the Competent Authorities. Wherever possible, attempts should be made to agree these in advance of their execution with the concerned Competent Authorities

8.27 It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned Competent Authorities. Taking account of its therapeutic use the risk of shortage of a medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the Competent Authority in advance.

8.28 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate. A formal disposition of all recalled batches should be made and documented. The rationale for any decision to rework recalled products should be documented and discussed with the relevant Competent Authority. The extent of shelf-life remaining for any reworked batches that are being considered for placement onto the market should also be considered.

8.29 The progress of the recall process should be recorded until closure and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.

8.30 The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.

8.31 In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects. Such actions may include the issuance of cautionary communications to healthcare professionals in relation to their use of a batch that is potentially defective. These should be considered on a case-by-case basis and discussed with the concerned Competent Authorities.

CHAPTER 9

SELF INSPECTION

PRINCIPLE

Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

9.1. Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.

9.2. Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

9.3. All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.