CHAPTER 2.3.3.

MINIMUM REQUIREMENTS FOR THE ORGANISATION AND MANAGEMENT OF A VACCINE MANUFACTURING FACILITY

SUMMARY

This chapter sets out the management requirements for the manufacture of veterinary vaccines in accordance with Chapter 1.1.8 Principles of veterinary vaccine production. *Manufacturers should use the chapter as a basis for the elaboration of specific rules adapted to their individual needs. Many of the general principles of laboratory management set out in Chapter 1.1.1* Management of veterinary diagnostic laboratories *are applicable to vaccine production, including accountability, executive management, infrastructure, human resources and compliance.*

There should be sufficient qualified personnel to carry out all the tasks that 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 (GMP) that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. Appropriate procedures should be in place for biorisk management, to protect the personnel, to prevent hazardous biological agents from leaving the plant, and to prevent contamination of products within the plant.

Premises and equipment should be located, designed, constructed, adapted and maintained to suit the operations. Their layout and design should 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.

Good documentation (including electronic records) constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The types of documents and electronic media used should be fully defined in the manufacturer's quality management system. The main objective of the system of documentation should be to establish, control, monitor and record all activities that directly or indirectly impact on the quality of products. The quality management system should include sufficient detail to facilitate a common understanding of the requirements, in addition to providing sufficient records of processes and evaluation of observations.

Any outsourced activity should be appropriately defined, agreed and controlled in order to avoid misunderstandings that could result in a product or operation of unsatisfactory quality. Written contracts should cover outsourced activities, products or operations to which they are related, and any connected technical arrangements. All arrangements for the outsourced activities including any proposed changes in technical or other aspects should be in accordance with regulations in force, and the marketing authorisation for the product concerned. Where the marketing authorisation holder and the manufacturer are not the same, appropriate arrangements should be in place to take into account the principles described in this chapter.

All complaints and other information concerning potentially defective products should be reviewed carefully following written procedures. A system should be in place to evaluate complaints and, if necessary, initiate a recall from the market promptly and effectively for products known or suspected to be defective.

Self-inspections should be conducted in order to monitor the implementation and compliance with GMP principles, and to propose necessary corrective measures.

1. Rules for personnel

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of veterinary vaccines relies upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks that 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 Practices (GMP) that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

1.1. General rules

i) The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

ii) The manufacturer must have an organisation chart. 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 GMP.

1.1.1. Key personnel

i) Key personnel include the head of production, the head of quality control, the head of packaging and distribution, the head of technical services and the person(s) responsible for the batch release. Normally key posts should be occupied by full-time personnel. The heads of production and quality control should be held by different individuals, independent from each other. In large organisations, it may be necessary to delegate some of the functions.

1.1.2. Training

i) The manufacturer should provide training for all the personnel whose duties take them into production 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.

ii) Besides the basic training on the theory and practice of GMP, 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 a qualified person. Training records should be kept.

iii) 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 (see Section 2.4 *Specific requirements for vaccine production*).

iv) 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.

v) The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

1.1.3. Personal hygiene

i) 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.

ii) All personnel should receive a 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.

iii) 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 vaccines.

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

v) 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.

vi) 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.

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

viii) Any specific requirements for the manufacture of aseptic or sterile preparations related to production are covered in 2.4 *Specific requirements for vaccine production*.

1.2. Specific rules for personnel involved in the manufacture of vaccines

i) All personnel (including those concerned with cleaning and maintenance) employed in areas where immunological products are manufactured should be given training in and information on hygiene and microbiology. They should receive additional training specific to the products with which they work.

ii) Responsible personnel should be formally trained in some or all of the required fields.

iii) Personnel should be protected against possible infection with the biological agents used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with the agent or with experimental animals.

iv) Where relevant, the personnel should be vaccinated and subject to medical examination.

v) Adequate measures should be taken to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include complete change of clothes and compulsory showering before leaving the production area.

vi) For immunological products, the risk of contamination or cross-contamination by personnel is particularly important.

vii) Prevention of contamination by personnel should be achieved by a set of measures and procedures to ensure that appropriate protective clothing is used during the different stages of the production process.

viii) Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. In the course of a working day, personnel should not pass from areas where contamination with live micro-organisms is likely or where animals are housed to premises where other products or organisms are handled. If such passage is unavoidable, clearly defined decontamination procedures, including change of clothing and shoes, and, where necessary, showering, should be followed by staff involved in any such production.

ix) Personnel entering a contained area where organisms had not been handled in open circuit operations in the previous 12 hours to check on cultures in sealed, surface decontaminated flasks would not be regarded as being at risk of contamination, unless the organism involved was an exotic.

2. Requirements for premises and equipment

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 and equipment used for critical operations must be qualified[1].

Added requirements for premises and equipment used in aseptic preparations are given in 2.4 *Specific requirements for vaccine production.*

2.1. General

i) 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. Research and development activities associated with organisms not authorised to be handled in the premises must be carried out in buildings completely separated from the manufacturing facility.

ii) 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.

iii) 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.

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

v) 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.

2.2. Storage areas

i) 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.

ii) 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 validated, checked and monitored.

iii) 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.

1 This qualification may be done according to the rules laid down in the PIC/S (see References).

iv) 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.

v) 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.

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

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

viii) Printed packaging materials are considered critical to the conformity of the vaccine and special attention should be paid to the safe and secure storage of these materials.

2.3. Production premises – general requirements

i) 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.

ii) 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.

iii) 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.

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

v) 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.

vi) 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.

vii) Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

viii) 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.

ix) Premises for the packaging of vaccines should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

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

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

2.3.1. Ancillary areas

i) Rest and refreshment rooms should be separate from other areas.

ii) 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.

iii) 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.

2.3.2. Quality control areas

i) 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.

ii) 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.

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

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

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

2.4. Specific requirements for vaccine production

2.4.1. Production areas

i) Premises should be designed in such a way as to control both the risk to the product and to the environment. This can be achieved by the use of containment, clean, clean or contained or controlled areas[2].

ii) Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the micro-organism and whether it has been classified as exotic.

iii) Inactivated biological agents should be handled in clean areas. Clean areas should also be used when handling non-infected cells isolated from multicellular organisms and, in some cases, filtration-sterilised media.

iv) Open circuit operations involving products or components not subsequently sterilised should be carried out within a laminar air flow work station according to the rules for aseptic preparation.

v) Other operations where live biological agents are handled (quality control, research and diagnostic services, etc.) should be appropriately contained and separated if production operations are carried out in the same building. The level of containment should depend on the pathogenicity of the biological agent and whether they have been classified as exotic. Whenever diagnostic activities are carried out, there is the risk of introducing highly pathogenic organisms. Therefore, the level of containment should be adequate to cope with all such risks. Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those used for production.

vi) Containment premises should be easily disinfected and should have the following characteristics:

a) the absence of direct venting to the outside;

2 Guidance on the qualification of the clean areas is given in ISO 14644 and described in the PIC/S GMP Guide (see References).

b) a ventilation system with air at negative pressure. Air should be extracted through HEPA (high-efficiency particulate air) filters and not be re-circulated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the re-circulated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAs, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;

c) air from manufacturing areas used for the handling of exotic organisms should be vented through two sets of HEPA filters in series, and that from production areas not re-circulated;

d) a system for the collection and disinfection of liquid effluents (see Section 2.4.4 *Disinfection – waste disposal*);

e) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;

f) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air lock should be of a size that enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.

g) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

vii) Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner that prevents microbial growth, for example by constant circulation at a temperature above 70°C.

viii) Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms should be supplied with air filtered to the same standard as that for the work area, and equipped with air extraction facilities to produce an adequate air circulation independent of that of the work area. Equipment passes should normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

ix) Production operations such as cell maintenance, media preparation, virus culture, etc., likely to cause contamination should be performed in separate areas. Animals and animal products should be handled with appropriate precautions.

x) Production areas where biological agents particularly resistant to disinfection (e.g. spore forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

xi) With the exception of blending and subsequent filling operations (for example with multi-valent vaccines), one biological agent only should be handled at a time within an area.

xii) Production areas should be designed to permit disinfection between campaigns, using validated methods.

xiii) Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat-sterilised equipment, all connections being also heat sterilised after making and before breaking. It may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used and there is no risk of leakage. The sterilisation parameters used before breaking the connections must be validated for the organisms being used. Different products may be placed in different biogenerators (fermenters), within the same area, provided that there is

no risk of accidental cross-contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

xiv) Access to manufacturing areas should be restricted to authorised personnel. Clear and concise written procedures should be posted as appropriate.

xv) The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly identified as well as the biological agents that are handled in them. The flow of people and product should also be clearly marked.

xvi) The activities carried out in the vicinity of the site should also be indicated.

xvii) Plans of contained or clean area premises should describe the ventilation system indicating inlets and outlets, filters and their specifications, the number of air changes per hour, and pressure gradients. They should indicate which pressure gradients are monitored by pressure indicator.

2.4.2. Animals and animal houses

i) Animal houses should be separated from the other production premises and suitably designed.

ii) The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in specific monographs (e.g. specific pathogen free [SPF] flocks).

iii) Animals, biological agents, and tests carried out should be the subject of an identification system so as to prevent any risk of confusion and to control all possible hazards.

iv) Animal houses where animals intended or used for production are accommodated, should be provided with the appropriate containment or clean area measures, and should be separate from other animal accommodation.

v) Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated, should be adequately contained.

vi) The animal species accommodated in the animal houses or otherwise on the site should be identified.

2.4.3. Equipment

i) The equipment used should be designed and constructed so that it meets the particular requirements for the manufacture of each product.

ii) Before being put into operation the equipment should be qualified and validated and subsequently be regularly maintained and validated.

iii) Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents.

iv) Where appropriate, the equipment should be designed and constructed as to allow easy and effective decontamination or sterilisation.

v) Closed equipment used for the primary containment of the biological agents should be designed and constructed as to prevent any leakage or the formation of droplets and aerosols.

vi) Inlets and outlets for gases should be protected so as to achieve adequate containment, e.g. by the use of sterilising hydrophobic filters.

vii) The introduction or removal of material should take place using a sterilisable closed system, or possibly in an appropriate laminar air flow.

viii) Equipment where necessary should be properly sterilised before use, preferably by pressurised dry steam. Other methods can be accepted if steam sterilisation cannot be used because of the nature of the equipment. It is important not to overlook such individual items as bench centrifuges and water baths.

ix) Equipment used for purification, separation or concentration should be sterilised or disinfected at least between use for different products. The effect of the sterilisation methods on the effectiveness and validity of the equipment should be studied in order to determine the life span of the equipment.

x) All sterilisation procedures should be validated.

xi) Equipment should be designed so as to prevent any mix-up between different organisms or products. Pipes, valves and filters should be identified as to their function.

xii) Separate incubators should be used for infected and non-infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type will only be acceptable if adequate steps are taken to seal, surface decontaminate and segregate the containers.

xiii) Culture vessels, etc., should be individually labelled. The cleaning and disinfection of the items can be particularly difficult and should receive special attention.

xiv) Equipment used for the storage of biological agents or products should be designed and used in such a manner as to prevent any possible mix-up. All stored items should be clearly and unambiguously labelled and in leak-proof containers. Items such as cells and organisms seed stock should be stored in dedicated equipment.

xv) Relevant equipment, such as that requiring temperature control, should be fitted with recording or alarm systems.

xvi) To avoid breakdowns, a system of preventive maintenance, together with trend analysis of recorded data, should be implemented.

xvii) The loading of freeze dryers requires an appropriate clean or contained area. Unloading freeze dryers contaminate the immediate environment. Therefore, for single-ended freeze dryers, the clean room should be decontaminated before a further manufacturing batch is introduced into the area, unless this contains the same organisms, and double door freeze dryers should be sterilised after each cycle unless opened in a clean area.

xviii) Sterilisation of freeze dryers should be done before use, preferably by pressurised dry steam. In case of campaign working, they should at least be sterilised after each campaign.

2.4.4. Disinfection – waste disposal

i) Disinfection or wastes and effluents disposal may be particularly important in the case of manufacture of immunological products. Careful consideration should therefore be given to procedures and equipment aiming at avoiding environmental contamination as well as to their validation or qualification.

3. Rules governing documentation

Documentation relating to the premises should be readily available in a **Site Master File**.

3.1. 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 used must be to establish, control, monitor and record all activities that directly or indirectly impact on all aspects of the quality of 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 on-going 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 or reports.

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. This includes electronic records from which data may be rendered in a human readable form.

3.2. Required documentation

i) **Site Master File:** a document describing the GMP related activities of the manufacturer.

3.2.1. Instructions

i) **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.

ii) **Manufacturing composition, 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.

iii) **Protocols** give instructions for performing and recording certain discreet operations.

iv) **Technical agreements** are agreed between contract givers and acceptors for outsourced activities.

3.2.2. Records or Reports

i) **Records** provide evidence of various actions taken to demonstrate compliance with instructions, including activities, events, investigations, and in the case of manufactured batches a history of each batch of product, from initiation of manufacture to final distribution. Records include the raw data that 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

ii) **Certificates of analysis** provide a summary of testing results on samples of products or materials together with the evaluation for compliance to a stated specification.

iii) **Reports** document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

3.3. Generation and control of documentation

i) 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 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 and authenticity of the record throughout the retention period.

ii) 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.

iii) 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.

iv) 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 (SOPs), work instructions and methods should be written in an imperative mandatory style.

v) Documents within the quality management system should be regularly reviewed and kept up-to-date.

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

3.4. Good documentation practices

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

ii) 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 vaccines are traceable.

iii) 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.

3.5. Retention of documents

i) 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.

ii) Specific requirements apply to batch documentation that must be kept for 1 year after expiry of the batch to which it relates or at least 5 years after certification of the batch by the authorised person, whichever is the longer. For investigational vaccines, the batch documentation must be kept for at least 5 years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

For other types of documentation, the retention period will depend on the business activity that 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.

More information and details can be found on documentation within the PIC/S GMP guide (PIC/S, PE 009-11 [Part I], see References).

4. Rules governing outsourced activities

4.1. Principle

Any activity that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings that could result in a product or operation of unsatisfactory quality.

4.2. General

i) 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.

ii) 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.

iii) 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.

4.3. The contract giver

i) 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.

ii) 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 are followed.

iii) 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 that might pose a hazard to his premises, equipment, personnel, other materials or other products.

iv) The contract giver should audit, monitor and review the performance of the contract acceptor and the identification and implementation of any needed improvement.

v) The contract giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure, either by himself, or based on the confirmation of the contract acceptor's qualified person, that all products and materials delivered to him by the contract acceptor have been processed in accordance with GMP and the marketing authorisation.

4.4. The contract acceptor

i) 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.

ii) The contract acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.

iii) The contract acceptor should not subcontract to a third party any of the work entrusted to him 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.

iv) The contract acceptor should not make unauthorised changes, outside the terms of the contract, that may adversely affect the quality of the outsourced activities for the contract giver.

v) The contract acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

4.5. The contract

i) A contract should be drawn up between the contract giver and the contract acceptor that 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 GMP. 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.

ii) The contract should describe clearly who undertakes 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).

iii) 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.

iv) The contract should permit the contract giver to audit outsourced activities, performed by the contract acceptor or his mutually agreed subcontractors

5. Rules governing complaints and products recall

5.1. Principle

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. A system should be designed to evaluate complaints and initiate a recall from the market, if necessary, promptly and effectively for products known or suspected to be defective.

5.2. Complaints

i) A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him.

ii) There should be written procedures describing the risk evaluation action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

iii) Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the study of such problems.

iv) If a product defect is discovered or suspected in a batch, ingredient or equipment used, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches that may contain reworks of the defective batch should be investigated.

v) All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

vi) Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

vii) Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

viii) The competent authorities should be informed as soon as possible if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product

5.3. Recalls

i) A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation.

ii) There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

iii) Recall operations should be capable of being initiated promptly, communicated effectively to customers and at any time.

iv) All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.

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

vi) Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

vii) The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

viii) The effectiveness of the arrangements for recalls should be evaluated regularly.

6. Rules governing self-inspection

6.1. Principle

Self-inspections should be conducted in order to monitor the implementation and compliance with GMP principles laid down in this guide, and to propose necessary corrective measures.

i) Personnel matters, premises, equipment, documentation, production, quality control, distribution of the vaccines, 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.

ii) 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.

iii) 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.

REFERENCES

INTERNATIONAL ORGANISATION FOR STANDARDIZATION (ISO) (1999). ISO 14644-1:1999. Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness. International Organization for Standardization (ISO), www.iso.org.

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PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S). Guide to good manufacturing practice for medicinal products. Pharmaceutical Inspection Convention, PIC/S, Geneva, Switzerland.

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