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Australian Pesticides and Veterinary Medicines Authority

Draft: Revised Australian code of Good Manufacturing Practice for veterinary chemical products

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Comments and enquiries regarding copyright:

Assistant Director, Communications
Australian Pesticides and Veterinary Medicines Authority
GPO Box 574
Canberra ACT 2601 Australia

Telephone: +61 2 6770 2300
Email: communications@apvma.gov.au.

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Introduction

Veterinary chemical products are subject to a registration process that requires them to be fit for their intended use and not place treated animals, users, consumers or the environment at risk due to inadequate safety, quality or efficacy. Veterinary chemical products must be manufactured in such a way that they comply with their registered particulars and that there is consistency in quality between batches.

The ultimate responsibility for attaining these quality objectives lies with senior management. Their attainment, however, requires the participation and commitment of personnel at all levels within the manufacturing organisation. To achieve these objectives, manufacturers must establish, maintain and continually improve a comprehensively designed, adequately resourced and effectively implemented quality management system incorporating the principles of good manufacturing practice (GMP).

Legal authority for GMP Code

The Good Manufacturing Practice (GMP) Code is legally operationalised through a multi-tiered legislative chain. First, section 23 of the *Agricultural and Veterinary Chemicals Act 1994* empowers the Minister or the APVMA to formally determine the Manufacturing Principles as a legislative instrument.

Next, these Manufacturing Principles legally mandate that a manufacturer must establish a quality management framework, explicitly stating that complying with the Australian Code of Good Manufacturing Practice for Veterinary Chemical Products (GMP Code) is how a manufacturer fulfills those principles.

Finally, Part 7 of the *Agricultural and Veterinary Chemicals Code Regulations 1995* (specifically Regulations 59 through 59E) provides the explicit administrative criteria, fees, and audit rules that the APVMA uses to police this licensing system.

The GMP Code will be further supported by officially produced guidance documents to assist manufacturers in achieving practical compliance with the code.

Quality assurance

Quality assurance is a broad concept covering all aspects of manufacture that individually or collectively influence the quality of a veterinary chemical product. It is the sum of the arrangements made to ensure that veterinary chemical products are consistently manufactured and controlled to quality standards appropriate for their intended use and regulatory requirements.

Quality assurance therefore incorporates GMP, quality control, quality risk management and continual improvement, together with other factors that may influence product quality.

Quality assurance requires manufacturers to establish and maintain a quality management system encompassing the organisational structure, responsibilities, procedures, processes and resources necessary to ensure product quality. The system must ensure that:

- facilities, utilities and equipment are suitable for their intended purpose,
- personnel are appropriately qualified, trained and competent,
- materials are sourced, controlled and used appropriately,
- manufacturing and quality control activities are defined, implemented and maintained in a state of control,
- risks to product quality are identified, assessed and managed,
- products are manufactured and tested in accordance with approved procedures and registered particulars, and
- continual improvement activities are undertaken to maintain the effectiveness of the quality management system.

The quality management system should be fully documented, monitored for effectiveness and periodically reviewed to ensure it remains suitable, adequate and effective.

Good manufacturing practice

Good manufacturing practice (GMP) is that part of quality assurance that ensures veterinary chemical products are consistently manufactured and controlled to the quality standards appropriate for their intended use and in accordance with approved registration particulars and specifications.

GMP is concerned with both production and quality control and is intended to provide confidence that veterinary chemical products are manufactured consistently and are of appropriate quality, safety and efficacy throughout their shelf life.

The basic requirements of GMP are that:

(a) manufacturing processes are appropriately designed, controlled and periodically reviewed to ensure they are capable of consistently producing products that meet established quality requirements,

(b) critical process steps, controls and significant changes are appropriately qualified, validated or otherwise justified,

(c) all necessary resources for GMP are provided, including:

(i) suitably qualified, trained and competent personnel,

(ii) adequate premises, facilities and utilities,

(iii) appropriate equipment and services,

(iv) suitable materials, containers and labels,

(v) approved procedures and instructions, and

(vi) appropriate storage and transport arrangements,

(d) procedures and instructions are written in clear and unambiguous language and are appropriate for the activities being performed,

(e) personnel are trained and competent to perform their assigned duties,

(f) records are generated and retained that demonstrate manufacturing, testing and release activities have been performed in accordance with approved procedures and that any deviations have been investigated and appropriately managed,

(g) records are maintained to enable the complete history of each batch to be traced,

(h) effective systems are maintained for complaints management, corrective and preventive actions, and product recall, and

(i) quality defects are investigated and actions taken to prevent recurrence.

Quality control

Quality control is that part of GMP concerned with specifications, sampling, testing, documentation and release procedures that ensure the necessary and relevant assessments are performed and that materials and products are not released until their quality has been determined to be satisfactory.

Compliance with GMP ensures that quality is built into a product throughout its lifecycle and not merely tested into the finished product. It requires veterinary chemical products to be manufactured under controlled conditions, by competent personnel, using validated or otherwise appropriately justified processes, supported by effective quality control and documentation systems.

This Code provides guidance on the standards expected to achieve acceptable GMP outcomes for veterinary chemical products manufactured for supply in Australia. It supports the APVMA Manufacturing Principles determined under section 23 of the *Agricultural and Veterinary Chemicals Act 1994* and forms the basis for the assessment and licensing of manufacturers under Part 8 of the Agvet Code.

The core chapters of this Code apply to all manufacturers of veterinary chemical products. Annexes describe any additional or specialised requirements for specific categories of products and manufacturing activities.

The intent of each core element is described through Manufacturing Principles. Manufacturers must comply with these Principles and implement systems and practices that demonstrate their effective application. The guidance contained within this Code is intended to assist manufacturers in meeting those Principles while allowing flexibility to adopt alternative approaches where they can be scientifically justified and shown to achieve an equivalent level of quality assurance.

Background to the review

The Australian Code of Good Manufacturing Practice for Veterinary Chemical Products was first published in 2007 following the consolidation of the Australian Code of Good Manufacturing Practice for Veterinary Preparations and the Australian Code of Good Manufacturing Practice for Home mixed Feeds, Feed-milling Industry and Stock-feed Premixes. The consolidation established a single GMP framework applicable across the veterinary chemical manufacturing sector while retaining additional requirements for specialised product categories through annexes.

Since publication of the 2007 Code, the legislative and regulatory framework governing veterinary chemical products has continued to evolve. Amendments to the *Agricultural and Veterinary Chemicals Code 1994*, the *Agricultural and Veterinary Chemicals Code Regulations 1995*, and the *Agricultural and Veterinary Chemicals Code (Manufacturing Principles) Determination 2014* have refined regulatory requirements, strengthened assurance and compliance activities, and reflected contemporary expectations regarding quality management systems, risk management, validation, data integrity and product lifecycle oversight.

Manufacturing technologies, quality systems and international GMP expectations have also evolved significantly. Greater emphasis is now placed on quality risk management, continual improvement, management oversight, validation and verification activities, supplier assurance, and the use of electronic systems and records. Regulatory authorities nationally and internationally have similarly adopted more risk-based approaches to the oversight of manufacturing operations.

This revision has been undertaken to ensure that the Australian GMP Code remains contemporary, scientifically based and aligned with current legislative requirements. The review has also sought to improve the clarity, consistency and usability of the Code while maintaining flexibility for manufacturers of different sizes, product types and operational complexity.

Consistent with previous editions, the revised Code provides a framework that supports the manufacture of veterinary chemical products that are fit for purpose and consistently meet the quality, safety and efficacy standards expected by regulators, industry, veterinarians, animal owners and the broader community.

PART 1 CORE ELEMENTS OF THE CODE

Important Information

Regardless of the size and nature of the manufacturing premises, all manufacturers of veterinary chemical products, unless exempt, are required to comply with the APVMA's Manufacturing Principles and the core elements of this Australian Code of Good Manufacturing Practice for Veterinary Chemical Products, considering the type of product being made and its intended use. Some additional guidelines for specific types of products/manufacturers are outlined in the Annexes.

Exempt persons or products are defined in Regulation 59 of the Agricultural and Veterinary Chemicals Code Regulations 1995.

CHAPTER 1 - QUALITY MANAGEMENT SYSTEM

Manufacturing Principle

Manufacturers of veterinary chemical products must have in place a quality assurance system to ensure that finished products are fit for their intended use, comply with registration requirements and do not place treated animals or users at risk due to inadequate quality, safety or efficacy.

The quality assurance system must ensure that:

(a) appropriate procedures are in place to ensure that relevant quality standards are met;

(b) all materials involved in the manufacturing process comply with required quality standards before they are released for use in manufacture;

(c) there are measures designed to prevent cross-contamination;

(d) there are safeguards and controls in place designed to prevent the occurrence of foreseeable errors or process failures; and

(e) finished products have been made and stored correctly, and they comply with required quality standards before they are released for supply.

The quality assurance system must be relevant to the nature and intended use of the product. It must be fully documented, monitored for effectiveness and provide for continuous improvement.

Quality Management System

Management of Quality

1.1 Management must ensure that a documented quality assurance system is in place and should ensure that quality requirements are understood, implemented and maintained at all levels of the organisation. Adequate resources should be provided to achieve this.

1.2 The manufacturer must identify and ensure the implementation of the quality standards approved in the relevant product registration.

Consideration should be given to any or all, of;

(a) Agricultural and Veterinary Chemicals Code (Agricultural Active Constituents) Standards 2022,

(b) Veterinary Labelling Code (VLC),

(c) Acute reference doses (ARfD) for agricultural and veterinary chemicals used in food producing crops or animals,

(d) APVMA Guidelines for the validation of analytical methods for Active Constituents, agricultural and Veterinary Chemical Products,

(e) APVMA Guidelines for the Generation of Storage Stability Data of Veterinary Chemical Products,

(f) Current Pharmacopoeial Monographs,

(g) State or federal government legislation or policy,

(h) Industry Standards (eg FAMI-QS, Feedsafe), and

(i) International Standards.

1.3 The manufacturer should have measures in place designed to prevent cross-contamination in every part of their operations. Special care is required where substances can cause adverse reactions in different species.

(a) Where the manufacturer produces veterinary chemical products for a range of different species, a documented risk assessment should be used.

(b) Segregation, campaign manufacture and validated cleaning procedures should be used in addition to the requirements detailed in Chapter 7.

1.4 The quality system should;

(a) be relevant to the nature and intended use of products,

(b) identify and implement safeguards and controls designed to prevent the occurrence of foreseeable errors and process failures,

(c) include systems and controls to ensure that finished products are;

(i) made with batch-to-batch consistency,

(ii) are stored correctly, and

(iii) comply with required quality standards before they are released for supply,

(d) ensure that facilities and equipment are suitable for the types of products made

(e) ensure that there are sufficient competent personnel, and

(f) define critical aspects of the GMP operations.

These requirements may be summarised in a quality manual.

1.5 The quality assurance system should facilitate compliance with GMP and ensure that:

(a) all manufacturing processes are clearly defined, are systematically reviewed in the light of experience, and shown to be capable of consistently producing veterinary chemical products that comply with their specifications and the required quality standards,

(b) critical steps of manufacturing processes and significant changes to the processes are validated,

(c) all necessary resources for GMP are provided, including:

(i) appropriately qualified, trained or experienced personnel,

(ii) adequate premises and space,

(iii) suitable equipment and services,

(iv) correct materials, containers and labels,

(v) approved procedures and instructions, and

(vi) suitable storage and transport.

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

(e) operators are trained to carry out procedures correctly,

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

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

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

(i) complaints about marketed products are examined, the causes of quality defects investigated, and

(j) appropriate corrective and preventive measures are taken in respect of the defective products / processes to prevent re-occurrence.

1.6 A nominated person with appropriate qualifications and experience should have responsibility for the overall direction and management of quality within the organisation.

1.7 Management should review the quality assurance system at stated regular intervals. The review should:

(a) determine compliance with the code,

(b) evaluate any changes to the quality system that have taken place,

(c) ensure the continued suitability, adequacy and effectiveness of the quality system, and

(d) facilitate continual improvement.

The management review process should be documented and records of the review maintained.

1.8 Relevant, controlled documentation should be available to cover manufacturing and associated activities at all locations. Records demonstrating compliance with controlled documents / GMP should be maintained. The specific requirements for controlled documents and records are detailed in Chapter 5.

1.9 Records should be kept of all validation studies carried out. In addition to the raw data, the records should include a technical report, set out in report format, providing details of the rationale for the study, the methods used, when and by whom it was carried out, the results and the conclusions.

Change Control

1.10 To facilitate compliance with clause 1.7, all changes made to a quality system should be recorded, and, where merited, subjected to a system of change control. Change control should include a risk assessment and an evaluation of the impact on all relevant key areas (Quality, Safety, Production, Maintenance/Engineering, Regulatory, Procurement, Vendor Management, etc.). Changes should be notified to key stakeholders prior to implementation, and, where applicable, retraining should be considered.

1.11 A change control system should be in place to manage significant manufacturing and product quality changes. This should include application to APVMA, as the registration authority, to vary product details where necessary (AgVet Code Regulation 1995 61 Licence condition—compliance with Manufacturing Principles. For the purposes of paragraph 126(4)(b) of the Code (which deals with conditions in licences), it is a condition of a licence that the licence holder comply with the Manufacturing Principles.). (see also clause 5.12 - 5.15)

1.12 All critical steps in the manufacturing process, and any changes to these steps, should be documented.

Management Review

1.13 Manufacturing processes should be reviewed at defined regular intervals and the outcome of that review documented and acted upon. This frequency should be annual, changes to frequency need to be justified. Review should meet ISO 22000 as a minimum requirement. Alternatively, product quality reviews (PQR) can be conducted against clauses 1.14 to 1.20. Records of the review should be maintained.

1.14 Regular periodic or rolling quality reviews of all authorised chemical 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, considering previous reviews, and should include at least:

(a) A review of starting materials including packaging materials used in the product, especially those from new sources, and particularly the review of supply chain traceability of active substances.

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

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

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

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

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

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

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

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

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

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

(l) A review of any contractual arrangements as defined in Chapter 9 to ensure that they are up to date.

1.15 Trending data from the previous product quality review should be included in cases where few batches of a product were manufactured in a 12-month review period. This is so that a more extensive set of data is used to assess the consistency of the process. In cases where a larger number of batches of a product is manufactured in a 12-month review period, it can also be useful to include trending data from the previous product quality review.

1.16 In cases where no batches of a product were manufactured during the annual review period, the product quality review should still be performed; this should address at least the following: stability results, returns, complaints, recalls, relevant deviations (including those arising from qualification and validation activities) and regulatory background (e.g. marketing authorisation variations submitted, granted or refused, including those for third country (export only) dossiers, and any relevant post-marketing commitments). A review of the last PQR should also be conducted.

1.17 Review timeframes can be appropriately adjusted based upon manufacturing and campaign duration, with adequate justification. The timeframe criteria should be established in an SOP. The trending performed in the review can include results gathered from the previous period to ensure its robustness.

1.18 The manufacturer and, where different, product registration 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 Quality Management 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.

1.19 Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, products containing the same (or similar) active substances, products manufactured using the same equipment or on the same production line, etc. Any such groupings should be scientifically justified. It should be demonstrated that the grouping of products enhances the overall review for related manufacturing processes, whilst at the same time facilitating review of all data associated with all of the individual products in the group. The grouping strategy should not impede detection of any adverse trends for an individual product. Reviewing only the data associated with a representative product or a worst-case product in a group is not considered acceptable.

1.20 Where the product registration holder is not the manufacturer, there should be a technical agreement (i.e. GMP agreement, see Chapter 9) in place between the various parties that defines their respective responsibilities and agreed strategies (e.g. product groupings) in producing the product quality review.

Quality Risk Management (QRM)

1.21 A documented QRM procedure covering both proactive lifecycle planning and retrospective event investigations is required. Each risk management activity should generate a written report detailing the identification, analysis, control, communication, and review of risks to product quality. Risk reports and final risk-based decisions should be approved by the Quality Department and reviewed annually.

1.22 Documented risk assessments should justify all decisions impacting chemical product quality, safety, and efficacy throughout the product lifecycle. Critical quality attributes should be monitored to ensure they are maintained within established specifications. Collected product data and knowledge should be reviewed annually to trigger necessary process re-evaluations and continual improvements.

1.23 The principles of QRM are that:

(a) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the user. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential harm. Each site in the manufacturing supply chain and distribution for a medicinal product should manage, within its area of responsibility, any manufacturing / quality risks that could impact upon product availability.)

(b) The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

1.24 An appropriate level of formality should be applied during quality risk management activities. Lower risk issues may be dealt with via less formal means, freeing up resources for managing higher risk issues and more complex problems that may require increased levels of rigour and effort.

1.25 Subjectivity can directly impact the effectiveness of quality risk management activities and the decisions made. Therefore, it is important that subjectivity is managed and minimized.

1.26 The output/results of the quality risk management process should be reviewed to consider new knowledge and experience. In this regard, a mechanism to review and monitor events should be implemented.

Validation Master Plan

1.27 Decisions on the scope and extent of qualification and validation must be based on a documented risk assessment. Retrospective qualification/validation should be avoided. Data supporting qualification and/or validation studies should ideally come from internal manufacturing programs. Data obtained from sources outside of the manufacturers own programmes may be used provided that this approach is justified and that there is adequate assurance of the reliability thereof to support the intended qualification/validation. The way in which risk assessments are used to support qualification, and validation activities should be documented.

1.28 A QRM approach should be used for qualification and validation activities. Where required, considering increased knowledge acquired during the life cycle, the risk assessments should be repeated. Qualification and validation activities should take into consideration the life cycle of the relevant equipment, facilities, utilities, systems and of the veterinary chemical product.

1.29 Any planned changes to the equipment, facilities, utilities, systems or manufacturing process that may affect the quality of the veterinary chemical product should be formally documented and the impact on the validated status or control strategy assessed.

1.30 Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures, including on reporting. There should be appropriate oversight over the whole validation life cycle.

1.31 Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.

1.32 The review and conclusions of the qualification/validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the qualification/validation

CHAPTER 2 - PERSONNEL AND TRAINING

Manufacturing Principle

Veterinary chemical products must be manufactured under the management and supervision of appropriately qualified, trained or experienced persons who:

(a) understand the specialised technical, quality and legal requirements relating to the manufacture of veterinary chemical products for which they have responsibility; and

(b) have their duties and responsibilities clearly defined by the manufacturer.

Manufacturing staff must be trained to a satisfactory level of competency in:

(a) the basic principles of good manufacturing practice; and

(b) the specific duties, in connection with the manufacture of veterinary chemical products, that they are required to perform.

There must be a sufficient number of competent personnel to carry out all required tasks.

Personnel and Training

General

2.1 The manufacturer should have adequate personnel with the necessary qualifications, training or practical experience. The responsibilities placed on any one individual should not be so extensive as to present a risk to quality.

2.2 The manufacturer should have an organisational chart showing the names of key personnel, as well as their areas of responsibility and lines of authority.

2.3 People in responsible positions should have written job descriptions describing their specific duties. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of GMP.

2.4 People in responsible positions should have adequate authority to carry out their responsibilities.

2.5 The duties of persons in responsible positions may be delegated to designated deputies with relevant qualifications and experience. Records should be kept of those delegations. Delegated responsibilities should be documented in the job descriptions. Designated deputies should receive appropriate training to enable them to complete the tasks (as required).

2.6 Operators' verbal and/or written communication skills need to be sufficient for them to respond to training, complete competency assessments, accept and implement instructions exactly and, where their duties require it, fill out forms correctly.

2.7 The responsibilities for Quality Assurance, Quality Control and for Production should be allocated to suitably trained, qualified, and/or experienced specific persons. The persons responsible for Production and Quality should have a relevant scientific qualification at tertiary level and/or have had relevant practical experience and the necessary competencies in the manufacture of products in accordance with GMP requirements.

2.8 Where practicable, different persons, will be responsible for Production and Quality; neither responsible to the other. Normally, these key positions should be occupied by full-time employees of the company (legal entity that has the licence). In some cases, the persons responsible for Production and Quality may have some shared or jointly exercised responsibilities provided their primary roles are not compromised.

2.9 The person responsible for release of products should be authorised by the person responsible for Quality. The person responsible for Quality may delegate the release responsibilities to other authorised employees who have the necessary experience and qualifications.

2.10 The persons responsible for Production should have effective control over any relevant manufacturing steps carried out at all premises covered by the manufacturing licence. The person with overall responsibility for Production should ensure that:

(a) products are produced and stored according to documented procedures,

(b) procedures relating to production operations are approved and are implemented,

(c) any subcontracted production work is approved and monitored,

(d) production records are evaluated and signed by an authorised person before they are submitted for product release,

(e) production areas, premises and equipment are maintained to an appropriate standard,

(f) appropriate validations are conducted, and

(g) initial and continuing training of production personnel.

2.11 The person nominated as having responsibility for Quality Assurance should have the necessary independence and authority to ensure that quality measures are employed in the production and testing of the product and that the product is not released until it has been judged to be compliant with specifications and product registrations. The person with overall responsibility for Quality Assurance should:

(a) ensure that the documented quality assurance system and all records, are relevant to the intended nature and use of the products,

(b) ensure that quality requirements are understood, implemented and maintained at all levels of the organisation,

(c) identify and ensure the implementation of the quality standards approved in the relevant product registration,

(d) ensure that measures designed to prevent cross-contamination are established, monitored and maintained,

(e) ensure that changes are appropriately managed,

(f) ensure that audits, including self-inspections and vendor supply comply with internal and external standards,

(g) lead investigation and resolution of quality events such as non-conformances, CAPA, OOS, and product,

(h) ensure that appropriate qualifications and validations are conducted,

(i) maintain oversight of secondary manufacturing sites and contract acceptors,

(j) assess and release (or reject) each batch of finished product before supply or delegate these responsibilities to an authorised person, and

(k) this person may also be responsible for Quality Control.

2.12 The person who is responsible for Quality Control should:

(a) establish adequate quality control specifications for all materials at all stages of manufacture and for the finished product,

(b) establish, document, validate and implement all quality control test procedures,

(c) assess and release/reject starting and intermediate materials for each batch,

(d) keep reference/retention samples of materials and products,

(e) ensure the correct labelling of containers of materials and products,

(f) monitor the suitability of packaging materials,

(g) monitor the stability of the products, the suitability of expiry dates and product storage conditions,

(h) check the maintenance of the quality control area, premises and equipment,

(i) monitor environmental control of quality control laboratories and test animal houses as appropriate,

(j) review trends in analytical results or yields,

(k) participate in the investigation quality events such as non-conformances, CAPA, OOS, and product complaints, and

(l) ensure that initial and continuing training of quality assurance / control personnel are conducted, according to need.

Other duties relating to quality control are summarised in Chapter 8.

Training and Competency

2.13 Personnel must have a clear understanding of their responsibilities. Responsibilities should be clearly documented, and all personnel must be fully trained.

2.14 Training should be provided for all personnel. Additional training may be required for employees whose duties take them into production areas or into quality control laboratories, including technical, maintenance and cleaning personnel. Training should also be given to other personnel whose activities could affect product quality. Manufacturers should ensure that all casual / temporary employees receive appropriate training and supervision. Contractors and visitors to the site should receive training relevant to their duties and access areas. The manufacturer should determine appropriate access rights for contractors and visitors, which may include restrictions on site access.

2.15 Training programs should be appropriate to the identified needs of staff and be approved by the head of either Production or of Quality, as appropriate. The effectiveness of the training program should be monitored.

2.16 Training programs should include initial / induction, and regular refresher training in the basic principles of GMP, Quality Assurance (QA), Quality Management Systems (QMS) (documentation, change controls, deviations, internal audits) and relevant Agvet legislative requirements, as well as training appropriate to the duties assigned to staff.

2.17 Records should be kept of all internal and external training programs and the various training activities undertaken by individual staff.

2.18 Training should involve a variety of techniques and staff should be assessed for their competence to perform the duties assigned to them. Records should be kept of those assessments.

2.19 Personnel working in areas where contamination is a hazard (e.g. cleanrooms or areas where highly active, toxic, infectious or sensitising materials are handled) should be given specific training in those aspects of manufacture, including Work Health and Safety (WHS) and Environmental requirements. Reporting processes should be in place to notify of any potential exposure.

2.20 Personnel should not be required, or allowed, to sign or initial a document unless they have been trained and assessed as competent in the work practices associated with the signature and in the significance of the signature.

2.21 A register of staff signatures and initials should be maintained. Entries should be updated at regular stated intervals and the previous records archived.

2.22 Visitors or untrained personnel preferably should not be taken into active production and quality control areas. If access is unavoidable, they should be adequately supervised and be given information in advance, particularly about personal hygiene and prescribed protective clothing.

Personal Hygiene and Health Issues

2.23 Detailed hygiene programs should be established and adapted to meet the needs of the different areas within the manufacturing facility. They should include procedures relating to:

(a) staff health,

(b) personal hygiene practices,

(c) clothing and personal protective equipment (PPE) of staff, and

(d) protective garments.

These procedures should be understood and followed by every person whose duties take them into the production and quality control areas.

2.24 Where relevant, production personnel should be subjected to medical examination to ensure that their health status does not pose a risk to product quality and that they are able to carry out required tasks (e.g. visual checks of labels or containers). The manufacturer should consider the need to monitor exposure.

2.25 Staff should be made aware of the need to draw management's attention to any health problems that might affect product quality. Steps should be taken to ensure that anyone affected by an infectious disease or having open lesions on an exposed surface of the body, is not engaged in activities where operator-borne contaminants may pose a risk to product quality.

2.26 Protective clothing should be cleaned and/or replaced at fixed intervals or when soiled. It should be kept in good condition. When necessary, soiled clothing should be decontaminated before being laundered (e.g. clothing from areas where live microorganisms are being cultured). Where garments are laundered off-site, any special precautions required to avoid harm to personnel, or the environment should be specified.

2.27 Protective clothing should not be worn outside the factory premises, or on toilet or meal breaks. Consideration should be given to cross contamination in different parts of the facility.

2.28 Eating, drinking, chewing, smoking, or the storage of food, drink, smoking materials or personal medication should not be allowed in the production, packaging, storage, or laboratory areas. Relevant signs should be displayed at prominent positions at entry points to these areas.

2.29 Direct contact should be avoided between the operator's bare hands and the exposed product or any part of the equipment that contacts the product.

2.30 There should be written procedures and records of actions taken or conclusions reached, where appropriate for personnel matters, including medical checks, training, clothing and hygiene.

CHAPTER 3 - BUILDINGS AND GROUNDS

Manufacturing Principle

Veterinary chemical products must be manufactured in buildings that are located, designed, constructed, maintained and utilised to:

(a) suit the operations carried out in them;

(b) ensure protection of the veterinary chemical products from contamination;

(c) permit effective cleaning and maintenance, including cleaning after processes have been completed; and

(d) minimise the risk of manufacturing error.

The products must also be manufactured in an environment, or in equipment fitted with precautionary measures, that:

(a) ensures a standard of hygiene appropriate to the class of veterinary chemical product being manufactured;

(b) minimises the risk of cross-contamination of the finished product, or of materials or components that are used or manufactured at the premises; and

(c) ensures the safety of operators and protects the outside environment.

Buildings And Grounds

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 The premises, including the surrounding grounds and gardens, should be kept in an orderly, neat and tidy condition.

3.3 Premises should be designed, constructed and maintained to minimise the effects of weather and ground seepage, the entry and accumulation of dust and other airborne materials, and the entry of insects, birds, rodents, vermin and other animals. Cavities and voids should be minimised and, where necessary, provided with access for pest control purposes.

3.4 Each part of the premises should be suitable for the operations being carried out and be kept in good repair. Repair and maintenance operations should not present any hazard to product quality.

3.5 Lighting, temperature, humidity and ventilation should be appropriate for the type of operations being undertaken. They should not directly or indirectly, adversely affect product quality during manufacture and storage, or the accurate functioning of equipment. Air intakes should be located away from sources of contamination.

3.6 Sinks should be made of stainless steel and preferably be situated to avoid uncleanable joins and crevices. They may require effective, easily cleanable traps and have air brakes to prevent backflow.

3.7 Floor drains should be avoided, as they are a potential source of contamination. Where they are necessary, they should be of adequate size, flush with the floor, screened and trapped. Drains should generally be underground. Open channels should be avoided, but, if necessary, should be shallow to facilitate cleaning and disinfection. Drains (open and closed) should be part of the cleaning process.

3.8 Production and quality control areas should not be used as passageways by personnel who do not work in them, or for the transport of materials not being currently used in them. They should not be used as storage areas for obsolete materials or equipment.

3.9 The premises should be secured against entry of unauthorised personnel or materials. Visitors to the premises, including external maintenance workers and contractors, should be supervised and restricted to an appropriate level of access.

Facility Hygiene

3.10 Processing areas, laboratories and storage areas should be kept in a clean, sanitary and orderly condition, defined by the manufacturer.

3.11 Documented cleaning and, where applicable, disinfection procedures should be available for all areas of the facility. These should describe:

(a) the areas to be cleaned, the frequency of cleaning, and specific requirements of individual areas,

(b) the materials, concentrations and equipment to be used, and

(c) the methods used to decontaminate cleaning equipment.

Records of this cleaning should be maintained.

3.12 Where the removal of traces of product is critical, evidence to demonstrate that the cleaning process is effective should be available. In these cases, unless standards of cleanliness are prescribed by a regulatory authority, manufacturers should define appropriate cleanliness threshold limits based on a documented assessed risk.

3.13 Waste material should be deposited in suitable, appropriately located and labelled containers and appropriately disposed of at frequent intervals. Where necessary, effluent should be treated before disposal.

3.14 The premises should be kept free of insects, birds, rodents, and other animals, either by containment or by appropriate control measures. A documented pest control program should be in place. This should preclude product contamination by treatment products and pest control should be monitored for effectiveness. Records should describe the location of bait stations, materials used, monitoring, frequency of treatment and effectiveness.

3.15 There should be written procedures and records of actions taken or conclusions reached, where appropriate, for environmental monitoring (including temperature and other controlled environments).

Storage Areas (including receipt and despatch)

3.16 Refrigerators, cold rooms and freezers should be regularly defrosted and cleaned. If a refrigeration storage facility is shut down, total cleaning should occur.

3.17 Receiving and despatch bays should secure materials and products and protect materials and products from the weather; and should be designed and equipped to allow containers of incoming materials to be cleaned, where necessary, before storage.

3.18 Storage areas should be organised and be of sufficient area to permit the effective separation and identification of the various materials and products stored in them. Materials or products that are rejected, returned or recalled should be segregated and secured.

3.19 Storage areas should provide storage conditions appropriate to the materials and products held in them. They should be clean, dry, and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature and humidity) these should be provided and monitored. These requirements do not preclude outdoor storage of materials where outdoor storage does not adversely affect quality.

3.20 Highly active, hazardous or toxic materials or products, or otherwise incompatible materials are to be stored and handled in such a way as to not pose a risk to people, facilities, environment, other materials or products.

3.21 Labels should be stored in segregated areas with restricted access. Other pre-printed packaging materials should be stored in such a way as to prevent mix-up.

3.22 Where quarantine status is ensured by storage in separate areas, these areas should be clearly marked. Any system replacing a physical quarantine system (such as a computerised access system) should provide at least an equivalent level of security.

Production Areas

3.23 Premises should be laid out in a way that allows the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different veterinary chemical 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.

3.24 Where starting and primary packaging materials, or intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be suitable for the class of product being manufactured. This will usually require surfaces that are nonporous, smooth, free from open joints, and do not shed particulate matter. They should also permit effective cleaning.

3.25 Sampling of raw materials should be conducted in designated areas designed to ensure material containment and prevent cross-contamination. Separation should be achieved physically or through validated operational segregation within a multi-purpose sampling room.

3.26 Manufacture of sterile, highly active, technical poisons, toxic or infective products should normally be performed using dedicated equipment in dedicated, self-contained facilities. Processes that may give rise to significant risk from cross-contamination may also require such controls. However, campaign manufacture in the same facilities may be accepted, provided that specific, validated precautions are documented, implemented, and monitored.

3.27 Where registered veterinary chemical products are manufactured using the same equipment or in the same areas as non-registered products, manufacturers should define and monitor appropriate cross-contamination threshold limits based on documented risk assessments.

3.28 The arrangements for weighing or measuring raw materials should minimise cross-contamination. This may require the use of separate weighing or dispensing rooms designed and reserved for that use. Dispensing rooms should not be used as storage areas for starting and other materials.

3.29 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of dry products), specific provision should be made and precautions taken, to avoid cross-contamination (e.g. efficient dust extraction, use of dedicated enclosed areas) and to facilitate cleaning.

3.30 Joints between walls and floors should be easy to clean, adequately sealed and where appropriate, coved to form a smooth curve between the floor and wall.

3.31 Wherever possible, wood or wood-based material should be avoided as a material of construction or support for equipment or materials in production areas, especially where it may be wetted. If used, it should be sealed with a coating that is resistant to chipping, disinfectants and cleaning agents, and that is easily cleaned.

3.32 The use of wood-based pallets or fibreboard in the production area should be closely monitored and managed in a way to avoid any contamination.

3.33 Pipe work, light fittings, ventilation points and other services should be designed and located to avoid the creation of recesses that are difficult to clean. As far as practicable, they should be accessible from outside the manufacturing areas for maintenance purposes.

3.34 Production areas should be effectively ventilated and allow, where necessary, control of airflow, temperature, humidity and filtration appropriate to the products handled, the operation undertaken and the external environment.

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

Laboratories

3.36 Quality control laboratories should be separated from production areas. This is particularly important with laboratories that handle potentially contaminating solvents, reagents or microorganisms.

3.37 Quality control laboratories should be designed to suit the operations carried out in them. Space should be sufficient to avoid mix-ups and cross-contamination. There should be adequate storage for samples and records. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

Ancillary Areas

3.38 Staff amenities, including lunchrooms, should be separate from storage, production and quality control areas.

3.39 Clean and well-ventilated toilets and changing rooms should be provided. These should be easily accessible and suitably isolated from any production, quality control or storage areas. They should be appropriate for the number of users and should be maintained in a tidy and hygienic manner, with an adequate supply of hot and cold water, soap and hygienic hand-drying facilities.

3.40 A sufficient number of clean hand basins, with a satisfactory supply of hot and cold water, soap or detergent dispensers, and hygienic hand-drying facilities should be provided near working areas for use by production personnel.

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

CHAPTER 4 - EQUIPMENT

Manufacturing Principle

Equipment used in the manufacture of veterinary chemical products should be suitable for its intended purpose and appropriately operated, maintained and cleaned. Equipment should be correctly installed and operated in accordance with written instructions that are appropriate for the equipment.

The design and layout of equipment should be such that:

(a) the risk of manufacturing error is minimised; and

(b) effective cleaning and maintenance are possible, in order to avoid cross-contamination of either intermediate materials or the finished product, the buildup of dust or dirt and, in general, to avoid any adverse environmental effect on the quality of the product.

Equipment

General

4.1 Equipment used for the manufacture (including testing) of veterinary chemical products, should be designed, located and maintained to suit its intended purpose and should be installed and positioned in such a way as to minimise any risk of error or cross- contamination.

4.2 Equipment should be uniquely identified. This identification should be traceable to all records pertaining to the equipment.

4.3 Sensitive instruments should be protected from adverse effects such as vibration, electrical interference, and humidity.

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

4.5 Where a controlled storage temperature is required for the maintenance of material or product quality, the environment should be controlled, monitored and recorded, as follows:

(a) there should be temperature recording devices, and records should be under regular review, and

(b) there should be an alarm and/or visual signal to indicate that a storage temperature control system has failed; the system should permit resetting only by authorised personnel and should be checked at regular, stated intervals.

Equipment Qualification and Validation

4.6 Production equipment should not present any hazard to the manufactured products (e.g. by contamination of processed materials or finished products, or their containers, with lubricants or other extraneous substances). The parts of the production equipment that contact materials being processed or the finished product should not be reactive, additive, or absorptive to such an extent that product quality is adversely affected.

4.7 Newly installed equipment that is critical to the manufacturing process should be formally commissioned. There should be protocols for installation qualification (IQ) and operation qualification (OQ) of equipment. These should include the development and implementation of procedures for operation (see clause 4.9), cleaning (see clause 4.13), maintenance (see clause 4.19) and calibration (see clause 4.23) IQ and OQ should be recorded.

4.8 Logs or equivalent records should be kept for major equipment, to record any validations, calibrations, maintenance, or repair operations, including dates and the identity of people who carried out those operations.

4.9 Qualification activities should consider all stages, from the initial development of the user requirements specification up to the end use of the equipment, facility, utility or system. While the specific stages/criteria are to be adapted to the specific project characteristics, the main stages and some criteria that can be included in each stage are indicated in following clauses, for orientation purposes.

4.10 Specifications for equipment, facilities, utilities or systems should be defined in a user requirements specification or a functional specification document. The essential elements of quality should be built in at this stage and any risks mitigated to an acceptable level. The user requirement specification is a point of reference throughout the validation life cycle.

Equipment Use

4.11 Equipment should be used in accordance with written instructions that are appropriate to the equipment and consistent with any operating instructions issued by the equipment manufacturer. Use of specific equipment should be recorded.

4.12 Balances and other measuring equipment required for production and quality control operations should be available and should have an appropriate range and degree of precision. Equipment should be properly positioned before use.

4.13 If prone to failure or variance, equipment used for critical steps in the manufacturing process should be monitored by devices capable of recording the necessary operating parameters or should be equipped with alarm devices to indicate malfunction. If such devices are not practical, the output should be monitored to ensure early detection of variance.

4.14 Log or equivalent records should also record, in chronological order, the use and cleaning of major equipment and of the areas where the products have been used.

Equipment Cleaning

4.15 Documented cleaning procedures should be available for all equipment These should consider the previous use / contents and describe or clearly reference:

(a) the equipment to be cleaned, the frequency of cleaning, and specific requirements of individual parts including, where merited, dis-assembly,

(b) the materials, concentrations and tools to be used,

(c) any risk assessments, residues monitoring or cleaning validations,

(d) precautions and controls for re-assembly,

(e) the methods used to decontaminate cleaning equipment, and

(f) records of this cleaning should be made.

4.16 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. Where necessary, it should be easily dismantled for cleaning. It should be cleaned according to detailed written procedures, and only stored in a clean, dry environment. Records should be kept of equipment cleaning operations.

4.17 To facilitate cleaning, equipment should be mobile or clear of walls and floors. Where this is not practical, equipment should be sealed to the surfaces it touches.

4.18 Washing and cleaning equipment should be chosen and used in such a way that it is not a source of contamination.

4.19 Equipment should be cleaned to the frequency and extent necessary to preserve product integrity. A cleaning record should be kept either on the batch record or in an equipment logbook.

4.20 Validation of cleaning procedures should be undertaken where traces of ingredient may pose significant contamination or toxicity risk in subsequent product batches. (see clause 1.3 and clause 3.14)

Equipment Maintenance

4.21 Where continued maintenance of specific equipment is essential to product quality, documented maintenance procedures and records should include the following:

(a) details and frequency of preventive maintenance requirements,

(b) action to be taken if equipment maintenance requirements cannot be met, and

(c) records of preventive maintenance, including the name of the serviceperson, any deviation from the procedure and a statement or authorising signature documenting the condition of the equipment following the service.

4.22 All equipment should be properly maintained, and records of this maintenance should be kept. In addition, equipment should be inspected for serviceability before any operation begins.

4.23 Repair and maintenance operations should not present any hazard to product quality.

4.24 Equipment that has been taken out of service, modified or undergone major repairs should be formally approved for re-entry into service (see clause 4.7)

Equipment Calibration

4.25 Each item of equipment used in manufacture or for quality control purposes that measures or depends on a physical parameter (e.g. measuring, weighing, recording and control equipment), should be calibrated at defined intervals, in accordance with a written procedure. That procedure should describe the method and frequency of calibration or observation, taking into account any statutory requirements, as well as the action to be taken when results deviate from defined acceptance limits.

4.26 Where appropriate, verification checks should be performed at a frequency consistent with the use of the equipment, in accordance with a written procedure.

4.27 Records should be kept of any calibrations, verification checks or observations carried out on such equipment. Those records should contain sufficient information to show that the required calibrations / observations have been carried out and provide details of any necessary corrective action taken.

4.28 Records of any equipment calibration should show the actual results observed and the acceptance criteria.

4.29 Where practicable, each item requiring calibration should bear a label or tag indicating that calibration has been carried out and when the next calibration is due. Alternatively, a computer-based maintenance system that flags the need for calibration can be accepted, provided that it can be shown to be working effectively.

4.30 There should be evidence to demonstrate that the calibrating devices used are themselves accurate. Contractors who calibrate equipment should be certified by a certification agency.

CHAPTER 5 - DOCUMENTATION

Manufacturing Principle

Manufacturers of veterinary chemical products should establish and maintain a system of documentation, document control and record keeping that:

(a) provides precise specifications for starting materials, intermediate materials and finished products, manufacturing formulae and instructions, and operating procedures for associated manufacturing and quality control activities;

(b) provides a complete history of each item, batch, or quantity manufactured in a specified timeframe, of veterinary chemical product produced at the premises; and

(c) establishes a traceable connection between raw materials and the finished product.

Documentation

General

5.1 All processes and associated activities in the manufacture of veterinary chemical products should be documented and the documents subjected to a system of document control.

5.2 Manufacturing documentation should be designed, prepared, reviewed and distributed with care. It should comply with the relevant parts of product registration applications and registered particulars for the product and should be regularly reviewed; and kept up to date.

5.3 Documents should be approved, signed and dated by appropriate and authorised persons. In the case of master manufacturing formulae, manufacturing instructions, and packaging and labelling instructions, a second authorised person should check, reconcile, endorse and date both the formula and instructions.

5.4 Documents should be legible, readily identifiable and retrievable. They should not include superfluous data and, at the working level, should be written in the imperative (i.e. as instructions rather than statements of what is desired). They should be laid out in an orderly fashion and be easy to check.

5.5 The contents of documents should be unambiguous.

(a) The title, nature and purpose should be clearly stated,

(b) The document should clearly identify the way in which it is to be used, and by whom it is to be used,

(c) It should include, or be identifiable to, the issuing premises and should also include the following information:

(i) a unique number identifying the document,

(ii) the version number and date it became effective,

(iii) the page number of the total number of pages of the document on each page, and

(iv) provision for authorisation.

5.6 Documents should not be handwritten.

(a) Records made may be handwritten or machine-generated, and must be clear, legible and permanent.

(b) Sufficient space should be provided for such entries.

Document Control

5.7 The system of document control should be documented. That document should define the procedures in place for:

(a) approval and regular review of documented procedures,

(b) distribution of documents,

(c) removal of obsolete documents from all points of issue and use, and

(d) prevention of inadvertent use of superseded documents.

5.8 The system of document control should include a list of all controlled documents and should identify the current revision status of any controlled document and the holder/location of that document.

5.9 Issue of working documents and forms should be controlled and recorded; any issued copy should reflect the full contents of the current authorised, master copy. The way that this is ensured should be documented by the manufacturer.

5.10 A documented procedure should be in place that defines the controls needed for the storage, protection, retrieval, retention time and disposal of records. (Refer to clause 5.19 for legal minimum baselines).

5.11 The way in which batch records and other critical records are stored (in a safe and secure environment) should be documented.

5.12 Where documentation is stored electronically only authorised persons should make changes. Access should be restricted by passwords or other means.

See Chapter 6 (Computer Systems) for details.

5.13 Required changes to controlled documents should be acted upon promptly.

(a) They should be reviewed, dated and signed by the authorised person(s) and formally implemented.

(b) There should be records to show that all relevant personnel have acknowledged subsequent changes to procedures.

(see clause 1.2)

5.14 Where appropriate, new or revised documents should be introduced following a formal commissioning and training period (see clause 2.13)

5.15 Where key documents (e.g. master manufacturing formulae or master manufacturing instructions, critical cleaning procedures) have been revised, all associated or linked documents (e.g. batch manufacturing instructions, batch documentation, forms) should be updated to reflect any relevant changes to the key documents.

5.16 All documents generated during qualification and validation must be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.

5.17 The inter-relationship between documents in complex qualification/validation projects should be clearly defined.

5.18 Qualification/validation protocols defining the critical systems, attributes and parameters and the associated acceptance criteria should be prepared.

Records Management

5.19 Records should be made or completed at the time each action is taken and should be permanent.

5.20 Any correction to a record should not cause the original information to be unreadable.

(a) Handwritten corrections should be clearly legible in permanent ink, and initialled and dated by an authorised person.

(b) The way in which corrections to electronic records are made will be defined by the manufacturer. Where appropriate, the reason for the alteration should be recorded.

5.21 Records may be in the form of electronic data, processing systems, photographic or other reliable means.

(a) Documents should describe the systems in use.

(b) The accuracy of electronic recordkeeping systems should be validated. (see Chapter 6)

5.22 Manufacturing records must be retained by the manufacturer for the period specified in the Agricultural and Veterinary Chemicals Code Regulations 1995, as cited below.

Regulation 61(3) A holder of a licence must make records showing:

(a) the materials used in the manufacture of the chemical products, the supplier and quantities of the materials used and details of the tests performed on those materials; and

(b) the procedures and controls employed in the manufacture of the chemical products, including the results of tests carried out during the processing of the chemical products; and

(c) details of tests performed on the chemical products and the results of those tests; and

(d) the stability studies (if any) that validate the recommended shelf life and appropriate storage conditions of the chemical products.

Regulation 61(5) A holder of a licence must keep at the premises to which the licence relates:

(a) the records in subregulation (3); and

(b) if it is not unreasonable in the circumstances – a sample from each batch of the finished products; for at least 12 months after the expiry date of the products to which they relate or, if there is no expiry date, for at least 6 years after the date on which the manufacture of the products was completed.

CHAPTER 6 - COMPUTER SYSTEMS

Manufacturing Principle

Where, in any step of manufacture, a computer is used for any activity that may affect the quality, safety or efficacy of a product, then the computer system should be subject to quality system management principles to ensure operational suitability.

The introduction of computer systems into any manufacturing process, including materials control, processing control, quality control and product distribution, should not adversely affect product quality or quality assurance.

Computer Systems

General

6.1 A written description of the system should be available and should be kept up to date. It should describe the objectives of the system and how it interfaces with other systems and processes.

6.2 Computer systems used in any GMP process including materials control, processing control, quality control and product distribution, should not adversely affect product quality or quality assurance processes. The use of electronic records should be controlled by policy or procedures.

6.3 An up-to-date listing of all relevant systems and their GMP functionality should be available. This should include any systems used for:

(a) materials control,

(b) documentation,

(c) record keeping, including distribution

(d) measuring,

(e) monitoring,

(f) controlling processes,

(g) maintaining environments,

(h) remote access, and

(i) and any other relevant process.

For critical systems an up-to-date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

6.4 Access to electronic documents and records should be controlled. The level of access of individuals should:

(a) be defined,

(b) ensure that authorised personnel can access required data, and

(c) exclude personnel not authorised to change or access data.

Creation, change, and cancellation of access authorisations should be recorded.

6.5 If a computer system is used for batch release, the authority to release should be clearly defined.

6.6 Electronic records may be signed electronically, in accordance with organisational policy. Electronic signatures are expected to:

(a) have the same impact as hand-written signatures within the boundaries of the company,

(b) be permanently linked to their respective record, and

(c) include the time and date that they were applied.

Computers and Validation

6.7 Before a new or upgraded computer system is launched, it must be thoroughly tested to prove it meets its operational goals. If a manual system is being replaced by a computer system, or the computer system is being upgraded, new and existing systems should be run in parallel for a time as part of this testing and validation. The extent of validation necessary will depend on a number of factors, including the intended outcomes, whether it is prospective or retrospective and whether novel elements are incorporated.

6.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.

6.9 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment. For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.

6.10 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.

Data Management

6.11 The system should provide a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.

6.12 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.

6.13 For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.

6.14 It should be possible to obtain clear printed copies of electronically stored data.

6.15 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry (see clause 6.11).

6.16 There should be a procedure for the reporting and assessment of incidents, including system failures and data errors. The procedure should include the need for Root Cause Analysis and CAPA of incidents that impact product and/or GMP compliance.

6.17 Records should be backed up regularly and progressively and the backup retained at a secure and remote location until the next backup is filed. Permanent archived electronic records should be transferred to new media at regular intervals to avoid loss.

6.18 Batch records that are stored electronically should be backed up by suitable means on a regular basis. It is particularly important that the data are readily available throughout the period of retention.

6.19 There should be contingency plans and recovery procedures for use in the event of a breakdown of the system. This may be part of a broader disaster recovery plan.

6.20 Data may be archived. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.

CHAPTER 7 - PRODUCTION

Manufacturing Principle

Veterinary chemical products must be manufactured to specifications in accordance with manufacturing information supplied as part of their application for registration including any subsequent approved variations.

Production operations must follow documented procedures that have been clearly defined by the manufacturer.

Any critical manufacturing process and any change to that manufacturing process, must be validated and formally approved by an authorised person. Where a change in the manufacturing process affects the registered specifications of the finished product, formal approval of such changes must be obtained from the registering authority before the affected product is released for supply.

Production

General

7.1 Each material used should be consistent with documented specifications and the master manufacturing formula, and each step of manufacture carried out (such as receipt and quarantine, quality assurance of raw materials, dispensing, processing, packaging, labelling and quality control procedures) should be in accordance with documented procedures and the master manufacturing instructions.

7.2 For each batch of product made, records should be kept of all materials used and of all critical steps and control procedures carried out.

7.3 All surfaces which come into contact with raw materials, intermediate materials and finished product should be maintained at an appropriate level of cleanliness at all stages of manufacture.

7.4 The identity and where relevant, the status of every material, including waste, should be clearly shown on the outside of its container.

7.5 The manufacturing process should be systematically monitored at all critical stages to ensure both the reliability of the manufacturing process and product quality, including microbial testing if relevant. Where a manufacturing process results in a product that no longer complies with the particulars or conditions of a relevant approval, formal approval of such changes must be obtained from the relevant authority before the affected product is released for supply.

Specific Requirements - Process Validation

7.6 When any new manufacturing formula, method of preparation or significant change 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.

7.7 Critical steps in the manufacture of each product or product group must be validated with supporting data. The extent and method of validation/revalidation should be appropriate for the manufacturing method and the type of product and its use.

7.8 Validation studies should be conducted in accordance with defined procedures. They should include the most challenging of any permitted ranges in process variables. Results and conclusions should be recorded as technical reports.

7.9 Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., must be documented as a deviation and be scientifically justified.

7.10 Results that fail to meet the pre-defined acceptance criteria should be recorded as a deviation and be fully investigated. Implications for the qualification/validation status should be discussed in the report.

Specific Requirements - Cross-Contamination

7.11 Cross-contamination should be minimised by appropriate technical or organisational measures, which may include:

(a) production in physically segregated areas (required for products such as live vaccines, live bacterial preparations and some other biologicals, as well as penicillins and other highly sensitising materials),

(b) adequately isolating plant and/or equipment by a suitable distance,

(c) production on a campaign basis, followed by appropriate and validated cleaning, or scheduling the manufacture of different products in an appropriate sequence,

(d) providing effective air/dust extraction systems and/or airlocks,

(e) keeping lids on mixing vessels,

(f) avoiding recirculation or re-entry of untreated, or insufficiently treated air,

(g) keeping protective clothing inside areas where products with special risk of cross- contamination are processed,

(h) using effective and validated cleaning/decontamination procedures, and using cleaning status labels, and

(i) using ‘closed’ production systems.

7.12 Where cross-contamination has the potential to cause a hazard to the treated animal, the effectiveness of cross-contamination control measures should be monitored periodically according to set procedures.

General Requirements - Starting Materials

7.13 There should be written procedures and records kept for the receipt of each delivery of each starting material, including intermediates, containers, bulk materials, printed packaging material and finished products.

7.14 All incoming raw materials and packaging materials should be checked to ensure that the consignment corresponds with the order. Containers should be cleaned where necessary and clearly labelled.

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

7.16 Incoming raw materials and finished products should be physically or administratively quarantined immediately after receipt or processing until they have been released for use or distribution. If physically quarantined, designated quarantine areas should be available for this purpose.

7.17 Materials received as intermediate or bulk products should be handled on receipt as though they were raw materials.

7.18 All materials and products should be stored under conditions that will minimise deterioration and should be stored in an orderly fashion to permit batch segregation and stock rotation.

7.19 Raw materials should be purchased only from approved suppliers named in the relevant specification.

7.20 Each delivery of starting material should be given a unique identifying number (UIN). If one delivery of material is made up of different batches, each batch should be considered as separate for sampling, testing and release and be given a separate UIN.

7.21 As soon as possible after receipt, each starting material should be assessed, in accordance with a written procedure, for its suitability for use, as set out in Chapter 8.

7.22 A stock rotation system should be implemented to ensure that raw materials are used by the nominated expiry/retest date.

7.23 There should be appropriate procedures or measures to ensure that the identity and status of all containers of raw materials can be recognised from their labelling at all times. Containers from which samples have been drawn should be identified.

Control of Starting Materials

7.24 On receipt, all starting materials (including chemicals and reagents, labels, printed cartons and other packaging material) should be subject to effective quarantine and release control.

7.25 The records of receipt should include:

(a) the name of the material on the delivery notes and the containers,

(b) the 'in-house' name and/or code of material if different,

(c) date of receipt,

(d) supplier's name and, if possible, manufacturer's name,

(e) original manufacturer's batch or reference number,

(f) total quantity, and number of containers received,

(g) the unique identifying number (UIN) assigned by the licensed manufacturer after receipt, and

(h) any relevant comment (e.g. state of the containers).

7.26 Raw materials should be appropriately labelled on receipt with at least the following information:

(a) the designated name of the starting material and the internal reference code where applicable (each starting material should be identified by and used under one name only),

(b) a number (UIN) given at receipt,

(c) the status of the contents (e.g. quarantined, on test, released, rejected), and

(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When computerised storage systems are used, all the above information need not necessarily be specified in text on the label.

7.27 Inspection records should also include confirmation that:

(a) the goods have come from an approved supplier or, if not, an explanation why,

(b) the nature and quantity of goods supplied is consistent with the order,

(c) the goods have been checked for damage,

(d) a valid certificate of analysis has been supplied for chemicals,

(e) at least a visual check for identity has been carried out,

(f) the material is consistent with documented specifications,

(g) each container is appropriately labelled and correctly identified,

(h) required samples have been taken for testing and/or retention, and

(i) the material has passed all required quality control tests.

The records should include the date of release by either Quality Control or an authorised person.

7.28 There should be written procedures for the internal labelling, be that paper or electronic (including status labelling to indicate whether under test, quarantined, passed for use or rejected), quarantine and storage of raw materials, packaging materials and other materials, as appropriate.

7.29 Records should be kept to confirm that materials have been kept under appropriate storage conditions.

Additional Controls for Receipt, Storage and Quality Control of Packaging Materials

7.30 Upon receipt, packaging materials, including printed labels, should be quarantined until checked against specifications and approved.

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

7.32 Pre-printed labels must not be overprinted with a different name, dosage, formula or strength of the product.

7.33 Labelling materials should only be issued for use by authorised personnel following an approved and documented procedure.

7.34 Stocks of labels and pre-printed packaging materials should be checked annually and outdated or obsolete material destroyed. This disposal should be recorded.

Water as a Starting Material

7.35 The quality of water required (potable or processed) should be specified and be consistent with approved registration details.

7.36 Where water is treated for use as an ingredient, a specification for this process water should be developed, based on sound physical, chemical and microbiological principles. Raw water should be purified before use to meet this specification.

7.37 Permanently fixed process-water pipelines should have sanitary couplings and be sloped for drainage. Pipes for distilled, purified and, where appropriate, other water should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken if action limits are exceeded.

7.38 Where process water is used, a water quality manual should be prepared. This document may be part of the manufacturer's quality manual and should include:

(a) a drawing of the purification, storage and (where applicable) reticulation system, showing all pipelines, valves, sample points, breather points, drain points, couplings, instrumentation, pipe slopes, flow rates and velocities of water flow,

(b) both a brief description of and a full specification for each element in the system, including manufacturers' recommended flow rates,

(c) standard procedures for use, including start-up, shutdown, backwashing, regeneration, sanitising and filter maintenance and testing,

(d) a log of system changes, routine and non-routine maintenance (unless routine maintenance is logged elsewhere and the log is readily available), investigations, corrective action and validation studies,

(e) chemical and microbiological specifications, including resample, action and shutdown limits,

(f) sampling instructions and testing procedures, including validation of procedures,

(g) results of tests, including graphical presentations,

(h) the positions of persons responsible for the operation and maintenance of the system and their deputies, and

(i) periodic reviews, conducted at least once per year.

7.39 Process water should be tested at a frequency consistent with the history of successful control. Sampling procedures should include 'worst case' sample points and production conditions. The sample size tested should be sufficient to demonstrate process control.

7.40 Microorganisms recovered from total counts should occasionally be separately identified. Atypical results should be investigated.

Dispensing and Production - General Requirements

7.41 The raw materials used for a particular product must conform to the master manufacturing formula. No substitution should be allowed unless the change is authorised in writing by an authorised person.

7.42 Only raw materials that have been released for use and which are within their shelf life, should be used.

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

7.44 The dispensing operation should be supervised or verified to the extent necessary to ensure the accuracy of the weight/volume and the identity of the materials and all checks should be recorded.

7.45 Materials dispensed for each batch should be kept together, isolated from other materials and be conspicuously labelled with the product batch number.

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

7.47 The product must be manufactured in full accordance with authorised batch manufacturing instructions. Any variation from those instructions should be authorised in writing by an authorised person.

7.48 Intermediate preparations, such as solutions used for pH adjustments or coating solutions, should be prepared following the same system of master formulae and processing instructions and their batch numbers should be carried forward onto the documents for the finished products in which they are used.

7.49 Where operations on different products are carried out simultaneously or consecutively in the same room, and where this is a product quality or safety issue, there should be measures in place to prevent mix-up and/or cross-contamination.

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

7.51 When working with dry materials and products, precautions should be taken to minimise the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

7.52 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 the name of the product or material being processed, its strength (where applicable) and batch number. Where applicable, the label should also mention the stage of production.

7.53 Labels applied to containers, equipment or premises should be clear, legible, easily understood and in the manufacturer's agreed format. Colours may be used in association with wording to indicate status.

7.54 Checks should be carried out to ensure that transfer lines and other pieces of equipment used for the transportation of products from one area to another are clean before use and are connected in a correct manner.

7.55 As far as possible, deviations from standard procedures should be avoided. Where deviations occur, they should be approved in writing by an authorised person.

7.56 The production of incompatible products should be avoided in areas and equipment destined for the production of veterinary chemical products, unless precautions are taken to ensure the integrity of these veterinary chemical products.

7.57 All intermediate yields and the final product yield should be checked and quantities reconciled against the theoretical or expected values by a competent person. Any discrepancy that exceeds acceptable limits should be recorded on the batch records and investigated, and the batch quarantined until its status has been determined.

7.58 Material must be transported between premises or buildings in a manner that ensures that the integrity and status of the material is maintained.

7.59 Delays in completion of the manufacturing process should be kept to a minimum. The maximum holding time for intermediate and bulk materials should be clearly defined and justified.

Specific Requirements - Batch Records

7.60 A batch manufacturing record must be established and kept for each batch processed and packaged. The record should;

(a) be based on the current, approved template(s),

(b) carry the number of the batch being manufactured (Each batch of product must be provided with a unique identifiable batch number, as specified in the Agvet Code Regulations),

(c) include the quantity of bulk and finished materials,

(d) include a copy of the label (including batch & expiry data),

(e) be a collated as a permanent, complete and correct record of the batch history including or referencing any records, forms, logbooks, sampling, testing, non-conformances, out-of-specifications, deviations, rework etc,

(f) be free from errors or omissions,

(g) have production operations signed off by the Production manager or authorised delegate, and

(h) have QC operations will be signed off by the QC Manager or authorised delegate.

The person Authorised for Release for supply (or their delegate) will evaluate the full record and include a copy of the release for supply (or rejection decision) in the batch record

7.61 During processing, information should be recorded at the time each action is taken, and, after completion, the record should be dated and signed showing agreement by the person responsible for the processing operations. The information to be recorded includes;

(a) a record to confirm that the equipment and workstation are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use,

(b) any relevant processing operation or event and major equipment used,

(c) dates and times of commencement of significant intermediate stages and of completion of production,

(d) name of the person responsible for each stage of production,

(e) the UIN, as well as the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added),

(f) initials of the operator of each significant step of production and, where appropriate, of the person who checked each of these operations (e.g. weighing),

(g) a record of the in-process controls, the initials of the person(s) carrying them out, and the results obtained,

(h) the final product yield, as well as yields obtained at pertinent stages of manufacture, and

(i) notes on special problems, including details, with signed authorisation, for any planned deviation from the manufacturing formula and processing instructions and authorisation for processing to continue in the event of unplanned deviations.

7.62 Where finished product has been rejected, the batch records should include a note as to the reason and should confirm that the batch has been status-labelled and appropriately quarantined and/or disposed of.

7.63 Log or equivalent records should also record, in chronological order each of the batches manufactured, and include the date of manufacture commencement, the name of the product, batch number of the product, the batch size, the quantity released and the date of the release.

Specific Requirements for Documents and Records - Dispensing and Manufacturing

7.64 Formally authorised master manufacturing formula and master manufacturing (or processing) instructions, that are appropriate for the type of product being made and consistent with data submitted for product registration, should exist for each product and batch size to be manufactured. They may be combined in one document.

7.65 The master manufacturing formula and master manufacturing instructions should be prepared, endorsed and dated by a competent person delegated by management. A second authorised person should check, endorse and date the instructions where possible. They should be kept up to date at all times and reviewed at specified intervals not exceeding three years. Any amendments should be checked by a second competent person.

7.66 The master manufacturing formula/master batch record template should include:

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

(b) a description of the pharmaceutical form (e.g. liquid, powder, cream), strength or potency of the product, and batch size,

(c) a list of all raw materials to be used, with the amount of each (quantity per unit dose and the quantity per batch), using the designated name and provision for entry of the manufacturer's UIN,

(d) a statement of the percentage excess, where a predetermined excess (overage) of any ingredient is used,

(e) provision for making any adjustments for potency, moisture etc. mention should be made of any substance that may disappear in the course of processing, and

(f) provision for entry of the expected final yield, with the acceptable limits and of relevant intermediate yields, where applicable.

Where practicable, batch sizes should be standardised.

7.67 The master manufacturing (or processing) instructions should include;

(a) a statement of the processing location and the principal equipment to be used,

(b) any special precautions to be observed with regard to product quality and personal safety (e.g. scheduling to prevent cross-contamination, clothing requirements, directions for dealing with spills, if relevant),

(c) controls that prevent cross contamination of starting materials,

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

(e) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures) with provision to record relevant data, such as time, pH, and temperature,

(f) the instructions for any in-process controls, with their limits,

(g) where necessary, the requirements for bulk storage of the products, including the container, labelling and special storage conditions and/or time limits, where applicable,

(h) provision for operator initials or signatures at suitable stages, and

(i) a summary of all necessary quality control tests and analyses, and at what stage they are to be carried out.

This should be used as a template for batch records.

Intermediate and Bulk Products

7.68 Intermediate and bulk products awaiting release by Quality Control must be segregated physically, or by an equivalent computer system, from other stock.

7.69 Intermediate and bulk should be stored under appropriate conditions that are clearly defined and documented.

General Requirements for Primary (filling) and Secondary Packaging Operations

7.70 Programs for packaging operations should be devised to minimise the risk of cross- contamination, mixups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the distance is great enough to avoid a mix-up.

7.71 Before packaging operations are begun, a line clearance should be undertaken 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.

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

7.73 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.

7.74 Containers should be clean before filling. Attention should be given to avoiding, and if necessary removing, any contaminants such as glass fragments and metal particles.

7.75 Filling and sealing should be followed as quickly as possible by labelling. Where this is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling occur.

7.76 The correct printing of, for example code numbers or expiry dates, done either separately or in the course of the packaging, should be checked and recorded. Printing by hand should be re-checked at regular intervals.

7.77 Special care should be taken when using cut labels and when over-printing takes place off-line.

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

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

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

(a) general appearance of the packages,

(b) whether the packages are complete,

(c) whether the correct products and packaging materials are used,

(d) whether any over-printing, such as batch numbering and expiry dating, is correct, and

(e) correct functioning of line monitors.

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

7.81 Products that have been involved in an unusual event (e.g. a mid-process breakdown in production or storage conditions) should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed records should be kept of this operation.

7.82 On completion of the packaging operation, yields should be determined and reconciliation conducted. Acceptable limits should be established. Any significant or unusual discrepancy should be investigated and satisfactorily accounted for before release.

7.83 Upon completion of a packaging operation, any unused batch-coded packaging materials must be destroyed and the destruction recorded. Unused printed material should be reinspected before being returned to stock.

Specific Requirements for Documents and Records - Primary (filling) and Secondary Packaging Operations

7.84 There should be formally authorised master packaging and labelling instructions for each product pack size and type. These may be combined with manufacturing records in one document.

7.85 The master packaging and labelling instructions should be prepared, endorsed and dated by an authorised person. An authorised second person should check, endorse and date the instructions, where possible. Instructions should be kept up to date at all times and reviewed at intervals of no longer than three years. Any amendments should be checked by an authorised second person.

7.86 The master packaging and labelling instructions should normally include, or have a reference to, the following:

(a) name of the 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 for a standardised batch size and, where required, an actual batch size, 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 or labels, or the APVMA label approval number(s),

(f) special precautions to be observed, including a careful examination of the area and equipment, in order to ascertain the line clearance before operations begin; any relevant scheduling and/or special cleaning instructions; and any relevant safety precautions,

(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used,

(h) details of in-process controls, with instructions for sampling and acceptance limits,

(i) the approved shelf life,

(j) provision for calculation of batch yield, and

(k) provision for label reconciliation.

This should be used as a template for batch records.

7.87 Before any packaging operation begins, there should be recorded checks that the equipment and workstation are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use (line clearance).

7.88 The following information should be entered at the time each action is taken, and, after completion, the record should be dated and signed showing agreement by the person(s) responsible for the packaging operations:

(a) the date and time of the packaging operation,

(b) the name of the responsible person carrying out the packaging operation and the initials of the operators of significant steps,

(c) a record to show that all packaging materials and labels have been assembled before starting and checked for identity and conformity with the packaging instructions and that the labels carry, or are to be printed with, the correct batch number and expiry date,

(d) details of the packaging operations carried out, including references to equipment and the packaging lines used,

(e) notes on any special problems or unusual events, including details with signed authorisation for any deviation from the master packaging instructions,

(f) the signature of the person responsible for the operation confirming that the operation has been carried out in accordance with the packaging and labelling instructions,

(g) where practicable, a sample of the label used showing the added batch number and expiry date and any other overprinting, as well as samples of any other pre-printed packaging materials used,

(h) the quantities and UINs/batch numbers of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, and

(i) results for batch yield from the bulk supplied to be packed and, unless otherwise justified, for reconciliation of labels and pre-printed packaging materials. Where practicable, any part-batch packed.

General Requirements for Finished Products

7.89 Finished products awaiting release by Quality Control must be held in segregated quarantine and stored under according to label conditions that are clearly defined and documented.

7.90 All product batches must be sampled for quality control and must not be released for supply until all specified tests are completed.

7.91 After release, finished products still under the control of the manufacturer, should be stored under conditions consistent with the approved product label.

7.92 Distribution records should be maintained for each batch of a product, in order to facilitate a recall (see Chapter 11).

7.93 A formal release for the next stage in the qualification/validation process should be authorised by the relevant responsible personnel either as part of the qualification/validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification/validation stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

Specific Requirements Release for Supply

7.94 Batch records should show the name and signature of the person responsible for releasing the product for supply and confirm:

(a) all manufacturing records have been reviewed,

(b) all QC records have been reviewed,

(c) all entries are complete and correct,

(d) there are no unexplained or unresolved deviations,

(e) the product meets all specifications,

(f) a final packed item has been visually examined and is correct,

(g) the final count of the product to be released, and

(h) the date of the release for supply.

Specific Requirements for Managing Residual, Recovered and Materials for Disposal

7.95 Product residues should not be incorporated into subsequent batches of product on a routine basis, except where this is provided for in the master formula or processing instructions and where limits are prescribed for the proportion of residue. In addition, a standard operating procedure should specify at least:

(a) limits on the age and total quality of residue that may be accumulated,

(b) limits on the number of batches of residue that may be incorporated in a single batch of product,

(c) limits on the total quantity or proportion of residue that may be incorporated in a single batch of product,

(d) a procedure for use and/or disposal that will facilitate overall reconciliation,

(e) any necessary testing or approval, and

(f) traceability records.

7.96 Recovery of all or part of earlier batches (that 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.

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

7.98 Finished product returned from the manufacturer's own stores or warehouse (e.g. because of soiled or damaged labels or outer packaging) may be relabelled, or bulked for repacking, provided that there is no risk to product quality and the operation is specifically authorised and documented. If such a product is relabelled, the operation should be regarded as a formal packaging operation. If bulked, the operation should be regarded as a formal processing operation. (see clause 11.14)

7.99 A suffix or batch number should be used to distinguish any bulked or relabelled material.

7.100 There should be documented procedures that describe precautions and controls for disposal of materials. Relevant records should be maintained.

Concurrent validation

7.101 In exceptional circumstances, where there is a strong benefit-risk ratio for the treated animal, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation can be used. However, the decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

7.102 Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the authorised person prior to certification of the batch.

CHAPTER 8 - QUALITY CONTROL

Manufacturing Principle

Manufacturers of veterinary chemical products should have in place an effective quality control system which is designed to ensure that before products are released from manufacture for supply, they meet specifications and have been manufactured in accordance with the manufacturer's documented procedures.

The person responsible for quality control should be sufficiently independent of other aspects of the manufacturing operation to allow effective implementation of the quality control function.

Manufacturers should ensure that analytical laboratories and animal testing facilities used in a step of manufacture follow the principles of good laboratory practice.

Quality Control

General

8.1 Adequate resources should be available to ensure that all the quality control arrangements are effectively and reliably carried out. All manufacturers should have an identifiable quality control function. This function should be;

(a) independent from other functions, and

(b) under the authority of a person with appropriate qualifications and experience, who has access to one or more laboratories.

8.2 Quality Control personnel should have access to production areas for sampling and investigation as appropriate. They should be empowered to take samples from any stage of the manufacturing process or from finished products at any time, and should take and retain samples, using documented procedures.

8.3 Quality Control should receive prompt information on any proposed changes or modification to material sourcing, specification, production procedures or written instructions.

8.4 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 should be recorded.

8.5 Any quality control documentation relating to a batch record should be retained for the period defined in clause 5.19.

Documentation - General

8.6 Quality Control documentation and records should follow the general principles given in Chapter 5. There should be documented systems in place to;

(a) establish quality control specifications for all materials,

(b) approve suppliers / manufacturers of starting materials,

(c) investigate complaints and issues related to the quality of the product, and

(d) facilitate laboratory operations.

Relevant records should be established.

Documentation Specific

8.7 The following should be prepared by, or be readily available to Quality Control:

(a) specifications,

(b) sampling plans and procedures, and

(c) procedures controlling to release or rejection of materials.

Documentation - Specifications

8.8 There should be authorised and dated specifications for starting and packaging materials, as well as finished products, appropriate for the type of product being made and consistent with data submitted for product registration. Where appropriate, they should also be available for intermediate or bulk products. Any special storage requirements (e.g. temperature) for individual materials should be documented.

8.9 Specifications for starting and primary or printed packaging materials should include, where applicable:

(a) a description of the materials, including:

(i) the designated name and the internal code reference,

(ii) the reference, if any, to a pharmacopoeial monograph, or any other document on which the specification is based,

(iii) the approved source of any active material,

(iv) the approved suppliers; and, if relevant, the original producer of the materials, and

(v) a specimen of printed materials.

(b) directions for sampling and testing, or reference to procedures,

(c) qualitative and quantitative requirements with acceptance limits,

(d) storage conditions and precautions,

(e) the maximum period of storage before re-examination, and

(f) any relevant safe handling instructions.

8.10 Where specifications for raw materials are based on a valid certificate of analysis provided by a supplier, a copy of that certificate of analysis should be suitably identified and authorised by an appropriate person and retained as part of the manufacturer's specifications.

8.11 Specifications for intermediate and bulk products should be available if these are purchased or despatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for raw materials or for finished products, as appropriate.

8.12 Specifications for finished products should include:

(a) the designated name of the product and the code reference where applicable,

(b) a description of the pharmaceutical form and package details,

(c) the qualitative and quantitative requirements, such as visual, organoleptic, physical, chemical and microbiological, with the acceptance limits, and

(d) the storage conditions, shelf life and any special handling precautions, where applicable.

Documentation – Sampling Plans

8.13 Sampling plans for starting materials (excluding packaging materials) should:

(a) * differentiate between certified, approved and other suppliers, including unknown suppliers, as appropriate,

(b) differentiate between starting materials that do not bear a manufacturer's batch number and those that do,

(c) * take account of the nature of each material, for example its potency and whether its place and method of manufacture may ensure against mix-up or even make mix-up impossible,

(d) take account of the intended use of the material (e.g. whether it is for injection),

(e) * differentiate between materials that may vary from container to container (e.g. by separation or moisture uptake) and those that may not,

(f) * prescribe the action to be taken where a delivery from a certified or approved supplier has failed,

(g) prescribe an increased sampling rate for damaged containers or for lots that do not appear to be homogenous,

(h) specify the extent of pooling of samples destined for tests other than identification, and

(i) require the sampling officer or analyst to initially examine each sample for homogeneity, evidence of deterioration or other visible defect.

8.14 Sampling plans for packaging materials should consider:

(a) the items shown as (*) listed in clause 8.13 for starting materials,

(b) the need to check the identity of each container or reel of labels and pre-printed packaging materials, and

(c) the number of samples needed to reach a valid decision to approve or reject a delivery in relation to quality-related defects.

8.15 Sampling plans for intermediate, bulk and finished product should consider:

(a) the batch size and any mixing validations conducted,

(b) parts of the batch that are least likely to be representative or are susceptible to adverse conditions,

(c) any delays or deviations, or time sensitive issues,

(d) any re-work done to the batch to bring it back into specification,

(e) the intended use of the material (e.g. whether it is for injection) and the number of samples needed to reach a valid decision to approve or reject,

(f) the quantity required for testing and retention,

(g) the need to visually examine the batch for any visible defects and for homogeneity,

(h) appropriate sampling equipment,

(i) appropriate sample containment and labelling, and

(j) requirements for storage and transport.

Documentation - Sampling Procedures

8.16 Samples should be taken in accordance with approved written procedures that describe:

(a) the method of sampling,

(b) the equipment to be used,

(c) the amount of the sample to be taken,

(d) instructions for any required subdivision or pooling of samples,

(e) the type and condition of the sample container to be used,

(f) the identification of containers sampled,

(g) any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials,

(h) the storage conditions, and

(i) instructions for the cleaning and storage of sampling equipment.

8.17 The sampling procedure should be justified, taking into consideration the nature of the material or the method of manufacture of the product being sampled.

8.18 Sample containers should bear a label indicating the contents, the batch number, the date of sampling and the containers from which samples have been drawn, these containers should also be identified.

Product Release and Rejection

8.19 The way in which the authorised person (or delegate) releases starting materials should be documented; this should include consideration of the

(a) approved specification,

(b) inwards goods records and inspections,

(c) history of compliance of the manufacturer/supplier. and

(d) any sampling or testing that has occurred.

8.20 The way in which the authorised person releases finished good should be documented. This should include or reference;

(a) a complete list of all documents, records, forms etc to be considered,

(b) the approved specification,

(c) the requirement to check critical calculations and yields,

(d) the requirement to identify and address deviations, non-conformances, out-of-specification and related issues, and

(e) the way in which the product release is to be certified.

8.21 Batch records should show the name and signature of the person responsible for releasing the product for supply and confirm:

(a) all manufacturing records have been reviewed,

(b) all QC records have been reviewed,

(c) all entries are complete and correct,

(d) there are no unexplained or unresolved deviations etc,

(e) the product meets all specifications,

(f) a final packed item has been visually examined and is correct,

(g) the final count of the product to be released, and

(h) the date of the release for supply.

8.22 The way in which the authorised person rejects any product should be documented and records kept. This should include due consideration of,

(a) on-going vendor assurance status,

(b) CAPA that may include increasing inspections, sampling or testing,

(c) validations and the need for revalidation,

(d) matters pertaining to customer complaints, returned product and recalls, and

(e) notification to APVMA.

8.23 Where finished product has been rejected, the batch records should include a note as to the reason and should confirm that the batch has been status-labelled and appropriately quarantined and/or disposed of.

8.24 Rejected materials and products should be clearly marked as such and be stored separately in clearly identified restricted (quarantine) areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Action taken should be approved and recorded by authorised personnel.

Laboratory - General

8.25 Where practicable, a quality control laboratory should be available and be adequately staffed and equipped for the performance of all quality control tests required before, during and after manufacture. Where there is no in-house facility, or the in-house facility does not have the capability of doing all required quality tests, satisfactory alternative arrangements for the required quality control testing should be made.

8.26 Where any quality control testing is contracted to an external laboratory:

(a) the records of this testing should indicate the source of the test results (see Chapter 9),

(b) this laboratory should comply with AS ISO/IEC 17025, or with any subsequent amendment, and /or

(c) this laboratory, if located in Australia, should be appropriately licensed by the APVMA to test veterinary chemical products in the manner required.

8.27 The QC laboratory should have documented systems in place that describe the processes used to;

(a) establish, document, validate and implement quality control test procedures,

(b) obtain and retain reference/retention samples of materials and products,

(c) ensure correct labelling of containers of materials and products,

(d) monitor the suitability of packaging materials,

(e) monitor the stability of the products, the suitability of expiry dates and product storage conditions, and

(f) review trends in analytical results.

8.28 Validation studies should be conducted in accordance with defined procedures.

(a) test method validation should meet the requirements of APVMA Guidelines for the validation of analytical methods for Active Constituents, agricultural and Veterinary Chemical Products,

(b) Equipment qualification and validation should meet relevant industry standards (for example WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-fourth report, Annex 4 Good chromatography practices) and should include provision for establishing and documenting relevant,

(i) operating instructions,

(ii) cleaning requirements,

(iii) requirements for maintenance and

(iv) requirements for calibration.

Results and conclusions should be recorded as technical reports.

8.29 Analytical laboratories facilities should follow the principles of good laboratory practices (GLP).

On-going stability programme

8.30 After marketing, the stability of the chemical product should be monitored according to an 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.

8.31 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.

8.32 This mainly applies to the chemical 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.

8.33 The ongoing stability programme should be described in a written protocol following the general rules of Chapter 5 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 4 and Annex 10.

8.34 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:

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

(b) Relevant physical, chemical, microbiological and biological test methods,

(c) Acceptance criteria,

(d) Reference to test methods,

(e) Description of the container closure system(s),

(f) Testing intervals (time points),

(g) Description of the conditions of storage (standardised VICH conditions for long term testing, consistent with the product labelling, should be used), and

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

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

8.36 The number of batches and frequency of testing should provide sufficient 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.

8.37 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.

8.38 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 regulatory authority.

8.39 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 regulatory authorities. The possible impact on batches on the market should be considered in accordance with Chapter 11 of the GMP Code and in consultation with the relevant regulatory authorities.

8.40 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.

Laboratory Documentation and Records

8.41 Written procedures, that comply with the requirement of Chapters 5 and 6 should be established for at least the following:

(a) testing procedures,

(b) controls applied to data and records (including analytical worksheets and/or laboratory notebooks),

(c) cleaning of quality control areas and equipment,

(d) preparation of materials and reagents,

(e) maintenance of reference substances,

(f) procedures for and records of, the calibration of instruments and maintenance of equipment,

(g) dealing with out-of-specification results and associated investigations,

(h) reviewing analytical performance,

(i) acceptance and generation of analytical reports and/or certificates,

(j) data from environmental monitoring, where required,

(k) validation records of test methods, and

(l) validation of equipment, where applicable.

8.42 In addition to the information that is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and be readily available.

8.43 To facilitate compliance with the requirements of clause 8.27 it is recommended that records of analytical test results, yields and environmental controls be kept in a manner permitting trend evaluation.

Retention Samples

8.44 Quality Control should take and retain samples of:

(a) at least each batch of active starting material, and

(b) each batch of finished product.

8.45 Retention samples of materials and products should be of a size sufficient to permit at least a full re-examination. In the case of active raw materials, the quantity taken should be at least twice the quantity required to establish identity and purity. In the case of finished products, the number of units retained will depend on the product and should be adequate to permit re-examination at a suitable time and investigation of possible complaints.

8.46 Retention samples from each batch of finished products should be retained for the period specified in the Agvet Code Regulations (see Chapter 5 ‘Records’). Where practicable, these samples should be kept in their final packaging. Where the finished product samples are not stored in their final packaging, the packaging chosen should be of the same materials as the manufactured product. Retention samples should be stored under the recommended conditions.

8.47 Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the release of the product, if their stability allows. This period may be shortened if their shelf life, as mentioned in the relevant specification, is shorter.

CHAPTER 9 - CONTRACT MANUFACTURE

Manufacturing Principle

Where all or part of the manufacture of a veterinary chemical product is contracted to another party, the licensed manufacturer should ensure that before manufacture commences all parties have signed a written 'GMP Agreement' that clearly specifies each party's responsibility in relation to every aspect of the manufacturing process, assurance of product quality and consistency with product registration particulars.

Arrangements for contracted steps of manufacture should not compromise the quality of the product.

Where a contractor is authorised to manufacture under the licence of another manufacturer, the licence holder should exert direct control and oversight of the quality management of the contracted step.

Contract Manufacture

General

9.1 Contract manufacture may only be undertaken by a manufacturer who is the holder of a relevant APVMA Manufacturer's Licence or an overseas manufacturer with GMP evidence that is equivalent to this Code of GMP, as determined by the APVMA; unless the work to be undertaken falls within the scope of the contract giver's licence as specified in Agricultural and Veterinary Chemicals Code Regulations 1995, cited below.

Regulation 59A A person who performs only a single step in the manufacture of a product is an exempt person in relation to the manufacture if:

(a) the step consists only of:

(i) packaging or labelling, or both packaging and labelling, the product; or

(ii) analysing or testing the product; and

(b) either:

(i) the licence that authorises the manufacture of the product (being a licence held by another person) permits the first-mentioned person to perform the step for the product; or

(ii) the step consists only of applying a label that contains only a name and address, or the registration number of the product, or both, to a package, or packages of the product.

9.2 Where a manufacturer or registrant of a veterinary chemical product (contract giver) engages any external party (contract acceptor) to conduct any step in manufacturing, for example the entire production and packaging processes, or steps such as tablet coating, packaging, labelling, sterilisation, analysis or testing and release for supply, both parties must agree on allocation and acceptance of GMP responsibilities.

The GMP Agreement

9.3 The GMP agreement should:

(a) clearly define the steps of manufacture, or scope of any analytical work, to be carried out, by the contract acceptor, and

(b) define the GMP responsibilities of each party for each aspect of the work.

All GMP Agreements should be kept up to date.

9.4 Technical aspects of the contract should be drawn up by competent persons with knowledge of veterinary chemical manufacture, analysis and/or GMP, as is appropriate.

9.5 All arrangements for manufacture and analysis must be in accordance with the appropriate product registration and be agreed to by both parties.

9.6 The GMP Agreement should describe clearly who is responsible for purchasing materials, testing and releasing materials and undertaking production and quality controls, including in-process controls, sampling, analysis, release for supply and the storage of records and retention samples.

9.7 Where qualification/validation protocols and other documentation are supplied by a third-party providing validation services, appropriate personnel at the manufacturing site shall confirm their suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

The Contract Acceptor

9.8 The contract acceptor should have adequate premises and equipment, knowledge and experience, quality management system and competent personnel to satisfactorily carry out the work ordered by the contract giver.

9.9 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

9.10 The contract acceptor should ensure, by quality assurance measures or by certification from another licensed manufacturer, that all raw materials received from any source meet relevant specifications and that all work in relation to those products or materials is carried out in compliance with requirements of this Code of GMP.

9.11 Where the contract acceptor is an analytical laboratory, the contract acceptor should make available to the contract giver details of all analytical procedures carried out on the contract giver's materials, as well as details of any relevant validation studies carried out on those procedures. Alternatively, where the contract acceptor considers an analytical method to be confidential property, that method and its validation should be available to the APVMA.

9.12 The contract acceptor should make available to the contract giver details of all manufacturing procedures and any quality control tests carried out on the contract giver's behalf, as well as copies of relevant manufacturing records.

9.13 The contract acceptor should notify the contract giver of any relevant deviations, out-of-specifications, non-conformances or similar quality events.

9.14 The contract acceptor should agree to participate in relevant investigations of customer complaints, suspected defects or similar quality concerns.

9.15 The contract acceptor should not pass to a third party any of the work entrusted to them under the contract without the prior evaluation and written consent of the contract giver.

9.16 Arrangements made between the contract acceptor and any third party should be subject to a GMP Agreement between either the original contract giver or the contract acceptor and the third party. Those arrangements should ensure that relevant manufacturing and analytical information is made available to the third party in the same way as between the original contract giver and contract acceptor. The third party must hold an APVMA Manufacturer's Licence, unless exempted under the *Agricultural and Veterinary Chemicals Code Regulations 1995* or be otherwise authorised by the APVMA, as in the case of overseas manufacturers, and accept the same responsibilities as the contract acceptor.

The Contract Giver

The contract giver is the legal entity who engages another legal entity to undertake one or more steps in manufacture of veterinary chemicals.

9.17 The agreement should require the contract giver to provide access to registration details of relevant;

(a) analytical methodology and validation studies,

(b) manufacturing procedures,

(c) quality control tests, and/or

(d) any other relevant data.

The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with registered particulars and any other legal requirements.

9.18 The contract giver should also ensure that the contract acceptor is fully aware of any aspects of the product or the work which might pose a hazard to the contract acceptor's premises, equipment, personnel, or other materials or products used or made on the premises.

9.19 The contract giver is responsible for:

(a) assessing the competence of the contract acceptor to successfully carry out the required work,

(b) ensuring that all arrangements for steps of manufacture, including any proposed changes of a technical nature, are in accordance with the registration particulars for the product concerned, and

(c) ensuring that all materials or processed products delivered to them by the contract acceptor comply with their specifications, and that they have been released by a competent authorised person.

Inspection of Contract Manufacturers

9.20 The Agreement should permit the contract giver, agreed third party or an APVMA-authorised GMP auditor to visit the facilities of the contract acceptor for auditing purposes.

9.21 Audits of contract manufacturers by the contract giver or an agreed third party should be carried out to ensure that work is carried out according to requirements in accordance with GMP and the registered particulars. The depth and frequency of inspections should be determined on a risk management basis.

CHAPTER 10 - INTERNAL AUDITS

Manufacturing Principle

Manufacturers of veterinary chemical products must regularly and systematically carry out internal audits of all aspects of their manufacturing operations, as well as of their quality assurance program, in order to monitor compliance with their authorised procedures, standards and requirements and ensure product quality. Steps must be taken to implement any necessary corrective and preventive action identified by those internal audits and to assess the outcomes.

Internal Audit

General

10.1 A program of planned and documented internal audits (self-inspections) should be in place to regularly and systematically assess all aspects of manufacture and quality control for compliance with this Code of GMP and to assess the effectiveness of the quality assurance system.

10.2 Internal audits should cover all aspects of GMP. The frequency and scope of audits should take into consideration the status and importance of the areas to be inspected, as well as the results of previous audits.

10.3 Internal audits should be conducted by staff who have been trained and are competent in internal audit procedures and should include, where practicable, staff who do not have direct responsibility for the processes being audited. Alternatively, independent external auditors may be used.

10.4 Where the need for corrective action has been identified;

(a) Steps should be taken to address any observed deviations from both;

i) the Code of GMP and

ii) the documented quality system.

(b) Corrective and preventive action should be monitored for effectiveness and modified if necessary.

(c) Documented procedures should be amended if there is an identified need to do so.

10.5 Records should be kept of all internal audits undertaken, the outcomes of those audits, details of any corrective and preventive action taken and the effectiveness of such action.

CHAPTER 11 – COMPLAINTS, PRODUCT RETURNS AND PRODUCT RECALLS

Manufacturing Principle

Manufacturers of veterinary chemical products should have in place a system of handling complaints regarding products they have manufactured or otherwise handled on the licensed premises. There should be a documented system of recording, investigating and, where appropriate, acting upon all complaints that may be related to product quality.

Manufacturers should also have in place a documented and effective procedure for recalling from the marketplace product that is known to be defective, or is suspected of being defective.

Complaints and Product Recalls

General

11.1 There should be in place a documented procedure for receiving, recording, reviewing and, where appropriate, acting upon all quality-related complaints received about veterinary chemical products manufactured or handled on the premises. The procedure should include

(a) the need to consider a recall in the event of a complaint concerning a possible product defect, and

(b) reference to the APVMA's requirements for adverse experience reporting.

11.2 Records should be kept of

(a) all complaints received,

(b) investigations carried out and their outcomes, and

(c) any corrective action taken to resolve the complaint and prevent the problem happening again.

11.3 All complaints related to product quality should be:

(a) registered in a complaints register, and

(b) retained for an appropriate minimum period, to be defined by the manufacturer.

11.4 Responsibility for handling complaints related to product quality and for deciding the measures to be taken should be delegated to a specified member or group of staff, who should be given adequate resources to carry out the task.

The individuals responsible for Quality Assurance, Quality Control and Production should be made aware of any complaint involving products manufactured or handled on the premises and, where merited participate in investigation and subsequent corrective actions.

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

Product Returns

11.6 Products returned from the market, which have left the control of the manufacturer, should be destroyed, unless their quality can be assured.

11.7 Returned products should be identified and be stored separately in a secure area while awaiting a decision on their fate.

11.8 Returned product may be considered for re-sale, relabelling or recovery with a subsequent batch, only after it has been critically assessed by Quality in accordance with a written procedure.

11.9 The nature of the returned product, any special storage conditions that it requires, its condition and history, potential for tampering, and the time elapsed since it was issued should all be taken into account in this assessment.

(a) there should be no adverse effect on the shelf life of the product batch, and

(b) where any doubt arises over the quality of the product, it should not be considered suitable for reissue or re-use, although basic chemical reprocessing to recover active ingredients may be possible.

11.10 Records should be kept for the period defined by the manufacturer. All actions taken, including the assessment of returned product should be appropriately recorded and authorised. Records should also be kept of all products returned for other reasons, the reason for the return (e.g. out of date product), and its disposal. Records should be also kept of any required corrective action.

11.11 Sterile / aseptic product that has been opened should not be reprocessed or returned to the market.

Suspected Product Defects

11.12 If a product defect is discovered or suspected in a batch, other batches should be checked in order to determine whether they also might be affected. Attention should be paid to other batches that may contain reworks of the defective batch. (see clause 7.96)

11.13 Records should be made detailing the investigations and any findings and corrective / preventative actions relating to suspected product defects.

Recalls

11.14 The APVMA should be notified if a manufacturer is considering recall action following possibly faulty manufacture, product deterioration, or any other serious quality problem with a product. The competent authorities of all countries to which defective products may have been distributed should also be notified.

11.15 There should be a written procedure for the initiation and management of any recall activity, which should be aligned with the APVMA's guidelines for the recall of agricultural and veterinary chemical products. Procedures should be regularly checked and updated when necessary.

11.16 Responsibility for execution and co-ordination of recalls should be delegated to a specific member or group of staff, who should be given adequate resources to handle all aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the person responsible for quality, the latter should be made aware of any recall operation.

11.17 Recall operations should be capable of being initiated promptly and at any time, including outside normal working hours. For that reason, the recalls co-ordinator should maintain a regularly updated list of emergency contact numbers, including after-hours contact details.

11.18 Distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on directly supplied customers, including those for exported products.

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

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

11.21 Records should be kept of all recalls initiated (including internal 'dummy runs'), all action taken, as well as of details of all product returned as a result of recalls and its disposal. Records should be in accordance with the APVMA's guidelines for the recall of agricultural and veterinary chemical products.

11.22 The effectiveness of the recall procedure should be evaluated annually by means of internal 'dummy runs' and the procedure revised if necessary. The outcome of these 'dummy runs' should be recorded, together with details of any corrective action considered necessary.

11.23 The manufacturer should define the retention time for these records.

PART 2 ANNEX

ANNEX 1 MANUFACTURE OF STERILE PRODUCTS

Manufacturing Principle

(1) Veterinary chemical products that are required to be, or are represented as being sterile, must be manufactured:

– *(a) in separate, controlled areas in the premises that have:*

(i) high standards of hygiene; and

(ii) a system of controlling particulate contaminants appropriate to the class of veterinary chemical product being manufactured.

– *(b) with special care and attention to detail; and*

– *(c) in accordance with procedures established and validated by the manufacturer.*

(2) The manufacturer must establish procedures and have equipment available (or in the case of bioburden, have access to equipment) to adequately monitor:

– *(a) the microbiological status of the environment in production areas; and*

– *(b) the microbial load of the veterinary chemical products that are to be sterilised.*

Introduction

Special precautions need to be taken when manufacturing sterile products in order to minimise the risks of microbiological, particulate and pyrogen contamination. Protection of both the product and the manufacturing environment is normally achieved through physical barriers, sanitation procedures and rigorous staff training, as well as the supply of clean filtered air. While regulatory audits frequently focus on cleanroom performance and validation, it needs to be appreciated that contamination of product is often associated with random events rather than with airborne contamination. Much depends on the skill, training and attitudes of the personnel involved. The greater the risks involved, the more stringent the precautions that should be undertaken. Typically, these stricter precautions include the use of ‘double barriers’ where processing and/or filling occurs under a unidirectional airflow within a cleanroom environment. While terminal sterilisation may reduce many of the risks, it will not eliminate them.

The requirements described in this Annex are divided into two sections: general guidelines that are applicable to all manufacturers of sterile products, including those that involve terminal sterilisation, and the more stringent guidelines that are associated with aseptic processing.

Periodic validation of key processes is necessary to demonstrate that such processes remain effective. The sterility of the finished product is assured by validation of the sterilisation cycle in the case of terminally sterilised products, and by ‘media-fill’ runs for aseptically processed products. It is not sufficient that a finished product passes a prescribed sterility test. The sum of the manufacturing precautions and the successful validation studies provides confidence in the quality of the product.

Parenteral preparations

Parenteral preparations are sterile preparations intended for administration into the animal body. They may be administered by injection, infusion or implantation. They are liquid, semi-solid or solid preparations containing one or more active substances in a suitable vehicle. Liquid preparations for injection or infusion are solutions, colloidal dispersions, emulsions or suspensions[1].

Parenteral Preparations prepared with an oily vehicle are suitable for intramuscular or subcutaneous administration only and are not given intravenously[1]

Ophthalmic preparations

Eye preparations are sterile preparations intended for application to the eyeball and/or to the conjunctiva, or for insertion into the conjunctival sac, to deliver active substances for a local effect.

They are liquid, semi-solid or solid preparations containing one or more active substances in a suitable vehicle. They may contain excipients, for example to adjust the tonicity or viscosity of the preparation, to adjust or stabilise the pH, to increase the solubility of the active substances, to stabilise the preparation or to provide adequate antimicrobial properties. The excipients do not adversely affect the intended medicinal action of the preparation or, at the concentrations used, cause toxicity or undue local irritation.

General

Premises

A1-001 Sterile products should be manufactured in areas that are designed and managed to minimise microbial and particulate contamination. The various operations of component preparation, product preparation and filling should be carried out in separate clean areas within the cleanroom.

A1-002 Wherever practicable, enclosed systems should be employed for product preparation and filling.

A1-003 Sinks and floor drains should be excluded from Grade B cleanrooms. In other areas, air breaks should be fitted prevent backflow and contamination of the clean water supply and production equipment.

A1-004 Changing rooms should be designed as airlocks and provide physical separation of the different stages of changing to minimise microbial and particulate contamination of operators and protective clothing.

A1-005 Separate airlocks should be considered for moving some materials into controlled areas. Where possible, material and personnel entries should be physically separated.

A1-006 An interlocking system or a visual and/or audible warning system should prevent the opening of more than one airlock door at a time.

[1] British Pharmacopoeia (Veterinary)

A1-007 Under all operational conditions, a filtered air supply to a particular area should maintain both a positive pressure and a positive airflow relative to surrounding areas of a lower grade and should flush the area effectively. Cleanrooms should be specified and documented as to their grading, air change rates, pressure differentials, temperature and relative humidity.

A1-008 A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

Production areas

A1-009 Access to buildings should be restricted to authorised persons. Visitors to buildings should be discouraged, kept to a minimum, and generally permitted only in areas not used for aseptic operations. Visitors' clothing should be in accordance with the area visited. All production areas should, as far as possible, be designed to avoid the entry of non-operational personnel.

A1-010 All exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and, where used, disinfectants. Timber and laminate are undesirable, as joints are hard to clean, timber is difficult to seal and laminate tends to lift, chip and crack.

A1-011 To reduce accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason.

A1-012 Pipes, ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.

A1-013 False ceilings should be sealed to prevent contamination from the space above them. Ceiling penetrations, such as lighting, visual alarms and filter boxes should also be sealed.

A1-014 Adjacent airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

A1-015 A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

A1-016 Areas for the manufacture of terminally sterilised product should be designed to prevent the mixing of sterilised and non-sterilised products.

Sanitation and hygiene

A1-017 Areas for the production of sterile products should be subjected to regular, thorough cleaning and disinfection. The effectiveness of controlling microbial content of the air and surfaces should be routinely monitored and trended. Microbial monitoring method should be verified for suitable recovery for the media used.

A1-018 Items brought into sterile manufacturing areas, including means of transport, should be of a standard of cleanliness compatible with the environmental standard for the area. Items brought into Grade B and A areas should be either sterilised or effectively sanitised before entry .

A1-019 There should be specific written procedures for the:

a) cleaning of bulk containers and their subsequent inspection for release for use in processing,

b) control of external contamination of bulk containers during use,

c) assembly of filters and the connecting of hoses and pipelines to eliminate potential mix-ups, and

d) dismantling, cleaning and decontamination of pumps, filters, pipelines, and filling heads and their subsequent inspection for release for use in processing.

A1-020 Fumigation (with humidified formaldehyde vapour or other validated methods) may be used to reduce microbial contamination in places inaccessible to surface disinfection. Fogging (such as with peracetic acid) may also be acceptable if the process is validated.

A1-021 Disinfectants and detergents should be monitored for microbial contamination unless pre-sterilised. Diluted disinfectants and detergents should be kept in previously cleaned containers and should only be stored for defined periods unless they are also sterilised. The effectiveness of sanitisers and disinfectants used in Grade A and B areas should be documented.

Environmental control

Air quality

A1-022 For the manufacture of sterile medicinal products, four grades of air quality are distinguished, as follows:

Grade A: The local zone for high-risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, aseptic connections. Normally such conditions are provided by a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air velocity in the range of 0.36–0.54 m/s (guidance value) at the working position in open cleanroom applications. The maintenance of unidirectional airflow should be demonstrated by air visualisation studies to assess the potential for turbulence or entrainment. A unidirectional airflow at lower velocities may be used in closed isolators and glove boxes.

Grade B: This is the background environment for a Grade A zone and is used for aseptic preparation and filling.

Grade C/D: Clean areas for carrying out less critical stages in the manufacture of sterile products. Grade C cleanrooms may be used for the manufacture and primary packaging of terminally sterilised products.

A1-023 The classification of airborne particulate levels for Grades A–D is given in the following table. Cleanrooms and clean air devices should be classified in accordance with EN ISO 14644-1.

Maximum permitted number of particles/m^3 of given size[a]

Grade	At rest [b]		In operation [b]	
	0.5 µm [c]	5 µm	0.5 µm [c]	5 µm
A	3,520	20[d]	3,520	20[d]
B	3,520	29[d]	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Not defined[e]	Not defined[e]

Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in the preceding table.

Notes:

(a) A discrete airborne particle counter is used to measure the concentration of particles of sizes equal to or greater than the designated threshold. Where consideration of particulate contamination is necessary to ensure product quality, a continuous measurement system during operation should be used for monitoring the concentration of particles in the Grade A zone and is recommended for the surrounding Grade B areas. For routine testing, the total sample volume should be not less than 1 m^3 for Grade A and B areas and preferably also in Grade C areas. If lower volumes are used these should be justified.

In order to reach the B, C and D air quality grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate terminal filters such as high efficiency particulate air (HEPA) filters for grades A, B and C.

(b) The particulate conditions given in the table for the ‘at rest’ state should be achieved after a short ‘clean up’ period of 15–20 minutes (guidance value) in an unmanned state after completion of operations. The particulate conditions for Grade A ‘in operation’ given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

(c) The guidance given for the maximum permitted number of particles in the ‘at rest’ and ‘in operation’ conditions correspond approximately to the cleanliness classes in the AS/NZS ISO 14644-1 at a particle size of 0.5 µm.

(d) These areas are expected to meet the limits for particles of size greater than 5 µm.

(e) The requirements and limits will depend on the nature of the operations carried out.

A1-024 Other characteristics such as temperature and relative humidity depend on the product and the nature of the operations carried out, as well as on personnel comfort. These parameters should not interfere with the defined cleanliness standard. Upper and lower limits should be specified.

A1-025 Cleanrooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

A1-026 For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management.

A1-027 Examples of operations to be carried out in the various air quality grades

Air quality grades

Grade	Operation for terminally sterilised products
A	Filling of products when unusually at risk
C	Preparation of solutions when unusually at risk and filling of products
D	Preparation of solutions and components for subsequent filling
Grade	**Operation for aseptic preparations**
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

A1-028 Operations preceding terminal sterilisation should normally be carried out in at least a Grade D environment. Where there are increased risks of microbial contamination to the product (e.g. filling of wide-necked containers, or where the product actively supports microbial growth or should be held before sterilisation), preparation of solutions and components should be carried out in at least a Grade C environment. Time limits should be documented and justified between filling and terminal sterilisation. Bioburden levels prior to terminal sterilisation should be established and regularly monitored.

A1-029 A floor plan of the manufacturing areas should be available, showing the points of entry and exit of air, classification of each room, number of air changes per hour and the differential pressure(s).

A1-030 Where an isolator is used, the air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least Grade D.

A1-031 Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, decontamination of introduced materials, sanitation of the isolator, the transfer process and isolator integrity.

A1-032 Monitoring of isolators should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system. Continuous monitoring of Isolator pressures and alarms is required.

A1-033 Blow/fill/seal equipment used for aseptic production that is fitted with an effective Grade A air shower may be installed in at least a Grade C environment, provided that Grade A/B clothing (see clause A1-041) is

used. The environment should comply with the viable and non-viable limits 'at rest' and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products for terminal sterilisation should be installed in at least a Grade D environment.

Environmental monitoring

A1-034 Cleanrooms and related areas should be monitored at planned intervals for airborne and surface microbiological contamination and the results obtained used to determine 'alert' and 'action' levels. Monitoring should be frequent and should take place while normal production operations are in progress. In the case of aseptic filling, it should provide the basis for the assessment of aseptic hygiene throughout the filling process. Results should be tabulated or graphed and assessed, and if necessary, prompt remedial action taken according to the standards established. Additional testing should be carried out to determine the effectiveness of such operations as cleaning and fumigation and the influence of disruptions such as spillage or maintenance.

A1-035 Environmental monitoring of clean areas should include the following components:

(a) particulate monitoring during routine operation, where relevant

(b) airborne microbiological monitoring,

i. air samplers should sample an adequate quantity of air to provide a meaningful result (see note Clause A1-021(a)),

ii. air monitoring using both volumetric (active air) and settle plate-sampling methods in aseptic fill and seal areas,

(c) regular microbiological monitoring of surfaces (e.g. walls, equipment surfaces, bench tops, trolleys and floors),

(d) regular microbiological monitoring of personnel (e.g. external surfaces on gloves, sleeves, and torso), and

(e) temperature and humidity monitoring; the recommended settings are 18-22°C and 35–60% humidity (too high a value on either setting will promote particulate and microbial shedding from personnel, and too low a setting will increase static electricity).

A1-036 Environmental monitoring methods used should be justified.

A1-037 Microbiological and particulate contamination should be controlled and monitored for each grade by a comprehensive procedure approved by quality management staff. Trend monitoring of viable results should be reviewed on a monthly basis.

A1-038 Media used for environmental monitoring should be able to recover yeasts, moulds, fungi and aerobic bacteria. Monitoring should include anaerobes where the type of product deems this necessary. It is recommended to use two types of culture media (usually agars) for the recovery of the above-mentioned organisms.

A1-039 Isolates found during environmental monitoring in Grade A and B areas should be regularly identified.

Personnel

A1-040 Management should delegate the supervision of the production process for sterile products only to persons who are qualified by training and/or experience in the relevant aspects of pharmaceutical/microbiological sciences. Where the person responsible for Quality is not a qualified microbiologist, arrangements should be made to obtain regular external expert microbiological advice.

A1-041 All personnel (including those concerned with cleaning and maintenance) should receive practical training in techniques, procedures and in disciplines relevant to the correct manufacture of sterile products, including hygiene (referred to in Chapter 2, clause 2.23 through to clause 2.30) and the basic elements of microbiology using expert microbiological advice. When external personnel who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

A1-042 Personnel required to work in clean and aseptic areas should be selected with care to ensure that they are not subject to any chronic disease or condition that would present an abnormal microbiological hazard to the product. The same principle should be applied to visitors to cleanrooms. Trend monitoring of viable results should be reviewed on a monthly basis.

A1-043 Staff who have been engaged in animal handling, processing of animal tissues or products/materials or culturing of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed. These entry procedures may include a period of quarantine exclusion from the manufacturing area.

A1-044 Entry procedures, including changing and hand washing, should follow written instructions designed to minimise contamination of clean area clothing or carry-through of contaminants to clean areas.

A1-045 The minimum protective clothing requirements for each grade of controlled area are as follows:

Grade A/B: headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit. A facemask should be worn to prevent the shedding of droplets. Sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

Grade C: Hair and, where relevant, beard and moustache should be covered. Nonpowdered gloves should be worn. A single or two-piece trouser suit, gathered at the wrists and with high neck and overshoes or dedicated shoes should be worn. They should shed virtually no fibres or particulate matter.

Grade D: Hair and, where relevant, beard and moustache should be covered. A suitable protective garment and overshoes or dedicated shoes should be worn. Gloves (non-powdered) may be required.

Equipment

A1-046 Unidirectional airflow equipment should be regularly tested and the results recorded.

A1-047 Where necessary, equipment should be sterilised before use. The effect of the sterilisation methods on the operation and durability of equipment should be considered. All sterilisation procedures should be validated and. where possible operating conditions continuously monitored. Monitoring records such as sterilising conditions should be verified and results recorded in the batch record.

A1-048 Equipment used in the stages of processing of sterile products before sterilisation should be designed and operated to minimise contamination by microorganisms and particulate matter. As far as practicable, equipment, fittings and services should be designed and installed so that maintenance and repairs may be carried out without personnel having to enter the cleanroom. If sterilisation is required, it should be carried out after complete reassembly wherever possible. Maintenance tools and equipment should be cleaned, disinfected or sterilised before use.

A1-049 Vessels containing bulk sterile-filtered water or product should be vented through bacteria-retaining filters. The filters should be periodically checked for integrity.

A1-050 Autoclaves, gas sterilisers, sterilising ovens, and lyophilisers should be equipped with automatic recorders that monitor the time and temperature and, where necessary, other parameters of the sterilising cycle. This equipment should be qualified upon installation, should be calibrated periodically and re-qualified annually, unless otherwise justified. Records should permit verification of achievement of these parameters with an appropriate degree of accuracy.

A1-051 A temperature-sensing probe for the automatic temperature recorder should be located at the position in the steriliser shown by previous studies to be the coolest part of the loaded chamber. Where sterilisers are fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilisation period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

A1-052 Heat sterilisers should have provision for the entry of leads from temperature-sensing devices placed in product packs or simulated product packs during heat penetration studies.

A1-053 The pressure during steam sterilising cycles should be recorded at least manually.

A1-054 Steam used for sterilisation should not contain additives at a level that could cause contamination of product or equipment. The use of ‘clean steam’ may need to be considered. Steam quality should be verified periodically.

A1-055 Where the quality of the product may be affected, air or any other gas admitted to an autoclave, hot air steriliser or lyophiliser or used to promote positive pressure for filtration, should be filtered through a bacteria-retaining filter. Compressed air used should also be filtered through a bacteria-retaining filter. Filter integrity should be periodically verified.

A1-056 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 should be produced, stored and distributed in a manner that prevents microbial growth; for example, by constant circulation at a temperature above 70 °C or at 4 °C or below.

A1-057 All water systems that supply process water to be used in the manufacture of products should be specified and monitored for:

(a) total organic carbon,

(b) conductivity,

(c) endotoxin, and

(d) microbial quality.

Monitoring should be frequent enough to determine trends or changes in quality. Monitoring methods should be verified as suitable.

Specification for materials

A1-058 Specifications for raw materials should consider microbial limits and any special storage requirements.

A1-059 Water used in the preparation of sterile products should comply with the relevant pharmacopoeial standards or registration requirements. It may not need to be sterilised before the product is manufactured.

A1-060 When distilled water is used in the final product, the time between distillation and the final production should not exceed 24 hours unless provision is made for it to be held at a temperature of at least 80 °C. A limit on the time that may elapse between solution preparation and sterilisation should also be set.

Processing

A1-061 Containers or other materials liable to generate particles or fibres should not be taken into areas supplied with Grade A, B or C air.

A1-062 The intervals between the washing, drying and sterilisation of components, containers and equipment should be as short as possible and subject to a time limit appropriate to the storage conditions. The interval between sterilisation and the use of these materials should also be subject to a time limit.

A1-063 The time between the start of the preparation of a solution and its sterilisation should be as short as possible and subject to a limit for each product that takes into account its composition and the prescribed method of storage. Unless special storage conditions are provided, bulk aqueous solutions should have no greater volume than can be used in one working day and should be filled into final containers and sterilised within one working day.

A1-064 The microbiological load of products should be as low as practicable before sterilisation. It should be monitored and an action level set that is related to the efficiency of the method of sterilisation to be used, the risk of pyrogens and previous validation results. All solutions. and in particular large-volume infusion fluids, should be passed through a filter of pore size ≤ 0.45 µm, where possible immediately before filling.

A1-065 Batch processing records for sterile products should include details of the sterilisation of the batch, and where the batch is aseptically processed, details of the sterilisation of the components and equipment used.

A1-066 The charts of automatic recorders of cycle parameters should constitute part of the batch processing records of sterile products and should be marked to identify the batch or batches to which each applies.

A1-067 Sterilisation records should be reviewed and approved as part of the batch release procedure.

A1-068 Each separate sterilising basket, package, pallet etc., of products or components undergoing sterilisation should be fastened, wired, sealed, lidded or otherwise secured to prevent mix-up and should bear, in a conspicuous position, a visual indicator to demonstrate whether it has passed through a sterilisation cycle.

A1-069 Microbiological (biological) indicators should be quarantined and subjected to quality control before use.

A1-070 Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products, unless justified by a written risk analysis.

A1-071 Components, containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated.

A1-072 Each procedure used for the sterilisation of a particular quantity or volume of a material, component or product should have been demonstrated by validation studies to be effective and reliable. The validation should be verified at scheduled intervals based on performance history, or when any significant change is made in the process or equipment.

A1-073 Where practicable, heat sterilisation is the method of choice. In any case, the sterilisation process should be in accordance with product registration.

A1-074 Validated loading patterns should be established for all sterilisation processes and periodically re-validated. A matrix or bracketing approach may be considered.

A1-075 Biological indicators should be considered as an additional method for monitoring the sterilisation and decontamination processes. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

Sterilisation by heat—general

A1-075 Each heat sterilisation cycle should be recorded on a time/temperature chart, or by equivalent electronic means, with a suitably large scale or by other appropriate equipment with suitable accuracy and precision.

A1-076 Chemical or biological indicators may also be used but should not take the place of physical measurements. Autoclave indicator tape, or equivalent chemical indicator, should be used to identify a sterilised load from an unsterilised load.

A1-077 Sufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time is commenced. This time should be determined for each type of load to be processed. Typical loading diagrams should be part of the standard operating procedures. Each sterilising load should contain one or more indicators to show that the cycle has been completed.

A1-078 After the high-temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised, unless it can be shown that any leaking container would not be approved for use.

A1-079 All sterilising equipment and processes should be initially qualified and validated then re-validated on an annual basis, unless otherwise justified. This includes autoclaves, hot air sterilisers and tunnels, irradiation processes, terminal sterilisation processes and steam in place systems.

Sterilisation by moist heat

A1-080 Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications, they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and evident to the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period.

A1-081 The items to be sterilised should be wrapped in a material that allows removal of air and penetration of steam but prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.

Sterilisation by dry heat

A1-082 Equipment for dry heat sterilisation should allow air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

Sterilisation by radiation

A1-083 During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. These dosimeters should be inserted in the load in sufficient number, close enough together to ensure that there is always a dosimeter in the irradiator. The position in the carrier receiving the lowest dose and, where appropriate, the highest dose should be represented. Where plastic dosimeters are used, they should be used within the time limit of their calibration. Dosimeter absorbances should be read soon after exposure to radiation.

A1-084 Biological indicators may be used as an additional control.

A1-085 Validation procedures should ensure that the effects of variations in density of the packages are considered.

A1-086 Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour indicators should also be used on each package to differentiate between packages that have been subjected to irradiation and those that have not.

A1-087 The total radiation dose should be administered within a predetermined time span. Where a third party conducts the radiation, they should provide a certificate indicating the lower and upper radiation doses.

A1-088 If an outside contractor carries out sterilisation by radiation, the contract giver is responsible for ensuring that the requirements for this type of sterilisation are met and that the process is validated. The responsibilities of the radiation plant operator (e.g. for using the correct dose) should also be specified; both dose and timeframe should be identified.

A1-089 Ultraviolet irradiation is not normally an acceptable method of sterilisation.

Sterilisation by ethylene oxide

A1-090 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

A1-091 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required for the process. The time required for this should be balanced against the opposing need to minimise the time before sterilisation.

A1-092 Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record. Where a third party conducts the radiation, they should provide a certificate indicating the lower and upper radiation doses.

A1-093 For each sterilisation cycle, records should be made of the time taken to complete the cycle, the pressure, temperature and humidity within the chamber during the process and the gas concentration and the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. These records should form part of the batch record.

Sterilisation by filtration

A1-094 Solutions or liquids should be filtered through a sterile filter of nominal pore size of ≤0.22 µm, or with at least equivalent microorganism-retaining properties, into a previously sterilised container. Consideration should be given to complementing the filtration process with heat or other treatment where the presence of filterable microorganisms is suspected.

A1-095 Positive pressure rather than negative pressure should be used in filtration processes. To enhance the assurance of sterility, a second filtration step, immediately before filling, may be advisable. Final filtration should occur as close as possible to the point of fill.

A1-096 Fibre-shedding characteristics of filters should be minimal. Asbestos-containing filters should not be used under any circumstances.

A1-097 The same filter should not be used for more than one working day, unless such use has been validated. The same filter should not be used for different products.

A1-098 The filter should not affect the product by removal of ingredients from it or by release of substances into it. This should be verified by pre/post filtration studies.

A1-099 The integrity of the sterilised filter should be verified immediately after use by an appropriate method, such as a bubble point, diffusive flow or pressure hold test. Integrity testing before and during use should also be considered. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter, should be determined during validation and any significant variation from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

Finishing (primary packaging)

A1-100 Containers should be closed by appropriately validated methods. Containers closed by fusion (e.g. glass or plastic ampoules) should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

A1-101 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

A1-102 Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is visual, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. The inspection process should be validated and the performance of the equipment and inspectors checked at intervals. Results should be recorded.

Quality control

A1-103 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

A1-104 Where required or appropriate, tests for the following should be carried out on each batch of product according to a written and approved specification:

(a) sterility,

(b) uniformity of contents,

(c) potency,

(d) pyrogenicity or endotoxin, and

(e) particulate matter.

For injectable and large-volume infusion solution products, such testing is essential.

A1-105 Test methods should be shown to be equivalent to a pharmacopoeial method such as the BP. If alternative methods are used, they should be validated.

A1-106 Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality as indicated by monitoring.

A1-107 Cumulative records of environmental control, the testing of manufacturing equipment, media fill runs and all other applicable quality control tests should be reviewed and maintained by Quality Control.

A1-108 Pharmacopoeial methods should be used for sterility tests. These methods should be validated for the product(s) concerned.

A1-109 Where parametric release has been authorised, all calibrations and controls that were specified in the application for authorisation should be rigorously maintained.

A1-110 Samples taken for sterility testing should be representative of the whole of the batch, but should include samples taken from parts of the batch considered to be most at risk of contamination, for example:

(a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention, and

(b) for products that have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

A1-111 Release of sterile product should include a review of:

(a) validation studies, including, in the case of aseptic filling, media fill results,

(b) environmental monitoring results,

(c) batch records including in-process test results,

(d) equipment monitoring and performance records,

(e) finished product test records, and

(f) any deviations from validated conditions. Products should not be released until all deviations have been closed.

Aseptic processing

Premises

A1-112 Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent microorganism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

A1-113 Aseptic filling should involve the minimum of human intervention. Where human intervention is unavoidable suitable monitoring procedures should be in place and reviewed before release of the batch.

A1-114 Sinks and drains should be excluded from Grade A /B aseptic filling/sealing rooms.

A1-115 Airlocks should be flushed effectively with filtered air. The final stage of the changing room should, in the 'at rest' state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general, hand-washing facilities should be provided only in the first (outer) stage of the changing rooms.

A1-116 Adjacent rooms of different grades should have a pressure differential of 10–15 pascals (guidance values). The air-flow pattern, location of equipment and movement of personnel should afford protection of the zone of greatest risk (i.e. the immediate environment to which a product and sterilised components that contact the product are exposed).

A1-117 Bioburden should be monitored before the final sterilising filtration, unless otherwise justified. There should be working limits on bioburden immediately before final filtration.

Production areas

A1-118 Products should be manufactured in a clean area up to the stage where they are sterilised, and thereafter processed and filled into their final containers under aseptic conditions, employing a double barrier system. The first barrier is provided by unidirectional flow workstations in which the actual filling operations are carried out. The second barrier is provided by the supply of filtered air into the room in which the operations are carried out. It is desirable to maintain this room at a positive pressure relative to the outside environment. Filters should be of HEPA standard and should be re-certified at least annually.

A1-119 Non-sterile products should not be processed in the same area as sterile products. Different products should not be processed concurrently in the same room.

A1-120 Grade B areas (see clause A1-022) should be designed so that all operations can be observed from the outside.

Sanitation and hygiene

A1-121 During aseptic operations, the areas should not be used for any other purpose. After any nonsterile operation such as maintenance, and before aseptic operations are commenced, the areas should be thoroughly cleaned and disinfected according to a written procedure.

A1-122 Clean and, where necessary, sterile protective clothing should be supplied and worn in production areas. Personnel working in associated areas not designated as clean or aseptic areas should change into clean over-garments before entering the clean or aseptic areas and remove these over-garments on exit. These outer garments should not be worn outside the cleanroom suite.

A1-123 Operators entering Grade B rooms should be instructed and qualified via written gowning procedures and their gowning verified at regular intervals.

A1-124 Clean over-garments should be made of such material and weave that they are comfortable to wear, do not shed fibres, and restrict the passage of particulate matter. These garments should not be fitted with pockets or cuffs.

A1-125 Disinfectants and detergents used in Grade A and B areas should be sterile before use.

Environmental control

A1-126 The 'in operation' and 'at rest' states should be defined for each cleanroom or suite of cleanrooms.

A1-127 Examples of operations to be carried out in the various clean zone grades.

Table 1 Clean zone grades

Grade	Operation for aseptic preparations
A	Preparation of solutions that are not to be filtered Handling of sterile starting materials and components that are not to be filtered Handling and filling of aseptically prepared products Transfer of partially closed containers, as used in freeze drying Preparation and filling of sterile ointments, creams, suspensions and emulsions
B	Transfer of partially closed containers in sealed transfer trays
C	Preparation of solutions to be filtered
D	Handling of components after washing

Environmental monitoring

A1-128 Sampling methods used during operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Viable monitoring results should be trended and reviewed regularly.

A1-129 Additional microbiological monitoring should be considered after activities such as major maintenance, interruption to production and equipment validation.

A1-130 Recommended action limits to be used in microbiological monitoring of clean areas during operation are given in the following table:

Table 2 Recommended action limits for microbial contamination[(a)]

Sampling method				
Grade	**Air sample cfu/m^3**	**Settle plates (diam. 90mm) cfu/4 hours[(b)]**	**Contact plates (dia. 55mm) cfu/plate**	**Glove print (5 fingers) cfu/glove**
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes: (a) These are average values.

(b) Individual settle plates may be exposed for less than four hours but should not be exposed for more than four hours unless validated. Additional plates may be used at a single location to sum to four hours exposure. The results from settle plates should not be interpreted as equivalent to those from volumetric sampling. cfu = colony forming units

A1-131 It should be demonstrated that airborne cleanliness classifications are met during operations. Appropriate alert and action limits should be set for the results of microbial and particulate monitoring. Operating procedures should prescribe corrective action, if these limits are exceeded.

Personnel

A1-132 Only the minimum number of personnel essential for production and in-process control operations may be allowed in aseptic or clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.

A1-133 Personnel engaged in servicing equipment or other non-routine activities should observe the same precautions and hygiene standards as production personnel.

A1-134 Wristwatches, make-up and jewellery should not be worn in clean areas.

A1-135 Outdoor clothing should not be brought into changing rooms leading to Grade B and C rooms. Clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session for every worker in a Grade A/B area. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session. Working sessions should generally not exceed 4 hours

A1-136 Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants that can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable.

Equipment

A1-137 A conveyor belt should not pass through a partition between a Grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).

Processing

A1-138 For each process line an aseptic process risk assessment should be conducted, documented and kept current. Any mitigations resulting from the risk assessment should be included in written procedures, environmental monitoring programs and quality control. The risk assessment should include material preparation, material, product and component sterilisation, transfers to higher classified areas, aseptic processes, potential for contamination and risks associated with process interventions.

A1-139 Maximum processing hold time should be included in any risk assessment and aseptic processing validation. This includes maximum bulk hold times, filtration times, pre-sterilisation hold times and aseptic filling times. Maximum hold times should be included and recorded in batch records.

A1-140 The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use should be minimised and subject to a time-limit appropriate to the storage conditions. The time between the start of the preparation of a solution and its sterilisation or filtration through a microorganism-retaining filter should be minimised.

A1-141 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum and movement of personnel should be controlled and methodical to avoid excessive shedding of particles and organisms as a result of over-vigorous activity. The ambient temperature and humidity should be set to provide a comfortable environment, taking into account the nature of the garments worn.

A1-142 Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double- ended sterilisers sealed into the wall, or by a procedure that achieves the same objective of not introducing contamination. Once sterilised containers, equipment and components should not be transited through lower grades (C or D) Non-combustible gases should be passed through microorganism-retentive filters.

A1-143 Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). The process simulation test should imitate as closely as possible the routine aseptic manufacturing process, including predictable interventions and worst-case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and be repeated at defined intervals not less than once annually) and after any significant modification to the heating, ventilation and air conditioning (HVAC) system, equipment, process or number of shifts. The number of containers used for media fills should be sufficient to enable a valid evaluation, with a confidence level of at least 95% for large batches. For small batches, the number of containers for media fills should at least equal the size of the product batch.

A1-144 The process simulation test (media fill) should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also consider various interventions known to occur during normal production as well as worst-case situations.

A1-145 The target should be zero growth, but production need not be halted if a contamination rate of less than 0.1% is observed provided an investigation is initiated.

A1-146 The manufacturer should establish alert and action limits. If action limits are exceeded a deviation and investigation should be raised.

A1-147 Care should be taken that any validation does not compromise the processes.

ANNEX 2 IMMUNOBIOLOGICALS AND OTHER PRODUCTS OF BIOLOGICAL ORIGIN

Manufacturing Principle

Veterinary immunobiological products and other chemical products of biological origin including those that are manufactured using a specified biological process should be manufactured:

(a) using only biological starting materials that are, or are derived from biological materials demonstrated to be as free as practicable from adventitious contamination;

(b) in premises designed, constructed and maintained so as to provide an appropriate level of containment of the biological or microbiological agents being handled and to permit effective decontamination from these agents or from toxic residues by procedures that:

(i) are established and validated by the manufacturer; and

(ii) maintain the safety of personnel.

(c) in cases where uniformity of product depends on deriving batches from a seed lot:

(iii) by maintaining the lots in secure and protective storage; and

(iv) by keeping meticulous records of their origin and disposition.

Essential information

The manufacture of veterinary immunobiological and other biological products is frequently complex, and the role of the quality assurance system is of the utmost importance. Due to the nature of biologics manufacture (e.g. cultivation of microorganisms), the products should be well protected against contamination and cross-contamination. This Annex should therefore be read in conjunction with Annex 1.

Stage of manufacture - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is this Annex. Guidance for the subsequent manufacturing steps of sterile biological products is covered in Annex 1.

The manufacture and control of genetically modified organisms need to comply with local and national requirements. Appropriate containment should be established and maintained in facilities where any genetically modified microorganism is handled. Advice should be obtained according to national legislation to establish and maintain the appropriate Biological Safety Level including measures to prevent cross contamination. There should be no conflicts with GMP requirements.

General

Premises

A2-001 Documentation relating to the premises should be readily available. 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, processes, waste and product should also be clearly marked.

A2-002 Animal species accommodated in the animal houses or otherwise on the site should be identified on the site plans or accompanying notes. Animal houses should be located in separate buildings to production areas.

A2-003 Activities carried out in the vicinity of the site should also be indicated on the site plans or accompanying notes. Plans of clean or contained areas should describe the ventilation system, indicating inlets and outlets, filters and their specifications, direction of airflow and any containment conditions, the number of air changes per hour and pressure differentials. They should indicate which pressure differentials are monitored by pressure indicators.

Segregation and containment

A2-004 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 using clean contained and/or controlled areas. The design and operation of premises should be justified by a documented risk-based contamination control strategy (CSS).

A2-005 Live biological agents should be handled in contained areas that may also be clean areas. The level of containment should depend on the pathogenicity of the microorganism and whether it has been classified as exotic. Where live biological organisms or GMOs are processed, these areas should conform to at least a PC2 containment standard, unless otherwise justified.

A2-006 Inactivated biological agents should be handled in clean areas. Clean areas should also be used when handling non-infected cells isolated from multi-cellular organisms and filtration-sterilised media. Dedicated production areas should be used;

(a) for the handling of live cells, capable of persistence in the manufacturing environment, until inactivation.

(b) for the manufacture of pathogenic organisms capable of causing severe disease.

A2-007 Open circuit operations involving non-viable products or components not subsequently sterilised should be carried out within a unidirectional Grade A airflow workstation in a Grade B area.

A2-008 Other operations where live biological agents are handled, such as quality management, research and diagnostic services, should be contained and separated if production operations are carried out in the same building. The movement of personnel and the level of containment should depend on the pathogenicity and origin of the biological agents. Where there is the risk of introducing highly pathogenic or exotic organisms (e.g. via quality management activities), the level of containment should be adequate to cope with all such risks. Containment may also be required if quality management or other activities are carried out in buildings in close proximity to those used for production.

A2-009 Contained areas should have the characteristics detailed below.

(a) They should be capable of easy disinfection.

(b) They should have no direct venting to the outside.

(c) Ventilation systems should have pressure differentials to contain organisms from the environment and protect the product from external contamination. Air should be extracted through filters appropriate to the organisms being handled and not be recirculated except to the same area. However, the recycling of air between areas may be permissible, provided it is appropriately filtered. Return air filters should be considered, justified via a contamination control risk assessment.

(d) They should have a system for the collection and disinfection of liquid effluents, including contaminated condensate from sterilisers, bioreactors etc. Solid wastes, including animal carcasses, should be disinfected, sterilised or incinerated as appropriate. Contaminated filters should be removed using a safe method.

(e) They should have changing rooms designed and used as airlocks and equipped with washing and showering facilities as 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 airlock system for the passage of equipment should be 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 airlock 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) There should be a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items, where appropriate. Decontamination cycles should be validated and monitored using biological indicators or equivalent.

A2-010 Transfer hatches 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 be exhausted to produce an adequate air circulation independent of that of the work area. Transfer hatches should be ventilated in the same way, but unventilated hatches, or those equipped with supply air only, may be acceptable if justified in the CSS.

A2-011 With the exception of blending and subsequent filling operations, only one biological agent at a time should be handled within an area. Production operations such as cell maintenance, media preparation, or virus culture likely to cause contamination should not be performed in the same area at the same time. Where the same room is used for more than one purpose, effective decontamination and line clearance between operations should be in place. These arrangements should be justified in a CSS.

A2-012 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.

A2-013 Killed vaccines should be blended, filled, and sealed under aseptic conditions and segregated from the processing areas where culturing is carried out.

A2-014 The filling of containers with live vaccines, including those prepared from attenuated strains, should be appropriately separated from other aseptic filling operations. This may be achieved by using separate areas or by elapsed time and effective decontamination procedures. These arrangements should be justified in a CCS.

Sanitation, disinfection and waste disposal

A2-015 Sanitation, disinfection, decontamination and disposal of wastes and effluents are particularly important in the manufacture of immunobiological and other biological products. Procedures and equipment should protect the product and avoid environmental contamination. Autoclaving and incineration are the preferred methods of decontamination of rubbish and waste material, although chemical inactivation may be acceptable in some circumstances.

A2-016 Production areas should be thoroughly cleaned and disinfected after any non-sterile operation, such as maintenance and before aseptic processing resumes. Cleaning and sanitation methods should be shown to be effective.

Personnel

A2-017 In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with live organisms or with animals. Where relevant, the personnel should be appropriately vaccinated and subject to regular medical examination. Personnel (including those concerned with cleaning, maintenance or quality management) employed in areas where biological medicinal products are manufactured and tested should receive training, including any specific measures to protect product, personnel and the environment.

A2-018 Adequate measures should be taken to prevent biological agents being carried outside the manufacturing plant by personnel. Dependent on the type of biological agent, such measures may include complete changing of clothes and compulsory showering before leaving the production area.

A2-019 Prevention of product contamination by personnel should be achieved by a set of measures and procedures that ensure that appropriate protective clothing is used during the different stages of the production process and ensure that personnel do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. These arrangements should be justified in a CSS.

A2-020 Only personnel essential for production and in-process control operations, maintenance and cleaning should be allowed into processing areas.

A2-021 Personnel working in areas designated as ‘clean/aseptic’ or ‘culturing’ should change into clean over-garments before moving from one area to another, and the over-garments should be removed on exit from the relevant area. The same principles should apply when staff move from other areas into clean/aseptic or culturing areas. The health status of personnel should be taken into consideration for product safety.

Equipment

A2-022 Any closed equipment used for the primary containment of biological agents should be designed and constructed to prevent any leakage or the formation of droplets and aerosols. Inlets and outlets for gases should be protected to achieve adequate containment (e.g. by the use of sterilising hydrophobic filters). The introduction or removal of material should take place using a sterilisable closed system, or possibly in an appropriate unidirectional airflow.

A2-023 Separate incubators should be used for infected and non-infected containers and also generally for different organisms or cells. Incubators containing more that one organism or cell type will only be acceptable if adequate measures are in place to seal, surface decontaminate and segregate the containers. All containers should be individually labelled. 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 be in leak-proof containers. Items such as seed stock (cell or organism) should be stored in dedicated equipment.

A2-024 The process of loading freeze-driers requires an appropriate clean or contained area. Unloading freeze-driers potentially contaminates the immediate environment. Therefore, for single-ended freeze-driers, the cleanroom should be decontaminated at the end of the process and before a further manufacturing batch is introduced into the area, unless this contains the same organisms. Double-door freeze-driers should be sterilised after each cycle unless opened in a clean area. Sterilisation of freeze-driers should be done at least after each campaign.

A2-025 Equipment used in the culturing of microorganisms should be capable of decontamination, either in situ or otherwise, and should be capable of effective cleaning before re-use and/or sterilisation. Cleaning and sanitation methods should be shown to be effective.

A2-026 In heat sterilising processes, it is essential that the whole load reaches the sterilisation temperature. Account should be taken of heat-up times for various loads and ‘typical loading’ diagrams should be part of standard operating procedures.

A2-027 Items to be sterilised by autoclaving should be wrapped in a material that allows the removal of air (either by free steam or evacuation of the chamber) and its replacement by steam, but does not permit recontamination when dry.

A2-028 Sterilisation by filtration should not be used when sterilisation by heat is acceptable. Positive pressure rather than negative pressure should be used in filtration processes. The integrity of the filter system should be tested immediately after each use. (See Section A1-073 and A1-095 for further clarification).

A2-029 When re-useable filters are used, they should be effectively cleaned and sterilised after each use. Consideration should be given to using individual filters for one type of solution only. Evidence of effective cleaning and integrity should be available.

A2-030 Unidirectional airflow equipment should be regularly tested and the results recorded. Cleanrooms and related areas should be monitored at planned intervals for microbiological contamination. Microbial trend results should be regularly reviewed by Quality Management.

Animals and animal houses

A2-031 The sanitary and health status of the animals used for production should be defined, monitored, and recorded. Animals should be handled in ways defined in specific monographs (e.g. Specific Pathogen Free [SPF] flocks), where these are available and relevant.

A2-032 Animals, biological agents and tests carried out should be identified in such a way as to prevent any risk of confusion and to control all foreseeable hazards.

A2-033 Animal testing facilities should be sufficiently secure to ensure that unauthorised entry is prevented and that animals cannot break in or escape. This applies particularly to facilities where live challenge tests are being carried out. Procedures should be in place to ensure that animals cannot be incorrectly identified or otherwise mixed up by staff. Attention should be given to decontamination and environmental requirements, where applicable.

A2-034 Animal houses accommodating animals used for, or intended to be used for, production purposes should be provided with appropriate containment and/or clean area measures and should be separated from other animal accommodation and production areas.

A2-035 Animal houses accommodating animals that are used for quality management purposes that involve pathogenic biological agents should be adequately contained.

Production

General

A2-036 Production of biological agents may take place in either clean or controlled areas, provided it is carried out in totally enclosed and heat sterilised equipment, with all connections being also heat sterilised after making and before breaking. It may be acceptable for connections to be made under local unidirectional airflow, 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 should be validated for the organisms being used. Different products may be placed in different bioreactors 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.

A2-037 Critical procedures, including methods for sterilisation, disinfection, virus removal and inactivation, should be validated and subject to monitoring and in-process controls.

A2-038 Substances of animal origin should be prepared from homogeneous bulk material, designated with a batch number. A batch may contain material derived from as many animals as is desired, but once designated and given a batch number, a batch should not be added to or contaminated in any way.

Starting materials

A2-039 Written specifications for starting materials should, where appropriate, include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials should be included. Microbiological controls are particularly important.

A2-040 The results of tests on starting materials should comply with the specifications. Where the tests take a long time, it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product should be conditional upon satisfactory results of the tests on starting materials.

A2-041 Where substances of animal origin (e.g trypsin and serum albumin) are used as ingredients of culture media, during processing or as added constituents of vaccines or diluents, batch records should allow traceability and confirmation with registered specifications and quarantine requirements for all such substances. Materials should be free from adventious or TSEs agents. Suppliers of animal derived materials should provide certification.

Media

A2-042 Media used in fermenters or bioreactors should preferably be sterilised in situ or in line. Heat is the preferred method. Gases, media, acids, alkalis, defoaming agents and other materials introduced into sterile bioreactors should themselves be sterile.

A2-043 Where heat-labile media components are required, these should be sterilised by other acceptable means (e.g filtration, gamma irradiation) and added aseptically to the heat-sterilised base medium.

Seed lot and cell bank system

A2-044 In order to prevent unwanted genetic drift, the production of immunobiological products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots and/or cell banks.

A2-045 The origin, history since receipt, preparation, form and storage conditions of seed material should be described in full. The number of generations (doublings, passages) between the master seed lot or cell bank and the finished product should be defined and be consistent with the product registration. Seed lots and cell banks should be adequately characterised and tested for contaminants. Acceptance criteria for new seed lots and cell banks should be established.

A2-046 During the establishment of a seed lot or cell bank, no other living or infectious material should be handled at the same time in the same area or by the same person. Seed lots and cell banks should be

established, stored and used in such a way as to minimise the risks of misidentification, contamination or any alteration.

A2-047 Evidence of the stability and recovery of the seeds and cell banks should be generated and recorded. Storage containers should be secure, clearly labelled and held at an appropriate temperature. Storage conditions should be properly monitored. An inventory of each seed lot and cell bank should be maintained and each container accounted for.

A2-048 Only authorised personnel should be allowed to issue and handle seed material. A log or register of use of master and working cell banks should be maintained for compete traceability.

A2-049 The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot or cell bank management system, the containers should not be returned to seed lot or cell bank.

Operating techniques

A2-050 The formation of droplets and the production of foam should be avoided or minimised during manufacturing processes. Centrifugation and blending procedures that may lead to droplet formation should be carried out in appropriate clean or contained areas to prevent transfer of live organisms.

A2-051 There should be documented procedures for the prompt handling of spillages of live organisms. Validated decontamination measures should be available for each organism. Where different strains of a single species of bacteria or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

A2-052 Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilised closed systems wherever possible. Where this is not possible, transfer operations should be protected by unidirectional airflow workstations. Checks should be made to ensure that vessels are correctly connected when adding of cultures. The methods used for sterilisation, disinfection, virus removal or inactivation should be validated.

A2- 053 After connection, before the flow of product, and again before disconnection, fermenter sampling, addition ports and connectors should be sterilised with steam. However, in some circumstances, chemical disinfection of ports and unidirectional airflow protection of connections may be acceptable.

A2-054 Equipment, glassware, the external surfaces of product containers and other such materials should be disinfected using a validated method before transfer from a clean or contained area. Only the absolute minimum of batch documentation required should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork should be adequately disinfected through an equipment transfer hatch, or the information transferred out by alternate means.

A2-055 Liquid or solid wastes should be sterilised or disinfected before transfer from a clean or contained area. However, alternative transfer procedures may be appropriate in some cases.

A2-056 Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only materials concerned with production are introduced.

A2-057 All materials entering a clean or contained area should be sterilised. Where practicable, heat-stable articles and materials entering a clean or contained area should do so through a double-ended autoclave or oven. Sterilisation of articles and materials elsewhere is acceptable, provided they enter through an airlock and appropriate precautions are taken (e.g., double wrapping, surface disinfection).

A2-058 Precautions should be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators.

A2-059 With the exception of blending and subsequent filling operations, or when totally enclosed systems are used, only one live biological agent should be handled within a production room at any given time. Production rooms should be effectively disinfected between the handling of different live biological agents.

A2-060 Addition of inactivating agent to the bulk material should be immediately followed by stirring or mixing to ensure even distribution of the agent. The bulk material should then be transferred to a sterile inactivation vessel to ensure all of the bulk material is exposed to the inactivating agent. Inactivation methods should be validated with monitoring of the validated conditions. Monitoring conditions should be included in each batch record and reviewed by the authorised person before batch release.

A2-061 Vessels containing inactivated product should not be opened or sampled in areas containing live biological agents. All subsequent processing of inactivated products should take place in Grade A/B clean areas or enclosed equipment dedicated to inactivated products.

A2-062 Containers of bulk material should be sealed, appropriately labelled and stored under specified conditions. Any prolonged storage conditions should be validated, including the sterility of the bulk where required.

A2-063 There should be a system to assure the integrity of all containers and their closures after filling. This requirement applies to containers of bulk materials, intermediates and finished products.

A2-064 The capping of vials containing live biological agents should be performed in such a way that contamination of other products or escape of the live agents into other areas or the external environment, does not occur.

A2-065 When there is a delay between the filling of final containers and their labelling and packaging, procedures should be specified for the storage of unlabelled containers so as to preserve product identity and to ensure satisfactory storage conditions.

Quality control

A2-066 In-process controls that are crucial to product quality, but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

A2-067 Where testing of bulk or intermediate materials is required, a sufficient quantity of sample should be retained, under appropriate storage conditions, to allow repetition or confirmation of the test result if necessary.

A2-068 Where production of a biological product involves continuous culture, the quality management requirements arising from such a production method should be appropriately addressed.

A2-069 Sufficient quality management testing should be undertaken to ensure that the product complies with the approved registration particulars. Critical test methods for finished product should be validated, including bioburden, endotoxin and sterility tests.

A2-070 Quality Control should maintain cumulative records of environmental control, the testing of manufacturing equipment and all other quality management tests where applicable, and should take into account the results of such testing before releasing any batch of product for distribution.

A2-071 Specifications for biological starting materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

ANNEX 2a CRUDE BIOLOGICALS AND IMMUNOLOGICALS

Manufacturing Principle

Veterinary immunobiological products and other chemical products of biological origin including those that are manufactured using a specified biological process must be manufactured:

(a) using only biological starting materials that are, or are derived from biological materials demonstrated to be as free as practicable from adventitious contamination;

(b) in premises designed, constructed and maintained so as to provide an appropriate level of containment of the biological or microbiological agents being handled and to permit effective decontamination from these agents or from toxic residues by procedures that:

(v) are established and validated by the manufacturer; and

(vi) maintain the safety of personnel.

(c) in cases where uniformity of product depends on deriving batches from a seed lot:

(vii) by maintaining the lots in secure and protective storage; and

(viii) by keeping meticulous records of their origin and disposition.

Essential information

The manufacturer should always adopt the highest possible standard of GMP, quality management, hygiene and safety. Products that can be manufactured under Annex 1 or Annex 2 will not be considered as 'Crude biologicals and immunologicals'.

Crude biological substances are supplied as extracts of animal derived materials, either 'as is' or as partially processed actives with or without appropriate excipients. Examples of 'crude biologicals and immunologicals' could include whole blood, plasma and other blood products or partially purified animal derived tissues, including milk, saliva and other non-tissue derivatives.

The manufacture of crude biologicals includes circumstances where the drug product is directly obtained from the biological source (eg whole blood) or is only partially processed from the animal derived raw source; such that the registration/permit has allowed for a range of proteins, or other biological substances to be presents as well as uncharacterised impurities intrinsic to the biological source that may potentially include carbohydrates, lipids, extraneous DNA or RNA, proteins, endotoxins etc. With the proviso that the presence of these uncharacterised impurities is demonstrated, empirically, not to be pathogenic.

Examples of appropriate processes could include

- Pulverisation, sonication, milling (etc)
- Washing (with or without surfactants)
- Dilution in water or an aqueous buffer
- Size exclusion, including by filtration and chromatography
- Concentration, including by dialysis, centrifugation, affinity chromatography and/or drying.

- Addition of appropriate excipients and
- Aseptic filtration.

Products that are not considered to be ‘crude biologicals or immunologicals’ include

- Products derived directly from fermentation or cell culture
- Products than can be sterilised or bioburden reduced by heat or chemical means
- Products subject to extended separation methods including ion-exchange chromatography, electrophoresis precipitation, used of solvents other than aqueous, endotoxin removal, polishing (Other examples to be added)
- Products that are labelled as sterile (because this implies freedom from subvisible particulate etc)

For crude biological active substances this annex provides the specific guidance including up to the point of the product being rendered aseptic.

Blood and blood products should also be manufactured using the relevant parts of PIC/S GOOD PRACTICE GUIDELINES FOR BLOOD ESTABLISHMENTS AND HOSPITAL BLOOD BANKS.

General

Premises

Refer to Annex 2

Segregation and containment

A2a-001 Dedicated production area should be used for the manufacture of pathogenic organisms capable of causing severe disease.

A2a-002 Open circuit operations involving non-viable products or components not subsequently aseptically filtered should be carried out within a unidirectional Grade A airflow workstation in a Grade B area.

A2a-003 External and internal production areas should have the characteristics detailed below. They should;

(a) be capable of easy disinfection,
(b) provide adequate protection of the product and the process,
(c) provide adequate ventilation,
(d) have a system for the collection and disinfection of wastes,
(e) have washing and showering facilities as appropriate, and
(f) have a system in place to precluded unauthorised entry.

A2a-004 Entry and exit of production areas should facilitate appropriate hygienic controls.

A2a-005 Production operations likely to cause cross contamination should not be performed in the same area at the same time. Where the same room is used for more than one purpose, effective decontamination and line clearance between operations should be in place. These arrangements should be justified in a CSS.

Sanitation, disinfection and waste disposal

A2a-006 Procedures and equipment should protect the product and avoid environmental contamination. Autoclaving and incineration are the preferred methods of decontamination of contaminated rubbish and waste material, although chemical inactivation may be acceptable in some circumstances.

A2a-007 External production areas should be adequately cleaned before production activities. Internal production areas should be thoroughly cleaned and disinfected before any aseptic processing. Cleaning and sanitation methods should be shown to be effective.

Personnel

Refer to Annex 2

Equipment

A2a-022 Any closed equipment used for the primary containment of biological agents should be designed and constructed to prevent any leakage or the formation of droplets and aerosols. Inlets and outlets for gases should be protected to achieve adequate containment (e.g. by the use of sterilising hydrophobic filters). The introduction or removal of material should take place using a sterilisable closed system, or possibly in an appropriate unidirectional airflow.

A2a-023 Separate incubators should be used for infected and non-infected containers and generally for different organisms or cells. Incubators containing more than one organism or cell type will only be acceptable if adequate measures are in place to seal, surface decontaminate and segregate the containers. All containers should be individually labelled. 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 be in leak-proof containers. Items such as seed stock (cell or organism) should be stored in dedicated equipment.

A2a-024 The process of loading freeze-driers requires an appropriate clean or contained area. Unloading freeze-driers potentially contaminates the immediate environment. Therefore, for single-ended freeze-driers, the cleanroom should be decontaminated at the end of the process and before a further manufacturing batch is introduced into the area, unless this contains the same organisms. Double-door freeze-driers should be sterilised after each cycle unless opened in a clean area. Sterilisation of freeze-driers should be done at least after each campaign.

A2-025 Equipment used in the culturing of microorganisms should be capable of decontamination, either in situ or otherwise, and should be capable of effective cleaning before re-use and/or sterilisation. Cleaning and sanitation methods should be shown to be effective.

A2a-026 In heat sterilising processes, it is essential that the whole load reaches the sterilisation temperature. Account should be taken of heat-up times for various loads and ‘typical loading’ diagrams should be part of standard operating procedures. Standard operating procedures should be available.

A2a-027 Items to be sterilised by autoclaving should be wrapped in a material that allows the removal of air (either by free steam or evacuation of the chamber) and its replacement by steam, but does not permit recontamination when dry.

A2a-028 Sterilisation by filtration should not be used when sterilisation by heat is acceptable. Positive pressure rather than negative pressure should be used in filtration processes. The integrity of the filter system should be tested immediately after each use.

A2a-029 When re-useable filters are used, they should be effectively cleaned and sterilised after each use. Consideration should be given to using individual filters for one type of solution only. Evidence of effective cleaning and resterilisation should be available.

A2a-030 Unidirectional airflow equipment should be regularly tested and the results recorded. Cleanrooms and related areas should be monitored at planned intervals for microbiological contamination. Microbial trend results should be regularly reviewed by Quality Management.

Animals and animal houses

A2a-031 The sanitary and health status of the animals used for production should be defined, monitored, and recorded. Animals should be handled in ways defined in specific monographs (e.g. specific pathogen free [SPF] flocks), where these are available and relevant.

A2a-032 Animals, biological agents and tests carried out should be identified in such a way as to prevent any risk of confusion and to control all foreseeable hazards.

A2a-033 Animal testing facilities should be sufficiently secure to ensure that unauthorised entry is prevented and that animals cannot break in or escape. This applies particularly to facilities where live challenge tests are being carried out. Procedures should be in place to ensure that animals cannot be incorrectly identified or otherwise mixed up by staff. Attention should also be given to decontamination and environmental requirements, where applicable.

A2a-034 Animal houses accommodating animals used for, or intended to be used for, production purposes should be provided with appropriate containment and/or clean area measures and should be separated from other animal accommodation and production areas.

A2a-035 Animal houses accommodating animals that are used for quality management purposes that involve pathogenic biological agents should be adequately contained.

Production

General

A2a-036 Production of biological agents may take place in either clean or controlled areas, provided it is carried out in totally enclosed and heat sterilised equipment, with all connections being also heat sterilised after making and before breaking. It may be acceptable for connections to be made under local unidirectional airflow, provided these are few and proper aseptic techniques are used and there is no risk of leakage.

The sterilisation parameters used before breaking the connections should be validated for the organisms being used. Different products may be placed in different bioreactors 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.

A2a-037 Critical procedures, including methods for sterilisation, disinfection, virus removal and inactivation, should be validated and subject to monitoring and in-process controls.

A2a-038 Substances of animal origin should be prepared from homogeneous bulk material, designated with a batch number. A batch may contain material derived from as many animals as is desired, but once designated and given a batch number, a batch should not be added to or contaminated in any way.

Starting materials

A2a-039 Written specifications for starting materials should, where appropriate, include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials should be included. Microbiological controls are particularly important.

A2a-040 The results of tests on starting materials should comply with the specifications. Where the tests take a long time, it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product should be conditional upon satisfactory results of the tests on starting materials.

A2a-041 Where substances of animal origin (e.g trypsin and serum albumin) are used as ingredients of culture media, during processing or as added constituents of vaccines or diluents, batch records should allow traceability and confirmation with registered specifications and quarantine requirements for all such substances. Materials should be free from adventious or TSEs agents. Suppliers of animal derived materials should provide certification.

Media

A2a-042 Media used in fermenters or bioreactors should preferably be sterilised in situ or in line. Heat is the preferred method. Gases, media, acids, alkalis, defoaming agents and other materials introduced into sterile bioreactors should themselves be sterile.

A2a-043 Where heat-labile media components are required, these should be sterilised by other acceptable means (e.g filtration, gamma irradiation) and added aseptically to the heat-sterilised base medium.

Seed lot and cell bank system

A2a-044 In order to prevent unwanted genetic drift, the production of immunobiological products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots and/or cell banks.

A2a-045 The origin, history since receipt, preparation, form and storage conditions of seed material should be described in full. The number of generations (doublings, passages) between the master seed lot or cell bank and the finished product should be defined and be consistent with the product registration. Seed lots and cell banks should be adequately characterised and tested for contaminants. Acceptance criteria for new seed lots and cell banks should be established.

A2a-046 During the establishment of a seed lot or cell bank, no other living or infectious material should be handled at the same time in the same area or by the same person. Seed lots and cell banks should be established, stored and used in such a way as to minimise the risks of misidentification, contamination or any alteration.

A2a-047 Evidence of the stability and recovery of the seeds and cell banks should be generated and recorded. Storage containers should be secure, clearly labelled and held at an appropriate temperature. Storage conditions should be properly monitored. An inventory of each seed lot and cell bank should be maintained and each container accounted for.

A2a-048 Only authorised personnel should be allowed to issue and handle seed material. A log or register of use of master and working cell banks should be maintained for compete traceability.

A2a-049 The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.

Operating techniques

A2a-050 The formation of droplets and the production of foam should be avoided or minimised during manufacturing processes. Centrifugation and blending procedures that may lead to droplet formation should be carried out in appropriate clean or contained areas to prevent transfer of live organisms.

A2a-051 There should be documented procedures for the prompt handling of spillages of live organisms. Validated decontamination measures should be available for each organism. Where different strains of a single species of bacteria or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

A2a-052 Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilised closed systems wherever possible. Where this is not possible, transfer operations should be protected by unidirectional airflow workstations. Checks should be made to ensure that vessels are correctly connected when addition of cultures takes place. The methods used for sterilisation, disinfection, virus removal or inactivation should be validated.

A2a-053 After connection, before the flow of product, and again before disconnection fermenter sampling, addition ports and connectors should be sterilised with steam. However, in some circumstances, chemical disinfection of ports and unidirectional airflow protection of connections may be acceptable.

A2a-054 Equipment, glassware, the external surfaces of product containers and other such materials should be disinfected using a validated method before transfer from a clean or contained area. Only the absolute

minimum of batch documentation required should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork should be adequately disinfected through an equipment transfer hatch, or the information transferred out by alternate means.

A2a-055 Liquid or solid wastes should be sterilised or disinfected before transfer from a clean or contained area. However, alternative transfer procedures may be appropriate in some cases.

A2a-056 Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only materials concerned with production are introduced.

A2a-057 All materials entering a clean or contained area should be sterilised. Where practicable, heat-stable articles and materials entering a clean or contained area should do so through a double-ended autoclave or oven. Sterilisation of articles and materials elsewhere is acceptable, provided they enter through an airlock and appropriate precautions are taken (e.g. double wrapping, surface disinfection).

A2a-058 Precautions should be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators.

A2a-059 With the exception of blending and subsequent filling operations, or when totally enclosed systems are used, only one live biological agent should be handled within a production room at any given time. Production rooms should be effectively disinfected between the handling of different live biological agents.

A2a-060 Addition of inactivating agent to the bulk material should be immediately followed by stirring or mixing to ensure even distribution of the agent. The bulk material should then be transferred to a sterile inactivation vessel to ensure all the bulk material is exposed to the inactivating agent. Inactivation methods should be validated with monitoring of the validated conditions. Monitoring conditions should be included in each batch record and reviewed by the Authorised Person before batch release.

A2a-061 Vessels containing inactivated product should not be opened or sampled in areas containing live biological agents. All subsequent processing of inactivated products should take place in Grade A/B clean areas or enclosed equipment dedicated to inactivated products.

A2a-062 Containers of bulk material should be sealed, appropriately labelled and stored under specified conditions. Any prolonged storage conditions should be validated, including the sterility of the bulk where required.

A2a-063 There should be a system to assure the integrity of all containers and their closures after filling. This requirement applies to containers of bulk materials, intermediates and finished products.

A2a-064 The capping of vials containing live biological agents should be performed in such away that contamination of other products or escape of the live agents into other areas or the external environment, does not occur.

A2a-065 When there is a delay between the filling of final containers and their labelling and packaging, procedures should be specified for the storage of unlabelled containers so as to preserve product identity and to ensure satisfactory storage conditions.

Quality control

A2a-066 In-process controls that are crucial to product quality, but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

A2a-067 Where testing of bulk or intermediate materials is required, a sufficient quantity of sample should be retained, under appropriate storage conditions, to allow repetition or confirmation of the test result if necessary.

A2a-068 Where production of a biological product involves continuous culture, the quality management requirements arising from such a production method should be appropriately addressed.

A2a-069 Sufficient quality management testing should be undertaken to ensure that the product complies with the approved registration particulars. Critical test methods for finished product should be validated, including bioburden, endotoxin and sterility tests.

A2a-070 Quality Control should maintain cumulative records of environmental control, the testing of manufacturing equipment and all other quality management tests where applicable and should take into account the results of such testing before releasing any batch of product for distribution.

A2a-071 Specifications for biological starting materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

ANNEX 3 NON-STERILE THERAPEUTIC PRODUCTS (OTHER THAN ECTOPARASITICIDES, PREMIXES, SUPPLEMENTS AND BIOLOGICAL FEED ADDITIVES)

Introduction

Additional guidance is required for some product types because of the wide range of non-sterile veterinary products subject to licensing and differences in consumer expectations relating to product quality. These products are often manufactured in facilities that are also used to make non-veterinary chemical products. This may pose additional risks for cross-contamination that need to be addressed.

Liquids, creams, pastes, gels and ointments

Liquids, creams, pastes, gels and ointments are particularly susceptible to microbiological contamination during manufacture and subsequent storage. Special measures should therefore be taken to minimise contamination. Water quality is of particular importance.

Powders and tablets

The manufacture of powders and tablets inevitably generates dust. Special attention should be paid to minimising cross-contamination and facilitating cleaning, either using dedicated facilities, sealed materials-delivery and mixing facilities or by effective dust extraction. However, the installation of such systems does not eliminate the need for regular cleaning of production areas and equipment.

Products containing penicillins and other highly sensitising antibiotics

The use of penicillins and other highly sensitising antibiotics in veterinary medicines does not present the same risks of hypersensitivity in animals as in humans. Nevertheless, when veterinary products containing penicillins and other highly sensitising antibiotics are not manufactured in dedicated facilities all necessary measures should be taken to avoid cross-contamination and any risk to operator safety.

Electrolytes

The term ‘electrolytes’ normally refers to solutions of mineral supplements that have various applications. ‘Electrolytes’, sometimes with vitamins and other medications added, may be used to treat serious dehydration associated with diarrhoea and other ailments. Such products can be administered either by injection, in which case they are required to be sterile (see Annex 1), or orally, in which case they are required to comply with any additional relevant requirements of this Annex.

In the racing industry, ‘electrolyte’ products are commonly used to treat dehydrated animals following racing. The products are usually added to drinking water or to feed after the race. Other ‘electrolyte’ products are simply vitamin and mineral supplements that are added to feed and water on a regular basis. In some cases, the products are manufactured in dry powder form. Such products are treated as vitamin and mineral supplements for GMP purposes (see Annex 6).

Bloat oils

This type of product usually consists of a mineral (petroleum) oil mixed with a detergent. It is administered to individual animals by drenching or painting it on the animal's flank or sprayed onto pasture or added to water in drinking troughs. These products are registered veterinary chemicals and consequently need to be manufactured in compliance with the manufacturing principles and the core elements of this GMP Code, taking into account the nature and use of the product. Where the product is manufactured in a petroleum refinery, only the relevant aspects of GMP need to be applied.

Slow-release intra-ruminal devices

These products vary widely in type and method of manufacture. They are usually large, heavy objects and may have some form of mechanical payout device as well as a mechanical device to prevent regurgitation. Examples include large anti-bloat capsules with spring-loaded payout mechanisms, large rubber-backed magnesium anodes that spring open on entering the rumen and slow-release mineral supplements in either large tablet or capsule form. In some cases, steps of manufacture are sub-contracted out to 'non-pharmaceutical' manufacturers, e.g. a metallurgical die-casting works or a rubber moulding facility. These facilities are required to be licensed, and the relevant manufacturing activities need be undertaken in compliance with the manufacturing principles and the core elements of this GMP Code. In applying the Code, consideration should be given to the nature of the product and the way it is to be used, as well as the nature of the manufacturing process.

Premises and equipment

A3-001 Production areas where the product or cleaned production equipment are exposed should be adequately protected from the outside environment.

Production

A3-002 The chemical and microbiological quality of water used for production should be specified and monitored.

A3-003 Mixing and filling processes should ensure homogeneity. Procedures should be in place to ensure that homogeneity is maintained during filling and after stoppages.

A3-004 When the finished product is not packaged immediately after processing, the maximum period of storage and the storage conditions should be specified and respected.

ANNEX 4 HERBAL PRODUCTS

Introduction

Control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products because of their often complex and variable nature, and the number and small dosage of defined active ingredients.

Premises

Storage areas

A4-001 Some plants, extracts, tinctures and other preparations may require special conditions of humidity, temperature or light protection. These conditions should be provided and monitored.

Documentation

Specifications for starting materials

A4-002 In addition to the requirements described in the core elements of this GMP Code (see Chapter 5), specifications for medicinal crude plants should include, as far as possible:

(a) the full botanical name (including, if appropriate, the name of the originator of the classification, e.g. Linnaeus),

(b) the preferred source of the plant (country or region of origin and, where applicable, method of cultivation, time of harvesting, collection procedure, pesticides that can/cannot be used etc.),

(c) plant description, including macroscopic and microscopic details, where a whole plant is sourced; an authentic reference specimen should be available for identification purposes,

(d) the part of the plant required (i.e. whether the whole plant or only a specific part such as the roots, leaves, whole tops etc.),

(e) the method used for drying,

(f) a physical description of the material,

(g) suitable identification tests, including, where appropriate, tests for known active ingredients, or markers, and the limits accepted,

(h) acceptable levels of possible chemical or biological contamination (pesticide, fungicide, herbicide, fungal or other microbial contamination, including aflatoxins, pest infestations, toxic metals, and other possible contaminants and adulterants), as well as the methods used to determine such contamination, and

(i) tests for foreign materials.

A4-003 Any treatment used to reduce fungal/microbial contamination or other infestation should be validated and documented. Specifications for such procedures should be available and should include details of processes, tests and limits for residues.

ANNEX 5 EXTERNALLY APPLIED ECTOPARASITICIDES

Introduction

Externally applied ectoparasiticides are those products applied externally to animals to control only external parasites.

Ectoparasiticides differ from most other veterinary chemical products in that they contain pesticides that may be toxic and generally incompatible with other forms of medicinal products. Consequently, ectoparasiticides should not be manufactured in the same area as other veterinary chemical products unless special precautions are taken to prevent cross-contamination. These precautions might include the use of dedicated equipment that is adequately separated from other processing areas or, where the same equipment is to be used for incompatible products, the use of scheduling and validated cleaning procedures.

Because some of the active materials are also used for agricultural chemicals, ectoparasiticides are occasionally manufactured in plants that also make agricultural chemicals. In those circumstances, rigorous precautions need to be taken to eliminate the risk of cross-contamination with pesticides, herbicides and incompatible materials.

Some of the products such as sheep dips, are made in large volumes using solvents and other materials that are sometimes stored in drums or specially constructed storage vessels. Outdoor storage of such materials may be acceptable, provided storage conditions such as temperature are appropriate for the materials involved.

Safety issues, such as the explosion hazard of excessive dust generation and the possibility of inhalation of chemical-laden dust by personnel (e.g. organophosphate pesticides), should be considered in the design and location of ectoparasiticide manufacture.

Attention is drawn to the need to comply with dangerous goods and hazardous substances legislation that may require special storage condition for goods that are of a dangerous or hazardous nature.

Buildings and grounds

A5-001 As a general rule, ectoparasiticides should not be manufactured in the same area as other veterinary chemical products. They should be made in segregated areas or separate buildings, using equipment that is dedicated to this type of product. However, use of common equipment may be accepted, provided that cross-contamination is controlled by scheduling and use of a validated cleaning procedure.

A5-002 Similarly, where ectoparasiticides are manufactured in a facility that also manufactures agricultural chemicals, they should be made in a separate area of the plant, using equipment dedicated to veterinary chemical manufacture. Special measures are needed to prevent cross-contamination with agricultural chemicals, particularly where shared facilities, such as packing rooms, are used.

A5-003 Bunding may be required in some situations to meet the requirements of dangerous goods and environment protection legislation.

A5-004 Outside storage of high-volume materials (e.g. solvents in 200 litre drums) may be acceptable, provided they are in adequately sealed containers and outside storage conditions are unlikely to adversely affect their quality.

Manufacture

A5-005 Manufacturing processes that involve the application of a liquid premix onto an inert carrier powder should ensure adequate dispersion of the liquid and, therefore, the active ingredient(s). Mixing times and methods should ensure batch homogeneity.

A5-006 Measures should be in place to prevent cross-contamination from hoses, fixed pipework and connections.

ANNEX 6 PREMIXES, SUPPLEMENTS AND BIOLOGICAL FEED ADDITIVES

Introduction

This Annex covers a range of products that are generally thought of as nutritional products required to be registered due to claims of therapeutic benefit, mode of oral administration, or contain an ingredient that are not considered END (Excluded Nutritional or Digestives) as per the 2015 Agricultural and Veterinary Chemicals Legislation Amendment (Animal Feed Reform and Other Measures). Consequently, they must be manufactured in compliance with APVMA GMP standards. All other products in this range that are not required to be registered must be manufactured in an approved quality system as per APVMA webpage "Stockfeed and petfood products which are excluded from registration".

The range of products includes:

Feed Additives: Any substance or agent added to a basic feed mix for continuous long-term administration to livestock for a specific purpose (e.g. enhancing production or maintaining health above levels obtained from the basic feed, improving storage qualities and/or palatability of the basic feed mix). This includes microorganisms, enzymes, acidity regulators, coccidiostats, and histomonostats (adapted from ISO20588).

Premixes: Means a mixture that: (a) contains vitamins, minerals, amino acids or other substances, and (b)is intended to be added to stockfood to form a finished feed for feeding to a group of animals.

Stockfood Supplements: means any substance or mixture of substances in the form of tablets, sachets or measures added to stockfood for administration to animals individually in order to supplement or balance that stockfood, but does not include a substance or mixture of substances in an injectable dose form, an intraruminal bolus, a block or a lick.

Stockfood means a basic food or food mixture that: (a) contains one or more nutritional ingredients; and (b) is intended to be fed to animals for the maintenance of life, normal growth, production, work, reproduction or performance.

General

Premixes are generally used to facilitate the addition of micro-ingredients and medications into larger volumes of final feed or drinking water for stock animals. These products can be a dry powder mix, a liquid preparation, salt or molasses block licks, or loose licks. These products are created according to a specific formulation. Some products also include mined minerals in powder form.

Because of the large amount of dust generated during the manufacture of dry preparations, special attention should be paid to cross contamination controls, either by physical separation from other aspects of manufacture or by effective dust extraction and hygiene. This is especially important for facilities that have minerals or ingredients that are toxic to one species of animals but not another.

Some preparations are referred to as 'electrolytes' and are mainly used to replace minerals and other electrolytes lost by racing animals (e.g. horses). Despite the therapeutic claims, most of these 'electrolytes' are more appropriately thought of as feed supplements from a manufacturing point of view.

Premix and supplement products

Buildings and grounds

A6-001 Processes are in place to prevent, control and detect potential cross-contamination especially from dust generation. Where appropriate separate facilities or zoning plans are implemented. Effectiveness of procedures are verified.

A6-002 Cleaning programs should specifically address the build-up of dust, sticky materials such as molasses, and corrosive materials such as salt.

A6-003 Premix production can involve the use of ingredients attractive insects, birds, rodents, and other pests. This should be addressed in the pest control program.

Personnel

A6-004 Personnel involved in the manufacture of animal feed products should be clearly identified and trained in elements of GMP appropriate to their needs.

Production

A6-005 Production areas where product or cleaned production equipment are exposed, should be adequately protected from the outside environment, especially when not in use.

A6-006 Where either process water or potable water is used in production, the quality of water used for production should be monitored.

A6-007 Mixing processes should ensure homogeneity. Validation records with relevant acceptable coefficient of variation (CV) or equivalent statistical analysis available.

A6-008 Parts of the process likely to have a significant adverse influence on the stability of the active ingredients (e.g. steam) should be controlled to ensure batch-to-batch consistency.

A6-009 Special attention needs to be paid to the prevention of microbial contamination during manufacture or storage of susceptible liquid formulations.

Equipment

A6-010 Compressed air and other gases that come into contact with product must be suitable to prevent contamination. Where possible food grade oils and lubricants are used.

A6-011 Complete cleaning may not be required between batches of the same or closely related products, provided that product integrity is maintained and cross-contamination risks between animal species has been considered. Controls such as flushing, sequencing, and cleaning between batches of feed ingredients are verified.

Materials control

A6-012 Where materials are stored in bulk, procedures are in place to prevent contamination from weather, pest contamination, and other foreign materials.

A6-013 Where mined mineral supplements are used, these meet the requirements regarding feed standard contaminants, especially regarding heavy metals and dioxins.

Feed products manufactured through Bioprocessing

Personnel

A6-014 Personnel responsible for the manufacture and quality of feed products made through bioprocessing should have appropriate qualifications in microbiology or related subjects and/or experience in the manufacture of such products.

A6-015 Personnel involved in the manufacture of animal feed products through bioprocessing should be clearly identified and trained in elements of GMP appropriate to their needs.

Materials control

A6-016 The taxonomic identity of microorganisms selected for production should be checked.

A6-017 The master seed culture should be checked for identity by morphological characterisation and comparison with the taxonomic characteristics originally identified. Its purity should be checked before transfer to the fermentation equipment by serial dilution, plating, and macroscopic and microscopic inspection for any foreign microorganisms.

A6-018 The master seed culture should be maintained in such a way as to minimise degeneration and maintain genetic stability.

A6-019 All seed cultures should be clearly labelled, and strict aseptic techniques applied in revival and subculture.

Production

A6-020 All operations should be designed to avoid contamination, formation of undesirable byproducts, deterioration, and handling errors.

A6-021 The culture liquid should be sampled and checked for purity at regular intervals throughout the fermentation process. However, in semi-solid surface cultivation, purity control may be restricted to visual inspection.

A6-022 Operational parameters such as enzyme activity temperature, pH, and oxygen content, should be monitored during fermentation and kept within predetermined ranges based on validation. Deviations from these ranges may indicate a contamination before it can be detected in microbial assays.

A6-023 Steps should be taken to ensure that contamination of the product during recovery is minimised.

ANNEX 7 SAMPLING OF STARTING AND PACKAGING MATERIALS

Introduction

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests that have been carried out on nonrepresentative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

This annex gives additional guidance on the sampling of starting and packaging materials.

Personnel

A7-001 Personnel who take samples should receive initial and ongoing regular training in the disciplines relevant to correct sampling. This training should include:

(a) sampling plans;

(b) written sampling procedures;

(c) the techniques and equipment for sampling;

(d) the risks of cross-contamination;

(e) the precautions to be taken with regard to unstable and/or sterile substances;

(f) the importance of considering the visual appearance of materials, containers and labels;

(g) the importance of recording any unexpected or unusual circumstances.

Starting materials

A7-002 The identity of a complete batch of starting materials can normally be ensured only if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly identified on its label.

A7-003 This validation should take account of at least the following aspects:

(a) nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements for veterinary medicines,

(b) the Quality Assurance system of the manufacturer of the starting material,

(c) the manufacturing conditions under which the starting material is produced and controlled,

(d) the nature of the starting material and the products in which it will be used.

Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:

(e) starting materials coming from a single product manufacturer or plant, and

(f) starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability, and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product), or by an officially accredited body.

It is improbable that a procedure could be satisfactorily validated for:

(g) starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited, and

(h) starting materials for use in parenteral products.

A7-004 The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples that may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

Packaging material

A7-005 The sampling plan for packaging materials should take account of at least the following:

(a) the quantity received,

(b) the quality required,

(c) the nature of the material (e.g. primary packaging materials and/or printed packaging materials),

(d) the production methods, and

(e) what is known of the Quality Assurance system of the packaging materials manufacturer based on audits.

The number of samples taken should be determined statistically and specified in a sampling plan.

ANNEX 8 REFERENCE AND RETENTION SAMPLES

Introduction

This Annex gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.

Samples are retained to fulfil two purposes; to provide a sample for analytical testing and also to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates that are transported outside of the manufacturer's control should be kept.

Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

It is necessary for the manufacturer, importer or site of batch release to keep reference and/or retention samples from each batch of finished product and, for the manufacturer to keep a reference sample from a batch of starting material (subject to certain exceptions – see A8-002 below) and/or intermediate product. Each packaging site should keep reference samples of each batch of primary and printed packaging materials. Availability of printed materials as part of the reference and/or retention sample of the finished product can be accepted.

The reference and/or retention samples serve as a record of the batch of finished product or starting material and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the marketing authorisation, a labelling/packaging query or a pharmacovigilance report.

Records of traceability of samples should be maintained and be available for review by regulatory authorities.

Duration of Storage

A8-001 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

A8-002 Unless a longer period is required under the law of the country of manufacture, samples of starting materials (other than solvents, gases or water used in the manufacturing process) should be retained for

at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned

Size of reference and retention samples

A8-003 The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions of the full analytical controls on the batch in accordance with the product registration which has been assessed and approved by the APVMA. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the APVMA.

A8-004 Reference samples should be representative of the batch of starting material, intermediate product or finished product 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). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the APVMA. The identity of a complete batch of starting materials can normally be ensured only if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly identified on its label.

A8-005 It should be ensured that all necessary analytical materials and equipment are still available, or are readily obtainable, in order to carry out all tests given in the specification until one year after the expiry of the last batch manufactured.

Storage conditions

A8-006 Storage conditions should be in accordance with the product registration (e.g. refrigerated storage where relevant).

Written agreements

A8-007 Where the product registration holder is not the same legal entity as the site(s) responsible for batch release, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 9 of this GMP code. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.

A8-008 The Authorised Person who certifies a batch for release should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.

A8-009 Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to controlling the taking and location of reference and retention samples.

Reference samples – General points

A8-010 Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials and packaging materials used for medicinal products, this is the original site of manufacture of the finished product. For finished products, this is the original site of manufacture.

Retention samples – General points

A8-011 A retention sample should represent a batch of finished products as distributed and may need to be examined in order to confirm non-technical attributes for compliance with the product registration. The retention samples should preferably be stored at the site where the Authorised Person (AP) certifying the finished product batch is located.

A8-012 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the APVMA.

A8-013 Where more than one manufacturing site is involved in the manufacture importation / packaging / testing / batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

Reference and retention samples in the case of closedown of a manufacturer

A8-014 Where a manufacturer closes down and the manufacturing licence is surrendered, revoked, or ceases to exist, unexpired batches of veterinary chemical products manufactured by that manufacturer remain on the market. For those batches to remain on the market, the manufacturer should make detailed arrangements for transfer of reference and retention samples (and relevant GMP documentation) to an authorised storage site. The manufacturer should satisfy the APVMA that the arrangements for storage are satisfactory and that the samples can, if necessary, be readily accessed and analysed.

A8-015 If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The product registration holder is responsible for such delegation and for the provision of all necessary information to the APVMA. In addition, the holder should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the APVMA in which any unexpired batch has been placed on the market.

ANNEX 9 COMPUTERISED SYSTEMS

Introduction

The introduction of computerised systems into systems of manufacturing, including storage, distribution and quality management does not alter the need to observe the relevant principles given elsewhere in the guide. Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality or quality management. Consideration should be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

Personnel

A9-001 It is essential that there is the closest cooperation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility utilising computerised systems. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of a computerised system.

Validation

A9-002 The extent of validation required should depend on the specific criticality of the system's application, whether the validation strategy is prospective or retrospective, and whether novel technical elements are incorporated. Validation should be integrated across the complete life cycle of a computer system, which includes the sequential stages of planning, specification, programming, commissioning, testing, documentation, operation, continuous monitoring, and change control management.

System

A9-003 Attention should be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.

A9-004 A written detailed description of the system should be produced (including diagrams as appropriate) and kept up-to-date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

A9-005 The software is a critical component of a computerised system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of quality management.

A9-006 The system should include, where appropriate, built-in checks of the correct entry and processing of data.

A9-007 Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results. If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.

A9-008 Data should be entered or amended only by persons authorised to do so. Suitable methods of deterring unauthorised entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined procedure for the issuance, cancellation, and alteration of authorisation to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorised persons.

A9-009 When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.

A9-010 The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorised and recorded with the reason for the change. Consideration should be given to building into the system the creation of a complete record of all entries and amendments (an 'audit trail').

A9-011 Alterations to a system or to a computer program should be made only in accordance with a defined procedure, which should include provision for validating, checking, approving and implementing the change. Such an alteration should be implemented only with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded. Every significant modification should be validated.

A9-012 For quality auditing purposes, it should be possible to obtain readable and complete printed copies of electronically stored data.

A9-013 Data should be secured by physical or electronic means against wilful or accidental damage, in accordance with item 4.9 of the guide. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above-mentioned checks should be performed at a frequency appropriate to the storage medium being used.

A9-014 Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.

A9-015 There should be available adequate alternative arrangements for systems that need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall should be available at short notice.

A9-016 The procedures to be followed if the system fails or breaks down should be defined and validated. Any failures and remedial action taken should be recorded.

A9-017 A procedure should be established to record and analyse errors and to enable corrective action to be taken.

A9-018 When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency (see Chapter 9).

A9-019 When the release of batches for sale or supply is carried out using a computerised system, the system should allow for only an authorised person to release the batches and it should clearly identify and record the person releasing the batches.

ANNEX 10 USE OF IONISING RADIATION IN THE MANUFACTURE OF VETERINARY CHEMICAL PRODUCTS

Introduction

This annex provides for requirements that are applicable when ionising radiation is used during the manufacturing process of a veterinary chemical product. While the specific requirements set forth in this annex apply only to the ionising radiation process, other aspects of the manufacturing process are subject to the requirements set forth in this Regulation as appropriate.

The required radiation dose to be applied, including relevant limits, should be provided for in the product registration.

Premises

A10-001 Premises should be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate materials intended for use in the production of chemical products from other type of materials, provided there is no risk of the former being contaminated by the latter. Any possibility of contamination of the products by radionuclides from the source should be excluded.

Equipment

Dosimeters

A10-002 Dosimeters used should be calibrated according to relevant standards. The period of validity of the calibration should be documented in writing with appropriate justification and be adhered to.

A10-003 The same instrument should normally be used to establish the calibration curve of the dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument should be established.

A10-004 Depending on the type of dosimeter used, due account should be taken of possible causes of inaccuracy including the changes in moisture content, changes in temperature, time elapsed between irradiation and measurement, and the dose rate.

A10-005 The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness should be subject to regular checks of calibration at intervals established having regard to the stability, purpose and usage.

Irradiators

Qualification

A10-006 It should be demonstrated, through appropriate documentation, that irradiators are able to perform consistently within predetermined limits when operated according to the process specification. In this

context, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It should not be possible for variations to occur in the operation of the irradiator which give a dose to the container outside these limits without the knowledge of the operator.

A10-007 When there is change to the process or the irradiator that could affect the dose distribution to the irradiation container (e.g. change of source pencils), it should be re-assessed whether the irradiator continues to consistently perform within the predetermined limits. The extent of assessment needed depends on the extent of the change in the irradiator or the load that has taken place.

Gamma Irradiators

Design

A10-008 The irradiator should be designed taking into account that the absorbed dose received by a particular part of an irradiation container at any specific point in the irradiator can be impacted by the following factors:

(a) the activity and geometry of the source,

(b) the distance from source to container,

(c) the duration of irradiation controlled by the timer setting or conveyor speed,

(d) the composition and density of material, including other products, between the source and the particular part of the container, and

(e) the path of containers through a continuous irradiator or the loading pattern in a batch irradiator, and on the number of exposure cycles.

Dose mapping

A10-009 The results of the dose mapping procedure should give minimum and maximum absorbed doses in the product and on the container surface for a given set of irradiator parameters, product density and loading pattern.

For the dose mapping procedure, the following elements apply:

a) The irradiator should be filled with irradiation containers packed with dummy products or a representative product of uniform density. Dosimeters should be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters should be placed in a larger number of containers.

b) The positioning of dosimeters will depend on the size of the irradiation container. For example, for containers up to 1 x 1 x 0.5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.

c) Ideally, reference dosimeters should be used because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty that can be estimated from the variations in replicate measurements.

d) The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the minimum required dose should be set having regard to the random variability of the routine dosimeters used.

e) Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

Electron Irradiators

Design

A10-010 The irradiator should be designed taking into account that the absorbed dose received by a particular portion of an irradiated product at any specific point in the irradiator can be impacted by the following factors:

(a) the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity,

(b) the conveyor speed,

(c) the product composition and density,

(d) the composition, density and thickness of material between the output window and the particular portion of product, and

(e) the output window to container distance.

Dose mapping

A10-011 The results of the dose mapping procedure should give minimum and maximum absorbed doses in the product and on the container surface for a given set of irradiator parameters, product density and loading pattern.

For the dose mapping procedure, dosimeters should be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. Requirements set forth in points (b) to (d) of A10-009 also apply.

Documentation

A10-012 The numbers of containers received, irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.

A10-013 The irradiator operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.

A10-014 Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained.

A10-015 The documentation associated with the validation and the qualification of the irradiator should be retained for one year after the expiry date or at least five years after the release of the last product processed by the irradiator, whichever is the longer period.

Processing

General

A10-016 Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.

A10-017 During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container should have been established during process validation and as part of the qualification of the irradiator.

A10-018 Radiation indicators should be used as an aid to differentiate irradiated from non-irradiated containers. However, they should neither be used as the sole means of differentiation nor be considered as an indication of satisfactory processing.

A10-019 Processing of mixed loads of containers within the irradiation cell should only be done when there is evidence supporting that the radiation dose received by individual containers remains within the limits specified.

A10-020 When the required radiation dose is -by design- achieved during more than one exposure or passage, this should be specified as part of the contract, including relevant details regarding predetermined time period. Unplanned interruptions during irradiation that extend the irradiation process beyond the specifications set forth in the contract should be notified to the contract giver, who should bring the information to the attention of the authorised person.

A10-021 Non-irradiated products should be always segregated from irradiated products. Methods of achieving this objective include the use of radiation indicators and appropriate design of premises.

Gamma irradiators

A10-022 For continuous processing modes, the following applies:

a) dosimeters should be placed so that at least two are always exposed in the irradiation, and

b) there should be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. The conveyor speed should be monitored continuously and recorded.

A10-023 For batch modes, the following applies:

a) at least two dosimeters should be exposed in positions related to the minimum dose position, and

b) source movement and exposure times for each batch should be monitored and recorded.

A10-024 For a given desired dose, the timer setting or conveyor speed should be adjusted for source decay and source additions. The period of validity of the setting or speed should be recorded and adhered to.

Electron beam irradiators

A10-025 A dosimeter should be placed on every container.

A10-026 There should be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, should be controlled within the pre-defined limits established pursuant to “Qualification”.

Process validation

A10-027 Through process validation it should be demonstrated that the delivery of the intended absorbed dose to the product will achieve the expected results.

A10-028 Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.

A10-029 The irradiation process specification should include at least the following:

(a) details of the packaging of the product,

(b) the loading pattern(s) of product within the irradiation container. When a mixture of products is allowed in the irradiation container, particular care should be taken that there is no underdosing of dense products or shadowing of other products by dense products. Each mixed product arrangement should be specified and validated,

(c) the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode),

(d) maximum and minimum limits of absorbed dose to the product, as well as associated routine dosimetry, and

(e) maximum and minimum limits of absorbed dose to the irradiation container and associated routine dosimetry to monitor this absorbed dose;

(f) other process parameters, including dose rate, maximum time of exposure, number of exposures, etc.

When irradiation is outsourced to a third party, items (iv) and (v) should form part of the contract.

Microbiological monitoring

A10-030 Microbiological monitoring is the responsibility of the manufacturer of the veterinary chemical product. Environmental monitoring and bioburden monitoring prior to irradiation may be required as specified in the product registration.

Subcontracting

A10-031 When treatment by irradiation is subcontracted, the subcontractor should hold an appropriate manufacturing licence.

A10-032 The manufacturer of the veterinary chemical product bears responsibility for the quality of the product, including the attainment of the objective of irradiation. The sub-contractor for the radiation process should ensure that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated)..

Acronyms and abbreviations

Shortened term	Full term
Agvet Code	Agricultural and Veterinary Chemicals Code
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
AS ISO/IEC	Australian Standard / International Organization for Standardization / International Electrotechnical Commission
AS/NZS ISO	Australian/New Zealand Standard / International Organization for Standardization
BP	British Pharmacopoeia
CAPA	Corrective and Preventive Action
CoA	Certificate of Analysis
CSS	Contamination Control Strategy
CV	Coefficient of Variation
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EN ISO	European Standard / International Organization for Standardization
EudraGMDP	European Union Drug Regulating Authorities Good Manufacturing and Distribution Practice
FAMI-QS	Feed Additive and Pre-Mixture Quality System
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GPS	Global Positioning System
HEPA	High-Efficiency Particulate Air (Filter)
HVAC	Heating, Ventilation and Air-Conditioning
IQ	Installation qualification
OMS1	Operations Management Software 1
OOS	Out of Specification

Shortened term	Full term
OQ	Operational qualification
PAT	Process analytical technology
PC2	Physical Containment Level 2
PIC	Pharmaceutical Inspection Co-operation Scheme
PPE	Personal Protective Equipment
PQ	Performance qualification
PQR	Product Quality Review
QC	Quality Control
QMS	Quality Management System
QRM	Quality Risk Management
QTA	Quality Technical Agreement"
RNA	Ribonucleic Acid
SOP	Standard Operating Procedure
SPF	Specific Pathogen Free
TOC	Total Orgainc Carbon
TSE	Transmissible Spongiform Encephalopathy
UIN	Unique Identification Number
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VLC	Veterinary Labelling Code
WHO	World Health Organisation
WHS	Work Health and Safety
WI	Work Instruction

Glossary

Term	Description
Agvet Codes	The Agricultural and Veterinary Chemical Code in each state and territory of Australia which, together with the Agvet Code Regulations, collectively form the legislative basis for the operations of the APVMA throughout Australia. The Agvet Code may be found as a Schedule to the Commonwealth Agricultural and Veterinary Chemicals Code Act 1994 as in force from time to time (that is, including all subsequent amendments). The Agvet Code scheduled to the Agricultural and Veterinary Chemicals Code Act 1994 applies to the Australian Capital Territory (including the Jervis Bay Territory). Each state and the Northern Territory has enacted legislation (the Agricultural and Veterinary Chemicals [State/Northern Territory] Act 1994) to apply the Agvet Code as in force from time to time to that jurisdiction. The Agvet Code of each jurisdiction may collectively be referred to as the Agvet Codes (see also Section 12 of the Agricultural and Veterinary Chemicals Act 1994). Agvet Code Regulations: the Agricultural and Veterinary Chemicals Code Regulations 1995 as in force from time to time, as referred to in the Agvet Codes.
Airlock	Airlock: an enclosed space with two or more doors (only one of which is opened at any time), which is interposed between two or more areas (e.g. of differing classes of cleanliness), for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock may be designed for either people or goods; in the latter case it may also be termed a ‘pass-through hatch’. An airlock may also be the ‘anteroom’ to a ‘cleanroom’ in which sterile goods are processed. It may have an air supply which may be single-pass or recirculated.
Approved supplier	a supplier of starting materials of known origin who is recognised as reliable, based on a history of deliveries that all met specifications and were well packaged and intact on receipt and, where possible, based also on a vendor audit.
Authorised person	a person recognised by the manufacturer as having the necessary basic scientific knowledge and technical experience to carry out specified tasks associated with quality management. Note that this definition is different from that given in the PIC/S code.
Batch	a defined quantity of material manufactured in one process or series of processes, from the same initial starting materials, so that it might be expected to be homogeneous (i.e. uniform with respect to composition and probability of chemical and/or microbiological contamination). However, to complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous processing, the batch is an arbitrarily defined fraction of the production that is characterised by its intended homogeneity (e.g. from one shift or one day, or derived from a particular lot of active ingredient).
Batch manufacturing formulae, manufacturing (or processing), and packaging instructions	are the working documents associated with each batch of product manufactured. They are based on, and are often authorised photocopies of, the master documents.
Batch number	a distinctive combination of numbers and/or letters that uniquely identifies a batch during all steps in the manufacturing process. • The batch number should allow a link to be established between the batch and all tests carried out on it in the course of processing and quality management. • A number of smaller batches may be combined by mixing to form a single batch. However, where the bulk batch is divided into lots that are processed or packaged

Term	Description
	separately during the final stage of manufacture, such lots should be distinguished from one another, for the purposes of product labelling, by a suitable means (usually by an affix to the batch number). • It is permissible to combine one unique series of numbers (processing numbers) on product up to the point of packaging, and another for the packed product, with or without an affix as described above), provided they are unambiguously correlated in batch records. • It is also possible to combine a series of batches of bulk product into a continuous series of packaging operations (not significantly separated in time, place or equipment) and apply a single batch number to the packaged batch, bearing in mind that if a fault occurs, or reconciliation fails, the whole series may have to be rejected or recalled. • Incoming materials will usually carry the batch or lot number of their manufacturer, but will be allocated a unique identifying number by which they are identified on the premises of the user. This avoids the use of the term 'batch number' with two different meanings. Other in-house terms for unique identifying number are acceptable.
Bulk product	any product that has completed all processing stages up to, but not including, final packaging.
Calibration	the process of confirming that the values indicated by a measuring instrument or measuring system, or values represented by a material measure, correspond with the known values of a reference standard.
Carton	a light box or pot made of thick card or plastic for holding goods, especially food or liquid; the contents of a carton.
Chemicals	a substance obtained by or used in a chemical process
Clean area	a suite of rooms (cleanrooms) with defined environmental control of particulate and microbial contamination, used in such a way as to minimise the introduction, generation or retention of contaminants within it.
Code of GMP	the Australian Code of Good Manufacturing Practice for Veterinary Chemical Products. A set of guidelines to assist manufacturers of veterinary chemical products to comply with the APVMA's Manufacturing Principles.
Contained area	an area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.
Containment	the action of confining a substance within a defined space (e.g. carrying out dusty operations in an enclosed room or containing spills within the confines of a bunded floor) or of keeping pests, airborne materials and other contaminants out of a building by effective sealing of entry points.
Contamination control strategy	A Contamination Control Strategy (CCS) is a comprehensive, risk-based system used in highly regulated manufacturing environments, such as pharmaceuticals, to prevent, detect, and mitigate the risks of chemical, microbiological, or physical contamination.
Critical	Extremely important because a future situation will be affected by it.
Cross-contamination	contamination of a starting material or of a product with another material or product.

Term	Description
Document control	the process by which important documents are approved, identified, dated, reviewed and updated as necessary, distributed on a restricted basis to where they are to be used and controlled so that only the current version is available for use.
End-use product: see 'finished product'.	
Filling	the process of filling primary packaging material with unprotected bulk product (e.g. filling a bottle with liquid, tablets or capsules).
Finished product	a completed product which has undergone all stages of production, and which is 'bottled' or packaged, sealed and labelled.
GMP Agreement	a written agreement between the primary manufacturer or registrant of a veterinary chemical product (the contract giver) and another manufacturer or laboratory that carries out a step in the manufacture of that product (the contract acceptor), that clearly specifies each party's responsibility in relation to every aspect of the manufacturing process, assurance of product quality and product registration particulars.
Good manufacturing practice (GMP)	a means of ensuring that veterinary chemical products are consistently manufactured in a safe and clean environment, by specified methods, under adequate supervision, with effective quality management procedures, so that the finished product meets the standards of safety, identity, strength, quality and purity that it is represented to possess.
Herbal medicinal products	medicinal products whose active ingredients are exclusively plant material and/or vegetable drug preparations.
In-process control	checks performed during production in order to monitor and, if necessary, adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.
Intermediate product	partly processed material which must undergo further manufacturing steps before it becomes a bulk product.
Manufacture	all operations (steps) involved in the manufacture of veterinary chemical products, including purchase and quality assurance of raw materials, processing and blending or assembly, quality management, packaging, labelling, sterilising and microbiological reduction, analysis and testing, in process storage, and releasing from manufacture for supply
Manufacturer	any person (individual or legal entity) involved in any step of manufacture of a veterinary chemical product.
Manufacturing premises	a place where any step in the manufacture of veterinary chemical products is carried out.
Manufacturing Principles	a legal instrument to be made by the APVMA which defines the basic principles that manufacturers of veterinary chemical products are required to comply with in order to be issued with and retain a manufacturing licence under the Agvet Codes. These principles form the basis of the Australian Code of Good Manufacturing Practice for Veterinary Chemical Products, with each manufacturing principle corresponding with a key element of the Code of GMP.
Master document	a document from which copies are made for use in the manufacture or testing of individual batches of product. The master is checked, authorised and filed until required

Term	Description
	for copying. It is convenient to distinguish it by having some of the printing or signatures in red ink: the red colour will not appear on copies.
Master manufacturing formulae, manufacturing (or processing) and packaging instructions	documents that list all the raw materials used and provide instructions for all processing and packaging operations.
Packaging	all operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note: sterile filling would not normally be regarded as part of packaging.
packaging material	Any material employed in the packaging of an agvet chemical product, including labels, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether they are in direct contact with the product: primary packaging material—packaging material that comes into direct contact with the product (eg a bottle or blister pack that contains liquids or tablets). secondary packaging material—packaging material that does not come into contact with the product (eg a printed cardboard carton that encases a sealed and labelled bottle of liquid or tablets).
Packaging materials	any material employed in the packaging of a veterinary chemical product, including labels, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether they are intended to be in direct contact with the product. • primary packaging material—packaging material that comes into direct contact with the product (e.g. a bottle or blister pack that contains liquids or tablets). • secondary packaging material—packaging material that does not come into contact with the product (e.g. a printed cardboard carton that encases a sealed and labelled bottle of liquid or tablets).
Person responsible for production	the person nominated on the Manufacturer's Licence as being responsible for production.
Person responsible for quality	the person nominated on the Manufacturer's Licence as being responsible for quality.
Primary packaging	see 'filling'.
Procedures	directions for performing routine operations, e.g. cleaning, clothing, environmental control, sampling, testing, equipment operation. They are often referred to as standard operating procedures (SOPs) or work instructions (WIs).
QA System	The sum total of arrangements made to ensure that products are consistently manufactured in an appropriate manner to the quality standards required for their intended use.
Qualification	the action of confirming that any equipment used or process step in the manufacturing process works correctly and actually leads to the expected results. The qualification process can be applied to equipment installation (installation qualification or IQ), equipment operation under different operating conditions (operational qualification or

Term	Description
	OQ), or equipment operation as part of a specific process (process qualification or PQ). Validation is often the sum of qualification steps.
Quality assurance	Is the sum of the arrangements made to ensure that products are consistently manufactured in an appropriate manner to the quality standards required for their immediate use. a
Quality control	Concerned with specifications, sampling and testing, and with the organisation, documentation and release procedures that ensure that the necessary and relevant tests are carried out so that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.
Quality control function	the procedures carried out by a manufacturer to ensure that effective quality management is carried out at all stages of the manufacturing process and that the finished product meets required specifications.
Quarantine	the status of starting materials, or intermediate, bulk or finished products that are isolated, whether physically or by a system, while awaiting a decision on their suitability for processing, or for sale and distribution.
Raw material	any chemical or physical substance used in the manufacture of a veterinary chemical product, but not including packaging materials.
Reagents	A substance, other than a starting material or solvent, that is used in the manufacture of an agvet chemical.
Reconciliation	the process of comparing, after making allowance for normal variation, the amount of product or in-process materials actually produced with the amount of starting materials used, and the theoretical or expected amount.
Records	confirm that a particular procedure has been carried out correctly. Collectively, they provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.
Reprocessing	the reworking from a defined stage of production of all or part of a batch of product of an unacceptable quality so that its quality may be rendered acceptable by one or more additional operations.
Risk	Risk is the possibility that harm (death, injury or illness) might occur when exposed to a hazard.
Secondary packaging	the process of placing filled, sealed, and labelled primary containers into an outer ‘secondary’ container.
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. They may include visual, organoleptic, physical, chemical and microbiological qualities.
Starting material	any substance used in the manufacture of veterinary chemical products, including both raw materials and packaging materials. (PIC/S definition is, ‘Any substance used in the production of a medicinal products, but excluding packaging materials’).
Step of manufacture	a single, discrete manufacturing activity, e.g. quality assurance of raw materials, blending, processing, primary and secondary packaging, labelling, analysis and testing, sterilisation, release for supply.

Term	Description
Sterile or sterility	freedom from viable contaminating microorganisms as described in the European Pharmacopoeia or other acceptable contemporary standards. The level of assurance provided by the absence of contamination in the sample, when applied to the quality of the batch, is a function of both the efficiency of the sampling plan adopted and the rigour of the test methods employed.
Technical poison	any substance or preparation included in Schedules 6 or 7 of the Standard for the Uniform Scheduling of Drugs and Poisons, published by the Commonwealth of Australia under the Therapeutic Goods Act 1989.
Unique identifying number (UIN)	a number allocated by the manufacturer to each 'separate material' received onto the premises. Materials within the one delivery, but bearing different manufacturers' batch or lot numbers, should each be regarded as 'separate materials'. In some instances, allocation of the raw material manufacturer's batch number may be acceptable.
Validation	the action of proving, in accordance with the principles of good manufacturing practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).
Veterinary chemical product	any substance that fits the legal definition of a veterinary chemical product in the Agvet Codes.
Yield	• theoretical yield—the quantity of material or product that would be produced at an intermediate or final stage of manufacture, assuming that all starting materials, intermediates and final products meet their average specifications and that no loss or error occurs in production. • expected yield—the quantity of material or product expected to be produced at an intermediate or final stage of manufacture, allowing for unavoidable losses (including moisture) under normal but controlled manufacturing practice, and allowing for any deliberate over-fill of product into its unit containers. 'Expected yield' may also be varied batch by batch to allow for factors such as actual moisture content, where this is a significant variable.

References

Visit the Australian Government Style Manual to view full referencing requirements.