

Australian code of
GOOD MANUFACTURING PRACTICE
for veterinary chemical products



Australian Pesticides &
Veterinary Medicines Authority

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Information about the APVMA

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government statutory authority responsible for the registration, quality assurance and compliance of pesticides and veterinary medicines up to and including the point of retail sale. Prior to their sale in Australia, all agricultural and veterinary chemical products must be shown to work, be safe for people, animals, plants and the environment, and not unduly jeopardise Australia's trade with other nations.

The Australian Government and all states and territories have agreed to a National Registration Scheme for Agricultural and Veterinary Chemicals. The Scheme sets out the regulatory framework for the management of pesticides and veterinary medicines in Australia by a single agency. The APVMA is responsible for managing and administering the Commonwealth's regulatory responsibilities under the National Registration Scheme.

The APVMA also manages a number of programs aimed at ensuring the safety and performance of pesticides and veterinary medicines. One of these programs involves the licensing of manufacturers of veterinary medicines.

The National Registration Scheme also provides for a national, uniform and cooperative legislative regime for agricultural and veterinary chemicals throughout Australia administered by the APVMA. The cooperative nature of the legislation is set out in the *Agricultural and Veterinary Chemicals Act 1994* and complementary *Agricultural and Veterinary Chemicals Acts* of each state and territory. The *Agricultural and Veterinary Chemicals (Administration) Act 1992* lays down the governance principles for the APVMA as an independent statutory authority of the Commonwealth. The centerpiece of the Scheme's legislation is the *Agricultural and Veterinary Chemicals Code* (the Agvet Code) scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*. The Agvet Code provides the operational details for the registration of chemical products by the APVMA as well as for quality assurance and compliance programs for pesticides and veterinary medicines up to and including the point of retail sale in Australia. Part 8 of the Agvet Code provides for the licensing of the manufacturers of veterinary medicines by the APVMA, where the manufacturer complies with the APVMA's Manufacturing Principles.

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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 to not place treated animals or users 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 batch-to-batch consistency.

The ultimate responsibility for attaining these quality objectives lies with senior management, but their attainment also requires the participation and commitment of all staff, at all levels, within the manufacturing organisation. In order to achieve these objectives, the manufacturer must have in place a comprehensively designed, adequately resourced and correctly implemented system of quality assurance, incorporating the principles of good manufacturing practice (GMP).

Quality assurance is a wide-ranging concept covering all aspects of the manufacturing process that individually or collectively influence the quality of a manufactured product. It is the sum total of the arrangements made to ensure that veterinary chemical products are consistently manufactured in an appropriate manner to the quality standards required for their intended use. Quality assurance therefore incorporates both GMP and quality control as well as other factors outside the scope of this Code of GMP such as environmental and occupational safety controls.

Quality assurance requires manufacturers to have in place a quality management system encompassing the organisational structure, responsibilities, procedures, instructions, processes and resources necessary for implementing quality management. That system must ensure that facilities and equipment are suitable for the types of products made, that there are sufficient competent personnel and that appropriate procedures are in place to ensure appropriate quality standards are met. In addition, the system must ensure that all materials involved in the manufacturing process (including raw materials, intermediate materials or samples from any material relevant to product quality) are checked and tested, where necessary, to ensure that they meet required quality standards before they are released for use. Procedures must be in place to ensure that the finished product has been made correctly and meets all the required quality tests before it is released for supply or sale.

The quality management system must be relevant to the needs of the product. It must be fully documented, monitored for effectiveness and incorporate an element of continuous improvement.

Good manufacturing practice (GMP) is the part of quality assurance that ensures that products are consistently manufactured to the quality standards appropriate for their intended veterinary use and in accordance with their registration particulars and specifications. GMP is concerned with both production and quality control. It is a means of giving consumers confidence that the products meet the required quality standards and are safe and reliable for the purposes for which they are intended.

The basic requirements of GMP are 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 facilities 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
 - (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 and investigated
 - (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 appropriate corrective and preventive measures are taken in respect of the defective products and to prevent re-occurrence.

Quality control is the part of GMP that is 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.

Compliance with GMP ensures that quality is built into the product at the time of manufacture. It requires products to be consistently manufactured in a safe and clean environment, by specified methods, under adequate supervision, with effective quality control procedures, and with a documentation trail that links starting materials, through the various manufacturing processes, to the finished product.

The various codes of GMP provide guidance as to what is required to achieve acceptable standards for manufacturing and handling veterinary chemical products. Such codes have been adopted in many other countries and are fundamental to maintaining the quality of veterinary preparations in international trade.

This revised *Australian Code of Good Manufacturing Practice for Veterinary Chemical Products* replaces both the *Australian Code of Good Manufacturing Practice for Veterinary Preparations* and the *Australian Code of Good Manufacturing Practice for Homemixed Feeds, Feed-Milling Industry Stockfeed Premixes*, which have formed the basis of the APVMA's Manufacturers' Licensing Scheme since its inception in March 1996. Unlike these earlier Codes, which provided different codes for different types of products, the core chapters of this revised Code of GMP apply to all types of products and to all types of manufacturing plants. The annexures describe any additional or specialised requirements relating to specific types of products, such as immunobiological and sterile products, ectoparasiticides, and premixes.

The intent of each core element has been clearly defined at the start of the relevant chapter in the form of a 'manufacturing principle'. This will clarify the intent (or objectives) of each element of the GMP Code and facilitate more consistent interpretation. These manufacturing principles will

be collated into a new set of APVMA Manufacturing Principles which therefore will be more closely aligned with the Code of GMP. Manufacturers of veterinary medicines must comply with the APVMA's Manufacturing Principles in order to be issued with and retain a manufacturers licence under Part 8 of the Agvet Code. The new APVMA Manufacturing Principles will be determined in accordance with Subsection 23(1) of the *Agricultural and Veterinary Chemicals Act 1994* and will be a formal legislative instrument made under the *Legislative Instruments Act 2003* and registered on the Federal Register of Legislative Instruments. The new principles, to be known as the *Agricultural and Veterinary Chemicals Instrument No. 1 (Manufacturing Principles) 2006* will commence on 1 May 2007. By a separate Instrument, the existing *Agricultural and Veterinary Chemicals Manufacturing Principles (Determination No. 1 of 1997)* made by the then National Registration Authority for Agricultural and Veterinary Chemicals (NRA) in April 1997 will be repealed on the same day.

To facilitate exports, this Code of GMP has been aligned with the *Guide for Good Manufacturing Practice for Medicinal Products*, September 2003 edition, published by the Pharmaceutical Inspection Convention Cooperation Scheme (PIC/S), which is increasingly being used by many of Australia's overseas trading partners, such as New Zealand, some Southeast Asian countries and Europe. This is also the code that is followed by Australian veterinary chemical manufacturers who also manufacture human pharmaceutical products.

The APVMA's revised GMP Code has been written specifically to meet the needs of all Australian veterinary chemical manufacturers. Despite the amalgamation of two codes into one, and alignment with the PIC/S code, many of the requirements of the original codes have remained essentially unchanged.

Background to the review

The *Australian Code of Good Manufacturing Practice Veterinary Preparations* and the *Australian Code of Good Manufacturing Practice for Homemixed Feeds, Feed-milling Industry and Stock-feed Premixes* were first published in 1992 as an initial step in the achievement of acceptable standards of GMP for Australian manufacturers and as a reference point for the acceptance of imported products. They were intended to be adopted voluntarily by industry prior to the introduction of the Manufacturers' Licensing Scheme by the former NRA. The NRA was established in June 1993 but is now known as the Australian Pesticides and Veterinary Medicines Authority (APVMA). The *Agricultural and Veterinary Chemicals Code* (the Agvet Code) scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994* came into effect in March 1995. The Agvet Code provides the operational details for the registration of chemical products by the APVMA as well as for its quality assurance and compliance programs. Part 8 of the Agvet Code provides for the licensing of the manufacturers of veterinary medicines by the APVMA, where the manufacturer complies with the APVMA's Manufacturing Principles. The Manufacturers' Licensing Scheme commenced in March 1996 and the existing Codes of GMP were adopted as the required standard.

An APVMA survey of veterinary chemical manufacturers in 2002 revealed industry support for a single code of GMP that was applicable to all sectors of the industry, but which also identified any special requirements that were specific to particular sectors (e.g. the manufacture of immunobiological and sterile products, ectoparasiticides, and premixes). There was also support for a code that was more closely aligned with the PIC/S Code, which would facilitate exports to countries that have adopted that GMP code (e.g. New Zealand, some Southeast Asian countries, and Europe) and that would also meet the particular requirements of the Australian veterinary chemical industry.

This revised GMP Code addresses those needs. It also addresses a number of shortcomings in the former codes. The intent of the various elements of the GMP Code is clearly defined and more detailed guidance is provided on some critical aspects of manufacture, such as documentation, use of computers and laboratory practice. Requirements for certain products, such as herbal products, direct-fed microbials and feed enzymes, have been clarified, and minor inconsistencies with current legislation have been corrected.

Interpretation of the Code

This Code of GMP is in two parts:

- Part 1 deals with the basic principles or core elements of GMP and applies to all sectors of the industry, all types of products and all sizes of manufacturing plant.
- Part 2 contains the Annexes. These describe additional or modified requirements and guidelines for specific sectors of industry, such as manufacturers of sterile and immunobiological products, ectoparasiticides, premixes and supplements. These Annexes supplement the core elements in Part 1. They do not replace them, and should be read and applied in conjunction with the relevant core elements.

The intent of each core element is described in the manufacturing principle(s) at the start of each chapter and all manufacturers are required to comply with these principles. The guidelines for each chapter provide guidance as to what manufacturers are expected to do in order to comply with the relevant manufacturing principle(s). Additional guidance material is provided in documents such as the European Pharmacopoeia, international and Australian standards, PIC/S guidelines and other relevant reference material, and manufacturers are expected to refer to such references where appropriate.

The revised GMP Code places greater emphasis on the need for manufacturers to maintain an effective quality assurance function and to periodically undertake a scientifically based risk assessment of their processes and procedures. In this regard, it is expected that manufacturers will embrace a culture of continuous improvement and that manufacturing practices will be progressively updated in line with technological developments.

The guidelines in the GMP Code are generally expressed in terms of 'should' and provide some element of flexibility. That is, manufacturers may use an alternative way of satisfying a particular guideline, provided they can demonstrate, on rational scientific grounds, that they meet the intent of the relevant core element. This is particularly important for small manufacturers and manufacturers of products that are not normally thought of as pharmaceutical, such as anti-bloat preparations sprayed onto pastures, salt licks, mined mineral supplements such as dolomite and limestone, therapeutic pet foods and some intra-ruminal devices. In those situations, the way in which the Manufacturing Principles are met might be quite different from what is done in a conventional pharmaceutical plant. For example, a small owner-operated business would not be expected to have an organisational chart or to have a separate person responsible for quality. However, it would be expected to have a suitably qualified/experienced person to release products in accordance with clearly defined and documented procedures.

In all cases, the nature and intended use of the product should be taken into account when interpreting the GMP Code, as well as the need to meet consumer expectations for a safe and

efficacious quality product. It is expected that procedures and practices employed in the manufacture of veterinary chemical products will be based on rational, scientific principles. If there is any doubt about whether a particular manufacturing practice complies with the Code, the critical test is always, 'Does it meet the intent of the Code of GMP and the relevant manufacturing principle?'

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, taking into account 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

Manufacturing principles

- 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:
 - appropriate procedures are in place to ensure that relevant quality standards are met
 - all materials involved in the manufacturing process comply with required quality standards before they are released for use in manufacture
 - there are measures designed to prevent cross-contamination
 - there are safeguards and controls in place designed to prevent the occurrence of foreseeable errors or process failures
 - 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 guidelines

Management of quality

- 101 Management should ensure that a documented quality assurance system is in place and that quality requirements are understood, implemented and maintained at all levels of the organisation. Adequate resources should be provided to achieve this.
- 102 A senior manager should have responsibility for the overall direction and management of quality within the organisation.
- 103 Management should review the quality assurance system at stated, regular intervals (no greater than every three years), to ensure the continued suitability, adequacy and effectiveness of the system, and its continual improvement. That review should evaluate any changes to the quality system that have taken place. The management review process must be documented and records of the review maintained.

Quality assurance

- 104 The quality assurance system should ensure that:
- (a) managerial responsibilities are clearly defined, documented and exercised
 - (b) production and control operations are clearly specified and good manufacturing and good laboratory practices are followed
 - (c) starting and packaging materials meet required specifications utilising, where possible, vendor assurance
 - (d) all necessary controls on intermediate products and in-process controls are carried out

- (e) all necessary validations are carried out
- (f) finished products are not supplied before an authorised person has certified that each batch has been produced in accordance with documented procedures, meets required specifications that are consistent with product registration, and meets all required quality tests
- (g) appropriate environmental and storage conditions are maintained
- (h) there is a procedure for conducting internal quality audits (self inspections) that regularly appraise the effectiveness and application of the quality assurance system.

Quality control

- 105 A system of quality control should be in place to ensure that products comply with their required specifications and standards. The basic requirements of that quality control system are described in Chapter 8.

Quality and production nominees

- 106 The responsibilities for Quality and for Production must be allocated to specific persons. Those nominated for these responsibilities should, where practicable, be different persons, neither responsible to the other. They should be suitably qualified, trained or experienced (see Chapter 2).
- 107 The persons responsible for Production and Quality should have effective control over any manufacturing steps carried out at all premises covered by the manufacturing licence.
- 108 The person nominated as having responsibility for Production must have the necessary authority to control manufacture of the product. The usual duties of that person are described more fully in Chapter 2.
- 109 The person nominated as having responsibility for Quality must 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 satisfactory. The usual duties of that person are described more fully in Chapter 2.
- 110 Where operational events and quality policy conflict, the person nominated as having responsibility for Quality must have the authority to make a decision to resolve the conflict. The circumstances and the decision must be recorded.

Process control and change control

- 111 All critical steps in the manufacturing process, and any changes to these steps, should be documented. Manufacturing processes should be reviewed at defined regular intervals and the outcome of that review documented and acted upon.
- 112 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.

CHAPTER 2

PERSONNEL AND TRAINING

Manufacturing principles

- Veterinary chemical products must be manufactured under the management and supervision of appropriately qualified, trained or experienced persons who:
 - understand the specialised technical, quality and legal requirements relating to the manufacture of veterinary chemical products for which they have responsibility
 - have their duties and responsibilities clearly defined by the manufacturer.
- Manufacturing staff must be trained to a satisfactory level of competency in:
 - the basic principles of good manufacturing practice
 - 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 guidelines

General

- 201 The manufacturer should have an adequate number of 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.
- 202 The manufacturer should have an organisational chart showing the names of key personnel, as well as their areas of responsibility and lines of authority.
- 203 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
- 204 People in responsible positions must have adequate authority to carry out their responsibilities.
- 205 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.
- 206 Operators' verbal and written communication skills should be sufficient for them to respond to training, accept and implement instructions exactly and, where their duties require it, fill out forms correctly.

Key personnel

- 207 Key personnel include the persons nominated as responsible for Production and for Quality and, if neither of these persons is responsible for product release, the person(s) authorised for that purpose. Normally, key positions should be occupied by full-time personnel.

- 208 The persons responsible for Production and for Quality should be independent from each other. In small operations where this may not be possible, the quality control function and procedures should be clearly documented and shown to be effective.
- 209 The person with overall responsibility for Production usually has responsibility to:
- (a) ensure that products are produced and stored according to documented procedures
 - (b) approve procedures relating to production operations and ensure their strict implementation
 - (c) approve and monitor any subcontracted production work
 - (d) ensure that production records are evaluated and signed by an authorised person before they are submitted for product release
 - (e) ensure that production areas, premises and equipment are maintained to an appropriate standard
 - (f) ensure that appropriate validations are conducted
 - (g) ensure that initial and continuing training of production personnel are conducted, according to need.
- 210 The person with overall responsibility for Quality usually has responsibility to:
- (a) evaluate and authorise master manufacturing and packaging documents
 - (b) approve specifications, sampling instructions, test methods and other quality control procedures
 - (c) approve or reject raw materials, packaging materials, and intermediate, bulk and finished products
 - (d) review completed batch records as part of the release procedures
 - (e) ensure that all necessary testing is carried out
 - (f) approve and monitor any contract analysts
 - (g) monitor quality performance of subcontract manufacturers
 - (h) check the maintenance of the quality control area, premises and equipment
 - (i) ensure that appropriate validations are conducted
 - (j) ensure that initial and continuing training of quality control personnel are conducted, according to need
 - (k) approve and monitor the suppliers of materials.
- Other duties relating to quality control are summarised in Chapter 8.
- 211 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.

Qualifications and experience

- 212 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.

Training and competency assessment

- 213 Training should be provided for all personnel 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. Particular attention should be given to the training needs of casual employees.
- 214 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.
- 215 Training programs should include initial training in the basic principles of GMP, as well as training appropriate to the duties assigned to staff. Programs should also include ongoing training and refresher training, including training in changes to the manufacturing process and procedures. Training programs should specifically address the concept of quality assurance, as well as relevant aspects of sanitation and personal hygiene.
- 216 Records should be kept of all internal and external training programs and the various training activities undertaken by individual staff.
- 217 Staff should be assessed for their competence to perform the duties assigned to them. Records should be kept of those assessments.
- 218 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.
- 219 Personnel should have a clear understanding of their responsibilities.
- 220 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.
- 221 A register of staff signatures and initials should be maintained. Entries should be updated at regular stated intervals and the previous records archived.
- 222 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

- 223 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 the health, personal hygiene practices and clothing of staff. These procedures should be understood and followed by every person whose duties take them into the production and quality control areas.

- 224 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).
- 225 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.
- 226 Every person entering the manufacturing or quality control areas should wear protective garments appropriate to the operations carried out there.
- 227 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. Protective clothing should not be worn outside the factory premises.
- 228 Eating, drinking, chewing, smoking, or the storage of food, drink, smoking materials or personal medication must 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.
- 229 Direct contact should be avoided between the operator's bare hands and the exposed product or any part of the equipment that comes into contact with the product.
- 230 The wearing of jewellery that may become detached or caught in machinery should be discouraged in manufacturing areas.
- 231 Specific hygiene requirements for the manufacture of special groups of products (e.g. immunobiologicals and sterile products) are covered in the relevant annexes.

CHAPTER 3

BUILDINGS AND GROUNDS

Manufacturing principles

- Veterinary chemical products must be manufactured in buildings that are located, designed, constructed, maintained and utilised to:
 - suit the operations carried out in them
 - ensure protection of the veterinary chemical products from contamination
 - permit effective cleaning and maintenance, including cleaning after processes have been completed
 - minimise the risk of manufacturing error.
- The products must also be manufactured in an environment, or in equipment fitted with precautionary measures, that:
 - ensures a standard of hygiene appropriate to the class of veterinary chemical product being manufactured
 - minimises the risk of cross-contamination of the finished product, or of materials or components that are used or manufactured at the premises
 - ensures the safety of operators and protects the outside environment.

Buildings and grounds guidelines

General

- 301 Premises should be situated in an environment that presents minimal risk of causing contamination of materials or products. For example, locations in close proximity to chemical works or trades likely to result in pollution or contamination of product should be avoided unless special precautions are taken.
- 302 The premises, including the surrounding grounds and gardens, should be kept in an orderly, neat and tidy condition.
- 303 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.
- 304 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.

- 305 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.
- 306 Sinks should be made of stainless steel, without overflow and preferably be spaced 50 mm away from walls so as to avoid uncleanable joins and crevices. They may require effective, easily cleanable traps and have air breaks to prevent backflow.
- 307 Floor drains should generally 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.
- 308 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.
- 309 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.

Cleaning and sanitation

- 310 Processing areas, laboratories and storage areas should be kept in a clean, sanitary and orderly condition.
- 311 Documented cleaning procedures should be available for all areas. 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
 - (c) the methods used to decontaminate cleaning equipment.
- 312 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 determine appropriate limits based on assessed risk.
- 313 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.
- 314 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, which should be monitored for effectiveness. Records should describe the location of bait stations, materials used, monitoring frequency and effectiveness.

Storage areas (including receipt and despatch)

- 315 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.
- 316 Storage areas should provide storage conditions appropriate to the materials and products held in them. In particular, 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. However, these requirements do not preclude outdoor storage of materials where outdoor storage does not adversely affect quality.
- 317 Where a controlled storage temperature is critical 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
 - (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.
- 318 Refrigerators, cold rooms and freezers should be regularly defrosted and cleaned. In the event that a refrigeration storage facility is shut down, total cleaning should occur.
- 319 Receiving and despatch bays should 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.
- 320 On receipt, all starting materials (including labels, printed cartons and other packaging material) should be subject to effective quarantine and release control.
- 321 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.
- 322 Sampling of raw materials should be conducted in such a way that contamination of the material, or cross-contamination of other materials, is prevented. There should be a separate sampling area for highly active, hazardous or toxic raw materials.
- 323 Highly active, hazardous or toxic materials or products, or otherwise incompatible materials should be stored in such a way as to not pose a risk to other materials or products.
- 324 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.

Production areas

- 325 The operations carried out in any particular area should be compatible so that the integrity of any product made in the area is not threatened.
- 326 Manufacture of sterile, highly active, toxic or infective products should normally be performed in dedicated, self-contained facilities. Processes that may give rise to significant risk from cross-contamination may also require such facilities. However, campaign manufacture in the same facilities may be accepted, provided that specific, documented precautions are taken.
- 327 Registered veterinary chemical products should not be manufactured in the same areas as poisonous, toxic or hazardous unregistered consumer products.
- 328 Veterinary chemical products containing technical poisons should be handled in segregated areas or separate buildings, usually with equipment dedicated to this class of product. However, common areas or equipment may be accepted, provided that cross-contamination is controlled by scheduling or use of a validated cleaning procedure.
- 329 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.
- 330 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.
- 331 Joins 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.
- 332 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.
- 333 The use of wood-based pallets should be avoided in production areas where there is a risk of contamination of the product.
- 334 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.
- 335 Production areas should be effectively ventilated and allow, where necessary, control of air flow, temperature, humidity and filtration appropriate to the products handled, the operation undertaken and the external environment.

- 336 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.
- 337 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.
- 338 Materials likely to shed fibres or other contaminants, such as wooden pallets or fibreboard, should not be taken into areas where products or clean containers are exposed.
- 339 Production areas should be well lit, particularly where visual on-line controls are carried out.

Quality control areas

- 340 Quality control laboratories should be separated from production areas. This is particularly important with laboratories that handle microorganisms.
- 341 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.
- 342 Sensitive instruments should be protected from adverse effects such as vibration, electrical interference, and humidity.

Ancillary areas

- 343 Staff amenities, including lunch rooms, should be separate from storage, production and quality control areas.
- 344 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.
- 345 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.
- 346 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.

Animal houses

- 347 Areas in which animals are housed should be adequately isolated from storage and processing areas, with separate access for animals and separate air handling facilities.

CHAPTER 4

EQUIPMENT

Manufacturing principles

- Equipment used in the manufacture of veterinary chemical products must be suitable for its intended purpose and appropriately operated, maintained and cleaned. Equipment must be correctly installed and operated in accordance with written instructions that are appropriate for the equipment.
- The design and layout of equipment must be such that:
 - the risk of manufacturing error is minimised
 - 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 guidelines

General

- 401 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.
- 402 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.
- 403 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 come into contact with materials being processed or the finished product must not be reactive, additive, or absorptive to such an extent that product quality is adversely affected.
- 404 Equipment should be uniquely identified. This identification should be traceable to all records pertaining to the equipment.
- 405 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.

- 406 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.
- 407 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow. Pipes should be adequately sloped for drainage and constructed without 'dead-legs'. There should be measures in place to ensure that materials transferred via pipelines are delivered to the correct destination.
- 408 Defective equipment should, if possible, be removed from production and quality control areas, or be clearly labelled as defective.

Equipment qualification and validation

- 409 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, calibration, maintenance and cleaning.
- 410 Equipment that has been taken out of service, modified or undergone major repairs should be formally approved for re-entry into service.

Maintenance

- 411 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.
- 412 Repair and maintenance operations should not present any hazard to product quality.
- 413 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
 - (c) records of preventive maintenance, including the name of the service-person, any deviation from the procedure and a statement or authorising signature documenting the condition of the equipment following the service.

Calibration

- 414 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.
- 415 Where appropriate, verification checks should be performed at a frequency consistent with the use of the equipment, in accordance with a written procedure.

- 416 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.
- 417 Records of any equipment calibration should show the actual results observed and the acceptance criteria.
- 418 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.
- 419 There should be evidence to demonstrate that the particular calibrating devices used are themselves accurate. Contractors who calibrate equipment should be certified by a certification agency.

Cleaning

- 420 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.
- 421 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.
- 422 Permanently fixed product and process-water pipelines should have sanitary couplings and be sloped for drainage.
- 423 Washing and cleaning equipment should be chosen and used in such a way that it is not a source of contamination.
- 424 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.
- 425 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 log book.
- 426 Validation of cleaning procedures should be considered where traces of ingredient may pose significant contamination or toxicity risk in following product batches.

CHAPTER 5

DOCUMENTATION

Manufacturing principles

- Manufacturers of veterinary chemical products must establish and maintain a system of documentation, document control and record keeping that:
 - 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
 - provides a complete history of each item, batch, or quantity manufactured in a specified timeframe, of veterinary chemical product produced at the premises
 - establishes a traceable connection between raw materials and the finished product.

Documentation guidelines

General

- 501 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.
- 502 Manufacturing documentation should be designed, prepared, reviewed and distributed with care. It should comply with the relevant parts of product registration dossiers and registered particulars for the product and should be regularly reviewed and kept up to date.
- 503 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.
- 504 Issue of working documents and forms should be limited to photocopying from current, authorised, signed, hard master documents or printing from access-controlled authorised electronic versions.
- 505 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.
- 506 Documents should not be handwritten. Data entries may be handwritten or machine-printed, and must be clear, legible and permanent. Sufficient space should be provided for such entries.

- 507 The contents of documents should be unambiguous. The title, nature and purpose should be clearly stated. The document should clearly identify the way in which it is to be used, and by whom it is to be used. It should include, or be identifiable to, the issuing premises and should also include the following information:
- (a) a unique number identifying the document
 - (b) the version number and date it became effective
 - (c) the page number of the total number of pages of the document on each page
 - (d) provision for authorisation.
- 508 Relevant documentation should be available to cover manufacturing and associated activities at all locations.
- 509 Reproduced documents should be clear and legible. The reproduction of working documents from master documents (e.g. by photocopying or by computer printout), should not allow error to be introduced through the reproduction process. A designated competent person should initial each reproduced document before issue to signify that it is complete, legible and appropriate.
- 510 Any correction to a document should permit the reading of the original information. Corrections should be handwritten clearly and legibly in permanent ink, and initialled and dated by an authorised person. Where appropriate, the reason for the alteration should be recorded.
- 511 Where appropriate, new or revised documents should be introduced following a formal commissioning and training period.

Document control

- 512 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
 - (d) prevention of inadvertent use of superseded documents.
- 513 A documented procedure should be in place that defines the controls needed for the storage, protection, retrieval, retention time and disposal of records.
- 514 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.
- 515 Changes to controlled documents should be acted upon promptly. They should be reviewed, dated and signed by the authorised person(s) and formally implemented. There should be records to show that all relevant personnel have acknowledged subsequent changes to procedures.

- 516 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) should be updated to reflect any relevant changes to the key documents, or be otherwise linked to the revised documents.

Records

- 517 Records should be made or completed at the time each action is taken.
- 518 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.

- 519 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked.
- 520 If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions. Access should be restricted by passwords or other means. See Chapter 6 (Computer Systems) for details.
- 521 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.
- 522 Consideration should be given to storage of batch records and other critical records in a safe and secure environment.

Documents required

Specifications

- 523 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.
- 524 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 preferred suppliers; and, if relevant, the original producer of the materials
 - (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
 - (f) any relevant safe handling instructions.
- 525 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.
- 526 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.
- 527 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
 - (d) the storage conditions, shelf life and any special handling precautions, where applicable.

Materials control (stores receipt, storage and disposal)

528 There should be written procedures and records for the receipt of each delivery of each starting material, including immediate containers and printed packaging material.

529 The records of receipt should include:

- (a) the name of the material on the delivery note and the containers
- (b) the 'in-house' name and/or code of material if different
- (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
- (h) any relevant comment (e.g. state of the containers).

530 The 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
- (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, competent person.

531 There should be written procedures for the internal labelling (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.

532 Any special storage requirements (e.g. temperature) for individual materials should be documented. Records should be kept to confirm that materials have been kept under appropriate storage conditions.

Master manufacturing formula, master batch records and master manufacturing processing instructions

533 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.

534 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.

535 The master manufacturing formula/master batch record 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
- (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.

536 The master manufacturing (or processing) instructions should include:

- (a) a statement of the processing location and the principal equipment to be used
- (b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising)
- (c) 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
- (d) the instructions for any in-process controls, with their limits
- (e) where necessary, the requirements for bulk storage of the products, including the container, labelling and special storage conditions and/or time limits, where applicable
- (f) 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)
- (g) provision for operator initials or signatures at suitable stages
- (h) a summary of all necessary quality control tests and analyses, and at what stage they are to be carried out.

Master packaging and labelling instructions

537 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.

- 538 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.
- 539 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
 - (k) provision for label reconciliation.

Batch manufacturing/processing records

- 540 A batch manufacturing record should be kept for each batch processed. It should be based on the current, approved master manufacturing formula/master batch record and manufacturing instructions and may be a photocopy of the master documents or a specially designed computer print-out. The method of preparation of such records should be designed to avoid transcription errors. The record should 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.
- 541 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) dates and times of commencement of significant intermediate stages and of completion of production
 - (b) name of the person responsible for each stage of production

- (c) 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)
- (d) 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)
- (e) 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
- (f) any relevant processing operation or event and major equipment used
- (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
- (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.

Batch packaging records

- 542 A batch packaging record should be kept for each batch or part batch processed. It should be based on the master packaging instructions and may be a photocopy of the master documents or a specially designed computer print-out. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the estimated quantity of finished product that will be obtained.
- 543 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).
- 544 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
- (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 should be subject to yield and reconciliation controls.

Where product is filled into unlabelled containers for later labelling, special precautions should be taken to maintain the identity of the product during storage.

Quality control sampling and testing

545 There should be written procedures for sampling and testing as specified in Chapter 8.

Release/rejection and distribution of finished product

546 Written release and rejection procedures should be available for materials and products and, in particular, for the release for supply of the finished product by the authorised person(s) designated for the purpose.

547 Batch records should show the name of the person responsible for releasing the product for supply and confirm by way of that person's signature that:

- (a) all manufacturing documents have been reviewed
- (b) all entries are complete
- (c) there are no unexplained or unresolved deviations
- (d) the product meets all specifications
- (e) a final packed item has been visually examined.

548 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.

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

Complaints, recalls and returns

550 Records of complaints, recalls and returned products should be retained for an appropriate period, to be defined by the manufacturer.

Computer records

- 551 Details of the records required where computer systems are used to store critical manufacturing information or control manufacturing processes are described more fully in Chapter 6.

Laboratory records

- 552 Details of the records required in quality control laboratories are described more fully in Chapter 8.

Validation records

- 553 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.

Other

- 554 There should be written procedures and records of actions taken or conclusions reached, where appropriate, for:
- (a) pest control (including details of any pest control program implemented, records of observations made as part of that program and any casual sightings, and details of any corrective action taken)
 - (b) general maintenance, cleaning and sanitisation (cleaning and sanitising instructions should include the name and strength of any cleaning/sanitising agent used)
 - (c) equipment installation and assembly, qualification and calibration (qualification and calibration records should show tolerance limits)
 - (d) equipment maintenance, cleaning and sanitisation (cleaning and sanitising instructions should include the name and strength of any cleaning/sanitising agent used)
 - (e) personnel matters, including medical checks, training, clothing and hygiene
 - (f) environmental monitoring (including temperature and other controlled-environment monitoring devices).
- 555 Clear operating procedures and, where appropriate, specific cleaning instructions, should be available for major items of manufacturing and test equipment.
- 556 Log books or equivalent records should be kept for major or critical equipment, to record any validations, calibrations, maintenance, or repair operations, including dates and the identity of people who carried out those operations.
- 557 Log books or equivalent records should also record, in chronological order, the use and cleaning of major or critical equipment and of the areas where the products have been processed.

CHAPTER 6

COMPUTER SYSTEMS

Manufacturing principles

- 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 must 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, must not adversely affect product quality or quality assurance.

Computer systems guidelines

General

- 601 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.
- 602 Before a system involving a computer is brought into use it should be thoroughly tested and shown to be capable of achieving the intended outcomes. If a manual system is being replaced by a computer system, or the computer system is being upgraded, both 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.
- 603 If software has been commissioned specifically for the manufacturer, its development should be documented at all stages and each step evaluated by expert review against the written objectives. The stages to be documented include planning, specification, programming, testing, installation and operational performance qualification.
- 604 If the software is 'off-the-shelf', but has been configured for the manufacturer's use, then installation qualification and operational qualification should be undertaken. This should include a list of the values/fields/variables/parameters that have been chosen, with detail of how this information is secured and made subject to change control and details of the tests for security that were applied. The operational qualification will show how the system successfully handles instructions and data.
- 605 If 'off the shelf' software has been partly or fully customised, its development should be treated as in 603 above.
- 606 If the software is 'off-the-shelf' and has *not* been configured or customised for use, then it should be precisely defined and an installation and performance qualification should be carried out to demonstrate that user requirements have been satisfied.

- 607 Alterations to a computer system should be made only in accordance with a change control procedure, which should include provision for checking and approving the changes and, to the appropriate extent, performing operational and/or performance qualification.
- 608 When outside agencies provide a computer service, there should be a formal agreement that includes a clear statement of the responsibilities of that outside agency.
- 609 A second authorised person should verify the entry of all critical data, such as master formulae, into a computer system.
- 610 The system should be capable of providing printed copies of all stored data relevant to product quality. Printed matter produced by computer peripherals should be clearly legible.
- 611 A procedure should be established to record and analyse errors and to enable corrective action to be taken.
- 612 The system should record the identity of persons who enter or confirm critical data and be capable of creating a time-stamped record of such entries or confirmations and of all amendments.
- 613 Data should be entered only by authorised persons and there should be methods of preventing unauthorised entry. There should be a defined procedure for the issue, alteration or cancellation of authority to enter and amend data.
- 614 If the computer system is used for batch release, the authority to release should be clearly defined.
- 615 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.
- 616 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.

CHAPTER 7

PRODUCTION

Manufacturing principles

- 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 guidelines

General

- 701 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.
- 702 For each batch of product made, records should be kept of all materials used and of all critical steps and control procedures carried out.
- 703 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.
- 704 The manufacturing process should be periodically monitored at all critical stages to ensure both the reliability of the manufacturing process and product quality, including microbial testing if relevant.
- 705 The identity and where relevant, the status of every material, including waste, should be clearly shown on the outside of its container.

Materials control (including storage)

General

- 706 Records should be kept of all incoming materials received in the store (whether raw materials, intermediate or bulk products or finished products).

- 707 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.
- 708 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.
- 709 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.
- 710 Materials received as intermediate or bulk products should be handled on receipt as though they were raw materials.
- 711 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.

Receipt, storage and quality assurance of raw materials

- 712 Raw materials should be purchased only from approved suppliers named in the relevant specification.
- 713 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.
- 714 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)
 - (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.

- 715 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 5.
- 716 A stock rotation system should be implemented to ensure that raw materials are used by the nominated expiry/retest date.
- 717 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.

- 718 The handling and treatment of animals used for production and testing purposes should comply with all the relevant animal welfare guidelines. Animals used for production purposes or for testing components, materials or products should, where appropriate, be quarantined before use. They should be maintained and controlled and, where necessary, subjected to testing to assure that they meet specifications and are suitable for the intended use. They should be identified and adequate records maintained showing the history of their use.

Receipt, storage and quality assurance of packaging materials

- 719 Upon receipt, packaging materials, including printed labels, should be quarantined until checked against specifications and approved.
- 720 Each delivery or batch of printed or primary packaging material received should be given a specific reference number or identification mark.
- 721 Pre-printed labels must not be overprinted with a different name, dosage, formula or strength of the product.
- 722 Labelling materials should only be issued for use by authorised personnel following an approved and documented procedure.
- 723 Stocks of labels and pre-printed packaging materials should be checked annually and outdated or obsolete material destroyed. This disposal should be recorded.

Cross-contamination control

- 724 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
 - (i) using 'closed' production systems.
- 725 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.

Process validation

- 726 Critical steps in the manufacture of each product or product group should 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.
- 727 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.
- 728 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.

Production procedure

Dispensing of raw materials

- 729 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.
- 730 Only raw materials that have been released for use and which are within their shelf life, should be used.
- 731 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.
- 732 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.
- 733 Materials dispensed for each batch should be kept together, isolated from other materials and be conspicuously labelled with the product batch number.

Processing operations

- 734 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.
- 735 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.
- 736 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.

- 737 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.
- 738 At every stage of processing, products and materials should be protected from microbial and other contamination.
- 739 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.
- 740 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.
- 741 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.
- 742 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.
- 743 As far as possible, deviations from standard procedures should be avoided. Where deviations occur, they should be approved in writing by an authorised person.
- 744 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.
- 745 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.

Intermediate and bulk products

- 746 Intermediate and finished products awaiting release by Quality Control must be segregated physically, or by an equivalent computer system, from other stock.
- 747 Intermediate and bulk products should be stored under appropriate conditions that are clearly defined and documented.
- 748 Material must be transported between premises or buildings in a manner that ensures that the integrity and status of the material is maintained.
- 749 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.

Process water

- 750 The quality of water required (potable or processed) should be specified and be consistent with approved registration details.
- 751 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.
- 752 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
 - (i) periodic reviews, conducted at least once per year.
- 753 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.
- 754 Microorganisms recovered from total counts should occasionally be separately identified. Atypical results should be investigated.

Primary (filling) and secondary packaging operations

- 755 Programs for packaging operations should be devised to minimise the risk of cross-contamination, mix-ups 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.
- 756 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.

- 757 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 758 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.
- 759 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.
- 760 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.
- 761 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.
- 762 Special care should be taken when using cut labels and when over-printing takes place off-line.
- 763 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 764 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 765 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
 - (e) correct functioning of line monitors.
- Samples taken away from the packaging line should not be returned.
- 766 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.
- 767 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.
- 768 Upon completion of a packaging operation, any unused batch-coded packaging materials must be destroyed and the destruction recorded. Unused printed material should be re-inspected before being returned to stock.

Release of finished products

- 769 Finished products should be held in quarantine, under conditions established by the manufacturer, until their final release.
- 770 All product batches must be sampled for quality control and must not be released for supply until all specified tests are completed.
- 771 After release, finished products still under the control of the manufacturer, should be stored under conditions consistent with the approved product label.

Residual, rejected, recovered and returned materials

- 772 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 quantity 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.
- 773 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.
- 774 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.
- 775 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 repackaging, 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.

- 776 Products returned from the market, which have left the control of the manufacturer, should be destroyed, unless without doubt their quality is satisfactory. They may be considered for re-sale, relabelling or recovery with a subsequent batch, only after they have been critically assessed by Quality Control in accordance with a written procedure. The nature of the product, any special storage conditions that it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. There should be no adverse effect on the shelf life of the product batch. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredients may be possible. Any action taken should be appropriately recorded.
- 777 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.
- 778 A suffix or batch number should be used to distinguish any bulked or relabelled material.

CHAPTER 8

QUALITY CONTROL

Manufacturing principles

- Manufacturers of veterinary chemical products must 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 must be sufficiently independent of other aspects of the manufacturing operation to allow effective implementation of the quality control function.
- Manufacturers must ensure that analytical laboratories and animal testing facilities used in a step of manufacture follow the principles of good laboratory practice.

Quality control guidelines

General

- 801 All manufacturers should have an identifiable quality control function. This function should be independent from other functions and under the authority of a person (with appropriate qualifications and experience), who has access to one or more control laboratories. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out.
- 802 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.
- 803 The principal duties of the head of Quality Control are summarised in Chapter 2 (Clause 210). Quality Control also has other duties, which may include:
- (a) establishing adequate quality control specifications for all materials at all stages of manufacture and for the finished product
 - (b) establishing, documenting, validating and implementing all quality control test procedures
 - (c) assessing and releasing/rejecting starting and intermediate materials for each batch
 - (d) assessing and releasing/rejecting each batch of finished product for supply
 - (e) keeping reference/retention samples of materials and products
 - (f) ensuring the correct labelling of containers of materials and products
 - (g) monitoring the suitability of packaging materials
 - (h) monitoring the stability of the products, the suitability of expiry dates and product storage conditions

- (i) participating in the investigation of complaints related to the quality of the product
- (j) monitoring environmental control of quality control laboratories and test animal houses as appropriate
- (k) reviewing trends in analytical results or yields
- (l) establishing or approving procedures for animal quarantine, animal testing and the recovery of biological material from animals for use in analysis, testing or production.

All these operations should be carried out in accordance with written procedures and be recorded.

804 Analytical laboratories and animal testing facilities should follow the principles of good laboratory practices (GLP). Written procedures should be established for at least the following:

- (a) cleaning of quality control areas and equipment
- (b) preparation of materials and reagents
- (c) maintenance of reference substances
- (d) calibration and maintenance of quality control equipment
- (e) dealing with out-of-specification results
- (f) reviewing analytical performance.

805 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 as required in Clauses 813–823).

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

807 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
- (c) this laboratory, if located in Australia, should be appropriately licensed by the APVMA to test veterinary chemical products in the manner required.

808 Animals used for testing components and products should be handled in the same way as those used in the manufacturing process (see Clause 718, Chapter 7).

Documentation

809 Laboratory documentation should follow the general principles given in Chapter 5 'Documentation'. The following information should therefore be prepared by, or be readily available to, Quality Control:

- (a) specifications
- (b) sampling procedures

- (c) testing procedures and records (including analytical worksheets and/or laboratory notebooks)
 - (d) analytical reports and/or certificates
 - (e) data from environmental monitoring, where required
 - (f) validation records of test methods, where applicable
 - (g) procedures for and records of, the calibration of instruments and maintenance of equipment.
- 810 Any quality control documentation relating to a batch record should be retained for the period defined in clauses 517–522, Chapter 5.
- 811 To facilitate compliance with the requirements of Clause 803, it is recommended that records of analytical test results, yields and environmental controls be kept in a manner permitting trend evaluation.
- 812 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.

Sampling

Sampling plans

- 813 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 be expected to 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
 - (i) require the sampling officer or analyst to initially examine each sample for homogeneity, evidence of deterioration or other visible defect.
- 814 Sampling plans for packaging materials should take into account:
- (a) the items shown as (*) listed in Clause 813 for starting materials

- (b) the need to check the identity of each container or reel of labels and pre-printed packaging materials
- (c) the number of samples needed to reach a valid decision to approve or reject a delivery in relation to quality-related defects.

Sampling Procedures

- 815 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
 - (i) instructions for the cleaning and storage of sampling equipment.
- 816 The sampling procedure should be justified, taking into consideration the nature of the material or the method of manufacture of the product being sampled.
- 817 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.
- 818 All samples taken for quality control purposes should be taken by Quality Control personnel, except samples for in-process control, which may be taken by authorised production staff.
- 819 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.

Retention samples

- 820 Quality Control should take and retain samples of:
- (a) at least each batch of active starting material
 - (b) each batch of finished product.
- 821 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.

- 822 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.
- 823 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.

Product release

- 824 Products should be released in accordance with the procedures specified in Chapter 5.

CHAPTER 9

CONTRACT MANUFACTURE

Manufacturing principles

- Where all or part of the manufacture of a veterinary chemical product is contracted to another party, the licensed manufacturer must 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 must not compromise the quality of the product.
- Where a contractor is authorised to manufacture under the licence of another manufacturer, the licence holder must exert direct control and oversight of the quality management of the contracted step.

Contract manufacture guidelines

General

- 901 Contracted manufacture may involve the entire production and packaging processes, or steps such as tablet coating, packaging, labelling, sterilisation, analysis or testing and release for supply.
- 902 When a manufacturer or registrant of a veterinary chemical product ('contract giver') contracts all or some of the steps of manufacture to another manufacturer ('contract acceptor'), both parties should authorise a written agreement (usually referred to as a 'GMP Agreement' or 'Specification of GMP Responsibilities') that clearly defines the steps of manufacture, or scope of any analytical work, to be carried out. It should also define the GMP responsibilities of each party for each aspect of the work. All GMP Agreements should be kept up to date.
- 903 Contract manufacture may be undertaken only by a manufacturer who is the holder of an APVMA Manufacturer's Licence, unless the work undertaken by the contract acceptor 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.*

The GMP Agreement

904 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.

905 The Agreement should permit the contract giver, agreed third party or an APVMA-authorized GMP auditor to visit the facilities of the contract acceptor for auditing purposes. The agreement should require the contract giver to provide, for this purpose, access to details of relevant analytical methodology and validation studies, or manufacturing procedures, quality control tests and manufacturing records.

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

The contract giver

907 Only APVMA-authorized manufacturers should be selected to carry out the specified steps of contract manufacture.

908 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. 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.

909 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
- (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.

The contract acceptor

- 910 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
- 911 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.
- 912 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.
- 913 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.
- 914 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.
- 915 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 Manufacturers 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.
- 916 Manufacturing, analytical and distribution records, and retention samples should be kept as specified in the GMP Agreement and in accordance with the *Agricultural and Veterinary Chemical Codes Regulations 1995* (see also Chapter 5 'Records').
- 917 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.

Inspection of contract manufacturers

918 Audits of contract manufacturers by the contract giver or an agreed third party should be carried out to ensure that work is carried out to requirements in accordance with GMP. 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 guidelines

General

- 1001 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 GMP and to assess the effectiveness of the quality assurance system. Those audits should cover all aspects of manufacture. 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.
- 1002 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.
- 1003 Where the need for corrective action has been identified, steps should be taken to address any observed deviations from the documented quality system and manufacturing procedures. Corrective and preventive action should be monitored for effectiveness and modified if necessary. Documented procedures should be amended if there is an identified need to do so.
- 1004 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 AND PRODUCT RECALLS

Manufacturing principles

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

Complaint and product recall guidelines

Complaints

- 1101 There should be documented procedures for the handling of all complaints, recalls and returned product.
- 1102 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 the need to consider a recall in the event of a complaint concerning a possible product defect.
- 1103 Records should be kept of all complaints received, investigations carried out and their outcomes and any corrective action taken to resolve the complaint and prevent the problem happening again.
- 1104 All complaints related to product quality should be registered in a complaints register.
- 1105 Records should also be kept of all product 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.
- 1106 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. If this person is not the person responsible for quality, the latter should be made aware of any such complaint or investigation involving products manufactured or handled on the premises.
- 1107 The complaints procedure should incorporate the APVMA's requirements for adverse experience reporting.

Suspected product defects

- 1108 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.
- 1109 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of products.

Recalls

- 1110 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.
- 1111 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 and the requirements of the *Trade Practices Act 1974*. Procedures should be regularly checked and updated when necessary.
- 1112 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.
- 1113 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.
- 1114 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.
- 1115 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 1116 The progress of a recall should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of products.
- 1117 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.
- 1118 The effectiveness of the recalls procedure should be evaluated from time to time 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.

PART 2

ANNEXES

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, taking into account the type of product being made and its intended use. Some additional guidelines for specific types of products/manufacturers are outlined in the following Annexes.

Note that these Annexes are intended to help with interpretation of this Code of GMP as it applies to the particular type of product referred to. They are not meant to replace the core elements of the Code and should be read in association with the relevant core elements.

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

ANNEX 1

MANUFACTURE OF STERILE PRODUCTS

Manufacturing principles

- Veterinary chemical products that are required to be, or are represented as being sterile, must be manufactured:
 - in separate, controlled areas in the premises that have
 - › high standards of hygiene
 - › a system of controlling particulate contaminants appropriate to the class of veterinary chemical product being manufactured.
 - with special care and attention to detail
 - in accordance with procedures established and validated by the manufacturer.
- The manufacturer must establish procedures and have equipment available (or in the case of bioburden, have access to equipment) to adequately monitor:
 - the microbiological status of the environment in production areas
 - the microbiological burden 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.

General

Premises

- A1-001 Sterile products should be manufactured in areas that are designed and managed to minimise microbial and particulate contamination.
- A1-002 Wherever practicable, enclosed systems should be employed for product preparation and filling.
- A1-003 Sinks and floor drains should be excluded wherever possible. Where this is unavoidable, air breaks should be fitted between the machine and sink or drain.
- 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 may be appropriate for moving some materials into controlled areas.
- 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.
- 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.
- 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 must 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 must 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.

A1-014 Areas for the manufacture of terminally sterilised product must be designed to prevent the mixing of sterilised and non-sterilised products.

Sanitation and hygiene

A1-015 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.

A1-016 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.

A1-017 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
- d) dismantling, cleaning and decontamination of pumps, filters, pipelines, and filling heads and for their subsequent inspection for release for use in processing.

A1-018 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.

A1-019 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.

Environmental control

Air quality

A1-020 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. 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.

A1-021 The classification of airborne particulate levels for Grades A–D is given in the following table.

Maximum permitted number of particles/m³ of given size^(a)

Grade	At rest ^(b)		In operation ^(b)	
	≥ 0.5 µm ^(c)	≥ 5 µm	≥ 0.5 µm ^(c)	≥ 5 µm
A	3500	1 ^(d)	3500	1 ^(d)
B	3500	1 ^(d)	350000	2000
C	350000	2000	3500000	20000
D	3500000	20000	See Note ^(e)	See Note ^(e)

- 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 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 m³ for Grade A and B areas and preferably also in Grade C areas.
- 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 be completely free from particles of size greater than 5 µm. As it is impossible to demonstrate the absence of particles with any statistical significance, the limits are set to 1 particle/m³. During the cleanroom qualification it should be shown that the areas can be maintained within the defined limits.
- (e) The requirements and limits will depend on the nature of the operations carried out.

A1-022 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.

A1-023 Examples of operations to be carried out in the various air quality grades

Grade	Operations 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	Operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

A1-024 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 must be held before sterilisation), preparation of solutions and components should be carried out in at least a Grade C environment.

A1-025 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).

A1-026 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.

A1-027 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, sanitation of the isolator, the transfer process and isolator integrity.

A1-028 Monitoring of isolators should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.

A1-029 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

- A1-030 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.
- A1-031 Environmental monitoring of clean areas should include the following components:
- (a) particulate monitoring during routine operation, where relevant
 - (b) airborne microbiological monitoring
 - air samplers must sample an adequate quantity of air to provide a meaningful result (see note Clause A1-021(a))
 - air monitoring using both volumetric and settle plate-sampling methods in aseptic fill and seal areas.
 - (c) microbiological monitoring of surfaces (e.g. walls, equipment surfaces, bench tops, trolleys and floors)
 - (d) microbiological monitoring of personnel (e.g. external surfaces on gloves, sleeves, and torso).
 - (e) temperature and humidity monitoring; the recommended settings are 18 °C and 35–50% 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).
- A1-032 Environmental monitoring methods used should be justified.
- A1-033 Microbiological and particulate contamination should be controlled and monitored for each grade by a comprehensive procedure approved by quality management staff.
- A1-034 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.
- A1-035 Isolates found during environmental monitoring should be regularly identified.

Personnel

- A1-036 Management must 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.

- A1-037 All personnel (including those concerned with cleaning and maintenance) should receive training in procedures and in disciplines relevant to the correct manufacture of sterile products, including hygiene (referred to in Chapter 2, Clauses 223–230) 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.
- A1-038 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.
- A1-039 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.
- A1-040 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.
- A1-041 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. Non-powdered 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

- A1-042 Unidirectional airflow equipment must be regularly tested and the results recorded.
- A1-043 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.

- A1-044 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.
- A1-045 Vessels containing bulk sterile-filtered water or product should be vented through bacteria-retaining filters.
- A1-046 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 and should be calibrated periodically. Records should permit verification of achievement of these parameters with an appropriate degree of accuracy.
- A1-047 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.
- A1-048 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.
- A1-049 The pressure during steam sterilising cycles should be recorded at least manually.
- A1-050 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.
- A1-051 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.
- A1-052 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 80 °C or at 4 °C or below.
- A1-053 All water systems that supply processed water to be used in the manufacture of products should be monitored for:
- (a) total organic carbon
 - (b) conductivity
 - (c) endotoxin
 - (d) microbial quality.

Specification for materials

- A1-054 Specifications for raw materials should consider microbial limits and any special storage requirements.
- A1-055 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.
- A1-056 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

- A1-057 Containers or other materials liable to generate particles or fibres should not be taken into areas supplied with Grade A, B or C air.
- A1-058 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.
- A1-059 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.
- A1-060 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 $\leq 0.45 \mu\text{m}$, where possible immediately before filling.
- A1-061 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.
- A1-062 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.
- A1-063 Sterilisation records should be reviewed and approved as part of the batch release procedure.
- A1-064 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.

- A1-065 Microbiological indicators should be quarantined and subjected to quality control before use.
- A1-066 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.
- A1-067 Components, containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated.
- A1-068 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.
- A1-069 Where practicable, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with product registration.
- A1-070 Validated loading patterns should be established for all sterilisation processes.
- A1-071 Biological indicators should be considered as an additional method for monitoring the sterilisation process. 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

- A1-072 Each heat sterilisation cycle should be recorded on a time/temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision.
- A1-073 Chemical or biological indicators may also be used, but must not take the place of physical measurements.
- A1-074 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time is commenced. This time must 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.
- A1-075 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.

Sterilisation by moist heat

- A1-076 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.
- A1-077 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

- A1-078 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

- A1-079 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.
- A1-080 Biological indicators may be used as an additional control.
- A1-081 Validation procedures should ensure that the effects of variations in density of the packages are considered.
- A1-082 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.
- A1-083 The total radiation dose should be administered within a predetermined time span.
- A1-084 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.
- A1-085 Ultraviolet irradiation is not normally an acceptable method of sterilisation.

Sterilisation by ethylene oxide

- A1-086 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.
- A1-087 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.
- A1-088 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.
- A1-089 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

- A1-090 Solutions or liquids should be filtered through a sterile filter of nominal pore size of $\leq 0.22 \mu\text{m}$, 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.
- A1-091 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.
- A1-092 Fibre-shedding characteristics of filters should be minimal. Asbestos-containing filters must not be used under any circumstances.
- A1-093 The same filter should not be used for more than one working day, unless such use has been validated.
- A1-094 The filter should not affect the product by removal of ingredients from it or by release of substances into it.
- A1-095 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 from this 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)

- A1-096 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.
- A1-097 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.
- A1-098 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. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

Quality control

- A1-099 Where required or appropriate, tests for the following should be carried out on each batch of product:
- (a) sterility
 - (b) uniformity of contents
 - (c) potency
 - (d) pyrogenicity or endotoxin
 - (e) particulate matter.
- For injectable and large volume infusion solution products, such testing is essential.
- A1-100 Cumulative records of environmental control, the testing of manufacturing equipment, media fill runs and all other applicable quality control tests should be maintained by Quality Control.
- A1-101 Pharmacopoeial methods must be used for sterility tests. These methods should be validated for the product(s) concerned.
- A1-102 Where parametric release has been authorised, all calibrations and controls that were specified in the application for authorisation must be rigorously maintained.
- A1-103 Samples taken for sterility testing should be representative of the whole of the batch, but should in particular 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
 - (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.

A1-104 Release of sterile product must 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.

Aseptic processing

Premises

A1-105 Aseptic filling should involve the minimum of human intervention.

A1-106 Sinks and drains should be excluded from aseptic filling/sealing rooms.

A1-107 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.

A1-108 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).

Production areas

A1-109 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.

A1-110 Non-sterile products should not be processed in the same area as sterile products.

A1-111 Grade B areas (see Clause A1-020) should be designed so that all operations can be observed from the outside.

Sanitation and hygiene

A1-112 During aseptic operations, the areas must not be used for any other purpose. After any non-sterile operation such as maintenance, and before aseptic operations are commenced, the areas must be thoroughly cleaned and disinfected.

A1-113 Clean and, where necessary, sterile protective clothing must 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.

A1-114 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.

A1-115 Disinfectants and detergents used in Grade A and B areas should be sterile before use.

Environmental control

A1-116 The 'in operation' and 'at rest' states should be defined for each cleanroom or suite of cleanrooms.

A1-117 Examples of operations to be carried out in the various clean zone grades

Grade	Operations 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

A1-118 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.

A1-119 Additional microbiological monitoring may be appropriate after activities such as major maintenance, interruption to production and equipment validation.

A1-120 Recommended limits to be used in microbiological monitoring of clean areas during operation are given in the following table:

Recommended limits for microbial contamination^(a)

Grade	Sampling method			
	Air sample cfu/m ³	Settle plates (diam. 90 mm) cfu/4 hours ^(b)	Contact plates (diam. 55 mm) 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

A1-121 It should be demonstrated that airborne cleanliness classifications are met during operations. Appropriate alert and action limits should be set for the results of particulate monitoring. Operating procedures should prescribe corrective action, if these limits are exceeded.

Personnel

A1-122 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.

A1-123 Personnel engaged in servicing equipment or other non-routine activities must observe the same precautions and hygiene standards as production personnel.

A1-124 Wristwatches, make-up and jewellery should not be worn in clean areas.

A1-125 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.

A1-126 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

A1-127 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

- A1-128 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.
- A1-129 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. Noncombustible gases should be passed through microorganism-retentive filters.
- A1-130 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. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth, but production need not be halted if a contamination rate of less than 0.1% is observed. The manufacturer should establish alert and action limits.
- A1-131 Care should be taken that any validation does not compromise the processes.

ANNEX 2

IMMUNOBIOLOGICALS AND OTHER PRODUCTS OF BIOLOGICAL ORIGIN

Manufacturing principles

- Veterinary immunobiological products and other chemical products of biological origin including those that are manufactured using a specified biological process must be manufactured:
 - using only biological starting materials that are, or are derived from biological materials demonstrated to be as free as practicable from adventitious contamination
 - 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:
 - › are established and validated by the manufacturer
 - › maintain the safety of personnel.
 - in cases where uniformity of product depends on deriving batches from a seed lot
 - › by maintaining the lots in secure and protective storage
 - › 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 nature of biologics manufacture (e.g. cultivation of microorganisms), the products must be well protected against contamination and cross-contamination. This Annex should therefore be read in conjunction with Annex 1.

Premises

General

- 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 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.

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, 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 by the use of clean contained and/or controlled areas.

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.

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.

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 control, 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 control activities), the level of containment should be adequate to cope with all such risks. Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those used for production.

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.
- (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 air locks 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 air lock 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 air lock should be of a size that enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.
- (g) There should be a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items, where appropriate.

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 normally be ventilated in the same way, but unventilated hatches, or those equipped with supply air only, may be acceptable.

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.

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, must be appropriately separated from other aseptic filling operations. This may be achieved by using separate areas or by elapsed time and effective decontamination procedures.

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 must be thoroughly cleaned and disinfected after any non-sterile operation, such as maintenance and before aseptic processing resumes.

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.

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.

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 must 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.

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 air flow.

A2-023 Separate incubators should be used for infected and non-infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type will only be acceptable if adequate 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.
- A2-026 In heat sterilising processes, it is essential that the whole load reaches the sterilisation temperature. Account must be taken of heat-up times for various loads and ‘typical loading’ diagrams should be part of standard operating procedures. Standard operating procedures must be available.
- A2-027 Items to be sterilised by autoclaving must 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 must be tested immediately after each use.
- 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.
- 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.

Animals and animal houses

- A2-031 The sanitary 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 also 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.

A2-035 Animal houses accommodating animals that are used for quality control 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 must 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 must be included. Microbiological controls are particularly important.

A2-040 The results of tests on starting materials must 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 must 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.

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.

Operating techniques

- A2-049 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.
- A2-050 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.

- A2-051 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 must be protected by unidirectional airflow workstations. Checks should be made to ensure that vessels are correctly connected when addition of cultures takes place.
- A2-052 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 air flow protection of connections may be acceptable.
- A2-053 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 must be adequately disinfected through an equipment transfer hatch, or the information transferred out by alternate means.
- A2-054 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.
- A2-055 Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only materials concerned with production are introduced.
- A2-056 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).
- A2-057 Precautions should be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators.
- A2-058 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 must be effectively disinfected between the handling of different live biological agents.
- A2-059 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.
- A2-060 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.
- A2-061 Containers of bulk material should be sealed, appropriately labelled and stored under specified conditions.

- A2-062 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.
- A2-063 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.
- A2-064 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

- A2-065 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.
- A2-066 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.
- A2-067 Where production of a biological product involves continuous culture, the quality control requirements arising from such a production method should be appropriately addressed.
- A2-068 Sufficient quality control testing should be undertaken to ensure that the product complies with the approved registration particulars.
- A2-069 Quality Control should maintain cumulative records of environmental control, the testing of manufacturing equipment and all other quality control tests where applicable, and should take into account the results of such testing before releasing any batch of product for distribution.

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 by the use of 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 Appendix 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 to 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 Apart from 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 and/or microbial, including aflatoxins, pest infestations, toxic metals, and other possible contaminants and adulterants), as well as the methods used to determine such contamination
- (i) tests for foreign materials.

A4-003 Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Specifications for such procedures should be available and should include details of processes, tests and limits for residues.

ANNEX 5

ECTOPARASITICIDES

Introduction

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, that are purported to have a therapeutic benefit and are therefore required to be registered. As a consequence, they must be manufactured in compliance with GMP standards. In most cases they are administered to animals in their feed or drinking water, which means that individual dosage is not controllable. The range of products includes:

- premixes
- supplements
- mined mineral supplements
- feed additives, such as probiotics and other direct-fed microbials, and enzymes derived from microbial cultures.

Premixes and supplements

General

Animal feed and water premixes facilitate the addition of medication to larger volumes of stockfeed. They are used when the active materials are difficult to weigh out or handle or are uneconomical to keep in a commercial or farm-based stockfeed mixing operation.

Supplements are usually mixtures of vitamins and minerals added to feed or drinking water. The products can be formulated either as a dry powder mix or as a liquid preparation. Others are formulated as self-administered products, such as solid salt or molasses block licks, or as liquid licks. Some products are simply minerals, such as limestone and dolomite, which are mined out of the ground, crushed, sieved and bagged as livestock mineral supplements.

Because of the large amount of dust generated during the manufacture of dry preparations, special attention should be paid to cross-contamination control, either by physical separation from other aspects of manufacture or by effective dust extraction and hygiene.

Some preparations are referred to as 'electrolytes', and are mainly used to replace minerals and other electrolytes lost by greyhounds and horses during exercise. Despite the therapeutic claim, most of these 'electrolytes' are more appropriately thought of as feed supplements from a manufacturing point of view.

Buildings and grounds

A6-001 The manufacture of dry premixes and supplements usually requires dedicated areas that are separated from other aspects of veterinary chemical manufacture either by distance or by physical barriers, in order to minimise the risk of cross-contamination.

- A6-002 Cleaning programs should specifically address the buildup of dust, sticky materials such as molasses and corrosive materials such as salt.
- A6-003 The manufacture of premixes often requires the use of large quantities of vegetable matter, which is likely to attract insects, birds, rodents and other pests. This should be addressed in the pest control program.
- A6-004 External driveways and paths surrounding the manufacturing area should be sealed to prevent the tracking of dirt and mud on the wheels of forklifts and other mobile equipment into the production areas.

Personnel

- A6-005 Where premixes and supplements are manufactured in premises also used to manufacture other products, the staff involved in the manufacture of premixes and supplements should be clearly identified and trained in those elements of GMP appropriate to their need.

Equipment

- A6-006 Complete cleaning may not be required between batches of the same or closely related products, provided that product integrity is maintained.

Process control

- A6-007 Parts of the process likely to have a significant adverse influence on the stability of the active ingredients (e.g. use of steam in pellet manufacture), should be controlled to ensure batch-to-batch consistency.
- A6-008 Special attention needs to be paid to the prevention of microbial contamination during manufacture or storage of susceptible liquid formulations.

Mined mineral supplements

Mineral supplements such as limestone and dolomite are often dug out of the ground by a front-end loader, crushed and ground, sieved and then bagged.

The identity and, where relevant, purity of the material being mined and of the processed material, should be checked using an appropriate level of testing, consistent with registered particulars. Care should be taken to ensure that stockpiled material is stored in such a way that contamination by stormwater runoff and other drainage materials is avoided, and that the bagged material is free from contaminants, such as pieces of metal, broken glass, bird and other animal droppings.

Direct-fed microbials and enzyme products

General

Direct-fed microbials (DFMs, sometimes known as probiotics) are essentially products that contain viable microorganisms (bacteria and fungi) for oral administration to livestock as an aid to digestion and to improve the efficiency of feed conversion, or to improve the health of the gut. The products are usually formulated as either a powder or pellet, or as a yoghurt type liquid. They may be administered as mass medications in feed, or individually administered to single animals.

Enzyme feed additives are specific, naturally-occurring enzymes that are usually derived from cultures of microorganisms similar to those used to manufacture direct-fed microbials, although some of them are derived from plant or animal tissues. They are usually formulated as a powder or pellet, although they can also be formulated as a liquid, and are usually added to stock feed as an aid to digestion and to improve the efficiency of feed conversion.

Direct-fed microbials and enzyme products are susceptible to microbial contamination during manufacture and subsequent storage and, in the case of enzyme products, heavy metal contamination from materials used in the fermentation process. For APVMA registration purposes, both types of products are required to meet minimum standards of potency, purity and activity of the active materials and to be free from or meet required standards for harmful organisms such as *Escherichia coli* and *Salmonella spp.* Enzyme products are also required to meet minimal standards for heavy metal contamination.

Particular attention should be paid to the uniformity and quality of the parent material (master and working seed cultures), media quality, and hygiene, both in the premises and during the manufacturing process. There should be an adequate level of quality control testing during the manufacturing process and of the finished product. A higher standard of manufacture is required where the manufacturing process involves fermentation and/or extraction of culture.

Where the product being made is essentially a premix of the active material with other materials, the standard of manufacture is essentially the same as that required for premixes and supplements, with particular attention being paid to sanitation and the quality of the raw materials.

Buildings and grounds

A6-009 The air supply to the areas used for the production of direct-fed microbials and enzyme products should be designed to minimise contamination.

Personnel

A6-010 Personnel responsible for the manufacture and quality of direct-fed microbials and enzyme products should have appropriate qualifications in microbiology or related subjects and/or experience in the manufacture of such products.

A6-011 Where manufacture of direct-fed microbials and enzyme products is carried out in premises also used to manufacture other products, the staff involved in the manufacture of direct-fed microbials should be clearly identified and trained in those elements of GMP appropriate to their need

Process control

Materials control

A6-012 The taxonomic identity of microorganisms selected for direct-fed microbials or enzyme production should be checked.

A6-013 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.

A6-014 The master seed culture should be maintained in such a way as to minimise degeneration and maintain genetic stability.

A6-015 All seed cultures should be clearly labelled and strict aseptic techniques applied in revival and subculture.

Production control

A6-016 All operations should be designed to avoid contamination, formation of undesirable by-products, deterioration and handling errors.

A6-017 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.

A6-018 Enzyme activity and operational parameters such as temperature, pH and oxygen content, should be monitored during fermentation and kept within predetermined ranges based on experience. Deviations from these ranges may indicate a contamination before it can be detected in microbial assays.

Enzyme recovery

A6-019 Steps should be taken to ensure that contamination of the product during recovery is minimised.

GLOSSARY

Please note: The definitions given below apply to the words as used in this Code of GMP. They may have different meanings in other contexts.

Action limit: established criterion (such as a microbiological count or a monitor reading) that requires immediate corrective action if exceeded. Frequently used in conjunction with

Alert limits.

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.

Air lock: 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 air flow between those rooms when they need to be entered. An air lock may be designed for either people or goods; in the latter case it may also be termed a 'pass-through hatch'. An air lock 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.

Alert limit: established criterion (such as a microbiological count or a monitor reading), that gives early warning of potential drift from normal conditions. **Alert limits** are not necessarily grounds for definitive corrective action, but require follow-up investigation.

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 control. 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 control.
- 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 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.

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.

Cross-contamination: contamination of a starting material or of a product with another material or product.

Crude plant (vegetable drug): fresh or dried medicinal plant or parts thereof.

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.

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 control procedures, so that the finished product meets the standards of safety, identity, strength, quality and purity that it is represented to possess.

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.

Herbal medicinal products: medicinal products whose active ingredients are exclusively plant material and/or vegetable drug preparations.

Intermediate product: partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

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.

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 control, 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 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.

Medicinal plant: a botanical plant, the whole or part of which is used for pharmaceutical purposes.

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 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).

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 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 total of the arrangements made to ensure that products are consistently manufactured in an appropriate manner to the quality standards required for their immediate use.

Quality control: is 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 control 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.

Reconciliation: the process of comparing, after making due 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.

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.

Standard name: a name assigned to a **starting material** that uniquely identifies it within the manufacturing establishment.

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.

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.

