

Good manufacturing practice for immunological veterinary medicinal products

J.I. Todd

Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey KT15 3LS, United Kingdom

Summary

Good manufacturing practice (GMP) is applied to the manufacture of immunological veterinary medicinal products (IVMPs) in a number of regions around the world. Within the European Union (EU) there are well-established requirements for GMP in the manufacture of IVMPs. Maintaining GMP when producing IVMPs is important because there are particular risks associated with their manufacture. These risks concern contamination and cross-contamination, environmental and operator protection, the variability of biological manufacturing processes and the limitations of some IVMP finished product tests. Whilst the general requirements of GMP are applicable to all medicinal products, guidance which addresses the specific concerns for IVMPs is provided by Annex 5 and also Annex 1 in *Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice* (referred to as the GMP Guidelines). Extending and harmonising GMP requirements for IVMP manufacture throughout the world will increase the availability of high quality, safe and efficacious IVMPs.

Keywords

Directive 91/412/EEC – Directive 2001/82/EC – Good manufacturing practice – Immunological veterinary medicinal products – Veterinary vaccine.

Background

This paper addresses the requirements of good manufacturing practice (GMP) for immunological veterinary medicinal products (IVMPs). IVMPs are defined as any veterinary medicinal product administered to animals in order to produce active or passive immunity or to diagnose the state of immunity (3). As such, this category covers a range of veterinary medicinal products including vaccines, immunosera, allergen products and diagnostic products administered to animals (e.g. tuberculin).

Good manufacturing practice requirements are applied to the manufacture of IVMPs in many countries around the world (7). Within the European Union (EU) there are well-established requirements for GMP in the manufacture of these products, with an EU-wide legal framework for GMP. The legislation also provides the legal basis to ensure compliance with the requirements of GMP, by means of inspection of manufacturers by regulators.

Legal basis of good manufacturing practice for immunological veterinary medicinal products within the European Union

The current legal requirements for GMP during the manufacture of IVMPs are embodied in two EU directives which are implemented by national legislation in EU Member States. These directives apply to all veterinary medicinal products including IVMPs. Directive 2001/82/EC (3), as amended by Directive 2004/28/EC (4), sets out wide-ranging requirements for veterinary medicinal products in the EU. Commission Directive 91/412/EEC (2) lays down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

Directive 2001/82/EC

This legislation requires that the manufacture of veterinary medicinal products within the EU be subject to the holding of a manufacturing authorisation for products intended for the EU market and also those intended for export to third countries. A further requirement is that the holder of a Manufacturing Authorisation is obliged to 'comply with the principles and guidelines on good manufacturing practice for medicinal products'. The Directive also requires Member States to ensure 'by means of repeated inspections' that 'the legal requirements relating to veterinary medicinal products are complied with'. This latter requirement also allows for the inspection of manufacturers established in third countries outside of the EU to ensure that the appropriate standards are met.

Commission Directive 91/412/EEC

This Directive reiterates that all veterinary medicinal products manufactured in or imported into the EU, including veterinary medicinal products intended for export, should be manufactured in accordance with the principles and guidelines of GMP. It then sets out these broad principles and guidelines and reiterates that it is the responsibility of Member States to ensure that manufacturers adhere to them. The Directive also refers to detailed guidelines published by the European Commission, these being entitled *Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice (6)* which are referred to hereafter as the GMP Guidelines. These guidelines are contained in volume 4 of the *Rules Governing Medicinal Products in the European Community*.

For adoption of the legislation for GMP, it was agreed by all Member States and the industry that the GMP requirements applicable to the manufacture of veterinary medicinal products were the same as those applicable to the manufacture of medicinal products for human use. However, certain detailed adjustments were set out in annexes to the Guidelines which concerned specific product types; one of these annexes covers the manufacture of IVMPs.

It should be noted that in addition to this legislation applying in EU Member States, provisions of the above directives have been implemented by Norway, Iceland and Lichtenstein. Thus, the requirements for GMP apply to the manufacture of veterinary medicinal products, including IVMPs, throughout the European Economic Area (EEA).

What is good manufacturing practice?

Whilst it is clear that EU legislation requires that veterinary

medicinal products are manufactured in accordance with GMP, a concise definition of the term good manufacturing practice is not provided. However, the following definition is provided in Chapter 1 of the GMP Guidelines:

'GMP is that part of Quality Assurance (QA) which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specifications.'

Thus, for IVMPs, as for other medicinal products, GMP effectively leads to a set of measures that are intended to ensure the manufacture of safe and efficacious products in a consistent manner in accordance with the requirements set out in their marketing authorisations.

Good manufacturing practice is applicable to both production and quality control (QC) aspects for medicinal products and the basic requirements can be summarised as follows:

- manufacturing processes should be defined, reviewed and shown to be capable of consistently manufacturing products of the required quality and in compliance with their specifications
- critical manufacturing steps and process changes should be validated
- necessary facilities for GMP should be provided, including:
 - i) adequate levels of qualified staff
 - ii) suitable premises
 - iii) suitable equipment and services
 - iv) correct materials, containers and labels
 - v) appropriate storage facilities
- clear, written instructions and procedures should be available
- operators should be trained to carry out procedures correctly
- full manufacturing records should be kept: deviations from procedures and instructions should be recorded and investigated
- records should be retained
- distribution methods should minimise risk to product quality
- a system should be in place to recall products from sale or supply
- complaints about products should be examined, the cause of quality defects investigated and appropriate measures put in place to prevent reoccurrence.

Importance of good manufacturing practice in the manufacture of immunological veterinary medicinal products

There are a number of potential issues, as considered below, which may be associated with IVMPs and their manufacture. These issues can have a negative impact on product quality and therefore, either directly or indirectly, affect the safety or efficacy of the product. Application of GMP principles to their manufacture plays an important role in reducing this potential negative impact.

Contamination and cross-contamination

A feature of IVMPs is the wide range of animal species for which products may be manufactured. At the current time, IVMPs available on the EU market include those for farm animals (e.g. poultry, cattle, sheep, pigs), aquatic species (e.g. salmon, trout), and companion animals (e.g. dogs, cats, horses, rabbits). As a consequence of this, IVMP manufacture (and in particular veterinary vaccine manufacture) may involve the handling and production of a wide range of pathogens associated with the range of target species to be treated. However, it is often the case that relatively small amounts of materials derived from each pathogen are required, as batches of finished product are often relatively small.

This situation contrasts with that of immunological medicinal products for human use, which may be produced in much larger batch sizes for a narrower range of pathogens. As a consequence of the potential wide range of pathogens handled during production of IVMPs and the smaller batch sizes, it is common for their manufacture to occur in premises where a range of products are manufactured on a campaign basis. Such campaign manufacture leads to an inherent risk of cross-contamination of products due to the handling of different pathogens in the same facilities.

Contamination of IVMPs with environmental or other contaminants such as bacteria, moulds or viruses is as much a concern as cross-contamination with other production organisms. This is a particular issue due to the production methods which are involved in IVMP manufacture: open aseptic processing steps are a frequent part of their production. Whilst these open process steps will normally be performed under a filtered air flow in a 'clean room' there is always a potential risk of products becoming contaminated. Furthermore, unlike the situation

for some sterile pharmaceutical products, terminal heat sterilisation of finished IVMPs is not normally an option due to their heat labile nature. Technological solutions to these issues are becoming more common, such as the use of steam-sterilised, closed systems for the culture, transfer and blending of products. However, open aseptic processing steps continue to be a common part of the manufacturing process for IVMPs; the filling and freeze-drying of IVMPs are both open processes.

Another potential route of contamination of IVMPs is via the raw materials that are used in their manufacture. Many raw materials may harbour bacterial or fungal contamination. In addition, there are potential risks that extraneous viruses or transmissible spongiform encephalopathy (TSE) agents could be introduced via animal-derived materials which are often used in IVMP manufacture (1, 5).

If an IVMP does become contaminated during its manufacture, then there is the potential that either the production process (e.g. virus culture), or the product itself might support the growth of the contaminant and allow its numbers to multiply.

The application of GMP principles to the manufacture of IVMPs is intended to reduce the potential risk posed by contamination or cross-contamination. If a contamination or cross-contamination problem is detected prior to the release of a product there will be significant costs involved, due to loss of the batch of product and downtime in the manufacturing facility whilst investigations and remedial action are performed. If such a problem is not detected prior to release, then there could be serious animal health and welfare implications. Although not due to a clear GMP compliance failure, a recent case was reported where a number of inactivated clostridial vaccines which had been released to the market were later found to be contaminated with live *Clostridium sordellii*. Of the 202,525 animals in affected herds, 41,767 animals were infected and 22,189 died (9).

Environmental protection concerns

Due to the virulent nature of some organisms handled during the manufacture of IVMPs, environmental protection measures are required. Accidental release of live biological agents to either the immediate production environment or the outside environment must be prevented. Release to other areas of the site gives rise to the potential for cross-contamination. Release to the outside environment may potentially pose both animal and human health issues. The animal health issues may be of particular importance when manufacture involves the handling of exotic organisms or notifiable disease agents (e.g. foot and mouth disease virus or bluetongue virus).

Operator protection concerns

Due to the zoonotic nature of some of the organisms handled, e.g. rabies virus, *Leptospira* spp. and *Mycobacterium bovis*, systems must be in place to ensure adequate protection of the staff. These systems will involve the use of containment facilities, protective clothing and, where appropriate, vaccination of staff.

Variability of biological manufacturing processes

It is a generally accepted aspect of biological manufacturing processes that the potential variability may be significantly greater than for pharmaceutical product manufacturing processes. As a result there is an inherent risk of inconsistencies arising in IVMPs when compared with their pharmaceutical counterparts and anecdotal evidence suggests that up to 10% of IVMP batches may be subject to minor deviations from the required specifications or details given in their marketing authorisation dossiers. The rigid application of GMP principles to the manufacture of these products plays a role in minimising the potential variability and ensures that any deviations are recorded and their potential impact investigated.

Relative inefficiency of some finished product tests in assuring the quality of immunological veterinary medicinal products

It should be noted that the inherent variability of biological systems (discussed above in relation to manufacturing processes) may also cause problems for the biological assay systems used in QC testing of IVMPs. Both *in vitro* and *in vivo* testing using biological methods are a frequent part of the testing of IVMPs. This aspect, along with issues of sample size, may limit the efficiency of finished product testing of IVMPs. An example of this is the European Pharmacopoeia sterility test: due to the sample size used it is possible that low-level contamination may not be detected. In addition, for tests based on the culture of any contaminants or live agents present (e.g. sterility, purity, inactivation, extraneous agents, etc.), the correct culture conditions are essential (e.g. media, incubation conditions, etc.) to ensure that any live microbial contaminants are detected. With reference to the example given above concerning contaminated clostridial vaccines, it should be noted that the *C. sordellii* contamination was not detected by the finished product sterility test.

Taking the above issues into account it is considered that the application of GMP to the manufacture of IVMPs is of paramount importance in ensuring the availability of

IVMPs of suitable quality that are safe and effective. Application of GMP principles to IVMP manufacturing processes effectively builds quality into the product from the outset rather than placing the emphasis solely on testing of the finished product, with the inherent limitations of this approach.

The good manufacturing practice guidelines and their structure

The GMP Guidelines consist of two parts which describe the basic requirements that are applicable to all medicinal products and their raw materials. The requirements are adapted and modified for some specific issues and product types by a set of annexes. Part 1 of the GMP Guidelines describes the basic requirements for the manufacture of medicinal products, whilst Part 2 describes the GMP requirements for active substances used as starting materials for medicinal products.

Part 1 consists of 9 chapters which reflect the key principles of GMP that are set down in Commission Directive 91/412/EEC. The chapter titles, along with some of the broad requirements, are included in Table I.

Part 2 of the GMP Guidelines addresses the GMP requirements for active substances used as raw materials for medicinal products. These requirements were previously voluntary and had been included as Annex 18. However, amendment of Directive 2001/82/EC by Directive 2004/28/EC made it mandatory for active substances for use as raw materials in medicinal products to be manufactured in accordance with GMP. However, it should be noted that the mandatory application of Part 2 of the GMP Guidelines had less impact on the manufacture of IVMPs than it did on the production of veterinary pharmaceuticals. Due to the nature of these materials and the fact that they are normally manufactured by the final product manufacturer, the production and testing of these antigens has routinely been subject to GMP and the requirements for their manufacture are provided in the relevant Annex to the GMP Guidelines.

Annexes 1 to 19 expand on the basic requirements. As indicated above Annex 18 has been changed to Part 2, but Annex 18 has not been reassigned to prevent confusion. The majority of the annexes address the manufacture of certain specific types of medicinal products, the remaining annexes providing more detailed information on a number of specific topics.

Table I
Chapters of Part 1 of the European Union Good Manufacturing Practice Guidelines and some of the key requirements for human and veterinary medicinal products

Chapter	Examples of key requirements
Quality management	An effective pharmaceutical quality assurance (QA) system should be in place Management and staff should be actively involved in the QA system The QA system should incorporate good manufacturing practice (GMP) and quality control (QC) The QA system should be adequately resourced
Personnel	There should be sufficient levels of competent and appropriately trained staff Job descriptions for key staff should be defined All personnel should be aware of the principles of GMP
Premises and equipment	These should be located, designed, constructed, adapted and maintained to suit their purpose Their design and layout should minimise the risk of error and permit effective cleaning and maintenance to prevent cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products
Documentation	Clear, accurate documents such as specifications and instructions should be in place Records should be kept
Production	Clear defined procedures should be followed to ensure that products of the requisite quality are produced in accordance with the relevant manufacturing and marketing authorisations These procedures should comply with the principles of GMP
Quality control	Sampling and testing should be performed as appropriate Release procedures should be in place to ensure that materials are not released for use, or products released for sale or supply, until their quality has been judged as satisfactory QC should be involved in all decisions which may concern the quality of the product
Contract manufacture and analysis	Systems should be in place to ensure that GMP requirements are met when work is contracted out by the manufacturer
Complaints and product recall	Complaints and other information concerning potentially defective products should be reviewed in accordance with written procedures A system should be in place to recall from the market, in an effective and timely manner, products known or suspected to be defective
Self inspection	A system of self-inspection should be in place to monitor compliance with GMP and propose necessary corrective actions

Of the specific product annexes, two are of direct relevance to the manufacture of IVMPs; these are Annex 5 'Manufacture of Immunological Veterinary Medicinal Products' and Annex 1 'Manufacture of Sterile Medicinal Products'. Annex 5 is applicable to all IVMPs; however, all parenteral and most liquid IVMPs are required to be sterile (or pure if they are live vaccines) and thus also fall under the scope of Annex 1. In addition, many other non-parenteral IVMPs including a significant number of freeze dried viral vaccines for use in poultry, although not required to be sterile, are not permitted to contain more than one non-pathogenic organism per dose. In order to comply with this limit it is, in practice, necessary to manufacture such products in accordance with Annex 1 requirements.

A number of other annexes may apply to the manufacture of IVMPs. These include Annex 8 'Sampling of starting and packaging materials', Annex 11 'Computerised systems', Annex 15 'Qualification and validation' and Annex 16 'Certification by a qualified person and batch release'.

The GMP Guidelines are subject to periodic review and update when necessary. Updates arise from initial input by EEA GMP inspectors with further input from industry and other interested parties, via a formal consultation process. Following finalisation, the revised chapter or Annex (or new Annex) is forwarded to the European Commission's Pharmaceutical and Veterinary Pharmaceutical Committees for adoption.

Annex 1 and Annex 5: specific good manufacturing practice guidance for immunological veterinary medicinal products

As highlighted earlier, in addition to the basic requirements in Parts 1 and 2 of the GMP Guidelines, there are specific requirements applicable to the manufacture of IVMPs, which are laid out in Annex 1 and Annex 5. The general requirements of Annex 1 which are applicable to the manufacture of IVMPs and the more specific requirements of Annex 5 are considered in this section.

The requirements of Annex 1 focus on minimising the potential for microbiological, particulate or pyrogen contamination. The skill and training of staff, and the role played by QA, are of particular importance in the manufacture of sterile medicinal products.

The manufacture of sterile products is required to be performed in 'clean areas' with microbial and particulate limits for these areas being set at levels dependent on the activities being performed. The lowest category of clean area (i.e. with the highest permitted particulates and microbial levels) is designated as Grade D, whilst the highest category is designated as Grade A. Grade A conditions are required for operations where the product is most at risk, i.e. during open manipulations such as filling. Frequent monitoring of clean areas should be performed to demonstrate the continued compliance with the stated air cleanliness grades. In addition, detailed requirements concerning clothing for staff working in clean areas are provided. Annex 1 also provides guidance on the requirements for premises and equipment, aseptic preparation, aseptic process validation, sanitation and sterilisation.

The requirements of Annex 5 concentrate on the areas highlighted earlier as being specific issues for the manufacture of IVMPs. These issues concern contamination and cross-contamination, protection of the environment and operators, the variability of biological manufacturing systems and the relative inefficiency of some finished product tests. Some examples of specific concerns and the applicable Annex 5 requirements which address them are provided in Table II.

Whilst the requirements of Annex 1 and Annex 5 generally complement each other there are some occasions where a balance may need to be struck between the requirements of the two annexes. For example, whilst inactivated materials and IVMPs should be handled in classical clean areas as required by Annex 1, live IVMPs and materials prior to inactivation should be handled only in containment facilities. However, as there is also the requirement to keep the live material or IVMPs pure, the air cleanliness grading and monitoring requirements of Annex 1, along with most other Annex 1 requirements,

generally apply to the Annex 5 containment conditions (e.g. where there is open processing this should be in a Grade A area with a Grade B background). Some care needs to be taken with this approach though, as there are a small number of cases where Annex 1 requirements are not appropriate for containment areas. An obvious example of this concerns the pressure cascades for clean and contained areas. In a clean area a positive air pressure cascade should be in place to protect the product. However, where live materials are handled, this approach would spread contamination and so a negative cascade (or suitable alternative arrangement designed to prevent the release of live agents) is required. Another Annex 1 requirement which is not appropriate for the operation of containment facilities is the use of continuous particulate monitoring systems in Grade A and B areas; in this case a stream of potentially contaminated air could be drawn into the system, thus causing a breakdown of containment.

Good manufacturing practice in different countries and regions

The manufacture of IVMPs is regulated in many countries around the world and the requirement for manufacture in compliance with GMP is often a key aspect of this regulation. The GMP requirements in place for IVMP manufacture in four key regions in the world (Europe, North America, Japan and Australia/New Zealand) are briefly considered.

Europe

The requirements of GMP as applied to the manufacture of IVMPs within the EEA have been discussed. In addition, manufacturers based in third countries which supply the EU market are required to manufacture in accordance with GMP and are normally subject to routine GMP inspection by EU inspection authorities. Inspections of IVMP manufacturers may be arranged in connection with nationally authorised products or for centrally authorised products. Inspections in relation to this latter group of products are coordinated by the Inspections Section of the European Medicines Evaluation Agency (EMA) (10).

With expansion of the EU the application of GMP has extended across Europe. New Member States are required to apply EU standards to the manufacture of IVMPs on accession to the EU.

In addition to the application of GMP by EU/EEA Member States, a Mutual Recognition Agreement (MRA) is in place between the EU and Switzerland, this covering veterinary medicinal products.

Table II
Specific concerns applicable to the manufacture of immunological veterinary medicinal products: examples of the requirements contained in Annex 5 of the European Union Good Manufacturing Practice Guidelines

Issue	Concern	Measures to address concern
Personnel	Personnel may be a significant source of contamination or cross-contamination	Appropriate protective clothing should be used at different stages of manufacturing Procedures should be in place governing movement between different manufacturing areas (movement restrictions)
Handling of live biological agents	Accidental release of live biological agents should be prevented	Live agents should only be handled in contained areas Containment facilities should include: <ul style="list-style-type: none"> – negative pressure work area – no direct venting of air out of the area – entry of staff and equipment via air locks – system for collection and disinfection or sterilisation of effluents and wastes
Handling of sterile and inactivated materials and products	Sterile and inactivated materials and products should be protected from contamination and / or cross-contamination	Sterile and inactivated materials and products should be handled in clean areas Clean areas should meet Annex 1 requirements, including positive air pressure cascade
Potential contamination due to certain manufacturing operations	Certain manufacturing operations may act as a source of contamination	Areas which are likely to be a source of contamination should be separated from other production areas, e.g: <ul style="list-style-type: none"> – QC laboratories – animal houses – virus culture areas – spore bearing bacteria culture areas – media preparation
Disinfection, decontamination and fumigation procedures	Contamination may be a concern if procedures are ineffective	Procedures should be validated to demonstrate their effectiveness
Potential cross-contamination during storage	One material or product should not pose a cross-contamination risk to another	Live or infected materials should be separated from sterile, non-infected or inactivated materials Separate, dedicated incubators or coolers should be used for the storage of live and inactivated products (although storage of live and inactivated finished filled products in the same area is accepted)
Product consistency	Measures should be taken to prevent or minimise variability between product batches	Seed lot and cell bank systems should be used where appropriate to ensure consistency of the seed material used for scale up Limits to the number of generations between the seed and the finished product should be in place, in accordance with the marketing authorisation dossier
Potential cross-contamination arising from a product	Contamination arising from product during manipulation should be avoided	The formation of aerosols, droplets and foam containing live agents should be prevented or minimised Accidental spillages should be handled in a prompt and safe manner Only one live agent should be handled in an area (or one virus and one cell line) at a time, unless closed systems are in use. An exception to this would be during the blending of live viral vaccines
Inactivation	Procedures should ensure complete inactivation	A double tank inactivation procedure should be followed
Consistency of production	Manufacturing yields should meet expected levels	Yield reconciliation should be performed following manufacture steps Deviations from expected yields should be investigated

United States of America

Immunological veterinary medicinal products fall under the scope of the Virus/Serum/Toxin Act of 1913 (10). A licence is required to manufacture these products at a specified facility, this being issued by the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture. This licence is required for manufacture for both the domestic and overseas markets. To obtain the licence, blueprints and blueprint legends for the facility must be submitted for approval. The Animal and Plant Health Inspection Service reviews these to ensure that the facility will operate in a manner consistent with GMP. If changes to the facilities occur, revised blueprints must be submitted immediately. Prior to issue of the licence, the applicant's premises are subject to inspection by APHIS examiners. The inspection is intended to ensure that the facility operates in a manner consistent with GMP by confirming that the establishment is configured in accordance with the blueprint and legends, that the production line is set up in accordance with the approved outline of production and that records are adequately kept. Following issue of the licence, APHIS routinely conducts unannounced post-licensing inspections ordinarily within 12 to 18 months of the last inspection. Special inspections may be performed prior to approval of changes to the facility or the production method.

Canada

The manufacture of IVMPs in Canada is subject to licensing and inspections in accordance with the country's Health of Animals Act and Regulations. Inspections of IVMP manufacturers are performed by the Veterinary Biologic Section of the Animal Health and Production Division of the Canadian Food Inspection Agency (www.inspection.gc.ca).

Japan

The regulation of IVMPs within Japan falls under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries. The Ministry issues licences to manufacture, import, and sell IVMPs. Conformity to GMP is stipulated as one of the conditions for obtaining a licence to manufacture (10).

Australia and New Zealand

Good manufacturing practice requirements for the manufacture of IVMPs are in place in Australia (for further details visit the website of the Australian Pesticides and Veterinary Medicines Authority: www.apvma.gov.au) and in New Zealand (see the New Zealand Food Safety

Authority website: www.nzfsa.gov.nz). These requirements along with the legislative basis for them are considered to be equivalent to those in the EU and vice versa. Equivalence was determined prior to the start of the operational phases of MRAs between each of these countries and the EU.

International bodies involved in good manufacturing practice and immunological veterinary medicinal product quality control

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) is an international body which is primarily involved in the spread and harmonisation of GMP standards throughout the world. Together, the Convention (a formal treaty between countries) and the Scheme (an informal arrangement between health authorities) provide the basis for active and constructive co-operation in the field of GMP.

The PIC/S mission statement is 'to lead the international development, implementation and maintenance of harmonised good manufacturing practice (GMP) standards and quality systems of inspectorates in the field of medicinal products' (www.picscheme.org).

The aim of PIC/S is to achieve this mission by 'developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations'. PIC/S has adopted the EU GMP Guidelines in their entirety as their own GMP Guidelines (with suitable modification to remove references to EU Legislation, etc. [8]).

Members of PIC/S include inspectorates from the EU and various countries around the world (e.g. Australia, New Zealand, Malaysia) and membership continues to expand. Among the current membership, the only inspectorate that is dedicated solely to veterinary inspection is that of the Czech Republic; however, a number of members are involved in the inspection of both human and veterinary products. Expansion of PIC/S membership by veterinary

inspectorates around the world would assist in the harmonisation of GMP standards for the manufacture of veterinary vaccines.

Other organisations

Various other organisations are involved in the standardisation and quality of veterinary vaccines and other IVMPs throughout the world. These include the World Organisation for Animal Health (OIE), the Food and Agriculture Organization (FAO) of the United Nations and the Veterinary International Cooperation on Harmonisation (VICH) (10). However, none of these organisations currently play a significant role with regards inspection or GMP for these products, concentrating more on the official testing of IVMPs. One organisation with a slightly wider remit on this issue is the Pan African Veterinary Vaccine Centre (PANVAC) which was set up in 1991 with FAO assistance and European aid. The main function of PANVAC has been the testing of various veterinary vaccines; however, it also provides training for specialists from African countries in the production and testing of veterinary vaccines.

Conclusions

Good manufacturing practice principles are applied to the manufacture of IVMPs in a number of countries and regions of the world. In the EU and other areas, legislation is in place to ensure the stringent application of GMP

requirements. It is considered that these requirements are of paramount importance in reducing the potential impact of the inherent risks which apply to the manufacture of IVMPs. These measures thereby ensure that IVMPs are of the appropriate quality, are safe and efficacious. The requirement for manufacture in accordance with GMP complements other regulatory safeguards such as the licensing requirements for these products.

The expansion of GMP to the manufacture of IVMPs in regions where it is currently not applied will bring significant benefits in terms of product quality, safety and efficacy. A key role in the development and promotion of harmonised GMP standards for all types of medicinal products is being played by PIC/S. However, other organisations, such as PANVAC, which already have an important part to play in the improvement of quality for veterinary vaccines may be candidates for a more prominent role in the future promotion of harmonised application of GMP standards for IVMP manufacture, particularly in developing countries. Whilst the application of these standards may have significant cost implications, it is considered that these should be outweighed in the long term by the benefits to animal health, and consequently to human health, in these regions through the availability of safe, efficacious veterinary vaccines, manufactured to high quality standards.



Bonnes pratiques de fabrication pour les médicaments vétérinaires immunologiques

J.I. Todd

Résumé

Dans nombre de pays, les médicaments vétérinaires immunologiques (MVI) sont produits en suivant des procédures appelées « bonnes pratiques de fabrication » (BPF). L'Union européenne met en œuvre depuis longtemps les BPF pour la fabrication des MVI. Il est essentiel de respecter ces exigences, compte tenu des risques particuliers associés à la fabrication des MVI, qui portent sur la contamination, la contamination croisée, la protection de l'environnement et des agents chargés de manipuler les médicaments, la variabilité des processus de fabrication de produits biologiques et les limites de certains tests applicables aux produits finis. Les exigences des BPF couvrent tous les médicaments, ceux à usage spécifiquement vétérinaire étant couverts par les Annexes 1 et 5 des Lignes directrices de l'UE relatives aux bonnes pratiques de fabrication des

médicaments à usage vétérinaire et humain. Il convient de développer et d'harmoniser les exigences des BPF partout dans le monde afin d'assurer une disponibilité de MVI de grande qualité, innocuité et efficacité.

Mots-clés

Bonne pratique de fabrication – Directive 91/412/EEC – Directive 2001/82/EC – Médicament vétérinaire immunologique – Vaccin vétérinaire.



Buenas prácticas de fabricación de productos inmunológicos veterinarios

J.I. Todd

Resumen

En varias regiones del mundo, la producción de medicamentos inmunológicos de uso veterinario se rige por una serie de buenas prácticas de fabricación. Dentro de la Unión Europea (UE) existen requisitos bien definidos en la materia. El hecho de atenerse a un conjunto de buenas prácticas en la fabricación de dichos medicamentos es importante por los particulares riesgos que el proceso conlleva, riesgos ligados a la contaminación, la protección del entorno físico y de los trabajadores, la variabilidad propia de los procesos de fabricación de productos biológicos y las limitaciones de que adolecen algunas de las pruebas a que son sometidos los productos finales. Si bien los requisitos generales de las buenas prácticas de fabricación son válidos para todo producto medicinal, en los anexos 5 y 1 de la guía comunitaria de normas de correcta fabricación de productos medicinales de uso humano y veterinario se sientan pautas referidas específicamente a los medicamentos inmunológicos veterinarios. La extensión de las buenas prácticas de fabricación a otras partes del mundo y su armonización acrecentarán la oferta de productos inmunológicos veterinarios seguros, eficaces y de calidad.

Palabras clave

Buena práctica de fabricación – Directiva 91/412/EEC – Directiva 2001/82/EC – Productos inmunológicos veterinarios – Vacuna veterinaria.



References

1. European Directorate for the Quality of Medicines (EDQM) (2005). – Section 5.2.5: Substances of animal origin for the production of veterinary vaccines. In *European Pharmacopoeia* 5th Ed., 460-462.
2. European Union (1991). – Commission Directive 91/412/EEC laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products. *Off. J. Eur. Communities*, **L228**, 70.
3. European Union (2001). – Directive 2001/82/EC of the European Parliament and of the Council on the Community Code Relating to Veterinary Medicinal Products. *Off. J. Eur. Communities*, **L311**, 1-66.
4. European Union (2004). – Directive 2004/28/EC of the European Parliament and the Council amending Directive 2001/82/EC on the Community Code relating to Veterinary Medicinal Products. *Off. J. Eur. Union*, **L136**, 58-84.

5. European Union (2004). – Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev. 2 – October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal Products (CVMP). *Off. J. Eur. Union*, **C24**, 6-19.
6. European Union (2006). – Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. *In* The Rules Governing Medicinal Products in the European Union, Volume 4. European Commission, Brussels, Belgium.
7. Luff P. & Soulebot J.-P. (1997). – Good Manufacturing Practices. *In* Veterinary Vaccinology (P.-P. Pastoret, J. Blancou, P. Vannier & C. Verschuere, eds). Elsevier Science, Amsterdam, The Netherlands, 201-202.
8. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). – Guide to Good Manufacturing Practice for Medicinal Products (PE009-5). PIC/S, Geneva, Switzerland.
9. Téllez S., Casimiro R., Vela A.I., Fernández-Garayzábal J.F., Ezquerro R., Latre M.V., Briones V., Goyache J., Bullido R., Arboix M. & Domínguez L. (2006). – Unexpected inefficiency of the European pharmacopoeia sterility test for detecting contamination of clostridial vaccines. *Vaccine*, **24**, 1710-1715.
10. World Organisation for Animal Health (OIE) (2000). – The role of official bodies in the international regulation of veterinary biologicals. Chapter I.1.9. *In* Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, 4th Ed. OIE, Paris.

