

**AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY**

**Regulation Impact Statement**

**ASSURING THE ENDURING GMP COMPLIANCE OF OVERSEAS  
VETERINARY CHEMICAL MANUFACTURERS**

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## Regulation Impact Statement

### ASSURING THE ENDURING GMP COMPLIANCE OF OVERSEAS VETERINARY CHEMICAL MANUFACTURERS

#### Background

The APVMA is the independent Australian government authority responsible for the assessment and registration of pesticides and veterinary medicines. Veterinary medicines include all veterinary chemical products such as vaccines, antibiotics, worming treatments, flea and tick washes and other parasiticides, for use on both domestic animals and animals for production.

As a Commonwealth Statutory Authority, the APVMA operates in accordance with governing legislation. The principal responsibilities of the APVMA are described in the *Agricultural Chemical (Administration) Act 1992* and the *Agricultural and Veterinary Chemicals Code Act 1994 (Agvet Codes)*.

In accordance with these Agvet Codes, the APVMA must be satisfied that veterinary chemicals are of a high quality; do not pose a threat to people, domestic or native animals, crops, plants, things or the environment; will not pose any unacceptable risk to trade with other nations; and will continue to work effectively.

The APVMA expects that all veterinary chemicals supplied in Australia are manufactured in accordance with the APVMA's Manufacturing Principles and associated codes of Good Manufacturing Practice (GMP). GMP is a system for ensuring that quality is built into products during manufacture rather than relying on testing prior to release. It is designed to minimise the risk of foreseeable errors and process failures so that all veterinary chemical products consistently comply with their approved registered particulars.

Australian manufacturers of veterinary chemicals must be licensed by the APVMA under Part 8 of the Agvet Codes. All manufacturers undergo regular audits, normally at intervals of 18 - 24 months, to ensure their continued compliance with GMP. Current GMP requirements for Australian manufacturers came into force in 1996 and those for overseas manufacturers in 1998. Prior to that date, manufacturers of imported products may not have been assessed for compliance with GMP.

Approximately one-third of all registered veterinary chemical products have at least one overseas manufacturer. Products manufactured overseas are usually sold in the same distribution channels as products manufactured locally. Registrants using overseas manufacturers are currently required to supply evidence of GMP compliance at product registration, or when applying for a new manufacturer. There are currently no arrangements for further submission of GMP evidence after product registration.

The APVMA currently takes a risk-based approach to the assessment of compliance for foreign manufacturing sites (see Attachment One, *Guidelines For Providing Evidence of GMP Status of Overseas Manufacturers* [[http://www.apvma.gov.au/qa/mls\\_overseas.shtml](http://www.apvma.gov.au/qa/mls_overseas.shtml)]). Where the manufacturer is located within the jurisdiction of an inspection authority recognized as being equivalent, the APVMA accepts certificates and/or audit reports provided by those authorities as

evidence of compliance with Australian GMP requirements. In the case of manufacturers in Europe, two treaty-level Mutual Recognition Agreements on Conformity Assessment describe the requirements for such certificates.

In countries where certificates from the local inspectorates are not accepted, audit reports may be accepted if the audits were conducted by recognised inspection authorities, such as the Therapeutic Goods Administration (TGA). Where no such alternative exists, the facility would need to be audited by an APVMA-authorised auditor. These audits are usually conducted at the expense of either the registrant or manufacturer. Certificates and audit reports are only accepted if the audit was within the previous three years.

The APVMA expects that any evidence of GMP should stipulate the date of the last audit as well as the steps of manufacture and the types of products inspected. No changes to the current evidential requirements are anticipated for the current proposal. The APVMA has estimated that 80% or more of the approximately 340 foreign manufacturing sites involved should be able to establish GMP compliance through the provision of certificates without the need for supplementary audits. The regulatory authorities in these countries are recognised as being equivalent to the APVMA. The remaining 20% of manufacturing sites would require regular audits from a recognised inspection authority.

Manufacturers of certain veterinary chemical products are exempt from the licensing requirements of Part 8 of the Agvet Code. These products are listed in Regulation 59 of the Agvet Code (see Attachment Two) and include external coat conditioners, any skin cleanser or shampoo, equine hoof protectants, sheep branding substances, and herb oils. To be consistent with the requirements for domestic manufacturers, foreign manufacturers of these licence-exempt products will be excluded from the proposed GMP requirements outlined in this document.

## **Part 1: Issues**

While it is assumed that registered veterinary chemical products manufactured overseas and supplied in Australia would be manufactured according to GMP, there is currently no legal requirement for this to occur and no requirement for registrants of imported veterinary chemical products to provide the APVMA with ongoing evidence of the manufacturer's compliance with GMP. This raises a number of significant issues.

### **Issue 1 – Concerns for product safety**

The primary concern is that the current differences in requirements for Australian and foreign manufacturers may be reflected in the quality of veterinary chemical products in the Australian marketplace. Australian-based manufacturing facilities are inspected on a regular basis to confirm their ongoing compliance with GMP. Foreign manufacturers are not necessarily subjected to the same scrutiny and the quality of the manufactured products cannot be similarly assured. From an international perspective, it is a fact that manufacturing standards vary. It also needs to be appreciated that major non-conformances can be observed in the most modern of facilities and regular audits are required to ensure that corrective actions are not only undertaken but also implemented effectively.

The consequences of poor GMP compliance may be reflected in reduced product quality, safety and/or efficacy. These effects are not quantifiable, but could occur if there was poor GMP compliance.

The following examples illustrate the dangers inherent in the breakdown of GMP compliance.

### ***Example 1***

In the mid-1980's, prior to the introduction of the APVMA's Manufacturers' Licensing Scheme and the need for GMP compliance, the then National Biological and Serum Laboratory demonstrated a high failure rate of veterinary preparations in the areas of potency, sterility and stability. Testing by NSW Agriculture in 1994 further demonstrated concerns about the quality of veterinary chemical products.

### ***Example 2***

In 2003, the manufacturing licence of one Australian company was suspended following significant concerns with GMP compliance. The breakdown in GMP led to serious product safety issues and the eventual recall of human and veterinary medicinal products on a massive scale.

### ***Example 3***

In 1998, the USA's Food and Drug Administration warned against the use of all large volume parenteral drugs manufactured by one Mexican company. Tests showed contamination with *Bacillus cereus* bacteria or related species, which can cause severe injury and death in cows. An import alert was also issued, to prevent importation.

### ***Example 4***

In 2000, the USA's Food and Drug Administration announced that one corporation was voluntarily recalling antiseptic sterile preparations after bacterial contamination in some lots of its sterile products for humans was discovered.

## **Issue 2 - Reduced equity in our requirements**

The inequity in our requirements also disadvantages local manufacturers who must maintain an APVMA Manufacturer's Licence. They must undergo at least one audit every 18-24 months and maintain compliance with GMP, that invariably necessitates investment in plant, equipment, personnel and/or quality system maintenance. They must pay licence fees as well as the cost of audits. The cost of an audit is approximately \$1000 - \$2000, and the annual licence fee payment varies from \$150 - \$1500 per annum, depending on category of manufacture and whether any concessions apply.

In contrast, the compliance costs of foreign manufacturers are dependent on the local authority and the extent to which GMP standards are enforced. The APVMA's understanding is that the standards required vary greatly both between and within some foreign countries. It is therefore crucial that commercial advantage gained through non-compliance with GMP is minimised in the interests of Australian consumers and all compliant manufacturers (both domestic and foreign).

### **Issue 3 – Veterinary chemical products manufactured overseas may not comply with legislative requirements**

The APVMA is required to implement legislation to regulate veterinary chemicals in the marketplace. Veterinary chemicals are currently registered only if they satisfy the requirements of Section 14 of the Agvet Code. Section 14 subsection 3 requires that, before registering a veterinary chemical product, the APVMA must be satisfied that it would be effective, that it would not be an undue hazard to animals or humans, and that it would not unduly prejudice trade. Section 14 subsection 5 of the Agvet codes requires that the APVMA must have regard as to how the product is formulated, the composition and form of the constituents, and the stability of the product.

It is also an offence to supply, or cause or permit to be supplied, a registered chemical product if the constituents, the concentration of the constituents, or the composition or purity of any constituent, differ by more than the prescribed extent from that shown in the registered particulars (Section 83 of the Agvet Code).

Without a process to ensure that manufacturing continues to comply with GMP for the registered life of a product, the APVMA cannot be satisfied that these requirements have been met for imported products.

### **Issue 4 - Lack of conformity with comparable national and overseas authorities**

The APVMA's control of veterinary chemicals throughout their life-cycle is not comparable to those of counterpart authorities in other developed countries. This potentially reduces public confidence in the APVMA and the APVMA's registration processes. In Europe and the USA, assurance of continuing GMP compliance for the life of a product, verified by inspections, is now an accepted requirement to ensure that veterinary medicines in the marketplace are of a high quality.

Australia's Therapeutic Goods Administration (TGA) has a separate scheme to provide product holders with "clearances" for each overseas manufacturer for a period of approximately three years (dependent on the evidence provided). Fees for assessment of this evidence start at AUD \$240. If an overseas audit is required, the total cost of two auditors for three to four days is typically in the range of AUD \$20,000-30,000. Audits are carried out, on average, every 20-24 months.

The USA's Food and Drug Administration (FDA) or, alternatively, the United States Department of Agriculture (USDA) Centre for Veterinary Biologics inspect veterinary chemical manufacturing sites, including foreign sites, approximately every two years.

Authorities in the EU issue *market authorisations* instead of *product registrations*, which last for five years. Every five years, these must be renewed by submitting a data package, including evidence of GMP compliance. In the UK, a fee of approximately AUD \$2,625 is charged for this renewal. Separate fees are charged for audits.

## **Part 2: Objectives**

The overriding purpose of this proposal is to introduce a mechanism for ensuring the enduring GMP compliance of overseas manufacturers supplying veterinary chemical products to the Australian marketplace. To achieve this, three objectives should be met.

### **Objective 1 - To ensure product safety.**

The first objective is to ensure as far as practicable, the ongoing safety of all veterinary chemical products that are registered for use in Australia, irrespective of their site of manufacture. GMP compliance is accepted by both the APVMA and industry as a method to ensure product quality and safety.

### **Objective 2 – To ensure compliance of veterinary chemical products with legislative requirements.**

Veterinary chemical products must comply with the APVMA's governing legislation, described in the *Agricultural Chemical (Administration) Act 1992* and the *Agricultural and Veterinary Chemicals Code Act 1994*. Products manufactured without assurance of enduring GMP compliance may not comply with current legislative requirements. It is also highly desirable for any new scheme to be consistent with existing legislation and allow the APVMA to take action if GMP compliance cannot be demonstrated.

### **Objective 3 – To improve stakeholder confidence in imported products**

The third objective is that the APVMA should maintain consumer confidence in imported products by applying requirements that are comparable to those required by other leading authorities and those required for domestic manufacturers.

## **Part 3: Identification of Options**

### **Introduction**

In the broadest context, options involve self-regulation, quasi-regulation and explicit regulation. The option of maintaining the *status quo* (ie doing no more than what is currently done) is not acceptable to the APVMA as it does not address the issues raised previously.

Options involving self-regulation and quasi-regulation, as defined by the Office of Regulation Review,<sup>1,2</sup> were explored but not considered appropriate for issues that were of major public health significance. Explicit regulation was explored more fully, but only options that comply with the current legislation were considered viable.

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<sup>1</sup> Office of Regulation Review 1998, *A Guide to Regulation (second edition)*, page D4

<sup>2</sup> Office of Regulation Review 1998, *A Guide to Regulation (second edition)*, page D5

Explicit regulation is defined by the Office of Regulation Review<sup>3</sup> as regulation underpinned by legislation. This is appropriate for issues that may be of high risk and high impact, such as a major public health and safety issue, where the government requires the certainty provided by legal sanctions and universal application.

## **Options not considered viable**

### ***Options involving self-regulation***

According to the Office of Regulation Review, self-regulation can occur when there is no major public health and safety concern, there is a low risk and the problems can be fixed by the market<sup>1</sup>. Self-regulation would mean that the veterinary chemical industry assumes full responsibility for the regulation of GMP compliance. Australian manufacturers already have legislative obligations to be licensed. Self-regulation options could not be considered for foreign manufacturing sites, as the public health and safety hazards arising from non-compliance could potentially be of high significance. The issues of concern are not addressed by market-based solutions such as the threat of commercial damage arising from product recalls or litigation. While the impacts of product recall and litigation can be severe, they have not, by themselves, proven to be effective deterrents. Further detailed consideration was not given to these options.

### ***Options involving quasi-regulation***

Quasi-regulation can occur when a less formal mechanism is required and government is not convinced of the need to mandate an entire industry<sup>4</sup>. Options involving quasi-regulation would mean that industry take substantial ownership of the scheme, with a viable industry association enforcing the scheme with effective sanctions. This could not be considered, because veterinary chemicals are already subject to explicit regulation due to public health and safety concerns, and there is no one over-arching industry body that could enforce such a scheme. Further detailed consideration was not given to these options.

### ***Options involving international co-operation***

Consideration was given by the APVMA to options involving international co-operation with notification of product defects. Under the Mutual Recognition Agreement with the EU, member states notify the APVMA of more serious recalls by issuing, "Product Alerts." However, the APVMA is not notified of quality defects and recalls in all foreign jurisdictions. Establishing memoranda of understanding with other national regulators, that included requirements for notification of recalls and changes to GMP licensing, would be complex and difficult to negotiate. They would also rely on the ability of foreign regulators to identify APVMA-registered products. Because of these limitations, further detailed consideration was not given to this option.

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<sup>3</sup>Office of Regulation Review 1998, *A Guide to Regulation (second edition)*, page B3

<sup>4</sup>Office of Regulation Review 1998, *A Guide to Regulation (second edition)*, page D5

### ***Options involving legislative change***

Consideration was also given by the APVMA to various options requiring legislative change, such as an option to create a requirement for regular submission of GMP evidence from overseas manufacturers.

Further detailed consideration was not given to these options as the process of legislative change can be prolonged and must be prioritised by government. The APVMA believes that a suitable option could be found within the APVMA's current legislative boundaries. It was therefore considered important to explore options within the current legislation rather than seeking legislative change.

### **Option considered viable**

#### ***The use of Conditions of Product Registration to ensure GMP compliance***

This option proposes that Conditions of Product Registration would be applied that require product registrants to be responsible for ensuring GMP compliance, maintaining current evidence and submitting evidence of GMP compliance when requested by the Authority. Proposed conditions of product registration are detailed more fully in Attachment Three.

This option places full reliance on the registrant of a product to ensure their overseas manufacturing sites remain GMP compliant after initial product registration. This would be legally enforced by the addition of Conditions of Product Registration that would require such compliance to be maintained and specific current evidence to be held by the registrant. The APVMA would underpin the integrity of the scheme by initiating a review/audit program where evidence of GMP compliance could be required by the APVMA at regular intervals. The APVMA would establish a schedule for routine request and evaluation of this evidence and there would also be a capacity for the APVMA to request evidence at any time if required.

These conditions would be imposed on both new and existing registrations for products manufactured at overseas sites. With regards to the latter, the APVMA plans to reconsider existing veterinary product registrations, in order to apply these conditions of product registration.

This option meets the objectives of the scheme in the following ways.

#### ***Objective 1***

This option ensures product safety, by requiring that each product is GMP compliant throughout its registered life, and that the evidence for this is checked regularly by the APVMA. If the manufacture of a registered product could not be shown to comply with GMP, the product registration could be suspended or cancelled, under s36 of the Agvet Codes for breach of a condition.

#### ***Objective 2***

This option will ensure the compliance of veterinary chemical products manufactured overseas with legislative requirements, by requiring GMP compliance in order to underpin product quality.

### *Objective 3*

The assurance of ongoing compliance with GMP for imported veterinary chemicals is likely to increase consumer confidence in the quality of such products. It also brings APVMA requirements into closer alignment with those of other leading regulatory authorities.

A variant of this option was also considered. In that option, the registrant would be required to submit current evidence of GMP compliance every three years, possibly via an “Application to Vary a Condition of Registration.” (s27-29 Agvet Codes). The due date for the submission of evidence would be specified in the Conditions. This option may allow cost recovery by the APVMA and the charges for evaluating the evidence and re-issuing registrations are likely to be in the order of \$600-2500/product. However, the legislative authority of the APVMA to impose conditions effectively requiring the applicant to lodge future applications for variation is questionable. Further detailed consideration was not given to this option.

## **Part 4: Assessment of the Costs and Benefits of the Preferred Option**

### **Impact Group Identification**

The main groups impacted by the proposed option are the community including the rural sector, industry and the APVMA. The community and the rural sector are the consumers of veterinary chemicals, for use on domestic animals and animals for production. Industry refers to the manufacturers and registrants of veterinary chemical products, which are manufactured in Australia and/or overseas. The APVMA is the government statutory authority responsible for regulating veterinary chemicals, and is funded by industry through fees and levies.

#### ***Benefits to the community and the rural sector***

The major benefit to consumers will be increased assurance in the safety and quality of veterinary products. It is not possible to quantify this effect, but the benefit is substantial when the risks associated with product quality defects are considered.

#### ***Costs to the community and the rural sector***

The community may experience a slight increase in the price of some veterinary chemicals manufactured overseas as a result of this option being adopted by the APVMA. However, it is not possible to predict whether this may occur, or to what degree it may occur.

#### ***Benefits to the APVMA***

This option provides the APVMA with assurance of GMP compliance for the products that are manufactured overseas. While the proposal may be marginally less rigorous than other mechanisms requiring formal submission and approval of all certificates/audit reports, the APVMA believes it would be a cost-effective and equitable way for managing the risks of non-compliance.

### ***Costs to the APVMA***

This option does not provide for fee recovery and the cost of the scheme would be funded by other funding mechanisms, such as annual levies. The frequency and extent of the APVMA program would be affected by the level of compliance observed. Evidence on approximately 120 sites per annum may be examined on a three-year cycle. It is anticipated that an additional staff member would be required, and related costs would have a minor effect on funding mechanisms.

This option would involve the establishment of processes to request the submission of evidence and to assess this evidence.

### ***Benefits to industry***

The major benefit to industry will be the greater regulatory transparency and the greater equity in our requirements, which will create a more level playing field. It will ensure that those registrants using Australian manufacturers, and those with overseas manufacturers who have ensured that their products continued to be GMP compliant post-registration, are not disadvantaged.

### ***Costs to industry***

For those products with overseas manufacturing sites, this option will incur administrative costs and the cost of obtaining satisfactory evidence of GMP compliance. That cost may be minimal where the APVMA considers a Certificate of GMP Compliance from a recognised authority to be acceptable. If an overseas audit is required, the cost may be up to \$10,000 per audit if an Australian auditor is involved. This may be substantially reduced if industry can co-operate to share the costs involved in overseas travel.

There will be an increase in time imposts placed on registrants in complying with an increase in regulatory requirements. Industry will need to establish and maintain administrative processes to comply with the new procedures.

If satisfactory GMP compliance cannot be established, industry may need to invest funds in order to meet APVMA requirements.

The effects of the new scheme will vary between companies. It will have no impact on some companies who use only Australian manufacturers. Small companies that use only overseas manufacturers may be affected. During public consultation, industry did not raise concerns over loss of product as a result of the new arrangements. The requirement for GMP compliance at the point of product registration has existed for a number of years. The APVMA does not consider that, as a result of the need for enduring GMP compliance, suppliers will leave the market and cause a reduction in supply of some veterinary chemical products manufactured overseas.

## Summary of outcomes for the option

The enduring GMP compliance of overseas veterinary chemical manufacturers				
<b>Objective: to assure the enduring GMP compliance of overseas manufacturers of vet chemical products</b>				
Option	Impact on			Likely Benefit/Cost
	the APVMA	the community	industry	
<i>The use of Conditions of Product Registration to ensure GMP compliance</i>	provides for up to 100% check rate every three yearly cycle; flexibility to reduce impost on workloads; no formal applications to be processed	good assurance of product safety and quality; may be slight (uncertain) rises in product costs	cost of obtaining evidence and submitting evidence; increased equity in requirements	Increased assurance of quality for products manufactured overseas balanced against the cost of obtaining and assessing such evidence.

## Part 5: Consultation

Consultation with the veterinary chemical industry began in July 2003 with the initial announcement of the project.

An industry meeting was held in July 2004 to discuss options and provide a forum for discussion. Comment was generally favourable and has been taken into account in formulating the Consultation (Draft) Regulatory Impact Statement. The industry representatives requested that evidence of compliance be collected in a coordinated way rather than, for example, on the anniversary date for each product. Under the proposed option, registrants will have the flexibility to collect the evidence of compliance at any time they wish, provided that the evidence collected is not more than three years old, based on the actual audit date. The same evidence can be used for multiple products manufactured at that site. The meeting also indicated that industry associations would have a useful role to play in notifying members of impending overseas audits so that costs could be shared.

A Consultation (Draft) Regulation Impact Statement was published in September 2004 to present options and assess their impacts. Comments from industry and the general public were invited in response to this, and a total of four responses were received (see Attachment Four). The responses were, in general, supportive of the proposed scheme. Issues raised in the responses were addressed in consultation with those who made submissions. It is anticipated that industry will continue to be consulted during implementation of the proposed scheme.

## **Part 6: Conclusion and Recommended Option**

### **The preferred option**

The APVMA's preferred option is provided and a timetable for implementation is given below.

### **Reasons for preferring this option**

This option is preferred because it avoids the need for legislative change, ensures veterinary chemicals manufactured overseas comply with GMP requirements on an ongoing basis and appears to be less costly than formal schemes used by other regulatory authorities. It also provides flexibility to both industry and the APVMA to accommodate workflow changes.

## **Part 7: Implementation and Review**

### **Timetable to implementation**

The following timetable outlines the process that will be undertaken in preparation for implementation of the new program in early 2005:

October-November 2004	Consultation between the APVMA and interested parties on the Consultation (Draft) RIS
November 2004	Presentation of the final RIS to the Office of Regulation Review for comment.
December 2004	Presentation of the final RIS to the Board of the APVMA for approval.
February 2005	Implementation of new program including the initiation of the Review/Reconsideration to impose Conditions of Product Registration for registered veterinary chemical products that are manufactured overseas.
2006-2007	Review and evaluate new program.
2007	Publish report on evaluation of new program.

## **Implementation of the preferred option**

The APVMA would seek to implement the preferred option by:

- i) imposing Conditions of Product Registration for new veterinary chemical products manufactured overseas as new products are registered;
- ii) re-considering existing product registrations for veterinary chemical products manufactured overseas in order to impose the Conditions of Product Registration;
- iii) developing a strategic program to request and consider evidence;

In developing a strategic program the APVMA would:

- i) determine the number of routine checks done per annum and the percentage of manufacturing sites checked each year, based on risks and available resources;
- ii) request evidence on a site-by-site basis for each registrant, where possible;
- iii) consider a transition period for collection of evidence.

## **Review of the preferred option**

A review of the new scheme will be conducted throughout 2006 and 2007. An assessment will be made against the objectives specified in the RIS. Any recommended improvements will be instituted before the end of 2007.

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## ATTACHMENT ONE

### GUIDELINES FOR PROVIDING EVIDENCE OF GMP STATUS OF OVERSEAS MANUFACTURERS

#### A. Recognised Agency and Acceptable Type of Evidence

Country	Type of product	Recognised agency (Competent Authority)	Type of certificate and/or other documentation required
<b>European Union (EU)</b> Austria Belgium Denmark Finland France Germany Greece Ireland Italy Luxembourg Netherlands Portugal Spain Sweden UK	Sterile and non-sterile medicinal products (including vaccines and other immunobiologicals, ectoparasiticides, medicated stock-feeds, premixes and supplements), <b>but not including</b> stock-feed additives or therapeutic pet foods (see below).	The relevant Competent Authority in the country of export. Refer to <i>EU-Australia MRA List of Competent Authorities</i> on the APVMA's web page.	<i>Certificate of GMP Compliance of a Manufacturer</i> , in the format agreed to by the Parties to the EU-Australia MRA.
	Stock-feed additives (eg direct-fed microbials, probiotics, enzymes).	Varies from country to country but is usually the national or regional Veterinary Service or Department of Animal Health. Sometimes it is the Department of Agriculture.	A certificate or other documentation that states that the facility has been inspected and that products are manufactured in accordance with requirements of EU Directive 95/69/EC.  Where the Directive requirements have been transposed into national legislation, it must be clear from the certificate/documentation that the national legislation relates to EU Directive 95/69/EC.
	Therapeutic pet foods (processed pet foods whose content has been modified to meet therapeutic requirements, eg low fat, low mineral content).	Varies from country to country but is usually the national or regional Veterinary Service or Department of Animal Health.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section
<b>European Free Traders Association (EFTA) countries</b> Norway Liechtenstein Iceland	Sterile and non-sterile medicinal products (including vaccines and other immunobiologicals, ectoparasiticides, medicated stock-feeds, premixes and supplements), <b>but not including</b> stock-feed additives or therapeutic pet foods.	Certifying agency to be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.

Country	Type of product	Recognised agency (Competent Authority)	Type of certificate and/or other documentation required
EFTA (cont)	Stock-feed additives.	Certifying agency to be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
	Therapeutic pet foods.	Certifying agency to be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
Switzerland	Sterile and non-sterile medicinal products (including vaccines and other immunobiologicals, ectoparasiticides, medicated stock-feeds, premixes and supplements), <b>but not including</b> stock-feed additives or therapeutic pet foods.	Swissmedic, Swiss Agency for Therapeutic Products.	<p>A certificate that clearly states that the manufacturer is authorised to manufacture veterinary medicinal products (or pharmaceutical products) in accordance with the laws and regulations of the Swiss Confederation and/or the particular Canton.</p> <p>The certificate should also state that the manufacturing plant is regularly inspected and that it complies with GMP requirements as recommended by World Health Organisation (WHO), the Pharmaceutical Inspection Convention (PIC) and, where issued by a Canton, the Intercantonal Office of the Controller of Medicines.</p> <p>There is usually no reference to EU requirements, although Swiss Regulations tend to be aligned with EU legislation.</p>
	Stock-feed additives.	Usually the national or regional Veterinary Service. Sometimes it is a Regional Agricultural Research Institute (where the regional vet service is based).	A certificate or other documentation that states that the facility has been inspected and that products are manufactured in accordance with requirements of the Swiss equivalent of EU Directive 95/69/EC. Note, in the case of Swiss certificates, it will not always be clear from the certificate/documentation that the national legislation relates to the EU Directive (95/69/EC). In that case, the manufacturer will need to provide a letter from the Swiss agency confirming that.
	Therapeutic pet foods.	Usually the national or regional Veterinary Service or Department of Animal Health. Sometimes it is a Regional Agricultural Research Institute (where the regional vet service is based).	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section

Country	Type of product	Recognised agency (Competent Authority)	Type of certificate and/or other documentation required
USA	Immunologicals (eg vaccines, antisera and other biological products of a therapeutic nature). Does not apply to biologicals of a performance enhancing nature (eg boar taint vaccines or hormones).	US Department of Agriculture (USDA) Centre for Veterinary Biologics.	A <i>Certificate of Licensing and Inspection</i> confirming that both the product and the manufacturing establishment have been inspected and licensed under the laws and regulations of the USA.
	Sterile and non-sterile medicinal products marketed in the USA, including medicated stock-feeds, premixes and supplements, <b>but not including</b> vaccines and other immunobiologicals (of a therapeutic nature), ectoparasiticides, stock-feed additives or therapeutic pet foods (see below). May include biological products of a performance enhancing nature (eg boar taint vaccines or hormone).	US Food and Drug Administration (FDA).	<i>Certificate to a Foreign Government</i> confirming that: <ul style="list-style-type: none"> <li>• the product and the manufacturing plant which produces it are subject to the jurisdiction of the FDA,</li> <li>• the manufacturing plant is subject to periodic GMP type inspections/audits, and</li> <li>• that the products and the manufacturing plant are in compliance with GMP (or words to that effect).</li> </ul>
	Immunobiologicals, sterile and non-sterile medicinal products manufactured for export purposes only and not marketed in the USA.	To be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
	Ectoparasiticides.	To be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
	Stock-feed additives and therapeutic pet foods.	State Agency responsible for the regulation of non-medicated stock-feeds and stock-feed additives (usually State Departments of Agriculture or University Extension Services). Certifying agency to be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.

Country	Type of product	Recognised agency (Competent Authority)	Type of certificate and/or other documentation required
Canada	Immunologicals (eg vaccines, antisera and other biological products of a therapeutic nature).	Veterinary Biologics Section of Canadian Food Inspection Agency	Both a <i>Veterinary Biologics Export Certificate</i> and a <i>Veterinary Biologics Establishment Licence</i> . In addition, a copy of the most recent inspection report may be required. Refer to the APVMA's Quality Assurance and Compliance Section for further information.
	Sterile and non-sterile medicinal products (including premixes and supplements), <b>but not including</b> vaccines and other immunobiologicals, ectoparasiticides, medicated stock-feeds, stock-feed additives or therapeutic pet foods.	Health Canada (Ministry of Health).	Both a <i>Therapeutic Products Establishment Licence</i> and the most recent <i>Inspection Exit Notice</i> .
	Immunobiologicals, sterile and non-sterile medicinal products manufactured for export purposes only and not marketed in Canada.	To be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
	Ectoparasiticides	To be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
	Stock-feed additives and therapeutic pet foods.	To be determined by prior arrangements with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.
New Zealand	All veterinary products other than those considered by NZFSA to be low risk (ie not pose a risk to trade or the environment).	Agricultural Compounds and Veterinary Medicines Group (AVCM) of the NZ Food Safety Authority (NZFSA).	<b>Certificate of GMP Compliance of a Manufacturer.</b>  Or if the facility has yet to be issued with the new certificate, an <i>Inspection Certificate</i> or a <i>Certificate of GMP</i> issued by the Animal Remedies Board that is no more than 2 years old.
	Low risk products, eg feed additives such as direct-fed microbials and enzymes, therapeutic pet foods, some products also approved for human use.	To be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.

<b>Country</b>	<i>Type of product</i>	<b>Recognised agency (Competent Authority)</b>	<i>Type of certificate and/or other documentation required</i>
Full members of PIC/S <b>(if not listed previously)</b> Czech Republic Hungary Malaysia Romania Singapore Slovak Republic	Sterile and non-sterile veterinary medicinal products (including vaccines and other immunobiologicals) made in facilities manufacturing products for human use.  Some PIC/S members may not be prepared to certify or inspect facilities used specifically for the manufacture of veterinary medicinal products, particularly products such as ectoparasiticides, medicated stock-feeds, premixes and supplements, stock-feed additives or therapeutic pet foods.	See list of PIC/S agencies on web ( <a href="http://www.picscheme.org/overview/picsauth.htm">http://www.picscheme.org/overview/picsauth.htm</a> ).	<i>Manufacturers' Licence or Certificate of GMP</i> (plus letter confirming currency of the certificate/licence if more than 3 years old).
All other countries	All types of products	Certifying agency to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.	Type of documentation to be determined by prior arrangement with the APVMA. Refer to Quality Assurance and Compliance Section.

## **B. Currency of Licence/Certificates**

Licences or GMP Certificates must be no older than the expiry date of the certificate or less than 3 years old (whichever is the earlier), unless accompanied by a letter from the relevant competent authority confirming currency.

## **C. Other requirements**

- The certificate provided must be either an original certificate, or a certified copy of the original certificate.
- Certified copies must be fully legible and entire (no missing edges).
- Faxed copies are not acceptable.
- The name and address of the manufacturer on the certificate must be the same as that shown on the application for registration. If different (eg certificate made out to an administrative address and not the street address of the manufacturing facility), a covering letter explaining the difference must be provided.
- The scope of the certificate must cover the type of product to which the application relates.
- There must be no qualifying statement on the licence rendering it invalid (eg a statement to the effect that 'the certificate is issued for the Government of the UK and must not be used for any other purpose').

## ATTACHMENT TWO

### Exert from *Agricultural and Veterinary Chemicals Code Act 1994 (Agvet Codes)*

#### 59 Manufacture of chemical products — exempt products

- (1) For the purposes of paragraph 121 (4) (a) of the Code (which deals with exempt products and persons in relation to manufacture), the following are exempt products:
  - (a) any agricultural chemical product;
  - (b) an ingredient used in the manufacture of a chemical product if the ingredient:
    - (i) does not have a therapeutic or biological effect on a plant or animal; or
    - (ii) is a herb, or an oil extracted from a herb, the sole use of which is as a starting material for use in the manufacture of a chemical product;
  - (c) any product prepared in a research facility or pilot plant solely for experimental use;
  - (d) any veterinary homeopathic preparation that:
    - (i) is more dilute than a one thousandfold dilution of a mother tincture; and
    - (ii) is not required to be sterile;
  - (e) any skin cleanser or shampoo;
  - (f) any coat conditioner intended for external use only;
  - (g) any equine hoof protectant;
  - (h) any sheep branding substance;
  - (i) a substance of any of the following kinds that is intended to be added to stockfood:
    - (i) organic acids;
    - (ii) antioxidants;
    - (iii) pellet-binding products;
    - (iv) mould inhibitors;
    - (v) preservatives;
    - (vi) feed handling improvers;
    - (vii) colouring agents;
    - (viii) anticaking agents;
    - (ix) deodorising agents;
    - (x) flavours;
    - (xi) flavour enhancers;
    - (xii) sweeteners;
    - (xiii) aromatic substances;
    - (xiv) appetising substances.

- (2) In paragraph (1) (d):

***mother tincture*** means a liquid prepared by the process of solution, extraction or trituration.

veterinary homeopathic preparation means a preparation:

- (a) formulated for use on the principle that it is capable of producing in a healthy animal symptoms similar to those which it is administered to alleviate; and
- (b) prepared according to the practices of homeopathic pharmacy using the method of:
  - (i) serial dilution and succussion of a mother tincture in water, ethanol, aqueous ethanol or glycerol; or
  - (ii) serial trituration in lactose.

## ATTACHMENT THREE

### **Proposed Conditions of Product Registration to assure the enduring GMP compliance of overseas manufacturers of veterinary chemical products**

(subject to further consideration, such as detailing of the requirements for a “record” in a Gazettal notice.)

This Chemical Product has been registered on the condition that:

1. The Registrant must not **Supply** the Chemical Product, or cause it to be supplied, unless the Chemical Product has been manufactured according to the NRA/APVMA Manufacturing Principles and associated Codes of GMP, or those of a Recognised Authority deemed to be equivalent by the APVMA.
2. The Registrant must, at or prior to the **Supply** of a **Batch** of the Chemical Product by the Registrant or by another person on behalf of the Registrant, make or have in its possession, a **Record** that the Chemical Product has been manufactured according to the NRA/APVMA Manufacturing Principles and associated Codes of GMP, or those of a Recognised Authority deemed to be equivalent by the APVMA.
3. The Registrant must produce, or cause to be produced, to the APVMA any **Record** within 10 working days of the request having been made by the APVMA, or other such period as determined by the APVMA.
4. The Registrant must keep, or cause to be kept, any **Record** for one year after the expiry date of any **Batch** that is made.
5. For the purposes of these conditions, **Records** are in the possession of the Registrant if **Records** are
  - (a) in the possession of the Registrant; or
  - (b) in the possession of another person pursuant to an arrangement with the Registrant.

#### *Definitions and Interpretation*

6. In these conditions the following words have the following meanings:

“**Batch**” means a defined quantity of material produced in a single series of operations;

“**Record**” means a document in written form that contains the particulars required by the APVMA; [*These particulars would be provided by Gazette Notice*]

**“Supply”** has the same meaning as given to it in Section 3 of the Agvet Codes and includes the doing of those things through, or pursuant to an arrangement with, another person;

**“Recognised authority”** means an authority described in *Guidelines for Providing Evidence of GMP Status of Overseas Manufacturers* ([http://www.apvma.gov.au/qa/mls\\_overseas.shtml](http://www.apvma.gov.au/qa/mls_overseas.shtml)).

# **ATTACHMENT FOUR**

## **Comments on the Consultation Regulation Impact Statement**

### **The level of response**

The APVMA received four written responses to the Consultation Regulation Impact Statement from the chemical industry and no responses from the community or chemical users. The following issues were raised and addressed with the individuals and industry group representatives.

### **Support for the proposed scheme**

Industry commented that it was largely supportive of the proposed scheme, particularly because it brings equality in requirements between Australian and overseas manufacturers.

They commented that the cost of the proposed scheme will be low for most manufacturers, registrants and products, as the only cost in many cases will be the provision of a current certificate acceptable to the APVMA, and the workload should be minimal. Industry believes the costs to the APVMA of this scheme will be minimal, and supports the recovery of those costs through the annual levies paid by registrants because there are benefits to all stakeholders. Issues 2-4 in the RIS, the issues of reduced equity in our requirements, the possible failure to comply with legislative requirements, and the lack of conformity with comparable national and overseas authorities, were supported by industry.

### **Specific concerns raised by stakeholders**

#### **Part 1: Issues relating to details of the evidence required**

Clarification was requested to confirm details of the evidence that will be acceptable to confirm GMP compliance.

##### Issue 1: Record Keeping

Industry suggested that in the conditions of registration, the timeframe for keeping records should align with the Code requirements for retaining samples of finished products (12 months past the expiry date of that product). This is found in Section 8.6 of the Code of GMP. If this was not possible, then the evidence should be maintained at least to the expiry date.

Response:

The APVMA has changed the timeframe for keeping records in the conditions of registration to twelve months past the expiry date of a product.

##### Issue 2: TGA Audits

Industry expressed concerns that the APVMA would require TGA audits as evidence of GMP compliance.

Response:

It is not essential to use TGA auditors for overseas audits. As an alternative, APVMA-authorized auditors, or auditors from other recognised authorities, are acceptable. However, where the overseas manufacturer is providing both human pharmaceutical and veterinary products into the Australian marketplace, the option of a TGA audit may minimise the costs of compliance.

### Issue 3: GMP Compliance Statements

Industry asked if the conditions of registration imply that each batch of product manufactured overseas must be accompanied by a current GMP compliance statement. It was felt that it would not be reasonable to require fresh originals of GMP certification for each batch of product.

Response:

A statement supplied by the manufacturer that the product was manufactured according to GMP would not be regarded as adequate evidence by the APVMA. Only evidence as detailed in APVMA guidelines would be regarded as acceptable. It would, however, not be necessary to supply original copies of such documentation with each batch of product. The conditions of registration stipulate that current evidence must be maintained, by either the registrant or another person pursuant to an arrangement with the registrant. For instance, if manufactured in the EU, the registrant could hold a Certificate of GMP Compliance and replace this every two to three years when that Certificate is updated.

### Issue 4: Delays with FDA Audits

Industry is concerned that US FDA inspection documents may appear to have expired, because US FDA inspections may be delayed, due to their risk-based approach to inspection frequency. In some cases, it may be several years between inspections.

Response:

Where there is a genuine reason why it is difficult to obtain current evidence, registrants should contact the APVMA, and this will be considered on a case-by-case basis.

### Issue 5: USDA

Industry commented that biologicals in the USA are regulated by the USDA, although the Consultative RIS only commented on the FDA.

Response:

The RIS has been amended to include this authority. The authorities that regulate veterinary chemicals in the USA are also listed in Attachment Three, and in the guidelines available on the APVMA's website. Updated guidelines will be released before the commencement of the scheme.

### Issue 6: ISO 9000 Certification

The question was raised by industry as to whether ISO 9000 certification would be acceptable, particularly in the case of ectoparasiticide products in the USA, as these are regulated by the US EPA.

Response:

The US EPA (Environmental Protection Agency) inspects sites on a regular basis, but audits to a standard that emphasises environmental issues. The APVMA requires additional evidence of compliance with the Australian Code of GMP. This usually involves an audit from a recognised authority, or an authority that is otherwise acceptable to the APVMA, subject to agreement on a case-by-case basis. ISO 9000 Certification by itself would not be acceptable evidence.

## **Part 2: Issues relating to the costs**

### Issue 7: Audit intervals

Industry expressed concerns that, in cases where an overseas audit was required, an audit every 2-3 years would be too costly. It was asked if this timeframe could be extended to as long as 5 years if the most recent audit had found the site to have no serious non-compliance. It was also asked if a declaration from the manufacturer, that no changes to the manufacturing process had been implemented, could be used to increase audit intervals to up to five years.

Response:

The APVMA considers 3 years to be the maximum time interval between audits that would be acceptable. Five years is too long an interval for assurance of GMP compliance. Australian manufacturers are required to have several audits within any five-year interval to maintain their Manufacturer's Licence, and countries with recognised authorities also conduct at least two audits within a five-year interval.

### **Part 3: Issues relating to the technical basis of the Consultative Regulatory Impact Statement**

Industry raised some concerns about the arguments presented in the RIS.

#### Issue 8: FDA fees

Industry commented that, "the report does not mention that the US FDA inspections do not result in any direct fee to the drug manufacturer."

Response:

The RIS has been amended to include this.

#### Issue 9: Quantifiable effects

Industry is concerned that quantifiable effects of the lack of GMP compliance are not demonstrated in the RIS. Another comment was made by industry that the first issue presented in the RIS, the issue of product safety that included examples, did not support the justification of the review and it would be preferable to delete this issue.

Response:

While poor GMP compliance may not be the only cause of compromised safety and efficacy of veterinary chemical products, it is an important issue for product quality after a product has been registered. The RIS has been amended to modify the statement, so it is not inferred that poor GMP compliance invariably results in reduced product quality.

#### Issue 10: The impact of GMP compliance

Industry believe that the RIS overplays the importance and impact of the potential for poor GMP compliance.

Response:

Australian manufacturers of veterinary chemicals are subject to explicit regulation via the Manufacturer's Licensing Scheme, and the proposed scheme establishes a comparable regulatory standard for overseas sites. The RIS has been amended to state that poor GMP compliance may be reflected in reduced product quality, safety and efficacy.

#### Issue 11: Reconsideration of existing veterinary chemical products

Industry would like more details about how the Reconsideration will be conducted fairly and equitably.

Response:

The Reconsideration will apply to all existing products with overseas manufacturers and according to established Reconsideration processes consistent with the Agvet Chemicals Code legislation.

Issue 12:

Industry commented that they would like the conditions of product registration to apply equally to locally manufactured products.

Response:

Conditions of registration for locally manufactured products have not been considered necessary as part of this proposed scheme. To assure GMP compliance throughout the life of a locally manufactured product, Part 8 of the Agvet Code requires Australian manufacturers of veterinary chemical products to have an appropriate licence with the Manufacturer's Licensing Scheme.