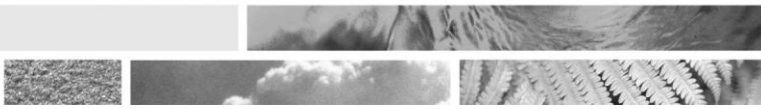
Environmental Protection Authority
Te Mana Rauhī Taiao

APPLICATION FORM
CONTAINMENT

Applicant:



Application Form: HS3 Import or Manufacture any Hazardous Substance in Containment

Under section 31 of the Hazardous Substances and New Organisms Act 1996

Send by post to: Environmental Protection Authority, PO Box 131, Wellington 6140 OR email to: info@epa.govt.nz
Payment must accompany application; see our fees and charges schedule for details. Please allow 10 working days for processing.

Argenta Manufacturing Ltd

Name of Substance:

Argenta Experimental Veterinary Medicines

APPLICANT CHECKLIST			
Mandatory sections filled out	X	**Appendices enclosed**	X
Initial fees Enclosed	X	**Signed and dated**	**X**
Electronic copy of application e-mailed to EPA	X		

Office Use Only

Application Code:

Date received:

EPA Contact:

Initial Fees Paid: $

Application Version No:

Important

You can talk to an applications advisor at the EPA who can help you scope and prepare your application. We need all relevant information early on in the application process. Quality information up front will speed up the process.

This application form may be used to seek approvals for more than one hazardous substance where the substances are related, for example a concentrated compound (active ingredient) and its related formulations, or a range of substances for similar purposes to be tested in a field trial.

Any extra material that does not fit in the application form must be clearly labelled, cross-referenced, and included in an Appendix to the application form.

Commercially sensitive information must be collated in a separate Appendix.

Unless otherwise indicated, all sections of this form must be completed for the application to be progressed.

You can get more information at any time by contacting us. One of our staff members will be able to help you.

Section One – Applicant Details

1.1 Name and postal address in New Zealand of the organisation making the application:

Name: Argenta Manufacturing Ltd

Address: P O Box 75 340 Manurewa Auckland

Phone: 09 250 3100

Fax: 09 268 1843

1.2 The applicant's location address in New Zealand (if different from above):

Address: 2 Sterling Avenue, Manurewa, Auckland

1.3 Name of the contact person for the application:

This person should have sufficient knowledge to respond to queries and either have the authority to make decisions on behalf of the applicant that relate to processing the application, or have the ability to go to the appropriate authority.

Name: Mitch Venning

Position: Product Development Manager

Address: Argenta Manufacturing Ltd, P O Box 75 340 Manurewa Auckland

Phone: 09 250 3100 DDI 09 250 3186 Mob 021 278 5852

Fax: 09 268 1843

Email: mitch.venning@argenta.co.nz

Section Two – Application Type and Related Approvals Required

This form is only to be used for an application to import a hazardous substance into containment or manufacture a hazardous substance in containment.

If you are making the application for some other reason, you will need a different form.

2.1 Is this application to manufacture or import a hazardous substance in containment for any of the following purposes:

Containment applications can only be made for a limited range of purposes. In particular it is not intended for commercial manufacture or sale.

Small amounts of any hazardous substance for use as an analytical standard where approval to import or manufacture that substance has been declined? ☐ No

Research on any hazardous substance to acquire information for use in assessing that substance for a HSNO approval? ☐ No

Research and development on any hazardous substance ☐ Yes

Use in an emergency? ☐ No

Other purposes? ☐ No

2.2 If you answered yes to one of the purposes listed above, please provide some supporting detail. If you answered yes to "other purpose", describe the purpose and explain why this purpose is appropriate to a containment application.

Approval is sought, pursuant to section 30(b) of the HSNO Act 1996, to manufacture or import animal health formulations for use in studies In Containment.

The objectives of the contained field studies is to provide information on medical device delivery performance, efficacy, safety and residues that will be used to help identify the candidate formulations to be selected for further development. In addition, the data generated in these studies may be used to support applications to register products under

the ACVM Act. It is proposed that under the current application a number of pilot and larger scale field studies will be carried out over a period of up to 7 years.

The investigational substances to be evaluated in New Zealand will contain active ingredient(s) and the necessary additional components (excipients) that will enable the ingredients(s) to be formulated into a suitable product.

It is expected that a proportion of these preparations may be classified as hazardous under the Hazardous Substances (Minimum degrees of hazard) Regulations 2001.

In some cases the information for these formulations may be limited, as they will have only been developed recently. However, it is likely that the individual components will be known and commonly present in other registered products. In each case, sufficient information will be provided to confirm the likely hazards and risks associated with the proposed use of the investigational substance(s).

The volume of the investigational substance both liquid and solid dose forms, directly involved in the In Containment animal studies is expected to be < 100 litres/ liquid substance and for solid compounds < 100 Kg/ substance over the 7 year period of approval. The compounds will be manufactured in New Zealand at Argenta Manufacturing Ltd an ACVM approved GMP facility.

It is proposed that the animal health formulations will be assessed in In Containment studies primarily in our research fistulate cattle herd at Waiuku near Pukekohe, but possibly at other sites around New Zealand and will only be used in compliance with the controls assigned to this approval.

The animal health investigational substances will include products with the following indications: Treatment of ectoparasites and endoparasites, mineral and vitamin deficiencies, endocrine correction, productivity improvers, rumen modifiers, mastitis, bloat, methane reduction, nitrate reduction. Additional test substances might also be indicated for a number of other health conditions affecting animals. The animal species treated will include sheep, cattle, deer, goats and possibly other farm and domestic animals. The test substances will be administered directly to the individual animals using specialised applicators like needles, syringes, drench guns and bolus applicators for oral dosing. The location of the study sites will be provided to the EPA as specified in the proposed controls (Appendix 2 in the confidential Appendices).

2.3 Is the information in this application relevant to import, manufacture or both?

Import the substance(s) only?	☐ No
Manufacture the substance(s) only?	☐ No
Import and manufacture the substance(s)	☐ Yes
If import only, indicate whether or not manufacture is likely in New Zealand	NA

2.4 If the information in the application relates to manufacture of the substance(s) in New Zealand, provide information on the proposed manufacturing process and any alternatives.

The manufacture of the investigational substances will take place at Argenta's manufacturing site that has been approved by the ACVM group and which conforms with the EPA's Exempt laboratory requirements. The details of the manufacturing facility are provided in confidence in Appendix 1.

2.5 If this substance(s) needs an approval under any other legislation, has an application for this approval been made?
(Optional)

Name of Approval	Application made
Agricultural Compounds and Veterinary Medicines Act 1997	**As required**
Food Act 1981	☐ NA
Medicines Act 1981	☐ NA
Chemical Weapons (Prohibition) Act 1996	☐ NA
Radiation Protection Act 1965	☐ NA
Biosecurity Act 1993	☐ NA

Resource Management Act 1991	☐ NA
Other (please specify):	No

Section Three – Information on the Substance(s)

Note all information that is commercially sensitive must be attached as an Appendix. The application form should be cross-referenced to the Appendix but should be able to be read as a stand-alone document which will be publicly available.

If approval is being sought for more than one hazardous substance, this section must be completed separately for each hazardous substance.

3.1 State the unequivocal identification of the substance(s).

This section should include all information necessary to unequivocally identify the substance(s) and may include:

- Chemical Name (Chemical Abstracts Preferred Index name or IUPAC name)
- Common Name
- Synonyms
- Trade Names
- CAS Registry Number
- Molecular Formula
- Structural Formula
- Impurities

For mixtures, in addition to the above information being provided on the actual mixture, information is also required on the composition of the mixture ie the chemical name, CAS number, function (eg active ingredient, emulsifier, surfactant, filler) and percentages of ALL components of the mixture (including non-hazardous components and impurities) should be provided. This information may be best expressed in tabular form. If the composition is variable, please ensure to state the limits.

If there are commercial reasons for not providing full information in the main part of the form, alternative approaches must be discussed with and agreed by the EPA. These must include the provision of a unique identifier of some kind.

The full formulation details of each investigational substance will be provided in confidence to the EPA before the commencement of a study

3.2 Provide information on the chemical and physical properties of the substance(s).

Provide as much information as possible on the chemical and physical properties of the substance(s) [at 20°C and 1 atmosphere unless otherwise stated] eg

- Appearance (colour, odour, physical state or form)
- pH
- Density
- Vapour pressure
- Boiling/melting point
- Solubility in water
- Water/octanol partitioning co-efficient

For mixtures, information is required on the chemical and physical properties of the mixture itself. However, if this information is not available, you should provide information on the chemical and physical properties of EACH hazardous component of the mixture.

The known chemical and physical properties of each investigational substance will be provided confidentially to the EPA before the commencement of a study, if this is required.

3.3 Provide information on the hazardous properties of the substance(s).

Information should be provided on the hazardous properties of the substance(s) known to the applicant. You should consider each of the six hazardous properties below and provide information on those hazardous properties. This information is needed in order to assess risks and determine whether or not and how the substance can be adequately contained.

- explosiveness

- flammability
- oxidising properties
- corrosiveness
- toxicity
- ecotoxicity

If your substance is a mixture and you cannot provide direct information on its hazardous properties, you can apply mixture rules to the hazardous components of the mixture. If you do this, then you will need to provide information on the hazardous properties of each hazardous component of the mixture, and show your workings.

The known hazardous properties of each investigational substance will be provided in confidence to the EPA, if required

3.4 Provide information on what will happen to the substance throughout its whole life from its introduction into New Zealand, its uses, through to disposal.

The information provided needs to reflect the containment character of the application. It will be used in the development of exposure scenarios and the assessment of risks and hence the specification of the containment conditions.

Specific details of the life cycle of a particular investigational substance will be provided to the EPA when required.

The life cycle of the investigational substance in New Zealand in general will be as detailed below:

1. **Manufacture or importation of a investigational substance**
2. **Storage of the investigational substance in a secure facility**
3. **Transportation of the investigational substance to the study site(s)**
4. **Administration of the investigational substance to the study animals**
5. **Disposal of surplus investigational substance will be by use, burial in a suitable landfill, or export for high temperature incineration.**
6. **Disposal of used containers will be by incineration (for plastic containers and if circumstances such as wind direction permit) or burying in a suitable landfill.**
7. **Retention of treated animals on the study sites for the period stipulated as one of the conditions of the ACVM Research Approval or Provisional Registration**

The packaging used will be appropriate for the manufactured investigational substance and will be known to contain the substance securely. Thus the potential for exposure to the investigational substance(s) by people handling the product while in the packaging within which it will be transported will be very low. Consequently, exposure during transport, storage and handling would only be possible if the packaging is breached.

3.5 Provide information on the quantity of the substance proposed to be imported or manufactured.

This information is used in the development of exposure scenarios and the assessment of risks.

Approval is sought to manufacture a maximum of 2000 litres and or 1000 Kg of solid formulations of each animal health substance over seven years. This product will be stored in properly approved facilities and a small quantity involving a maximum of 100 litres or 100Kg (solid formulations) will be dosed to animals In Containment over the 7 years of the approval. The remaining product will be produced to validate the manufacturing process and to provide samples required to carry out stability testing in the proposed commercial pack sizes over an extended period. .

Section Four: – Information on the Proposed Containment System

4.1 Provide information on the proposed containment system.

It is essential that good information is provided on the containment system because the adequacy of containment in conjunction with the hazardous properties of the substance will have a major impact on whether or not approval is given.

You will need to provide a description of the containment proposed AND information on how you intend to address the following issues (proposed controls):

- methods for preventing the escape of the contained hazardous substance and preventing the contamination of the facility.
- methods for excluding unwanted organisms from the facility or to control organisms within the facility
- methods for excluding unauthorised people from the facility
- methods for preventing unintended release of the substance by experimenters
- methods for controlling the effects of any accidental release of the substance
- inspection and monitoring requirements of the containment facility

A management plan may be attached as an appendix. This plan should specify the procedures for implementing the above methods for containing the substance(s), and provide details of the qualifications of the person responsible for implementing those controls.

The proposed containment system for the studies will be based on the controls contained in Appendix 2.

However the essential aims of this system can be summarised as below:

1. **To limit the likelihood of escape of any contained hazardous substance or contamination by any hazardous substance**
2. **To exclude unauthorised people from having access to the contained hazardous substance**

3. **To prevent unintended release of the substance by researchers working with the substance**
4. **To prevent treated animals or their produce entering the food chain before the time stipulated by the ACVM**
5. **To control the effects of any accidental release of the substance**
6. **To ensure that the inspection and monitoring requirements have been met**
7. **To ensure that the person responsible for implementing the controls has the required qualifications**

These aims of the containment system will be achieved because:

1. **The investigational substance(s) will be stored in a locked facility to which access is only available to authorised suitably trained personnel.**
2. **Only limited quantities of the investigational substance will be taken to the study site(s) and any remaining after administration of the treatment, will be immediately returned to the secure locked facility**
3. **The investigational substance will only be provided in packaging that is suitable for its safe storage and transport**
4. **Only very small quantities of the investigational substance will be administered**
5. **The investigational substance will only be administered by experienced, suitably trained people, using appropriate equipment.**
6. **The investigational substance will only be administered at the dose rates detailed in the approved protocols**
7. **The investigational substance will only be administered using suitable safety equipment that may include gloves and the wearing of appropriate protective clothing**
8. **The investigational substance will only be administered to the species specified on the conditions of approval of the ACVM Research Approval or ACVM Provisional Approval and Ethics Approval .**
9. **The study will be carried out on farms that are securely fenced**
10. **It is expected that testing of the investigational substance will involve the treated animals being managed by farmers who are experienced in the running of the types of studies contemplated**

11. **The farmers or managers of the study sites will reside on the property, thus giving the study site a high level of security and limiting access to the treated animals to people authorised by the study directors or the farm managers**

Section Five – Identification and Assessment of Risks

In completing this section, it is important that you take account of the proposed containment system you described in Section 4. We are particularly interested in knowing about risks that may still remain with the containment system in place. You will need to consider the effects on the environment and public health including any social effects.

You should also take account of the quantity of material involved and the number of different locations that may be involved.

Complete this section as far as you can.

5.1 Identify all of the risks of the substance(s)

Include information on potentially significant possible risks of the substance and whether or not these risks are likely to be significant. It is important to think about the source of the risk ie the way in which the risk is created (the exposure pathway), and then the consequences of exposure. Risks should be considered in relationship to:

- the sustainability of native and valued introduced flora and fauna
- the intrinsic value of ecosystems
- public health (including occupational exposure)
- the relationship of Maori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna and other taonga
- the economic and related benefits to be derived from the use of the hazardous substance
- New Zealand's international obligations.

The main risks associated with the investigational substance(s) can be considered under a number of headings as shown below:

Manufacture and Storage:

The investigational substance(s) will be manufactured in Argenta's secure GMP facility with effective quality control and quality assurance procedures in place. The personnel will be skilled and knowledgeable about the management and minimisation of the risks associated with the production of potentially hazardous substances. The investigational substances and the raw materials that are used in the manufacture will be stored in a secure facility that is approved for storage of substances of this type and which has in place all the appropriate procedures and documentation to effectively manage any possible risks to the environment and to those handling the substances.

Transport:

Insecure packaging or an accident could result in spillage of the investigational substance during loading or unloading or during transport to the contained facilities. In the event of an accident of this type the environment could be exposed to the substance. Spillage is also possible at the study site or storage facility. The risk of spillage during transport is expected to be low, because the substance(s) will only be transported by suitably trained and approved carriers (eg, Chem Couriers), or by staff directly involved in the studies. In addition the packaging will be known to be secure and suitable for the purposes of containing the investigational substance under normal transport and storage. To further reduce the risk only relatively small quantities (< 20 litres liquids, < 20 Kg solids) will be transported and used at any one time.

Administration of the Investigational Substance:

The substance will only be administered to animals by a suitably trained and qualified person (in most cases a veterinarian) who has been given all the required information to manage the substance safely. In addition the test substance(s) will usually be administered by a closed system (eg. Injection, capsule applicator, oral drench applicator, pour-on applicator) using suitable calibrated equipment and at the doses approved by the ACVM. This minimises the risk to the animals the users and the environment.

Disposal of Treated Produce:

Where an investigational substance is administered to food animals all treated produce will be disposed of in accordance with the conditions set by the ACVM Group for the substance. This will remove any risk of residues of the investigational substance entering the food chain.

Disposal of Surplus Investigational Substance:

Surplus substance will be disposed of by high temperature incineration (off shore), burying, or other suitable disposal method (acid/alkali degradation) and therefore will be rendered to a form that is not hazardous before being discharged to the environment. Alternatively the product may be stored and subsequently disposed of by use once the requisite permits and approvals (ACVM and HSNO) are obtained. The risks associated

with disposal will be very low as it will only be carried out by qualified people or companies and facilities appropriate for this function.

Contamination of the Study Site:

There is a small risk of contamination of the study site by spills or possible residues from dung or urine of the treated animals. However, the fact that the investigational substance will not be stored at the study site and that only small volumes will be administered to a small number of animals, mostly using a contained application system (Drench applicator, capsule applicator, syringe) means the risk of spillage is minimal. The risk is further minimised by the use of suitably qualified and trained personnel whom are aware of all necessary precautions to take to minimise the risk to the environment. The faecal and urine risk will also be low as only relatively small volumes of substance will be administered to each animal (typically < 50 mL or 50 grams but up to 500 grams for density retained bolues for mature >300 Kg cattle) and also because only a small number of animals (likely < 40) will be treated with the investigational substance at any one site. In addition metabolising of the substance by the animal will further reduce the quantity of residues excreted.

Accidents, Natural Hazards and Sabotage:

Risks may arise from accidents, natural hazards such as earthquakes and floods, and through sabotage or through deliberate misuse of the substance. However the secure packaging, secure and restricted sites of storage and the fact that the investigational substance, is only administered by trained professionals will minimise those risks.

The main benefit of the approval of this application is that Argenta (an animal health contract formulation development and contract manufacturing business) will be able to offer their clients both formulation development in the laboratory and then proof of efficacy via clinical studies. Thus providing a more cost effective way of controlling the important conditions affecting the health of New Zealand farm and domestic animals.

5.2 Provide an assessment of the potential risks identified in Section 5.1.

An explicit risk assessment only needs to be provided for those risks which might be significant. The assessment should consider whether the identified risks can be adequately managed by the proposed containment system and the substance(s) itself adequately contained.

The assessment should include the nature, probability of occurrence and magnitude of each adverse effect. The uncertainty bounds of the information contained in the assessment should also be discussed.

Risk Assessment and Management

Activity	Hazard Low/Medium/High	Risk Low/Medium/High	Managed	Controls used in Management
Manufacture and storage	Low	Low	Yes	GMP manufacturing facility Secure facility (Swipe cards) no unauthorized access
Sample transportation	Low	Low	Yes	Small amounts of substance Suitable packaging
Application of sample	Low	Low	Yes	Trained personnel Appropriate equipment
Disposal of treated animals	Low	Low	Yes	Trained personnelProject plan including ACVM approval requirements
Remaining sample Disposal	Low	Low	Yes	Trained personnel Return of surplus substance to secure facility for correct disposal
Site Contamination	Low	Low	Yes	Trained personnel Small doses used Substance not stored at site
Accidents, Natural disasters, Sabotage	Low	Low	Yes	Trained personnel Secure storage facility Secure packaging

Risk to Māori:

Assessment of the known and possible adverse effects throughout the life cycle of the investigational substance(s) on the relationship of Maori and their culture and traditions and their ancestral lands, water, sites, waahi tapu, valued floras and fauna and other taonga has been conducted in accordance with the assessment framework contained in the ERMA New Zealand User Guide "Working with Maori under the *HSNO Act 1996*".

It is concluded that there are no significant cultural effects likely from the manufacture over 7 years of up to 2000L (liquids) or 1000 kg (solids) of each of the new formulations into containment for use in animal studies located on selected sites that will comply with the proposed ERMA controls.

The contained use of the test substances at only a few secure locations where public access is prevented together with compliance with the requirements of the ACVM approval mean that there will be no involuntary community exposure and there will not be any significant exposure to the environment.

Section Six – International Considerations

6.1 The EPA is interested in whether this substance (or any of its components) has been considered by any other regulatory authority in New Zealand or by any other country. If you are aware of this, please provide details of the results of such consideration.
(Optional)

It is likely that the same or similar substance(s) or one or more of the component active pharmaceutical ingredients will have been approved by the ACVM Group and the EPA. Additionally, most if not all of the non-active excipients will also have been approved by the EPA.

Section Seven – Miscellaneous

7.1 Provide a glossary of scientific and technical terms used in the application.

7.2 Provide here any other information you consider relevant to this application not already included.

Not Applicable

Section Eight – Summary of Public Information

The information provided in this section may be used in the Authority's public register of substances required under Section 20 of the HSNO Act.

This summary information will be used to provide information for those people and agencies (eg Ministry for the Environment, Department of Conservation, Regional Councils, etc), who will be notified of the application, and for potential submitters who request information. This information will also be used to prepare the public notice of the application.

For these reasons, applicants should ensure that this summary information does not contain any commercially sensitive material.

8.1 Name of the substance(s) for the public register:
Please use a maximum of 80 characters.

Argenta Manufacturing Ltd Experimental Veterinary Medicines

8.2 Purpose of the application for the public register:

This should include (in a maximum of 255 characters) an abstract giving information on the intended use of the substance and why an application is needed based on its hazardous properties.

To import or manufacture in containment Argenta Manufacturing Ltd Experimental Veterinary Medicines. These will be used in animal studies under tightly controlled conditions and to confirm product stability and to validate the production process.

8.3 Use Categories of the substance(s):

The EPA has adopted the system of use categories developed by the European Union, which identify various functional uses of substances. This information is pertinent to the assessment of exposure scenarios and the determination of risk and is also useful for building up a profile of the substance. There are three sets of use categories. Within each of these, applicants should state which use categories are relevant to all intended uses of the substance(s).

- Main category: There are four main categories.
- Industry category: There are 16 industry categories.
- Function/Use category: There are 55 function/use categories.

Main category: 3 – Non-dispersive use
Industry category 1 – Agricultural industry
Function/Use category: 41 – Pharmaceuticals

8.4 Executive Summary:

In this section, the applicant should provide a summary of information contained in this application, including:

- the identification of the substance, its hazardous properties, intended uses, and disposal
- an assessment of the adverse effects of the substance
- information on the proposed containment

This is a generic application to import or manufacture Argenta Manufacturing Ltd Experimental Veterinary Medicines for testing. The intention is to conduct small-scale contained field studies that will provide the information required for the development of these investigational substances.
The proposed containment controls and procedures that accompany this application are designed to contain the investigational substances and manage any hazards and risks that may be associated with their importation, manufacture, storage, transport, use and disposal. The disposal of surplus investigational substance(s) will be by use or by burying in a suitable landfill or by high temperature incineration (export), or by acid/alkali degradation (Argenta Manufacturing Ltd) and disposal of used containers will be by incineration (for plastic containers and if circumstances such as wind direction permit) or by burying in a suitable landfill.
The containment system will involve the following procedures:
1. The storage of the investigational substance in locked facilities to which access is only available to authorised suitably trained personnel.
2. The taking of only limited quantities of the investigational substance to the study site and the returning of any that is not administered to secure locked storage.

3. The providing of the investigational substance in packaging that is suitable for its safe storage and use

4. The administration of only very small volumes of the investigational substance

5. The administration of the investigational substance at the approved dose rates by experienced, suitably trained people using appropriate equipment.

6. The dosing of the investigational substance, using suitable safety equipment that may include gloves and the wearing of appropriate protective clothing

7. The administration of the investigational substance to the species specified on the Conditions of approval of the ACVM Research Approval or Provisional Registration

8. The carrying out of the studies on farms that are securely fenced and to which access will only be provided to people authorised by the study directors or the farm owners/managers

Signature **Date**

Mitch Venning
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