Ministry for Primary Industries
Manatū Ahu Matua

Guidance Document

Risk to Benefit Analysis to Support ACVM Registration

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Title

Guidance Document: Risk to Benefit Analysis to Support ACVM Registration

About this document

This is a guideline for carrying out an adequate analysis of the risks and benefits in support of registration of a trade name product under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997. You must carry out and document such an analysis, and include it in your registration application.

Document history

This document is being issued for the first time. It does not replace any other versions.

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Disclaimer

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1 Purpose

This is a guideline for carrying out an adequate analysis of the risks and benefits in support of registration of an agricultural compound trade name product. You must carry out and document such an analysis and include it in your registration application.

2 Background

The ACVM Act specifies the risk areas that you must consider in your analysis. Harms in any other risk areas are not relevant.

The comparison of risks to benefits focuses on a balance between the positive outcomes from using your product and the potential for causing harm in particular risk areas. Acceptability of risks is actually an expression of the balance between benefit and harm. If the benefits from using your product are significant, it may be more acceptable to take a risk of causing a particular harm. Conversely, any risk of harm is unacceptable if there is not some certainty that benefits will be achieved. In all cases there must be more potential to achieve benefits than to cause harm.

If you are unfamiliar with the concept of risk and benefit analysis, particularly how it applies to the registration of agricultural compound products, this guidance should help. You should also refer to the ACVM Registration Information Requirements and the information guidelines for your product type (available on our website). The guidelines focus on the risk of causing harm. Apart from showing adequate efficacy in regard to the claims you make about your product, the MPI guidelines do not focus on analysis of other types of benefits because they are often relative and subjective. Nevertheless, you need to describe what you consider are the collective benefits, particularly if your product poses significant risks of harm.

3 Risk analysis

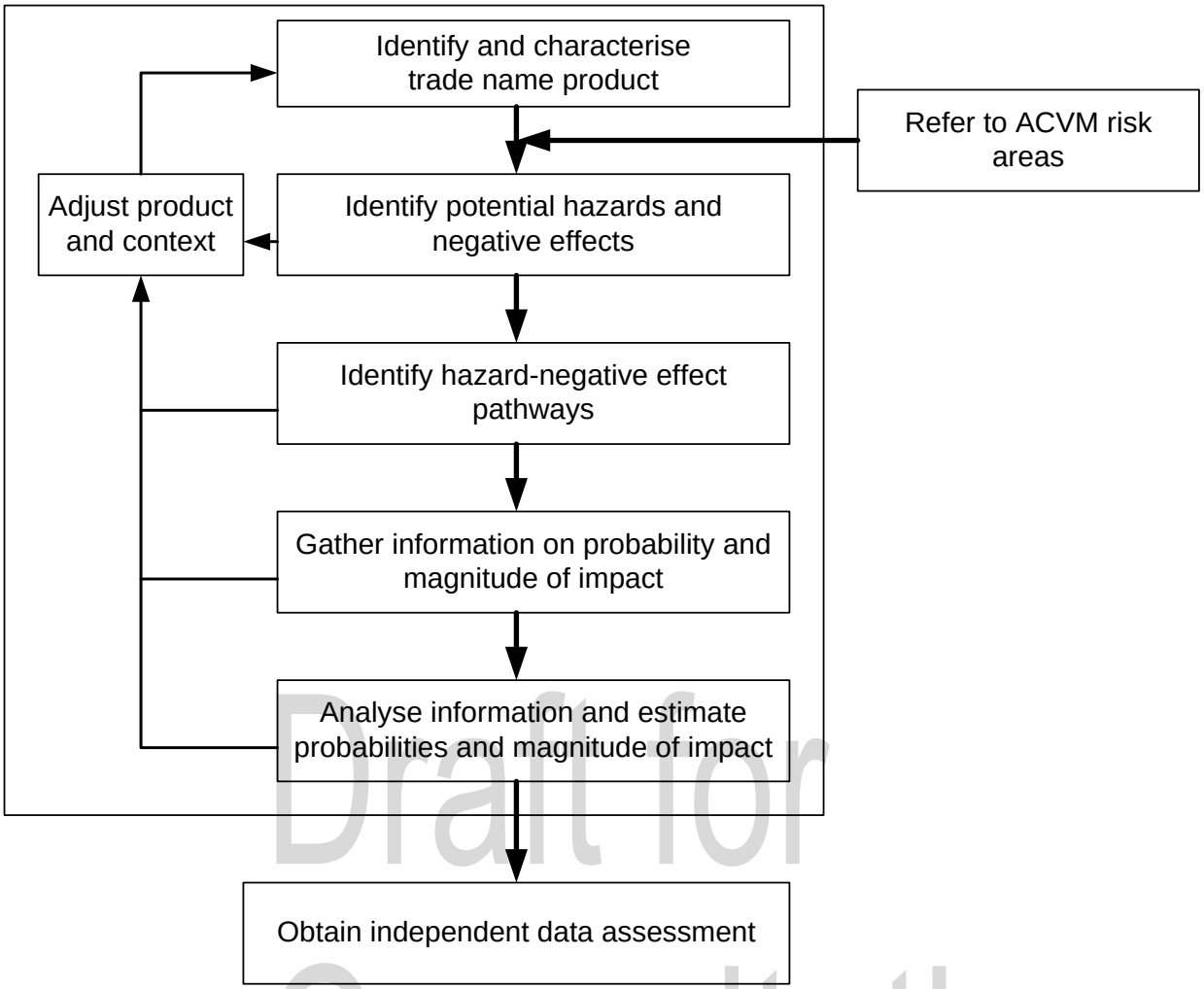
Risk analysis is the part of risk management that focuses on identifying and estimating the level of risks before they are tempered by any regulatory intervention to reduce the probability of harm or to mitigate the impact of that harm.

It is MPI's responsibility to:

- make the level of acceptable risks clear;
- specify the information that is most likely required from you to put the risks posed by your product into perspective (see section 6);
- appraise your risk analysis and supporting information; and
- decide if registration is appropriate and under what conditions.

While MPI has issued registration information requirements, it is essential that you understand the context of the risk analysis and the intent of the analysis. This is your responsibility. You are responsible for your product and you must have confidence that you can produce your product in a specific and consistent manner. You must be aware of the risks associated with the use of your product and take the steps you think are necessary to reduce those risks to an acceptable level as judged by MPI's ACVM risk management framework (see Risk Management under the ACVM Act Overview).

Graphically, your risk analysis looks like this:



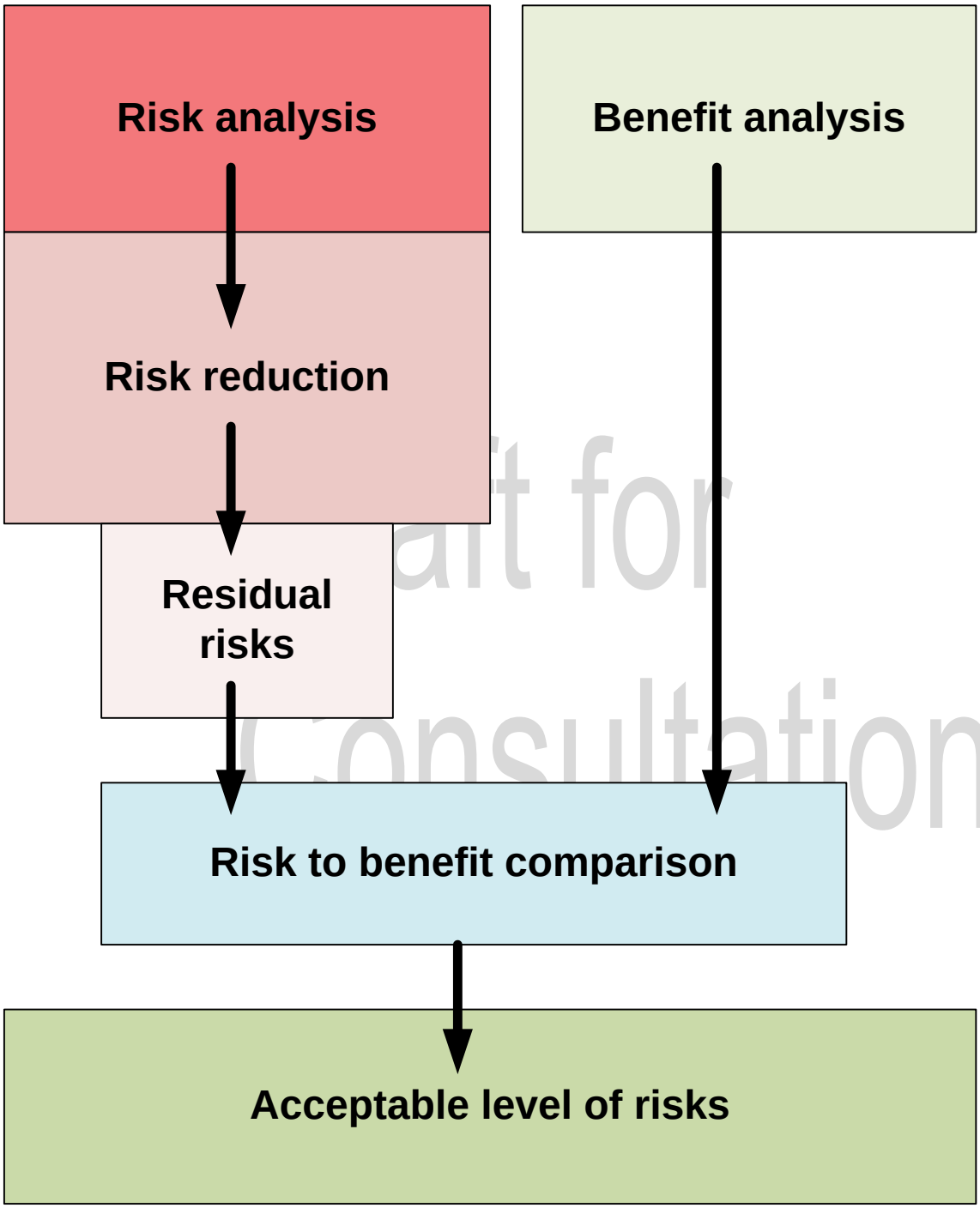
The risk analysis must be done and included in an application for registration. It should also be used in the development of the product in the first place so that it, and the context in which the product is intended to be used, can be adjusted to bring the risks down to acceptable levels. Please note the risk analysis must be provided along with the independent assessment[1] of any data you have generated to support the analysis.

Based on the information, independent assessments and risk analysis provided by the applicant, MPI will appraise and impose risk management conditions on a registration. However, you are expected to design and manufacture your product in a way that minimises risks in the first place.

[1] MPI maintains a list of independent data assessors you may wish to contract to review your data.

4 Benefit analysis

Benefit analysis is a necessary counter-balance to risk analysis. The important matter that must be considered is whether or not the risks are acceptable (i.e. the risks are tolerable given the benefits that are expected). To do this, risks have to be viewed in light of the expected benefits (probability and magnitude).



The initial risk analysis may prompt a redefinition of the product to reduce the risk. Additionally, registration conditions will be imposed to reduce the risks even further. However, the risks can never be reduced to zero. There will always be residual risks. Note that there is a subjective component of perceived risks that has to be considered. A combination of the real and perceived residual risks could be seen as intolerable. For the risks to be considered acceptable, there has to be some certainty that the benefits that could be realised are going

to be sufficient to counter-balance the concerns about the risks the product poses. Any application for registration should provide a statement about the expected risk, particularly if the residual risks are significant or there is particular public concern about or resistance to your product.

Remember that there is a public consultation requirement built into the appraisal of applications for registration of agricultural compounds and veterinary medicines. Failure to describe the benefits may compromise the outcome of the appraisal of your application.

Unrealised benefit cannot be measured quantitatively, so the benefit analysis can usually be no more than a quantitative description except for confirmation of efficacy, which can be shown via efficacy trials.

5 Specifying the product

All risk and benefit analyses of agricultural compound trade name products must begin with careful and specific identification of the product. This is because the product is the point of reference for the analyses and for subsequent registration.

You must first state the claims you are making for the product. It is these claims that make your product relevant to the ACVM Act. (For guidance on what is and is not an agricultural compound, refer to What is an agricultural compound.) The claims also set the expectations regarding what the product is intended to do and how it is to be used, and prompt what benefits might be expected.

You must also be specific about the chemical/biological makeup of your product, and provide its chemical (or biological) and physical characteristics. For further information on how to specify the chemical (or biological) and physical characteristics of your trade name product, refer to:

- Veterinary medicine registration information guidance on chemistry; or
- Agricultural chemical registration information guidance on chemistry and manufacturing; or
- Microbial Agricultural Chemicals; or
- Vertebrate toxic agent (VTA) registration information guidance on chemistry

Some questions to ask yourself
• Is the product an agricultural compound? • Are the intended use and use instructions clearly stated? • Is the description of the product complete and clear with appropriate product specifications for that type of product? • Is the description of the manufacture of the product complete and clear with appropriate manufacturing specifications and controls?

6 Supporting information

Once you have specified your product, you must assess the relevant risks managed under the ACVM Act that could be posed by the use of your product for the purpose(s) you have indicated. The risk analysis conclusions you draw must be supported by technically sound evidence.

The risk analysis should be for the product that is the one to be registered. All trial work should therefore be conducted using that product. Using any other product or even a variation on your product introduces doubt about the relevance of the analysis to your product. If you have to (or choose to) use some other product or variation of your product, you must address the differences and explain why they will not be significant. MPI will decide if your justification for equivalence and relevance is acceptable.

The evidence supporting your assessment of risk can be generated by carrying out appropriate trials designed to estimate both the probability and the magnitude of harms relevant in each of the ACVM risk areas. Further guidance on possible harms and risk areas is given below.

Alternatively, you may be able to refer to evidence that was generated on some other product(s) or refer to previous regulatory decisions made by MPI, or public domain information about some other product(s) that supports your estimates of the risks. However, you must explain why that evidence is equally relevant to your product when it is used for the same purpose(s) and in the way you intend your product to be used.

6.1 Equivalence and relevance

If you support your risk analysis by referring to information generated using a reference product that is not the same as your product, you must provide a robust case for equivalence. *(Guidance on equivalence is currently being updated.)*

If your risk analysis is based on previous regulatory decisions made by MPI or other information on similar products, you must present the differences between your product and the other products referred to and explain why the decisions or other information are relevant to your product. If your product is not exactly the same as the reference product, you will have to address each difference and demonstrate that these do not invalidate your argument for relevance.

Remember, your intention is to prove that the evidence you are referring to supports your risks analysis. If you cannot prove equivalence and relevance, then you should carry out appropriate trial work on your product.

It is your responsibility to include all the information you are referring to in your application. You cannot simply provide references to the information in the application.

6.2 Cross-referencing information

You may be able to cross-reference information MPI holds on a reference product rather than include the information in your application[2]. To do this you will have to prove equivalence between your product and the reference product. Importantly, you are not cross-referencing the product. You are cross-referencing the information MPI holds on that product. If MPI does not hold the information you are referring to (e.g. the product you have chosen to reference was registered by cross-referencing some other product so the evidence is not in the file) the cross-reference cannot be done. MPI will advise you if the information is not in

[2] You cannot cross-reference information that is currently protected confidential information. For more information about protected confidential information refer to Protection of Confidential Information about ACVM Trade Name Products.

the file, but it will not search through other files to find an appropriate reference product. You must choose the reference product that has the information you want to refer to.

Some questions to ask yourself
• Is there adequate evidence to support the estimates of risks in each of the ACVM risk areas? • Is the evidence relevant to the risk estimates? • Is the reference product chosen justified on the basis of equivalence between your product and the reference product? • Has all the information been included (and properly indexed) in the application? • Has each cross-reference to information held by MPI on a registered reference product been justified on the basis of equivalence between your product and the reference product? • Is the information actually in the reference product file? • Has each reference to a previous regulatory decision or public domain information about another product(s) been justified on the basis of equivalence and/or relevance?

7 ACVM risk analysis

The purpose of the Act (ref section 4) is to prevent or manage the following risks associated with the use of agricultural compounds:

- risks to public health;
- risks to trade in primary produce;
- risks to animal welfare; and
- risks to agricultural security.

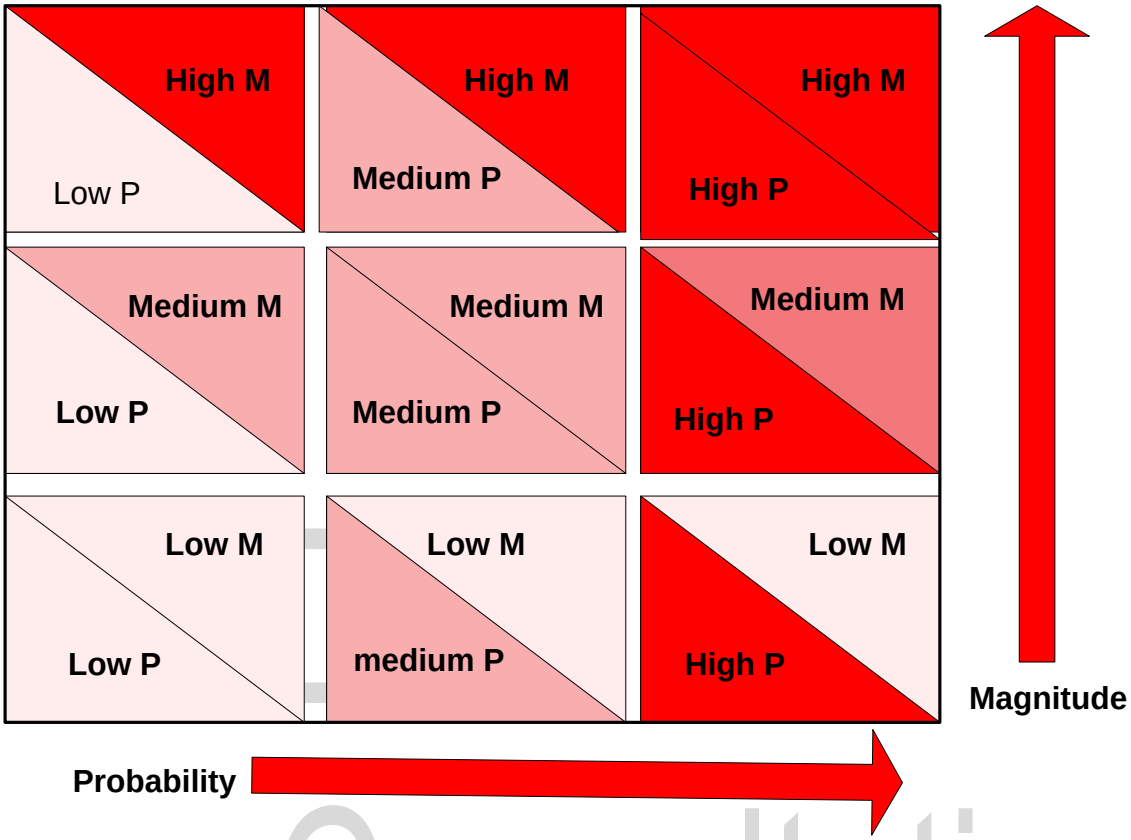
While managing these risks down to an acceptable level, registration decisions must also ensure that:

- the use of agricultural compounds does not result in breaches of domestic food residue standards; and
- when agricultural compounds are offered for sale there is sufficient consumer information provided so people can use them without causing harm.

The ACVM Act aims to achieve its purpose by providing that no agricultural compound may be used (including imported, manufactured, or sold) in New Zealand unless the agricultural compound is authorised (in this case registered) under the Act. The analysis of the risks is considered when authorising the product. Therefore, your risk analysis must focus on the risk areas specified in the ACVM Act. Your product may pose other risks but they are not managed under the ACVM Act (see guidance on the risk areas below).

Risk is a combination of probability that the use of the product will cause harm and the magnitude of that harm. While the probability can be expressed numerically, the combination cannot. A quantitative estimate of the level of risk is preferred but, at times, you may have to resort to a qualitative description of the risks. MPI accepts that your estimates will only be approximate but it expects the estimates to be supported by technically sound and robust evidence.

The following shows the spread of risk estimates.



As the probability and magnitude increase, the acceptability of the risk decreases to the point where even imposing conditions cannot reduce the risks to an acceptable level.

You must address each of the risk areas in turn and provide evidence that supports your estimates of the risk posed. What you need to investigate and analyse are:

- each of the characteristics (i.e. hazards) of your product that could cause harm;
- the kinds of harm that could be caused;
- the way the harm could come about (i.e. hazard/harm pathway); and
- estimates of the probability and magnitude of each harm.

For example, if you are recommending that your product be used on animals or plants used to produce food for humans or feed for animals, an ingredient could persist in the animal or plant and cause a non-compliant residue in the produce for human consumption. It would be an offence to sell that produce as food for human consumption (harm). That ingredient is a characteristic of the product that turns out to be a residue hazard. The fact that the product is intended to be used on animals or plants creates a residue hazard/harm pathway. You need to show the likelihood and the level of residue that would be in the produce when it is offered for sale, when the product is used as per label instructions.

You need to consider each characteristic of your product that could be a hazard in each of the risk areas. You must estimate both the probability of harm and the magnitude of the harm for each hazard to create a

comprehensive picture of the overall risk profile. For example, a risk area managed under the ACVM Act is risk to trade in primary produce. Therefore, after establishing the likelihood and level of residue in the produce, which will be used to set a maximum residue level (MRL), you should also provide a comprehensive picture of the risks of rejected produce due to non-compliant residues. At the same time the product could compromise the management of a pest for biosecurity reasons. Each of these matters should be addressed.'

Some of the common product characteristics that can be hazards are:

- ingredients (chemical/biological substance and concentration of all significant ingredient not just the stated active ingredients);
- packaging and labelling; and
- use pattern (e.g. target animal or plant, mode of administration/application, dosage/application rate, frequency of administration/application).

For guidance on harms, see guidance on risk areas below.

Some questions to ask yourself

- Are there any ingredients in the product that could pose a risk in any of the ACVM risk areas?
- Is there any combination of ingredients that poses a risk in any of the ACVM risk areas, or that alters the risk profile of each ingredient on its own?
- Is there any aspect of the way the product is manufactured that introduces hazards that pose a risk in any of the ACVM risk areas?
- Is there anything about the packaging that poses a risk in any of the ACVM risk areas?
- Is there anything about the way the product is intended to be used (how, when, how much, how often, on what animals or plants) that poses a risk in any of the ACVM risk areas?
- Is there any aspect of the information that is to be provided with the product that may jeopardise the safe and effective use of the product?

8 ACVM risk areas

The following is a more detailed description of the ACVM risk areas and the matters you should take into consideration in your analysis. While you have to consider each of the risk areas, they may not all be relevant to your product. If you concluded that your product does not pose risks in one of the risk areas, you just have to include the logic of that conclusion in your risk analysis. MPI will advise you if it holds a different opinion.

You will note that in each of the threshold descriptions there is a reference to 'ministerial direction'. It is MPI's responsibility to make such directions as public as possible. To date there are no ministerial directions in any of the risk areas.

8.1 Public health

Public health as a risk area is defined as the health of:

- all of the people of New Zealand, or
- a community or section of such people.

In New Zealand, aspects of public health are managed by a number of government departments under different legislation (that is, the Ministry of Health under the Health Act 1956, the Medicines Act 1981 and the Misuse of Drugs Act 1975; WorkSafe New Zealand under the Health and Safety at Work Act 2015; and the Environmental Protection Authority under the Hazardous Substances and New Organisms [HSNO] Act 1996).

To avoid overlap, the public health risk area under the ACVM Act specifically relates to aspects that fall **outside** the scope of the other legislation dealing with public health. In other words, the hazards and harms/negative effects to the health and safety of people that are relevant to the ACVM Act are those that are directly attributable to the use of agricultural compounds and not considered (or not able to be considered) under any other legislation.

8.1.1 Threshold

The threshold that is used to determine an acceptable level of public health risk is an unacceptable probability (and magnitude of harm) that the use of the agricultural compound would:

- reduce effectiveness of human health care;
- reduce the safety of food and food-related products (commercial, non-commercial/home grown and recreationally gathered produce/food);
- fail to achieve claims to maintain or improve human health status or health care via its use as an agricultural compound, including the management of pests;
- reduce the effectiveness of public health programmes; or
- be inconsistent with any written ministerial direction on public health.

8.1.2 Harms/negative consequences

Public health negative consequences would include failure to achieve the level of human health protection expected from the use of an agricultural compound product. For example, a product does not produce the immunity in animals to prevent the spread of zoonotic organisms from animals to people.

Another negative consequence would be reduction in the effectiveness of human health care. The obvious example of this is the possible development of resistance to antimicrobial active ingredients and the transfer of resistant bacteria from animals (or plants) to people.

Inefficacy of agricultural chemicals or vertebrate toxic agents intended to control either invertebrate or vertebrate pests that pose risks to the health and safety of humans[3] could be a negative consequence, particularly if the product is to be used in public health programme to eradicate or control pests.

[3] If the pest is exclusively a pest or pathogen of humans, it is possible that its management cannot be considered under the ACVM Act, simply because the definition of pest specifically excludes humans and any living organism that affects only humans. If there is a demarcation issue, consult with MPI to get the matter sorted.

Some questions to ask yourself
• Would use of my product interfere with diagnostic tests, undermining attempts to identify a disease of public health significance? • Would its use reduce the effectiveness of measures to control pathogens or disease hosts/vectors? • Would its use undermine the safety of human foods, resulting in unsafe residues of substances (or their metabolites), or be a source of biological contamination? • Would its use facilitate the transfer of zoonotic pathogens to humans? • Would specific innovative technologies such as genetic modification or nanotechnology associated with my product introduce health hazards that would cause unacceptable levels of public health risk?

8.1.3 Negative consequences irrelevant to the ACVM Act

Because of the diffuse responsibilities for public health, it is useful to know what negative consequences are **not** relevant to the ACVM public health risk area, for example:

- health problems in people caused by exposure to agricultural compound products, which are managed under the HSNO Act 1996 and the Health and Safety at Work Act 2015; or
- ineffectiveness of products used on humans or to control exclusively human pests or pathogens.

8.2 Trade in primary produce

This risk area involves both international and domestic trade in New Zealand primary produce.

Primary produce is defined in the ACVM Act as any animal or plant, or any derivative of any animal or plant, intended for sale.

Market preferences for quality of the produce are not relevant to this risk area unless the preferences are specified in official requirements (that is, required under New Zealand law or specified in importation requirements by other countries, or specified in a direction from the Minister). For example, there are no official requirements for wool to meet any residue limits for agricultural compounds, so agricultural compound residues in wool do not jeopardise the official acceptability of wool overseas or in the New Zealand market, even though some consumers would prefer to buy wool that is known to be free of residues. Conversely, there are organoleptic (i.e. affecting senses such as taste or smell) quality characteristics of milk and milk products that must be addressed to meet international trade requirements. The difference is that the organoleptic requirements are specifically stated in official import requirements.

8.2.1 Threshold

The trade threshold is an unacceptable probability (or impact) resulting in:

- non-conformance to international trade requirements
- non-conformance to bilateral trade requirements
- non-conformance to agreed New Zealand requirements

- non-conformance to requirements imposed to give effect to a written New Zealand ministerial direction.

8.2.2 Harms/negative consequences

The relevant immediate negative consequences are ones that would prevent the produce from conforming to official overseas import requirements or New Zealand minimum requirements. The downstream negative consequences are rejection (or delays in acceptance) of New Zealand primary produce in the overseas marketplace. Downstream negative effects could be any official government action taken against New Zealand exported primary produce.

There are also other actions, such as restrictions, delays or rejections due to a failure to comply with any other international standard, bilateral import requirement or control programme or restrictions/ prohibitions on the use of certain substances or types of agricultural compound product.

However, the immediate consequences of concern are findings that would lead to sanctions against primary produce from New Zealand. For example, the European Union import requirements prohibit animal produce from animals that have been treated with hormonal growth promotants (HGPs). A rejection of an export consignment of New Zealand beef because some animals had been treated with HGPs would be a negative consequence.

There are also negative consequences closer to home. Failure to conform to New Zealand minimum requirements could result in restrictions, distribution delays, or even statutory offences when nonconforming produce is offered for sale here.

Non-compliant residues are a particular negative consequence.

You should also be aware that:

- certain substances are prohibited in agricultural compounds;
- processes of manufacture or directions for use could be unacceptable; and
- even inadequate levels of regulatory control of use could jeopardise the acceptability of primary produce in some cases.

Trade requirements change from time to time. MPI attempts to maintain up-to-date information on trade requirements, so check with us about current requirements if you are unsure.

Some questions to ask yourself

- Does the product contain ingredients that jeopardise trade in primary produce?
- Does the intended use of the product (how, where, when, how much, how often, on which animals or plants) jeopardise trade in primary produce?
- If the product is to be used on animals or plants that are intended for use as food for humans or feed for animals, what are the residue profiles for significant ingredients when the product is used as directed?
- Would specific innovative technologies such as genetic modification or nanotechnology associated with my product jeopardise trade in primary produce?

8.3 Animal welfare

For the purpose of identifying relevant animal welfare risks, the target animal must be within the scope of the Animal Welfare Act 1999 definition, which includes all vertebrate animals and a few specified invertebrate animals. A target animal is defined as the animal purposefully treated with the agricultural compound and, in the case of a pregnant animal, the foetus or neonate potentially affected by the compound administered to a pregnant animal.

Pain and distress are the parameters for animal welfare and unnecessary/unreasonable has become the point of unacceptability for those parameters. This takes into consideration the fact that some pain or distress may be necessary to achieve a benefit to the animal.

The intended outcome in managing risks to animal welfare under the ACVM Act is to prevent unnecessary and unreasonable pain or distress in the target animal. In many cases involving agricultural compounds, animal welfare is a question of balance between the unavoidable pain and distress caused and the benefit to be realised for the animal(s). The balance must be in favour of benefit to the animal.

The animal welfare risk area is not generally relevant to the use of agricultural chemical products because animals are not the intended target. Some welfare issues are associated with subsequent and inadvertent exposure, but these non-target effects are addressed under the HSNO Act (as negative impacts on the environment rather than as animal welfare per se).

In regard to vertebrate toxic agents (VTAs), death of the target animal is the intended outcome so the animal welfare concern is that death is achieved in the most humane manner possible, minimising the associated pain or distress. Once again, effects of VTAs on non-target species is a HSNO Act matter (as negative impacts on the environment rather than as animal welfare per se).

8.3.1 Threshold

The animal welfare threshold is an unacceptable probability (or impact) that:

- the use of the agricultural compound would result in unnecessary/unreasonable pain or distress in the target animal
- the product would fail to achieve claims to prevent, treat or cure conditions characterised by significant (greater than mild and transient) pain or distress
- the use of the agricultural compound would be inconsistent with any written ministerial direction on animal welfare.

The following are circumstances in which it is considered that inefficacy may jeopardise animal welfare and efficacy analysis is required.

Clinical signs of moderate pain or distress is the usual point at which welfare risks are not acceptable. Conditions for which the clinical signs are no more than transient, mild pain or distress and for which there are alternative products available would not prompt animal welfare concerns because judgements can be made or advice taken about the appropriateness of a particular product for a particular animal. Therefore, welfare concern is partially based on the ability of persons using your product to observe clinical signs and to take action to alleviate pain or distress before they progress to a more significant level, and the ability to take the time to choose between products or take advice on products, without compromising the welfare of the animal.

However, in striking an animal welfare balance, the determinant factor for you to consider will be the severity of the pain or distress that the product is intended to prevent or alleviate. The following definitions should be used.

- **Mild pain or distress** is insufficient to alter normal behaviour except in a very transient way. The animals are easily distracted from the pain or distress.

- **Moderate pain or distress** does not prevent normal behaviour but the animal remains aware of the pain or distress and is not easily distracted.
- **Severe pain or distress** debilitates the animal and prevents normal behaviour.

Products that are promoted or sold to prevent, treat or cure any condition that is commonly characterised by at least moderate pain or distress, especially if clinical signs can develop rapidly, must be efficacious. Therefore, efficacy information must be considered when assessing such products for registration.

If specific levels of efficacy have been highlighted in ACVM registration information guidelines, it should be confirmed that those levels will be achieved. If levels are not specified, you must show that a treated animal is better off (either alleviating clinical signs, or preventing, treating or curing the condition), having taken into consideration the pain or distress caused by the treatment.

MPI recognises that there are other conditions that are usually characterised by only mild pain or distress and there is time to choose between alternative products to achieve the most relief for the treated animal(s). There are also products that are used on animals to achieve an effect (for example, oestrus control) that may have nothing to do with treating conditions of animal welfare concern or alleviating clinical signs of pain or distress. Nevertheless, efficacy must be addressed in order to show that there is sufficient benefit to the animal to offset any pain or distress from treatment.

The only time efficacy does not have to be considered in such cases is when it is confirmed that the risk of pain or distress is approaching zero. In those very rare occasions where the risk is approaching zero, confirmation of efficacy would not be relevant to the ACVM Act. However, failure to support claims of efficacy for such products may result in breaches of the Fair Trading Act 1986.

Conditions of welfare concern

As examples of conditions of welfare concern, the following can be characterised by at least moderate pain or distress and commonly by severe clinical signs. Clinical signs can also develop very quickly, providing no opportunity to make judgements about alternative products. MPI considers that efficacy information would be required in all cases for registration of products marketed for use to prevent, treat or cure any of these conditions.

- Any infectious disease
- Any parasitic (internal or external) infestation characterised by at least moderate pain or distress and which can escalate to more severe clinical signs and shock
- Any gastro-intestinal disorder characterised by any of the following: abdominal pain, distension, tympani, vomiting, diarrhoea, unusual peristalsis or physiological dysfunction
- Any urogenital disorder characterised by any of the following: pain, distension, anuria, obstruction or physiological dysfunction
- Any in-utero condition that causes post-natal pain or distress in the offspring
- Any respiratory disorder characterised by any of the following: pain, compromised respiration, coughing, compromised oxygen/carbon dioxide exchange or physiological dysfunction
- Any musculoskeletal disorder characterised by pain or compromised movement
- Any cardiovascular disorder characterised by any of the following: pain, compromised oxygen/carbon dioxide exchange (either general or localised), compromised blood flow (either general or localised), or physiological dysfunction
- Any central nervous system disorder characterised by any of the following: pain, irritation (either general or localised), compromised senses (either general or localised), disorientation or motor dysfunction
- Any neoplasia characterised by any of the following: pain, compromised physiological functions or homeostasis, compromised immunity or resistance to secondary infections (either systemic or localised)
- Any immune system disorder characterised by any of the following: pain, compromised immunity or resistance to secondary infections (either general or localised), irritation (either general or localised), or auto-immune reactions
- Any disorder of the eye or conjunctiva characterised by any of the following: pain, spasms, intra-ocular pressure, or unusual lacrimation
- Any disorder of the middle or inner ear characterised by pain or loss of hearing or balance;
- Shock
- Any trace element or nutrient deficiency requiring parenteral administration of the deficient element, nutrient or precursor to alleviate pain or distress
- Trauma characterised by at least moderate pain or distress
- Any behavioural condition resulting in hypersensitivity, marked irritability or anxiety, or self-mutilation
- Any skin abnormality characterised by pain or distress or which compromises the integrity of the skin as a barrier to disease.

8.3.2 Harms/negative consequences

Animal welfare negative consequences include:

- chronic pain or distress;
- delayed development of symptoms or abnormalities in the animal treated; and
- immediate pain and distress in the treated animal.

The negative effects can be divided into two kinds. The first kind relates to pain or distress to the animal due to treatment with, or exposure to, the agricultural compound. The negative consequence could take the form of death, toxicity, physical injury; infection, abnormal or unintentional physiological responses or functions, undesirable pharmacological effects, carcinogenicity, teratogenicity, or any other abnormality that can be related to treatment or exposure to the agricultural compound.

The second kind of consequence relates to pain or distress caused by failure of the product to achieve the claimed effects. Consequently, the animal suffers the pain or distress that the agricultural compound was intended to prevent or alleviate.

Some questions to ask yourself

- Does the intended use of the product (how, where, when, how much, how often, on which animals – age, class, condition, physiological state) jeopardise the welfare of the animals to be treated?
- Does the product offer sufficient benefit to the animals treated to off-set any uncertainty as to whether it will cause any pain or distress?
- If the product does not work as claimed will the animals treated consequently suffer pain or distress?
- If there is potential to cause pain or distress in the animals treated, would the benefit to the animals be greater than the pain or distress caused?

8.4 Agricultural security

The term 'agricultural security' refers to the zoosanitary and phytosanitary safety of animal and plant populations respectively. It relates to:

- eradication or control of pests or unwanted organisms as per the Biosecurity Act 1993; and
- management of organisms that may be undesirable to certain parties.

In the first bullet point, the terms 'pest' and 'unwanted organism' have the specific meanings used in the Biosecurity Act 1993. They relate to organisms in risk goods or ones specified in official pest management plans. However, the scope of the ACVM Act is broader and includes any organism that is undesirable by a sector managing the productivity of the national herd/flock. For example, the endemic contagious bovine leukaemia virus is not a pest or unwanted organism in terms of the Biosecurity Act but it is considered an undesirable organism by the dairy industry and dairy farmers. Another example relates to the clostridial organism that causes tetanus and is endemic in New Zealand. The agricultural security risk threshold is used

as the basis for considering regulatory intervention in regard to tetanus vaccines even though the organism is neither a pest nor an unwanted organism under the Biosecurity Act.

So endemic pests or pathogens do have to be considered in your risk analysis in light of disease or pest control programmes of other affected parties as well as the incursion of exotic organisms and national and regional pest management goals.

8.4.1 Threshold

The agricultural security threshold is an unacceptable probability (or impact) that:

- use would allow exotic pests, unwanted organisms or undesirable organisms to become established in New Zealand;
- inefficacy would allow pests, unwanted organisms or undesirable organisms already present in new Zealand to spread and become established in other areas;
- use would undermine control measures;
- inefficacy would undermine control measures;
- unintended harm to non-target plants or animals would jeopardising control measures;
- use would be inconsistent with any written ministerial direction on agricultural security.

You must also address whether or not your product will undermine pest and disease control. For example, if your product is an antimicrobial agent, is it likely to encourage the development of animal pathogens resistant to that agent or a similar agent?

Some questions to ask yourself

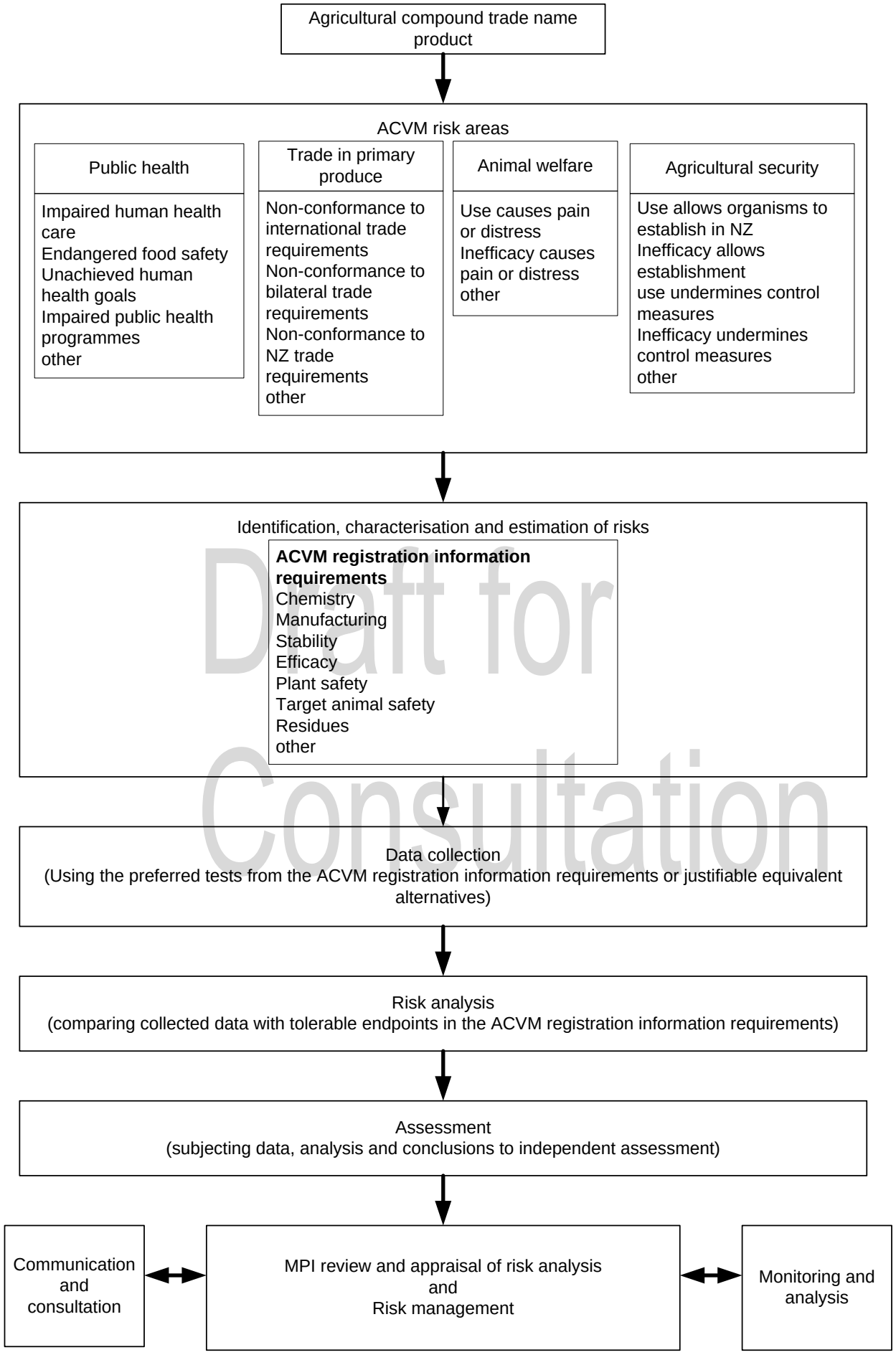
- Would use of the product interfere with diagnostic tests, undermining attempt to identify a disease that is the subject of biosecurity attention?
- Would its use reduce the effectiveness of measures to control pathogens or disease hosts/vectors or pests?
- Would its use facilitate the dissemination of pathogens or pests?
- Would specific innovative technologies such as genetic modification or nanotechnology associated with the product introduce hazards that would cause unacceptable levels of biosecurity risk?

9 Risk analysis and information requirements for registration

In summary, risk analysis is investigating what hazards associated with your product are likely to cause harm or negative consequences, given the description of the ACVM risk areas. To do this:

- You have to think through all the possible pathways that could lead to harm/negative consequences.
- You have to design trials that will show how those hazards are likely to cause the negative consequences and how significant the consequences will be. For example, if your product is to be used on food-producing animals, you have to design residue trials that will show the level of residue (for any significant ingredient) when your product is used as directed.
- You have to set the trial parameters and specify reliable/proven testing and analytical processes to generate the trial data.
- You have to subject the data to sound analysis and draw conclusions that are supported by the data/evidence.
- You have to do all this in accordance with good clinical/field practices and the analytical work must be done in accordance with good laboratory practices for veterinary medicines and under the principles of GLP for agricultural chemicals.
- Finally, you must subject your trials and analyses to independent data assessment.

Your risk analysis process should be as follows (note that the three boxes at the bottom are MPI's responsibility).



Refer to the ACVM registration information requirements and guidelines for more detail on the information you should include. These documents will give you what MPI considers common best practice in generating data to support the average registration. Note that the requirements cannot anticipate areas of analysis that should be included to address hazard/negative consequence pathways/risks posed by innovative compounds or technologies. It is your responsibility to proactively and comprehensively address the relevant risks posed by innovative compounds and technologies.

10 Identifying and describing benefits

Benefits are positive outcomes that could or would be achieved from use of your product. The analysis of benefits is necessary to counterbalance risks of harm. Note that showing there are benefits to be achieved from the use of your product that works is not to protect the consumer from wasting their money on products that do not work. Consumer protection from worthless products is not a risk area that is relevant to the ACVM Act. The reason you must describe the benefits of your product is to counterbalance any risks of causing harm. This could mean that, if your risk analysis shows that there are no risks of causing harm in any of the ACVM risk areas, you do not have to identify and estimate any benefits, not even basic efficacy. However, if your risk analysis shows that there are relevant risks then you must counterbalance them with evidence of benefits, starting with adequate efficacy. If your product does not work, then any harm is likely to be unacceptable. The greater the risks are, the more important it is for you to show the additional benefits as well as basic efficacy to balance those risks.

Some benefits such as efficacy can be measured relatively easily and accurately. Other benefits are more subjective and difficult to quantify or to attribute to the use of your product in particular. In your benefit analysis you could highlight (with justification) those other benefits, claiming that your product poses fewer unacceptable risks (in either probability of harm or in the magnitude of that harm) than other available products; or that your product achieves a better or more consistent positive outcome, such as long-term pest control. However, this is not the same as saying your product works better than some other product. It is better to focus your analysis on the desired outcome, not on product to product comparisons. If you choose to make claims about the relative performance of your product compared to some other product, you must specifically justify those claims in robust comparison trials.

MPI considers that having a choice of safe and effective products is a significant benefit to the public in itself. So even if there are products similar to yours that are already registered, MPI will consider your product on its own merit as presented in your application. It will not refuse your application just because there are other similar products already registered. Nor will it disregard your claims about benefits simply because those benefits are already being achieved via other products.

Keep your risk analysis in mind as you work through your analysis of the benefits. Remember you are trying to show that, in balance, your product is more beneficial than harmful. Be as informative as you need to be to make that balance obvious.

10.1 Identifying and estimating benefits

While at times benefits can be vague and hard to measure, they can generally be described in the following types.

Efficacy

The most apparent benefit is that your product will do what is claimed. Efficacy is at least the minimum benefit that should be expected. So you need to show that your product will do what you claim. It is recommended that you confirm efficacy as recommended in the MPI's efficacy guidelines.

Reduced risks

The purpose of regulatory control under the ACVM Act is to manage the relevant risks down to an acceptable level. So reducing risks is definitely a benefit. Your product and the way it is intended to be used should be consistent with good agricultural practice (GAP). There are aspects of your product that you could highlight that reduce the relevant risks and still adhere to GAP, such as:

- changing significant ingredients to ones with less potential to cause harm;
- lowering exposure rates for significant ingredients;
- shortening exposure periods;
- adjusting use patterns to safer exposure periods;
- reducing any tendency to cause tolerance or resistance that compromises on-going efficacy.

Many other factors could reduce risk, and they could be identified and their impact estimated in your benefit analysis.

Perception of risk

Public preferences or public resistance to certain types of products, ingredients or agricultural practices could make them more or less acceptable and, therefore, your product could be perceived as more or less beneficial. While relative and subjective, these perceptions do have a place and should be considered in your benefit analysis.

Improved outcome

Your benefit analysis could show the positive aspects of your product. For example, you could include evidence that use of your product will improve overall control or maintain effective control for a longer time.

Cost effectiveness

The relative costs of alternative intervention options may be an important factor in choosing to use a particular product. You may be able to show that using your product results in more cost-effective results while adhering to GAP. This could be an appropriate benefit.

10.2 Risk to benefit comparison

Risk management's optimal target is **not** zero risk. In fact, extreme risk aversion is unsustainable because aiming for zero risk is neither practical nor affordable. The most desirable outcome must be a balance between potential harm, potential benefit and affordability to the nation.

To put your product into perspective, refer to your risk analysis conclusions and your benefit analysis conclusions and provide an explanation as to why you consider that in balance, the risks are at an acceptable level given the benefits that access to and use of your product will be afford.

If the risks are not zero for your product, you will have to address the efficacy of your product as a minimum benefit. However, if significant risks are apparent (either real or perceived) you may consider addressing benefits in a more rigorous and comprehensive manner than just efficacy as suggested in the ACVM guidance to provide a more informative and compelling application, and more acceptable in context of the obligatory public consultation.

11 Conclusion

MPI must have confidence that risks can be managed down to acceptable levels, and must refuse to register a product if either:

- the risks cannot be managed; or
- there are too many uncertainties and information gaps in the risk analyses you provide in your application.

Follow the ACVM registration information requirements and guidelines so that your application is as complete and informative as possible. Ultimately, you are responsible for your product and you are in the best position to know what impacts its use might have. You must explain that as clearly as possible.

If you have questions, contact us (approvals@mpi.govt.nz).