APVMA Risk Analysis Framework

Comments on Draft Published November 2011

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INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has invited comments on the draft Risk Analysis Framework published November 2011.

Competitive Advantage is a consulting practice that provides services to organisations wishing to gain approvals for products to be sold in Australia. These include products requiring registration by the APVMA.

The principal consultant, Michael Tichon, established Competitive Advantage in 2002 after working in Australia and internationally in various roles within the agrochemical and related industries. Immediately prior to returning to Australia, he worked in the US with global regulatory responsibility for agrochemical, public health products and related businesses.

The business was named 'Competitive Advantage' based on a belief that organisations can obtain competitive advantage by understanding and complying with regulatory requirements. Unfortunately, the regulatory system, which the then Minister for Agriculture described in 2010 as being bogged down in red tape, has prevented compliant companies from enjoying a benefit from their investment in understanding requirements and in complying with requirements.

The Minister for Agriculture further stated that the framework under which APVMA was operating at the time (2010) was not the 'optimal landing point'.

APVMA has now published a risk analysis framework. It is encouraging to see the willingness of Government and APVMA to change. Hopefully these changes will result in APVMA becoming a truly world-class regulator of agricultural and veterinary chemicals that ensures unsafe products are removed from the market quickly and encourages efficient registration and approval of appropriate products.

This document comments on the draft risk analysis framework.

WHAT IS A 'FRAMEWORK'?

A 'framework' is a foundation. It provides the 'skeleton' around which actual procedures can be developed and implemented.

The published Risk Analysis Framework does provide good foundations for an effective risk assessment process. However, there are concerns about some aspects of the framework.

As with any framework, its success will ultimately be gauged by the procedures and practices that are implemented to build on the framework.

THE CONCERNS ABOUT THE FRAMEWORK

Scope of APVMA's responsibility

The Risk Analysis Framework states APVMA's areas of responsibility include:

- Protecting human health.

- Protecting plants, animals and the environment.
- Protecting Australia's international trade in agricultural commodities.
- Verifying the effectiveness of agvet chemical products.

In addition, the Framework states the areas of responsibility include:

- Assuring the quality of agvet chemical products.

We agree with the first four areas which are listed in section 14 of the *Agricultural and Veterinary Chemicals Code Act 1994*. However, we have not been able to find any specific requirement in legislation or regulations that specifically states APVMA must assure the quality of agvet chemical products.

While we are unable to find specific requirements in legislation or regulations that requires APVMA to assure the quality of agvet chemical products, it is accepted that protecting human health, plants, animals, environment, international trade and ensuring efficacy of agvet chemical substances requires that products and the actives used to produce those products are of a known and acceptable quality. The *Agricultural and Veterinary Chemicals Code Act 1994* (AgVet Code) at section 14 acknowledges this.

It is also noted that the *Agricultural and Veterinary Chemicals Act 1994* at section 23 states APVMA may specify manufacturing principles, including 'procedures for quality assurance and quality control to be employed in the manufacture of chemical products' (s23(2)(b)). However, Section 23 does not apply to agricultural chemical products (*Agricultural and Veterinary Chemicals Code Regulations 1995* reg 59(1)(a)).

***Concern 1**: APVMA should not assume roles and responsibilities not required of it by the relevant legislation and regulations.*

Ensuring active constituents supplied are of acceptable quality

We agree APVMA must be satisfied about the manufacture of actives and formulated chemical products before granting registration, as required by section 14 of the *AgVet Code*.

The Risk Analysis Framework states that, to assess quality of products, APVMA must be convinced that the product (or active) can be manufactured consistently. This includes manufacturing according to a specific method and employing effective quality control procedures.

***Concern 2**: It is critical that APVMA be able to determine if products of acceptable quality are produced and supplied. The current processes and procedures do not achieve the objective of ensuring only quality actives and products are supplied in Australia. Radical change to the current processes and procedures is required.*

The current process for approval of active constituents results in:

1. An 'approval holder' being responsible for the active. This means the approval must ensure that any changes to manufacturing method are notified to APVMA.
2. Any registrant of a product containing the active being able to obtain the active from the approved site of manufacture without knowledge of the approval holder.
3. While the approval holder is required to notify the APVMA of changes to manufacturing processes, etc, the manufacturing site is not (unless the manufacturing site is the approval holder).
4. Those who source the approved active from an approved manufacturing site, other than the approval holder, are not required to ensure the active is produced using approved manufacturing processes (but do need to ensure the active complies with the APVMA Standard for the active).
5. As many actives only state a minimum purity of the active without reference to permitted/not permitted impurities, there is no guarantee the active supplied by an approved site of manufacture will be produced using the manufacturing method disclosed to APVMA.

***Concern 3**: Individual manufacturing sites should not be published, although APVMA needs to keep a record of the sites. Only the approval holder should be published. Sourcing active from a specific manufacturing site should require agreement of the approval holder, to ensure any changes to manufacturing process, quality control procedures, etc are notified to APVMA.*

Definition of Risk

The Risk Analysis Framework describes APVMA's approach to risk assessment.

The Risk Analysis Framework defines risk as the product of Hazard and exposure, i.e.

$$Risk = Hazard \times Exposure$$

Human Health and the Environment

In contrast with the above definition of risk, the Framework states that, in relation to human health and environment, risk is the probability that a chemical or biological agent will cause harm, i.e.

$$Risk = P(Harm), \text{ or}$$
$$Risk = P(\text{A particular hazard being observed})$$

We agree with the probabilistic approach to risk assessment rather than the relatively simplistic product of hazard and exposure, which ignores the probability of the hazard causing harm.

Efficacy

APVMA states that, in relation to efficacy, risk is associated with the ability of a product to meet specific performance criteria determined by APVMA.

***Concern 4**: APVMA should not set specific efficacy criteria for products. Applicants should be able to set the desired performance criteria, justify them and ensure they are adequately communicated on the label.*

Modern products may not be able to provide the level of control that was previously achieved with broad-spectrum, long-lasting chemicals. Modern products are increasingly used as part of a program. Individually, the products in a program may not achieve the 'specific performance criteria determined by the APVMA'. However, in a program, these products may contribute to effective, sustainable control of pests, diseases, etc.

International Best Practice

APVMA claims international guidelines, best available data and best available methodology are used in assessing risk. The Framework further states the assessment procedures used by APVMA are 'consistent with international best practice'.

***Concern 5**: The claim that international best practice is used in Australia is not correct. Publication of the Framework will not result in best practice, guidelines and methodologies being accepted unless APVMA adopts the practices used in other advanced countries.*

An example of internationally accepted processes not being adopted in Australia is demonstrated by the Framework stating the No Observed Effect Level (NOEL) is relied upon to determine 'safe' levels of a chemical. Most advanced countries have adopted the No Observed Adverse Effect Level (NOAEL). As an example, the *OECD Manual for Investigation of HPV Chemicals* states at 4.3.1:

> '*response (effect) assessment is the estimation of the relationship between dose, or level of exposure to a substance, and the incidence and severity of an effect. At this step the no observed adverse effect level (NOAEL), or if this is not possible, the lowest observed adverse effect level (LOAEL), shall, where possible and appropriate, be determined*'.

Similarly, the *OECD Guidance Document for the Derivation of an Acute Reference Concentration (ARFC)* discusses NOAELs and its limitations. This document states:

> '*There is now an appreciable body of thought that there should be a move away from the use of the NOAEL as the POD towards the use of the Benchmark dose methodology*'.

I have previously raised with APVMA/OCS the use of Benchmark dose methodology and have been informed APVMA/OCS does not use this methodology.

***Concern 6**: The Framework should be amended to require use of best practice including internationally accepted measures such as NOAEL and Benchmark dose methodology.*

Uncertainty

The Framework states that APVMA places strong emphasis on minimising uncertainty. The Framework then defines 'acceptable' uncertainty as being 'beyond reasonable doubt'.

***Concern 7**: The procedures and policies that arise from the Framework must define the criteria that give rise to 'doubt'.*

Unless criteria that give rise to doubt are defined and communicated to stakeholders, the regulated community will not be able to determine if information to be submitted in support of a registration application is adequate or not.

The 'Precautionary Principle', where defined by some groups as meaning that approvals should not be granted where 'safety' has not been proven is not acceptable. No product, not even water, is completely 'safe'. There is never complete information.

The Productivity Commission published a paper in 2007 (Weier, A, and Loke, P (2007). Precaution and the Precautionary Principle: two Australian case studies. Downloaded from http://www.pc.gov.au/ data/assets/pdf_file/0005/67271/precautionaryprinciple.pdf 15 January 2012) which discusses definitions of the Precautionary Principle. The authors of the paper state 'The purpose of flexible versions of the Principle is very specific – to act as a "rebuttal to the mistaken claim that uncertainty warrants inaction"' (p 7).

***Concern 8**: APVMA should confirm its intentions with respect to uncertainty. Uncertainty should not be an excuse for inaction in relation to decision-making'.*

There are numerous options available to APVMA when faced with uncertainty including approval with controls on use of the product.

In assessing 'uncertainty' we note APVMA uses a weight of evidence approach and, wherever possible, aims to minimise the use of laboratory animals.

***Concern 9**: The aim to minimise use of laboratory animals is supported. Weight of evidence should be considered before requiring animals to be subjected to suffering and death due to one or more specific studies not being available.*

Substances that are used in other situations, have been assessed and are allowed to be used by other regulatory authorities without there being any evidence of

adverse effects should not be required to conduct studies listed in guidelines but not available, if other available data indicate the probability of harm is low.

Similarly, in relation to potential effects on the environment, the probability of harm must be assessed in light of data available for other species and use of the same or similar products in other situations. Total elimination of 'harm' is no more achievable than proving a substance is 'safe' to people.

Unacceptable risk of injury or harm

APVMA claims an objective of its assessments of environmental data is to ensure non-target animals and plants are not exposed to an 'unacceptable risk of injury or harm' (p31).

What is 'acceptable' and what is 'unacceptable' risk needs to be clearly articulated, e.g. is death of a spider in a crop sprayed with an insecticide unacceptable harm? Does yellowing and stunting of non-target plants growing along a fence around a crop sprayed with a herbicide constitute 'unacceptable harm'?

Concern 10: A clear policy of what constitutes 'unacceptable' harm needs to be communicated to stakeholders.

POSITIVE ASPECTS OF THE FRAMEWORK

The publication of the Framework will help all stakeholders understand the basis for APVMA decision-making.

Aspects of the Framework which are considered to be to the benefit of all stakeholders include:

1. Confirmation that APVMA relies on and uses scientific, structured and systematic methods for decision-making.
2. Risks, and not hazard alone, are the basis for regulatory decision-making.
3. A willingness to apply a level of protection that is proportional to the risk. Based on the previous two points, this is interpreted to mean the actual risk and not perceived risk.
4. A willingness to communicate in a transparent manner.
5. A willingness to share information with other regulatory authorities and accept appropriate information from other regulatory authorities.

The confirmation that APVMA will continue to use scientific risk assessment in determining regulatory actions is most welcome.

CONCLUSIONS

The publication of the Risk Analysis Framework is welcomed and will help all stakeholders understand APVMA's decision-making process. Confirmation APVMA will continue to use scientific risk assessment is welcome. However, the draft Framework contains information that raises concern.

The key concerns raised by the draft Framework are:

1. APVMA apparently assuming roles and responsibilities not required of it by the relevant legislation and regulations.

2. While it is critical that APVMA be able to determine products of acceptable quality are produced and supplied, the document does not indicate a willingness to introduce more effective procedures to achieve the objective of ensuring actives and products of acceptable quality are supplied for use in Australia. Suggested changes to current procedures to help ensure products of appropriate quality are supplied include:
    a. Individual sites of manufacture of active constituents not being published (although APVMA needs to keep a record of the sites).
    b. Only the approval holder being published, and
    c. Sourcing active from a specific manufacturing site requiring agreement of the approval holder (to ensure any changes to manufacturing process, quality control procedures, etc are notified to APVMA).

3. APVMA stating it will set specific efficacy criteria for products. Applicants should be able to set the desired performance criteria, justify them and ensure they are adequately communicated on the label.

4. The claim by APVMA that it uses international best practice is not correct. Publication of the Framework contains examples of approaches that are no longer considered 'best practice' being used e.g. use of NOEL (No Observed Effect Level) rather than the internationally accepted measures such as NOAEL (No Observed Adverse Effect Level) and Benchmark dose methodology.

The Risk Analysis Framework does provide guidance on APVMA's general approach to risk analysis. To be truly effective, the Framework will need to be supported by comprehensive documentation on the procedures and policies that arise from the Framework. The policies and procedures need to articulate:

1. The criteria to be used by APVMA in determining when there is acceptable versus unacceptable doubt.
2. How APVMA will deal with uncertainty, remembering that uncertainty should not be an excuse for inaction in relation to decision-making.
3. APVMA's approach to 'weight of evidence' especially in relation to the need to do 'guideline' toxicity studies and APVMA's stated aim to minimise use of laboratory animals.
4. What APVMA considers to be 'unacceptable' harm.