The registration and label approval process for sheep ectoparasiticides

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Summary

Before agricultural and veterinary chemical products can be sold, supplied, distributed or used in Australia, they must be registered and their labels approved by the NRA. A separate approval is also required for active constituents either before, or at the same time as a product is registered. This paper will describe the assessment process for registration and approval of a chemical product and will cover such aspects as the legislative criteria that must be satisfied, the advice the NRA may seek from external agencies as well as the consultation process with stakeholders. The paper will also outline the NRA information services available to assist applicants when preparing their application.

For an overview of the NRA please refer to O'Brien (2001) (these proceedings)

Keywords

Registration, sheep ectoparasiticides, label approval

What the Legislation Requires of the NRA

The NRA is required by legislation to approve active constituents, register products and approve labels.

In order for the NRA to approve an active constituent e.g. Diflubenzuron, the NRA must be satisfied that the active constituent would not be an undue hazard to persons who are exposed to it, nor would it be likely to have an effect that is harmful. Further, the legislation requires the NRA to have regard to the toxicity of the constituent and its residues, the method used for manufacturing the constituent, the level of impurities in the constituent, the analysis of the chemical composition of the constituent and the results of that analysis.

In order for the NRA to grant registration of a product e.g. an ectoparasiticide, the NRA must be satisfied that:

1. The intended use of the ectoparasiticide would not be an undue hazard to the safety of persons exposed to the product;
2. Nor would it be likely to have an effect that is harmful to human beings;
3. The ectoparasiticide would not have an unintended harmful effect on the target animals (in this case, sheep), non-target animals and plants, and the environment;
4. The product is effective and safe for its intended purpose; and,
5. With respect to trade between Australia and its overseas trading partners, the product would not unduly prejudice Australia's export trade of live sheep and sheep commodities.

With respect to approving a label, the NRA must be satisfied the label contains adequate instructions relating to:

1. The circumstances in which the product should be used;
2. How the product should be used;
3. The times when the product should be used;
4. The frequency of the use of the product;
5. The withholding period after the use of the product;
6. The re-entry period after the use of the product;
7. The disposal of the product when it is no longer required;
8. The disposal of containers of the product; and,
9. The safe handling of the product and first aid in the event of an accident caused by handling of the product.

The Legislative Criteria

To be satisfied as required by legislation, the NRA subjects each application that is received to a screening process that determines whether an application is acceptable for evaluation. During the assessment process, each application is evaluated against set criteria of Chemistry and Manufacture, Public Health, Occupational Health & Safety, Environment, Residues & Trade, and Efficacy and Safety. The data requirement for each criterion is outlined in Parts 1 to 10 of the Vet Requirement Series [(1)]. The NRA must be satisfied of all criteria before registration is granted.

Who May Apply
Under the Agricultural and Veterinary Chemicals Code Act 1994 (AgVet Code), any person or company may submit an application to the NRA for approval of an active constituent for a new or existing chemical product; for registration of a chemical product and for approval of a label for a chemical product. Applications may also be submitted for approval of variations to an existing product. Examples of variations include formulation changes and extensions of use. Each application must consist of a completed NRA application form that is signed by an approved person, the relevant information/data package, and the appropriate fee.

Screening Process

Administrative Screening
On receiving an application for the registration of a new veterinary chemical product, for example a new ectoparasiticide, a Registration and Customer Service officer will check the application for completeness in a process referred to as Administrative Screening. An electronic record and a physical file are established for the application and a unique product number and a tracking system application number assigned. The applicant is notified of any current reviews that are in progress for the active constituent or class of products. Administrative screening ends when the electronic record and file have been prepared for technical screening.

Technical Screening
Product Evaluators collectively screen new applications, responses to deficient applications and those applications that have returned with advice from the NRA's external agents. For the hypothetical ectoparasiticide application, an Evaluator would check the accompanying cover letter to establish the purpose of the application and to determine the appropriate category of evaluation and fees. In instances where a similar product with a similar use pattern is already registered, the Evaluator confirms that the nominated registered product is a suitable reference product. The application is checked to ensure that details of the formulation, manufacturing standards of the active constituents and excipients, manufacturing site and sources of the active constituents are provided. Where constituents are not manufactured to a compendial standard, manufacturing specifications or equivalent for those constituents are sought.

Local manufacturing sites are checked for evidence of compliance with the Codes of Good Manufacturing Practice (GMP) by verifying the NRA GMP Licence as recorded in the NRA's Manufacturing Licence database. Overseas manufacturing sites are checked for compliance in accordance with the gazetted guideline titled, *NRA Recognition of Overseas Manufacturers of Veterinary Chemical Products* [(2)]

Product Evaluators will check whether data and/or scientific argument relevant to toxicology, metabolism, occupational health and safety, the environment, residues and trade have been provided. The Product Evaluator may request that relevant internal agencies (e.g. Chemistry and Residues Evaluation Section; Quality Assurance & Compliance), and external agencies (e.g. National Occupational Health and Safety Commission; Therapeutic Goods Administration; Environment Australia) screen the application and associated data.

The Product Evaluator will also scrutinize the efficacy and safety dossiers submitted for relevancy of field, laboratory and pen studies, and assess whether sufficient numbers of studies have been conducted and whether confirmatory trials were conducted in Australia. Should the data be incomplete or clarifications in the application required, the Product Evaluator would request the information through a technical deficiency letter. Depending on an individual application circumstances, a deficiency letter may contain the combined requests from the Product Evaluator and one or more agencies.

Agency Screening

Chemistry Evaluators provide specific advice on formulation chemistry, manufacturing and quality control issues, product specifications, and shelf life. Their Residue counterparts advise on the occurrence of chemical residues in produce from treated animals for human consumption, the risk to human health from consuming such produce, setting of maximum residue limits (MRLs) and withholding periods (WHPs), and trade issues. Quality Assurance & Compliance determines whether the evidence of GMP compliance for an overseas manufacturing facility is equivalent to the Australian GMP Code. National Occupational Health and Safety Commission (NOHSC) and Therapeutic Goods Administration (TGA) advise on any impact that the proposed new product may have on human safety and health, while Environment Australia (EA) comments on the impact of the product on the environment.

Again, where data are insufficient or incomplete, the agencies may request additional information through a technical deficiency letter. Once satisfied with the information, each agency would indicate the level of assessment that is required, or in some instances, indicate that no detailed assessment is required, but provide comments instead.

Having considered the advice or comments from the agencies, the Product Evaluator decides on the category of evaluation that is required. The Agvet Code provides specific categories together with fees and timeframes under which an application is to be evaluated. For example, a category 1 assessment with an associated fee of $20,620 and a timeframe of 15 months will apply to a new active to be used on food /fibre producing animals; category 34 ($10,310, 8 months) for an extension of use of an existing active to a new food/fibre producing species, while a generic product may be category 26 ($1030, 3 months). If there are no deficiencies, or the responses to deficiencies are satisfactory, the application is accepted for evaluation and is assigned to a Product Evaluator. Each agency is given a specific timeframe to provide an evaluation report to the NRA.

Simpler and straightforward applications, for example repacks, are finalised during the technical screening process, provided that there are no outstanding registration issues pending for the reference product or technical deficiencies identified.

Assessment Process

Chemistry and Manufacture

A Chemistry Evaluator, who may evaluate an application for a new active constituent or a new source separately or concurrently with the product application, assesses Part 2 of the data submission. When reviewing the new active constituent, the Evaluator will consider the synthetic process used to manufacture the chemical, the quality of the reagents and the levels of any impurities present; the likelihood of any toxic micro-impurities, the stability and the physiochemical character of the active constituent. To assess batch-to-batch reproducibility, the Chemistry Evaluator will consider batch analysis results for commercially produced batches, and the analytical methods used to generate the batch analysis results. Thus, the Chemistry Evaluator will have regards to the active's composition, its properties, source, stability, production processes and packaging. These are outlined in detail in Part 2 [(3)]. If the criteria for approval are met, the active constituent is approved and the applicant is issued a notice of approval of an active.

When evaluating the product application, the Chemistry Evaluator will have regard to the composition and form of all constituents in the formulation, how the product is formulated, the quality control measures implemented to ensure batch-to-batch reproducibility, batch analysis results to demonstrate compliance with the product specifications, the analytical methods and corresponding validation data, and the stability of the product when stored in the marketing containers. This chemistry evaluation enables the Product Evaluator to be satisfied that the product is stable and that subsequent batches can be manufactured to the same high quality. The quality and reproducibility aspects of the product are an integral part of the assessment for human and environmental safety, related trade issues as well as the efficacy and safety in the target animal.

Public Health

Therapeutic Goods Administration assesses the toxicological data in Part 3 [(4)] and Part 4 [(5)]. This agency advises the NRA on the toxicity of the formulation and its active constituents in relation to public health. Advice on a new active constituent may be given on request during the approval process of an application for technical grade active constituent or during the product registration process. Based on the toxicological evidence of the active, including its metabolism and pharmacokinetics, Therapeutic Goods Administration determines the poison schedule classification for the active and some excipients such as solvents. Poison scheduling determines which signal heading appears on the label, for example, POISON for schedule 6 (S6) and CAUTION for schedule 5 (S5). To arrive at the appropriate schedule, TGA would consider the risk that the hypothetical ectoparasiticide may pose to human health, and its associated hazards. Depending on the hazards (e.g. eye and skin irritation caused by diflubenzuron), TGA may recommend first aid instructions that are to be observed on the product label. The NRA is satisfied when the product demonstrates that it will not have a harmful effect on users.

Occupational Health & Safety

NOHSC assesses Part 6 [(6)] and considers the hazards that the formulation poses to persons who are exposed by handling the product or animals treated with the product, the occupational exposure and the margin of safety. NOHSC uses a tiered approach to risk assessment. Where indicated by risk assessment, NOHSC may propose measures to control occupational exposure before and during end use of the product. For an ectoparasiticide, rehandling restrictions may be necessary. Should a preliminary assessment of wool residues indicate an unacceptable safety margin, NOHSC will require wool residue dissipation information on the ectoparasiticide, percutaneous absorption study and a worker exposure study to refine their risk assessment.

Having considered the Therapeutic Goods Administration's report, NOHSC may recommend safety directions to be observed on the product label, personal protective equipment to be used, and a suitable rehandling period. Specific guidelines for addressing occupational exposure to an ectoparasiticide are outlined in section 6.6 of Part 6. The NRA is satisfied when the product demonstrates that it is not an undue toxicological hazard to the safety of people who are exposed to it during handling and use, or sheep that have been treated with the product.

Environment: Environment Australia (EA) assesses environmental data in Part 7 (8), and will take account of the environmental chemistry and fate as well as the toxicity of the active constituent on non-target animals including birds, plants, soil organisms and aquatic life. EA will make an assessment of the extent of, and potential for, environmental exposure; including the estimated market share for the product, the biological, physical and chemical properties of the chemical; the method of application and use-pattern; the method of disposal; as well as an assessment of the environmental hazard including disposal of spent or unused product. Based on the data provided EA may recommend environmental statements and/or specific disposal instructions to be incorporated into the label.

In their assessment, Environment Australia will consider the implications for the environment when fleece that is treated with an ectoparasiticide is scoured. EA requires data on the amount of fleece residue that is discharged in aqueous effluents after fleece is scoured so as to determine the level of environmental exposure. Since the residue level in fleece at shearing depends on the

degradation rate of the chemical in the fleece and the periods between applications and shearing, an applicant will be required to provide fleece degradation data to support a wool withholding period. Guidance on establishing the environmental hazard posed by sheep ectoparasiticides is outlined in section 7-4.3 (c) (iv) of Part 7. The NRA is satisfied when the product demonstrates that its proposed use pattern will not adversely affect the environment.

Residues in Food Commodities

The Residue Evaluator assesses the metabolic fate of the chemical, the nature of the chemical residue present in tissues of treated animals, and identifies the target organ for residue accumulation (Part 4 of Requirements Series) [(5)].

The applicant is required to submit residue data generated in trials in which animals have been treated with the maximum dose rate permitted under Good Agricultural Practice (Part 5 of Requirement Series) [(8)]. A Residue Evaluator then assesses this data and determines when changes to the existing Australian MRLs for that residue in animal tissues are required. Based on the residue data, the Residue Evaluator is able to determine if residue levels would exceed the established MRLs when the applicant's proposed withholding periods are observed.

For a new active constituent, where there are no existing MRLs, the residue results are used to promulgate MRLs that reflect Good Agricultural Practice in Australia. At the time of setting MRLs, the Residue Evaluator will assess the risk to human health due to ingestion of residues in tissues of treated animals by estimating the dietary intake as a percentage of the Acceptable Daily Intake. Additionally, the Residue Evaluator considers the impact that the product may have on Australian export trade by reviewing the MRLs established for that constituent by importing countries and by Codex. The NRA is satisfied when the product demonstrates that its proposed use pattern will not result in tissue residue violation or adversely affect trade in animal commodities.

Residues in Wool

The Chemical and Residue Evaluation section of the NRA does not assess residue levels in wool. Key aspects of this assessment are included in Parts 6 [(6)] and 7 [(7)] and are assessed by National Occupational Health and Safety Commission (NOHSC) and Environment Australia. The wool industry currently observes an Australian Maximum Acceptable Residue amounts for organophosphates and synthetic pyrethroids in wool of 9 mg/kg and 7 mg/kg respectively. The NRA is satisfied when the product demonstrates that its proposed use pattern will not unduly prejudice trade in wool.

Efficacy and Safety

The State Reviewer considers efficacy and safety data described in Part 8 [(9)]. All relevant data from trials, published literature, peer reviews and scientific arguments are evaluated. The initial report is distributed to the States for their comments, which are consolidated into one report. Registration of the product is supported if the data demonstrate that the product is effective for the purposes claimed and is safe for the intended species and non-target species. The NRA is satisfied when the product demonstrates efficacy and safety.

Label

After all reports and comments have been received and considered, the text-formatted, version-controlled product label is amended as required. Attention is paid to signal headings/scheduling, product name, claims and active constituents. The Product Evaluator will check that that the label contains all information outlined in page 1. Appropriate meat, milk and wool withholding periods or restraint statements are included based on the assessment of the data provided. Other details that are checked include the applicant's contact details, batch number, expiry date and NRA Approval Number. These aspects of the label are assessed in relation to the Vet Labelling Code, and attention is paid to where specific blocks of information are located on the label. There are other labelling requirements that are specific for ectoparasiticides that are used on

sheep. These requirements are outlined in Appendix 5 of the Vet Labelling Code and pertain to the claims, withholding period statements, critical comments and tabulation of application rates.

The Product Evaluator is satisfied when the applicant has addressed all the legislative label requirements. The labels are approved concurrent with the product registration. At finalisation, the label is given a NRA Approval Number, which is a combination of the product number separated by a forward slash from the month and year of approval.

Consultation Process

For new products based on existing active constituents and involving an extension in use to a new food/fibre producing species, the NRA will gazette a notice that outlines the outcome of the residues and trade risk assessments. This notice and a Trade Advice Note are available to the public, peak industry bodies for meat, milk and fibre, and the States for 28 days during which the NRA accepts written comments. At the end of the gazettal period, all residues, trade and related label issues raised will be considered and used in deciding whether to grant approval of registration of the product. Each respondent receives a reply from the Product Evaluator. For food related residues, should the Australian MRLs be higher than overseas and/or international standards, a peak body may establish and recommend an Export Slaughter Interval that may be different from the domestic withholding period. The Product Evaluator would then ensure that the label include an appropriate Export Slaughter Interval statement. A similar statement relating to other overseas standards does not currently exist for wool.

For new products based on new active constituents the NRA will publish in the NRA Gazette, a full Public Release Summary [10] covering all aspects of the toxicology, occupational health and safety, residues, environment, trade and efficacy and safety. The public is invited to submit written comments within 28 days of the notice on whether the NRA should approve the application on hand. Trade issues are addressed as per the Trade Advice Notice described above.

Consultative Committees are set up through which the NRA consults on policies. The committees provide a forum where the States, industry and the community respectively participate in developing policies that Evaluators apply during the registration process.

Approval/Refusal Notice

At the end of the consultation phase, all comments from the public, peak bodies and States together with the reports from the internal and external agencies are considered. Risk analysis is used where issues are contentious. Should the Product Evaluator be satisfied that the legislative criteria are met, he or she would recommend that the product be registered and the label approved. If the recommendation is accepted and signed as accepted, the product information will be entered into the NRA database, and a Notice of Registration and Approval is issued. This notice together with the approved label is distributed to all State and Territory Coordinators. Approval is valid for 12 months and is renewable at the beginning of every financial year.

Where registration is not granted on account of the Evaluator not being satisfied on any one or more of the criteria, the applicant will be issued a written notice of refusal and a statement of reasons for the refusal. If the refusal to grant registration is disputed, the applicant may opt to apply for a reconsideration of the initial decision by the Chief Executive Officer of the NRA. Alternatively, the applicant may lodge an appeal directly to the Administrative Appeals Tribunal.

Information Services [11]

Applicants may contact the NRA staff by phone, facsimile, e-mail or mail [12] for advice prior to submitting an application for registration. Alternatively, information may be downloaded from the NRA's homepage [13]. Most of the NRA's Publications [14, 15] are available on the website. Included are various guidelines, the Requirement Series, and NRA application form. Other publications available are the MRL Standard and the NRA Gazette. Notices and invitation for

public comment for new product applications are announced in the NRA Gazette, as are Public Release Summaries for new actives, draft Chemical Review reports for comments or final reports of Chemical Reviews. The process module [16] developed by the NRA is particularly useful in guiding applicants through the application processes. In the near future, the Vet Labelling Code will be accessible on the website.

The public version of the NRA's register and database [17] is accessible to the public via the NRA website. This database provides basic information on registered products from which a reference product may be chosen. It provides a link to Queensland Department of Primary Industry and Energy register of labels. For a nominal fee, the NRA will provide copies of the most recently approved labels of registered products.

References

Agricultural and Veterinary Chemicals Code Act 1994

National Registration Authority Web Site
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