Summary of the UK efficacy evaluation process and requirements for biological products

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ABSTRACT

The evaluation of efficacy forms part of the statutory regulation of pesticides. Approval depends on demonstrating a measurable benefit, through control of the target or reducing harmful effects. For most situations there is no absolute minimum level of control that must be achieved. The evidence presented in the application for approval should support the label claims, which must reflect both product performance and the conditions required to achieve this. The Pesticide Safety Directorate (PSD) operates a flexible system to address efficacy requirements, accepting relevant data from a range of sources including non-UK data, public domain information, and evidence from grower’s trials. In addition, and particularly relevant for biological products, there is scope to use reasoned cases in certain areas. An alternative approach that may be available is mutual recognition of approvals or data packages from other Member States. PSD recognises the importance of biological products in developing a strategy for sustainable plant protection products. To lessen the regulatory burdens for biological and other ‘alternative’ products, there is currently a pilot scheme based around reduced data requirements and registration fees. Applicants are encouraged to meet with PSD at an early stage in product development, including discussion with efficacy specialists on requirements and appropriate trials design.

INTRODUCTION

Biological products can be a valuable component in integrated control programmes, one aim of which is to limit the use and impact of chemical plant protection products on non-target organisms and the environment. Their importance has increased in recent years, both with pressure to reduce conventional pesticide use, and as an additional tool in pesticide resistance management strategies. However there are currently relatively few biological products on the UK market. One of the main reasons given is the apparent regulatory burden, both in terms of data requirements and costs. To encourage more products onto the market, PSD set up a pilot scheme for alternative products. This is designed to assist in the compilation of reduced data requirement packages and is based on significantly reduced fees for pheromones, biological (microbial), and plant extract products. This experience will be used in the longer term to produce a reduced fee structure where appropriate. The first product to complete the registration process via this scheme was a pheromone mating disruption product approved in 2004. The pilot scheme also supports part of PSD’s development of a ‘National Strategy for the Sustainable Use of Plant Protection Products’ (see
One aim is to examine ways to encourage the development and uptake of alternatives to chemical pest control. A perceived barrier in the registration of biological products is the efficacy requirements, both in terms of the standards applied and amount of data required. This paper gives an overview of the efficacy evaluation process and the approaches that can be used to address the data requirements, including specific issues facing biological products.

REGULATORY BACKGROUND

One question asked is why efficacy is evaluated under the regulatory process instead of ‘allowing the market to decide’. The statutory control of pesticides came into force as part of the Food and Environment Protection Act (FEPA) (1985). The mechanisms of the approval process were detailed in the Control of Pesticides Regulations (COPR) (1986). Efficacy consideration was defined by one of the aims of the act to ‘secure safe, efficient and humane methods of controlling pests’. The harmonisation of regulation within the European Union was introduced in 1991 (Directive 91/414/EEC). Further directives detail the data requirements including efficacy (93/71/EEC), and guiding principles for Member States to ensure a consistent approach (97/57EC, 2005/25EC). Important efficacy concepts were introduced regarding good experimental practice (GEP), use of guidelines, dose justification, and consideration of resistance. In the UK the directives were implemented by the Plant Protection Products Regulations (PPPR) which applies to new active substances, and subsequently those existing active substances re-registered following their review. The approval of pesticides is a risk/benefit analysis, evaluating risk of exposure to consumers, operators and the environment. Consideration of efficacy determines the benefit of use, balancing effectiveness against negative impacts (e.g. crop safety). The independent assessment of product performance prevents unnecessary exposure to the environment, users or consumers, and unnecessary costs to the grower (including economic/resources). It is therefore not only a statutory requirement, but a key element in supporting the UK policy on the minimisation and sustainable use of pesticides.

ADDRESSING DATA REQUIREMENTS

The efficacy data requirements will not be discussed in detail, full information is available on the PSD website (www.pesticides.gov.uk) in ‘Chapter 8’ of the ‘Data Requirements Handbook’. There are also a wide range of accompanying guidelines, addressing both specific crop/target situations and general issues e.g. numbers of trials and writing a biological dossier. The requirements examine both effectiveness and crop safety (including yield) and, where appropriate, impacts on succeeding and adjacent crops. Under PPPR there is further emphasis on various aspects of crop safety, and a need to submit preliminary data. Two significant new requirements, as mentioned above, relate to the principles of sustainable pesticide use. Dose justification is required for key label targets, whether economically important or difficult to control. Evidence must demonstrate inferior performance (lower or inadequate levels of control; shorter persistence of effect) at doses lower than those proposed (EPPO 1/225(1)). This can be addressed by including lower doses (e.g. 0.6 – 0.8N) in the field trials. A resistance risk analysis is also required, based on resistance history of target and
active, mode of action, and proposed use. In high risk situations modifying factors may be required to limit exposure (e.g. number of applications), and an appropriate resistance management strategy. For biological products their novel mode of action usually makes them positive contributors in resistance management programmes.

a) Use of preliminary data

Preliminary data includes laboratory based research, glasshouse screening data and small scale trials. Biological products often involve novel techniques and background information is helpful to the evaluator in assessing the data and understanding how the product will be used. More importantly, such data can be used along with reasoned cases to address various areas of the data requirements. For products targeting pests and diseases this approach is relevant for various aspects of crop safety. Standard glasshouse pre- and post-emergence screens on a range of plant species can provide sound evidence of the lack of plant activity. This, alongside appropriate observations in effectiveness trials, could address crop phytotoxicity and impacts on succeeding/adjacent crops without the need for designated crop safety trials. (In contrast products with herbicidal activity will require specific crop safety trials at both 1N and 2N, with some taken to yield (EPPO guideline 1/226(1)). Preliminary data can also be used as evidence for dose justification when required, as well as supporting the effectiveness claims.

b) Location of trials

PSD has always accepted non-UK trials, indeed some product approvals are based entirely on such data, provided there is an appropriate case demonstrating comparability of relevant conditions (agronomic, edaphic, target, climate). Those conditions which are relevant will depend on the product’s mode of action and use e.g. soil type is relevant to soil applied but not foliar applied products. Even where not comparable the data may still be acceptable provided the conditions are at least as challenging. For example, in warmer climates pest pressure may be greater because it allows for more generations per season and is, therefore, a more challenging situation to deliver effective control. Climate will need to be considered for all field applied products. The Crop Protection Association (CPA) prepared a climate comparability paper in liaison with PSD defining a zone across Northern Europe where climate is considered comparable to the UK. For trials conducted in this area applicants may simply refer to the zone without the need to submit any further specific meteorological data. The UK has encouraged this approach to be taken forward through EPPO, and a draft version of defined zones across Europe is awaiting final approval in the autumn.

b) Trial design and conduct

PSD provides guidance both on general principles of trials design and also specific crop/target situations. Under PPPR trials should be conducted in accordance with relevant European and Mediterranean Plant Protection Organisation (EPPO) guidelines. Guidelines set out minimum standards on key issues such as including untreated controls and standard treatments, plot size, number of replicates, and assessment methods. A common problem for biological products is that existing guidelines are either inappropriate or unavailable. PSD (and EPPO) recognise that
deviations may be necessary (e.g. no available standard) or guidelines may not be relevant, particularly for products with novel modes of action. Therefore non-standard trials designs are acceptable provided there is a full explanation and appropriate justification of methods used (UK Efficacy Guideline 113, EPPO guideline PP1/223(1)).

Lepidopteron pheromone mating disruption products illustrate where alternative methodology is appropriate. Treated plots need to be large scale (around 5 ha) and separated from untreated areas to prevent continuous migration into treated plots. Monitoring flight activity to identify application timing cannot be done using standard pheromone traps because of potential target interference from the test products. Assessments focus on damaged fruit because the target itself is not controlled, and the site history of typical fruit damage is very important, particularly when there is significant distance between plots. The methodology is therefore radically different to a standard randomised small plot trial for a conventional insecticide, but justified because of the mode of action and type of benefit being assessed (Efficacy Guideline 640).

Under 91/414 efficacy trials must be conducted according to GEP by testing organisations which are officially recognised. In the UK the scheme was introduced on 1st January 1998 (UK guideline 110) and the same principle applies in other Member States. Data generated after the relevant date by organisations not officially recognised cannot be considered as part of the core package of required trials. In some circumstances it may be permissible to accept as supporting data. Data from non-EU countries may be accepted where there is evidence that GEP was used. This requirement should be considered during the initial planning of developmental work. For research organisations involved in biological products it may be appropriate to consider applying for official recognition. This can be seen as a long term investment beneficial to all areas of development by ensuring maximum (regulatory) value for the data generated.

c) Data from other sources including other Member State approvals

Applicants may submit public domain evidence from e.g. published papers to support label claims provided their relevance is clearly explained. For microbial products this may include data on related microbial species. Factors to consider would include relevance of test conditions, dose, and formulation to the proposed use, and justification for any non-UK data. Evidence from grower’s trials may also be accepted, provided they are actively supervised to ensure appropriate conduct and reporting of results (UK Guideline 112). An alternative approach may be to ‘mutually recognise’ an existing approval or previously evaluated data from another Member State. PSD consider these on a case by case basis to determine their relevance to UK conditions but there is no re-evaluation of any data. Details provided by the applicant on the conditions/location under which the supporting data were generated are very useful in determining their relevance. Where there are significant differences such data may still provide the basis for an approval with some limited confirmatory data to address particular concerns.

d) Amount of data required

Applicants need to address each area detailed in the relevant legislation. For biological products the use of preliminary and public domain data in some areas, particularly those relating to crop safety and other adverse effects, may be sufficient. Furthermore,
for naturally occurring substances a comparison of dose/exposure levels with natural background levels can also be used as a reasoned argument instead of submission of data. This approach forms the basis of the OECD guidance document on pheromones and other semiochemicals. Arguments can be made in many areas of risk assessment (e.g. fate and ecotoxicology) and crop safety based on exposure levels being below those released naturally by organisms.

The main areas to be addressed will be effectiveness and supporting the product label. As a guide, for chemical pesticides the number of trials for a major target is normally ten spread over a two year period to demonstrate performance over a range of climatic and environmental conditions. An appropriate distribution of trial sites across main growing areas is important to ensure factors such as plant cultivar and target pressure are included. Minor targets/crops require only three trials. PSD guidance identifies specific major and minor targets for cereals, top fruit, oilseed rape and other brassicas, and will discuss individual crop/target situations with applicants. Some claims are for a target group rather than individual species e.g. ‘caterpillars’ which can be supported from a range of 2-3 trials on each of the key species. Various situations allow scope for a reduction in the number of trials necessary. In protected situations where environmental conditions are more controlled fewer trials may be appropriate and can be conducted in one season. Other factors allowing a reduction include significant difficulties in trials conduct, a sporadic target, or, as with pheromones, the need for large areas when testing. It is important to stress that the number of trials required is flexible depending on the quality of data provided and supporting evidence available. For biological products the same approach can be taken of using evidence from a wide range of sources. Using all available information the applicant can then use a smaller number of appropriately conducted trials to confirm field performance and draft their label. The latter is important in providing specific guidance to users on appropriate conditions, for example any agronomic practices which help to maximise the effectiveness.

Extrapolation of existing data to support either new claims or formulation changes is a common approach. In some cases the extrapolation may require no further data e.g. closely related target/crop or minor formulation change. In others some confirmatory data over one season will be required. The extent of the existing database along with factors relating to the similarity in proposed new use will determine whether and what additional data may be required. For new actives, particularly when development resources are limited, it is worth considering supporting just one or two key uses/targets during registration. Once approved and marketed it then becomes more cost effective, and is a simpler registration process, to add additional uses.

LEVELS OF ACCEPTABLE EFFICACY

A key misconception is that approval is dependent on having high levels of control and being comparable to an existing standard. The approval of any product, regardless of mode of action, is dependent on evidence demonstrating a measurable benefit. The important point is that the label reflects the level of control (or benefit) achieved, which can be wide ranging, and any conditions under which lower or more variable levels of effectiveness may occur. The UK approach follows the EPPO principles of acceptable
efficacy (guideline 1/214 (1)). Products should provide statistically significant benefits compared to the untreated control, reflecting the need to limit exposure of all products. Product performance should be of the same order as existing commercial standards (where available). However, lower effectiveness is acceptable when the product has other advantageous properties. These include a wider range or greater flexibility in uses, fewer limiting conditions, greater compatibility with cultural or other plant protection measures, lower resistance risk and fewer undesirable effects. Biological products meet many of these criteria and in addition their approval may also be justified by providing important alternatives in resistance management strategies for existing chemicals. Only in certain specific situations are high levels of control a requirement e.g. seed borne disease control must be at least 98% to comply with certified seed claims. The label claims for biological products can be tailored appropriately reflecting their mode of action. It may be more relevant, for instance, to refer to limiting or reducing levels of damage rather than control of populations, particularly where the target effects are on crop quality. As a guide, for fungicides and insecticides, claims for full control refer to control over 80%, 60-80% may be described as ‘useful’ or ‘partial’ control, and 40-60% as ‘reduction’. Control levels less than 40% are still acceptable provided that there is a defined and proven benefit.

SUMMARY

Efficacy testing for biological products can present particular challenges but the regulatory requirements should not be seen as a barrier. Applicants should consider the requirements early in the development stages so that data are both relevant and generated in an appropriate fashion. Data requirements can be addressed by a combination of evidence from wide ranging sources, reasoned cases and, particularly for effectiveness, some field trials data. Alternatively, an approach based on approvals and data evaluated in other Member states may be possible. The need for non-standard trials design is accepted and applicants are advised to discuss their proposals with PSD initially. Trials should supplement existing evidence and be used to draft appropriate label claims with information, if relevant, on conditions where control may be more variable. Generally, a wide range of claims are acceptable provided a measurable benefit can be demonstrated. The more extensive the database, the greater is the potential to extrapolate to additional claims either directly or with some limited further data. It is recognised that biological products are an important tool in the sustainable use of pesticides and food production. PSD are looking to build on the experience of the pilot scheme and in the area of efficacy have used it to provide guidance on trials for pheromone products. More recently an efficacy working group has been set up with the International Biological Manufacturers Association (IBMA). The aims include developing more specific guidance with experts in relevant fields, as well as providing closer links with a sector of the crop protection industry that it is recognised is less familiar with the registration process. PSD is also involved in several European initiatives designed to reduce the amount of efficacy data required and to encourage the availability of more active substances, particularly for minor crops. This includes an EU contract to draft efficacy extrapolation guidance based on existing knowledge from all Member States.
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