EFFICACY ASSESSMENT UNDER THE BIOCIDAL PRODUCTS DIRECTIVE: AN UPDATE FROM THE ICUP, EDINBURGH 1996

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Abstract - In 1993 the European Commission put forward a proposal for a mandatory authorisation scheme to cover the supply of biocides. The Directive aims to establish a single market in biocides and provide a high level of control for man and the environment by ensuring that requirements for authorisation are equal across Member States. An integral part of such controls is the requirement that products will be effective in use. Negotiations have been completed and The Biocidal Products Directive (98/8/EC) was adopted by the European Parliament and Council in February 1998 and entered into force on 14 May 1998. All Member States now have until May 2000 to implement this complex and technical Directive.

To facilitate implementation of the Directive, technical guidance is being prepared by Sweden, Finland and the UK under contract from the Commission, concerning listing of actives substances on Annex I, data requirements and procedures for authorisation and registration of biocidal products. The HSE as Competent Authority for the UK, is preparing the technical guidance for risk assessments for authorisation of biocidal products. This contains guidance on assessment of efficacy. The UK has experience of producing guidance documents and has produced detailed documents outlining efficacy data requirements for wood preservatives, antifouling products, public hygiene insecticides and surface biocides. These documents are aimed at compliance with current national legislation, i.e. the UK Control of Pesticides Regulations 1986. Technical guidance drafted for efficacy assessment is in two parts: a generic chapter providing general guidance for assessment and evaluation of data required to substantiate a label claim; a series of technical annexes relevant to specific product types.

Key words - Biocidal registration, regulations, European Commission

INTRODUCTION

In 1993 the European Commission put forward a proposal for the introduction of a mandatory authorisation scheme to cover the supply of biocides. The Directive aims to establish a single market in biocides and to provide a high level of control for man and the environment by ensuring that requirements for authorisation are equal across Member States. An integral part of such controls will be the requirement that products will be effective in use. Prior to the Biocides Directive there were already in existence within the EU a plethora of chemical control schemes covering: new and existing substances; medicines; veterinary medicines; cosmetics; food additives; plant protection products.

The Biocidal Products Directive (BPD) has its origins in the Plant Protection Products Directive (91/414/EEC), a Directive to control what are better known as agricultural pesticides. As this Directive was being finalised it was considered that a Directive to control "non-agricultural pesticides" should be proposed and that such a scheme should encompass all products marketed to control harmful organisms (excluding those that were already regulated by other Directives). In other words the Biocidal Products Directive is a "catch-all" Directive.

The BPD was first proposed by the EU Commission in 1993 and the final text was formally adopted by the Parliament and Council on 14 May 1998. The Directive has two main aims: to provide a high level of protection for humans and the environment; harmonisation of the EU market for the biocidal products and their active substances.

The Directive will impose for the majority of products a 2 stage procedure whereby: active substances are evaluated and approved at EU level; individual products containing them are evaluated and authorised by Member States.

This means that suppliers seeking authorisation would have to submit data on health and environmental effects and efficacy. Data assessment would be on the basis of "Common Principles"; these are criteria to ensure consistency of approach to evaluation and authorisation across all Member States. In most cases authorisation would be mutually recognised by Member States.

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This presentation aims to give an insight as to the work being undertaken to implement the forthcoming Biocidal Products Directive (98/8/EC), with emphasis on the consideration of the efficacy data required to authorise biocidal products under this Directive. In addition it will be discussed how HSE, as the nominated UK Competent Authority for biocides, has set out assessment guidelines for biocidal products. The presentation will begin with a brief background to the Directive and will consider the efficacy requirements and general considerations as set out in the Directive's body text and Annexes, and the impact that these requirements will have on the Commission, Member States and industry in implementing the Directive. Finally the presentation will discuss the nature of the general guidance being prepared for applicants and Competent Authorities; guidance such that Competent Authorities can evaluate data to determine their acceptability in supporting label claims for biocidal products.

Before beginning to examine closely the issues as they apply to the efficacy assessment of biocidal products, it would be helpful to explain how the Directive is structured (Box 1).

THE BIOCIDAL PRODUCTS DIRECTIVE 98/8/EC

Body text of Directive - Articles 1 - 36 concerns the placing of biocidal products on the market (including conditions of authorisation, transitional arrangements, information exchange, confidentiality, data protection, classification and labeling etc.).

Annex I - will comprise a positive list of active substances that have been evaluated & approved at EU level. This list will start empty and fill up gradually. Annex IA and IB will comprise active substances incorporated into low risk products and basic substances, respectively.

Annexes II-IV detailed lists of data requirements for active substances and biocidal products (inc. toxicological, environmental, physico-chemical and efficacy data).

Annex V - A list of the 23 product types together with brief indicative descriptors.

Annex VI - better known as the Common Principles. These contain guidelines and criteria used by Member States when considering authorisation of biocidal products.

Box 1. The structure of the Biocidal Products Directive 98/8/EC

Product types included in biocidal products directive

There are 23 product types included under the scope of the Directive and these are split into 4 main groups of biocides: Disinfectants - Food hygiene, veterinary, domestic, hospital, drinking water, etc.; Preservatives - Wood preservatives, slimicides, film, in-can, textiles, etc.; Pest Control - Insecticides and acaricides, rodenticides, avicides, other vertebrate control products, repellents, etc.; Specialised - Antifouling products, embalming and taxidermist fluids etc.

Efficacy data requirements and assessment criteria

What does the Directive state about the effectiveness of biocides? What is required of an applicant? (Box 2).

Article 5.1(b)

The biocidal product should be:

- sufficiently effective, and;
- have no unacceptable effect on the target organism.

Box 2. Body text - Article 5(1) b

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It is not elucidated in the text as to what is meant by "sufficiently effective" although Annex IIB and the Common Principles discuss assessment of efficacy data against product label claims. The data requirements necessary to support the authorisation of biocidal products are presented in Box 3 and Box 4.

BPD Annex IIB - Efficacy Data Requirements for Biocidal Products

Dossiers for Biocidal Products

- Product type
- Fields of use envisaged
- Target organisms
- Method of application
- Effects on targets
- Mode of action
- Number and timing of applications
- Application rate/final concentration in system

EFFICACY DATA

The proposed label claims for the product and efficacy data to support these claims, including any available standard protocols used, laboratory tests, or field trials, where appropriate. Any other known limitations on efficacy including resistance.

Box 3. Efficacy data requirements for biocidal products (Annex IIB)

Paragraph 51:

Data shall be submitted and evaluated to ascertain if the efficacy claims of the biocidal product can be substantiated. Data submitted by the applicant or held by the Member State must be able to demonstrate the efficacy of the biocidal product against the target organism when used normally in accordance with the conditions of authorisation.

Paragraph 52:

Testing should be carried out according to community guidelines if these are available and applicable. Where appropriate, other methods can be used as shown in the list below. If relevant acceptable field data exist, these can be used.

- ISO, CEN or other international standard method
- National standard method
- Industry standard method (accepted by Member State)
- Individual Producer Standard (accepted by Member State)
- Data from actual development of the Biocidal Product (accepted by Member State)

Box 4. Annex VI (Common Principles) - Paragraphs 51 and 52

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The Directive is one of the most complicated to have come out of Brussels so what challenges will its implementation pose for the Commission, Member States and Industry?

EU COMMISSION

- Ensure adoption of the Directive across EU Community
- Produce guidance documents
- Establish a committee on biocides
- Write and adopt a review regulation
- Publish a list of existing actives
- Allocate actives for review
- Review (& modify) the operations

MEMBER STATES

- Implement the Directive into law (BPR 2000)
- Set up a Competent Authority (HSE)
- Review active substances
- Apply mutual recognition
- Enforce any non-compliance

INDUSTRY

- Produce a list of active substances
- Submit data for review
- Cooperate internally: data sharing (task forces); standardisation of tests (EFFICACY)
- Report any problems

Box 5. BPD - Responsibilities/challenges for the various "players"

Standardisation of efficacy test methodology

With respect to development and harmonisation of efficacy test methods, activity for biocides is on-going in several quarters: Within Europe, the Commite Europeen de Normalisation (CEN) has technical committees in several product areas working towards the development of test methodology for efficacy test protocols. Examples of these are CEN's Technical Committees 38 (Wood Preservation) and 216 (Disinfectants & Antiseptics) who are currently producing new standards and guidelines for the use of these test methods to support label claims. Additionally, in preparation for the introduction of the Directive both Member States and Industry (via the European Chemical Industry Council, CEFIC) are also being proactive in this area. On a more global scale, the OECD's Pesticide Forum has recently undertaken a survey of biocidal control schemes and data requirements amongst its members with a view to harmonisation of test methods and requirements. The next phase for efficacy will include the collation of available test methods, an assessment of their acceptability and the preparation of proposals to develop "new" ones. All players in these activities share the same problems, which include the time that will be required not only to develop test methods and guidance but also the time needed for agreement and validation of any new methods. This problem is further compounded by the many potential use patterns and possible label claims for biocidal products.

Member state activity

Since January 1997 three Member States, Finland, Sweden and the United Kingdom have, under contract from the EU Commission, been involved in the production of technical guidance documents to

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facilitate the implementation of this complex Directive. The allocation of responsibility is: Sweden - Criteria for entry onto Annex I; Finland - Data requirements for 23 product types; United Kingdom - Amplification of the Common Principles (Annex VI). For the UK the contract requires the production of detailed practical guidance on the assessment of risk and efficacy for the purposes of authorisation/ registration of products. The aim of all three documents is to provide assistance to regulators and applicants alike in the operation of the Directive.

United Kingdom Technical Guidance Document (UK TGD) and efficacy guidance

Paragraph 52 of the common principles indicates what methods may be used for efficacy testing but does not consider how such data are assessed against a label claim. The UK TGD seeks to address this. In the consideration of efficacy, it is important to note that compared to assessment of data addressing risk to man and the environment arising from the use of biocides, a number of important differences exist: 1) there is no international agreement as to what data are needed to provide sufficient evidence of efficacy in support of label claims for biocidal products; 2) there are few internationally agreed test guidelines or test methods for use in efficacy testing across the range of product types under scope (this includes no criteria for study design, complexity, conduct or reporting); 3) as efficacy testing does not consider testing for safety (with respect to human health or the environment) the application of the principles of Good Laboratory Practice (GLP) is not considered to be appropriate. However, the UK TGD considers the spirit of such principles should be applied to efficacy testing.

The UK TGD outlines a flexible and pragmatic approach to the assessment of efficacy data but at the same time attempts to provide practical, illustrative guidance so that both applicants and Competent Authorities can evaluate data to determine their completeness and adequacy with respect to an evaluation. In particular it addresses: 1) what information is needed to make up a label claim; 2) the idea of robustness as applied to individual studies (e.g. in terms of types of study that may be available, use of controls, replicates, details, etc.); 3) the Quality Assurance procedures to be adopted; 4) the overall evaluation of the data package when completeness and adequacy of data submitted is compared against the label claim; 5) the decision making process. In view of the wide diversity of product types and potential use patterns, the nature and extent of data required to demonstrate efficacy and fulfillment of label claims will vary from one product to another. Consequently the guidance for efficacy contained within the UK TGD is in 2 parts: Part 1 is a generic guidance chapter for the assessment of data; Part 2 comprises a series of supplementary technical annexes specific to different groups of product types. This paper concentrates on the generic guidance on the assessment of efficacy data for biocidal products.

Information in a label claim

Claims for biocidal products are highly variable and dependent on product type, use pattern and desired effect. Biocides are produced and used within a diverse range of industries where the products, processes and biological challenges vary enormously. Label claims for products can be very broad or very specific with respect to target organisms and use patterns. A label claim can be considered to be a matrix of information that normally comprises the following parameters: 1) product type; spectrum of biological activity (including target organisms); 2) mode of action (destroy, deter, render harmless, prevent/inhibit the action of, etc.); 3) area of use/site of application; end point; 4) directions for use (including dose rate, application method). Not all of these parameters will be relevant or applicable to all product types.

Target organisms/spectrum of activity

The range of target organisms for which claims are made and from which principal organisms representative of the biological challenge can be selected should, wherever possible, be identified on the label. It follows that efficacy claims within a particular product type may often be very specific in nature with

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respect to target organisms or alternatively they can be very broad. In the case of broad label claims it is not always appropriate or realistic to include on the product label and associated literature the entire range of organisms against which the product is intended to be used.

Mode of action/effects on target organisms

The data supplied must be relevant to the claimed mode of action or intended effect on the target organisms.

Areas of use/site of application

The data supplied must reflect the intended use pattern/area of use for the candidate product.

Directions for use

The label will also include the information that defines the way in which the biocidal product is handled and applied and typically will encompass some or all of the following: 1) preparation of the formulation for use; 2) application method/delivery technique; 3) dose rate/treatment frequency; 4) other information/ limitations pertinent to the efficacy of the candidate product. The Competent Authority should ensure that the appropriate information relevant to the application is provided.

Available test methodology

Apart from wood preservative products and disinfectants very few recognised (international) efficacy test standards exist. Much of the available data therefore are currently in the form of producer standards and product development data, i.e. they are ”non-standard”. This requires the competent authority to assess efficacy data on their own merits (i.e. whether the test be an EN, ASTM, AOAC, a national standard, or non-standard data).

In the UK it is considered that applicants should have the opportunity to provide other supplementary data to support products, either in the form of reliable field data or some other supporting evidence (such as product development data) as appropriate. Assessment therefore of individual studies or groups of studies should be considered in terms of: robustness; quality; adequacy; completeness.

Guidance on robustness

When looking at individual studies for their robustness it is necessary to determine what information is available to the assessor. This will include the type of study conducted (lab, field, etc.), the experimental design, whether it is conducted to a recognised guideline, the information source (test house, company research, literature) and in particular the amount of detail included in the test report.

Quality assurance (QA)

Although it is not mandatory to conduct efficacy tests in accordance with GLP, it is the UK view (and others) that efficacy tests (and the data generated from them) should be based on sound scientific principles and practice. Competent Authorities should ensure that satisfactory QA procedures are encouraged and in place such that information regarding study personnel, test methods, documentation, archiving/storage and retrieval of raw data are readily available if requested.

Guidance on overall evaluation with respect to adequacy and completeness

These criteria and procedures are designed to assist the Competent Authority in their evaluation of efficacy data for the purpose of arriving at a decision as to whether or not to grant an authorisation of a biocidal product application. (they are also intended to assist applicants in their understanding of the assessment process and the basis for acceptance or rejection of a proposed authorisation). The purpose of the efficacy assessment is to ensure that the proposed use of a biocidal product is supported by adequate scientific information.

Adequacy of data

In many situations data based on either single studies or based on simple laboratory tests alone will be unlikely to be considered adequate to support the commercial authorisation of a product. Whereas the

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provision of additional types of data (simulated use or actual field studies) are more likely to lead to a successful application. Often therefore conclusions will be drawn on the efficacy of a biocidal product based on the results of a series of studies submitted in support of a label claim.

The adequacy of data is evaluated on the basis of their usefulness, i.e whether the test is designed and conducted following appropriate test procedures. Elements for consideration should include; does the method adopted measure response appropriate to an end point relevant to the label claim; does the method chosen use chemical/physical/biological conditions relevant to the application; and does the method chosen employ appropriate controls? Adequacy of data can be further considered to be underpinned by two elements: reliability and relevance. Reliability is the inherent quality of the data (test methodology/the way the tests are reported) and is determined by the confidence that a Competent Authority has in individual studies and data packages. Generally the more details that are documented, then the easier an evaluation of their reliability should be. Relevance is the extent to which data and/or tests are appropriate for assessment against label claims. Data are contrasted against the various parameters that make up a label claim.

The Competent Authority will assess the efficacy in order to grant authorisation in their territory. Data generated from outside the territory in which authorisation is sought may be provided. In this situation the Competent Authority should consider the relevance of the proposed use of a biocidal product with respect to the climatic conditions, target organisms and/or breeding periods of the target species in their territory.

Having considered the reliability of the data and their relevance against each of the points above (as appropriate) the Competent Authority will consider the overall efficacy evaluation. The data should demonstrate that, when used in accordance with the label instructions, the use of the biocidal product will result in a measurable beneficial effect. The data should demonstrate that an acceptable, consistent level and duration of control or protection or other intended effect is likely to result from use of the biocidal product at the recommended dose rate (the evaluation should determine a dose rate that is considered to be effective but not excessive). The acceptable level of control may vary depending on the intended purpose of the proposed use and the label claims. For broad label claims the Competent Authority should ensure that the data available are on organisms representative of the claim as a whole. These data should be relevant to the challenge posed by all organisms likely to be within the broad label claim and should include a full consideration of the biology, morphology and behaviour as appropriate. Therefore, due to the variability of label claims and intended effects, expert judgement will have an important place in all evaluations.

Conclusions as to the performance of the product must be valid for all areas of the Member State in which it is to be authorised and must hold for all conditions under which it is proposed, except where the proposed label specifies that the preparation is intended for use in certain specified circumstances.

Decision making

Based on the assessment of all the available information, the Competent Authority will decide which of the following will apply: 1) the application is acceptable as the data submitted demonstrate an acceptable level of control and support all the label claims and statements; 2) the application is not fully supported by the available data; the biocidal product may still be authorised or registered subject to specific conditions/ restrictions e.g. changes to the draft label may be made, in consultation with the applicant, either to revise (or delete) certain label claims or to improve use directions; 3) additional data/information are required to support claims (or to resolve a particular point or item of concern) before a decision on authorisation or registration can be made; 4) the biocidal product cannot be authorised or registered. There could therefore be a number of conclusions for each application (e.g. one use of the product can be authorised with restrictions, another cannot be authorised at all, and yet another cannot be authorised without more information).

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