

Efficacy Guideline 105

UK Efficacy Guidance on Plant Protection Product (PPP) formulation changes, and Use of EPPO PP 1/307

Contents

Aim of the Guideline2

Introduction.....2

Changes in the active substance content of the PPP2

Criteria for Significant Changes in PPP Co-formulants3

Generating data to support significant formulation changes4

 5.1 Use of small-scale pot trials under protected conditions.....4

 5.2 Field trials5

Specialised product types, and specific situations of use considerations.....6

APPENDIX 1: Example of UK comparability field trials6

Further information.....7

Aim of the Guideline

The UK had long standing established guidance on efficacy considerations and requirements for formulation changes to PPP. This has now been replaced by EPPO standard PP1/307 '*Efficacy Considerations and data generation when making changes to the chemical composition or formulation type of plant protection products*'.

The purpose of this guideline is to provide further explanation on using EPPO PP 1/307 to support proposed UK PPP formulation changes, including highlighting any changes from the previous superseded UK requirements or circumstances not within EPPO standard scope (particularly active substance content, where UK guidance remains relevant).

This guideline only relates to efficacy considerations of changes in PPP formulations. Other aspects of the risk assessment will also require appropriate consideration and reference should be made to the relevant guidance.

Introduction

The criteria on significant formulation changes, and advice on any supporting data that may be required, described in EPPO PP 1/307 and below in this UK guideline, are also relevant where an applicant wishes to demonstrate comparability of formulations to support generic products (bridging to data out of protection for the original authorised PPP).

EPPO PP 1/307 does not address data protection issues, which is a regulatory matter not within its remit. Where the text discusses the possibility of bridging approaches, it is for the applicant to identify relevant available data from an appropriate UK authorised product. The decision making principles for relevant criteria are outlined, with comparability based on relative effectiveness and crop safety properties to the authorised formulation.

The standard also introduces the possibility of using glasshouse studies as an optional additional approach to field trials, where relevant. This is discussed below.

Changes in the active substance content of the PPP

The original published PP 1/307 (2018) discussed changes in active substance content (with reference to FAO manufacturing tolerance limits). However, it was subsequently identified that using FAO was not directly relevant to efficacy properties. However, no alternative harmonised approach could be agreed and the scope of PP 1/307 (revised 2020) was restricted to consideration of formulation components only. Addressing changes to active substance content therefore remains a National issue, and the existing UK guidance remains valid:

- Changes in the source of active substance do not require further consideration of efficacy.

- Changes of up to and including +/- 10% in the amount of the active substance, are minor and as such require no further efficacy data. (NB it is the amount of active substance applied to the target that is important, not the content in the formulation itself).
- Attempting to significantly change a formulation, by making a series of minor changes in content (i.e. each within 10%) that would not in themselves require supporting data, is not acceptable. CRD will refer to the original authorised formulation for each change and where appropriate request supporting data.

Some products contain more than one active substance. Where changes are made to the ratios of the active substances within a product, even if these changes are less than 10% for each active substance, further efficacy consideration may be required, particularly in terms of effectiveness and dose justification. It is not appropriate to make successive small changes to the active substance content which ultimately results in a significant difference in the ratio, unless there is appropriate data to address the issues of efficacy, dose justification and crop safety, as relevant. (PP 1/306 '*General principles for the development of co-formulated mixtures of plant protection products*' discusses provides further information on justification of active substances in mixed active PPP)

Criteria for Significant Changes in PPP Co-formulants

EPPO Guideline PP 1/307, Part I, describes those changes in co-formulants which are either considered minor and can be addressed by provision of an appropriate reasoned case, or those considered significant and may require supporting effectiveness and crop safety data. Part I considers both quantity of existing components, or changes in the co-formulants themselves.

PP 1/307 emphasises that with all changes, the applicant should clearly explain the function of each co-formulant and provide a detailed justification for any changes. For example, even where CAS numbers are identical, the degree of ethoxylation can vary significantly. Different isomers may also have identical CAS numbers. In both cases, this could impact on biological activity, and therefore an appropriate case/explanation will be required. CRD Efficacy team work closely with chemistry colleagues, who will advise on equivalence.

Any comparison of a proposed change in formulation should always be made with the originally authorised formulation. If the overall changes (compared with the originally authorised and tested formulation) are beyond those considered as non-significant then some data will be required to confirm that the effectiveness and crop safety of the formulation are not adversely affected. The impact of a series of individually nonsignificant changes may be cumulative.

Changes in individual or cumulative content, of greater or less than 10% are considered biologically significant. (There is a subtle change from UK, where absolute 10% change was the applied criteria).

In terms of co-formulants, as with previous UK guidance, the key components remain the surfactant and solvent systems. There is one new criteria compared to previous UK guidance, which is **changes in pH buffer agents are also considered potentially significant**. This may be relevant particularly to adversely impacting on crop safety properties of herbicide products. However, it may be possible to argue equivalence, in terms of maintaining pH, by reference to the chemical properties.

The EPPO standard also notes that experience may have been gained from similar changes and it may be possible to make a case to justify the change without the need for specific additional testing. For example, it may be possible to demonstrate that a range of formulations of the same active substance are similarly effective and crop safe; or that the intended change may be similar to one already made with that active substance. Where the applicant has access to existing data which shows that this change in formulation did not affect effectiveness and crop safety, then comparability testing may not be required.

(NB the criteria described can also be used to support reasoned cases for the relevance of trials data generated with early, development formulations).

Generating data to support significant formulation changes

EPPO PP 1/307 **Part II** describes the principles for the type and quantity of efficacy data required to support formulation changes which are biologically significant.

5.1 Use of small-scale pot trials under protected conditions

The EPPO standard describes the possibility of supporting biologically significant changes by using protected trials (pot tests), as an alternative, or providing further support, to field trials. This could include both glasshouse studies as well as tests conducted in polytunnels. This is a new approach compared to UK requirements (unless of course the product in question was authorised for protected uses).

If generating data using protected, small pot trials, it is important to consider what aspect of formulation comparability has been identified as requiring further investigation. For example, if crop safety is the concern, then protected tests may provide a more challenging environment, with young 'soft' foliage being more susceptible to expressing damage symptoms. Where comparable effectiveness of the formulations is being assessed, the crop/targets selected should be suitably representative/challenging EPPO 1/307 recognises this by recommending that lower doses may be useful in detecting possible lower performance, which might then indicate the need for field trials to determine if this effect is seen in fully realistic conditions. Consideration should also be given to the practicalities of application and assessment at the relevant crop growth stages. For example, foliar insecticide sprays applied shortly after crop emergence to control virus vectors may be suitable for some crops to test in small scale studies; but oilseed rape (OSR) pests attacking flowers/pod stage are more appropriately tested under field conditions.

For herbicides, there are standard described OECD methods for pre- and post-emergence tests, but standard methodologies for fungicides and insecticides may not be available. It may also be relevant to consider pot tests without protection for disease

pathogens. Any use of small-scale trials should be accompanied by an appropriate reasoned case. **Applicants are advised to discuss with CRD efficacy team before conducting small scale protected tests.**

Where differences in efficacy compared to the authorised formulation are observed within these small-scale trials, then further field testing will be required.

5.2 *Field trials*

The EPPO standard describes supporting comparability by using field trials, including a guide on the minimum number of fully supportive results (Table 3). For example, on a single crop, a major target requires a minimum of 5 results, with additional targets requiring a further 3-5 results. However, where there are multiple crops and targets, the number of results reduces to 2-4. Most importantly, the standard notes that with knowledge and experience this number can be further reduced.

The previous UK guidance for comparability trials was based around a 'minimum' of 5 bridging trials. However, in practice, and particularly where there are a range of crop/targets, this number increased. Taking account of experience and basing comparability on key major/challenging targets, the overall number of acceptable results arising from use of the EPPO guidance may not be substantially different to previous UK requirements. (An example is provided in Appendix 1).

The location of the trials can include non-UK sites, but as always it is important to justify the relevance of these trials. This includes not only comparable conditions, but relevance of reference products used. EPPO PP 1/307 notes that there will be differences in target challenge (for example UK represents particularly challenging conditions for development of cereal diseases, but less challenging for pests). And therefore it is important to carefully consider these factors and impact on the validity of comparisons, and the selection of the key targets.

Trials can be typically conducted over one year provided they are carried out to reflect the label directions of use and with sufficient target pressure. Where long-term control of a target organism is claimed, then assessment may need to be carried out over a reasonable period as a change in formulation may affect longer term control, e.g. for perennial weeds control in the following year will need to be assessed.

EPPO PP 1/307 recognises that the original authorised formulation may no longer be commercially available, and as such direct comparisons in trials are not possible. In such cases, a bridging approach to another authorised product containing the same active substance may still be possible, but the extent of required data is likely to be more than that needed where direct comparisons are available. This approach is dependent on comparisons across a broad and representative range of uses and demonstrating that the proposed formulation performs as expected for such a product type, on the basis of existing knowledge on the formulated active substance.

For certain herbicidal products, vapour drift is an important concern when considering effects on adjacent crops. Existing data on this aspect can be used if the applicant can establish, either by way of a reasoned case or tests, that the vapour drift of the 'new' formulation is no greater than that of the 'old' formulation.

When considering the results, it is difficult to draw conclusions where the existing authorised formulation results indicates lower than expected effectiveness, even if the proposed formulation provides comparable control to the authorised product. This may be a function of trial conditions or an indication of resistance but does not necessarily provide evidence that the proposed formulation is inherently as effective as the authorised product. As such, evidence is still needed of appropriate or expected control under suitable trial conditions. Where differences between results are observed, appropriate statistical analysis should normally be carried out. Where comparability is demonstrated, this allows other aspects of efficacy to be addressed via reference to any unprotected data supporting the authorised formulation. If comparability is not demonstrated, it may be required to submit a full data package to support the proposed new formulation.

Specialised product types, and specific situations of use considerations

Appendix 1 of EPPO PP 1/307 describes certain product types and situations of use where different considerations may be relevant, and/or although formulations are not comparable data may not necessarily be required: simple salts in water; preemergence use of herbicides, soil applied fungicides/insecticides, baits/molluscicides, seed treatments, fumigants, and consideration of taint for stored produce PPP. The circumstances described are the same as that previously described under the superseded UK guidance, apart from taint which is a new factor to address.

APPENDIX 1: Example of UK comparability field trials

UK Insecticide Example using EPPO PP 1/307 Table 3:

Below is an illustration of using the EPPO standard on the number of supportive trials results generated in field trials. The insecticide authorised formulation has a wide range of claims including aphid control on cereals, a range of oilseed rape (OSR) pests, and a range of other pests in various horticultural crops. To demonstrate comparability against these diverse pests, data should be generated representative of different insect groups (e.g. sucking pests/beetles/Lepidoptera), and include challenging/major crops.

Within the planned trials programme to demonstrate comparability, a **minimum** of eight fully supportive efficacy trials, which must include the following:

- Control of aphids on autumn and summer cereals (two fully supportive results on each). Where autumn timings are targeting aphid vectors (e.g. BYDV), assessments must include both aphid population and spring assessments of virus symptoms.
- Control of pollen beetle and one other oilseed rape pest (minimum 2 fully supportive results)
- Control of caterpillars on brassicas (or other vegetable crops with waxy leaved surface to provide challenging situation)

- Control of at least one other representative pest from a different insect group and different crop

Crop safety may be addressed by appropriate observations in the effectiveness trials (unless significant adverse symptoms occur above that observed in the reference product, which might then necessitate further specific crop safety trials).

Further information

For information about health and safety, or to report inconsistencies or inaccuracies in this guidance, visit www.hse.gov.uk.

This guidance is issued by the Health and Safety Executive. Following the guidance is not compulsory, unless specifically stated, and you are free to take other action. But if you do follow the guidance you will normally be doing enough to comply with the law. Health and safety inspectors seek to secure compliance with the law and may refer to this guidance.

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