Efficacy Requirements for the UK Re-registration of Products considered under the Transitional arrangements of Regulation 1107/2009

Scope

This guideline applies only to the completion of the 91/414/EEC review of existing active substances and subsequent UK re-registration of associated existing products.

Background

91/414/EEC introduced harmonised EU data requirements, assessed in accordance with Uniform Principles. The Efficacy evaluation centred on the Annex III data for the proposed product and uses, and was conducted at Member State (MS) level to take account of local conditions (e.g. the relative importance of crop/target). This approach was also taken in the review of existing actives for Annex I inclusion, and subsequent product re-registration.

91/414/EEC was replaced in June 2011 by EU regulation 1107/2009, transposed in the UK into the Plant Protection Products Regulations (PPPR) (2011). This has introduced zonal product authorisations with evaluations conducted by a Zonal Rapporteur Member State (ZRMS). The efficacy data requirements are unchanged, but the data is now assessed by the ZRMS on its relevance to the MS in the zone where an application has been.

However, the 91/414 review is not yet complete, with a few actives waiting a final decision on Annex I listing, and many existing products still undergoing re-registration in individual MS. These actives and associated existing products are covered by the transitional measures described in Article 80 of 1107/2009. The measures specify that consideration remains in accordance with 91/414 and National law in place before the regulation (Article 80.5(b)). Therefore the efficacy assessment remains based at individual MS level, using the MS existing 91/414 requirements. This applies even if the existing product is being considered via the voluntary work share arrangements. It is not appropriate (or practical) to conduct a ‘voluntary efficacy zonal assessment’ because the individual MS 91/414 efficacy requirements will still apply. Where the UK is the ‘zonal rapporteur’ for a voluntary work share application, the UK efficacy evaluation will follow the procedures laid out in this guideline. Data will only be considered in relation to the proposed and current UK uses for the existing product. The UK assessment will be available to other MS but may not involve a comprehensive evaluation of all the data submitted, only that which is required to complete re-registration in the UK. It may be useful to discuss this further if holding a pre-submission meeting with CRD. (Individual MS have varying approaches to address efficacy at re-registration under 91/414, and you should discuss these directly with them).

1 EU Guidance on the renewal of actives approved under 1107/2009 is under development

2 http://www.hse.gov.uk/pesticides/topics/pesticide-approvals/pesticides-registration/applicant-guide/product-authorisations-the.htm

3 http://www.hse.gov.uk/pesticides/topics/pesticide-approvals/pesticides-registration/applicant-guide/voluntary-re-registration-w.htm
Overview of UK Efficacy Requirements at Re-registration

This guideline explains how to address the UK efficacy requirements for existing products at re-registration and should be followed for all products completing their 91/414 re-registration in the UK under Article 80. First issued in 2005, it has been updated in 2012 not only to clarify the procedures now that 1107/2009 has been implemented, but also to reflect the experience gained since re-registration started. The UK approach is based on making use of available relevant existing data supporting UK COPR4 approvals, and then specifically addressing the additional requirements that 91/414 introduced. The extent of the need for new/more recent data depends on factors such as how similar the proposed uses and formulation are to those approved under COPR, and whether resistance concerns may have impacted on performance over time. It is extremely important that the re-registration submission clearly explains how the proposed uses relate to the existing UK COPR product and label uses. Re-registration is a two-stage process:

a) ‘Step 1’

This follows on from the publication of the Annex I inclusion Directive for the reviewed active substance. The approval holder must demonstrate both compliance with the conditions of the listing, and support of an appropriate Annex II package. Within six months CRD will revoke any products not meeting the criteria, or where necessary issue amended COPR approvals to comply with the conditions of the Annex I listing. However, consideration must be given to the impact of any amendments on the effectiveness of the product and associated label claims. Supporting evidence and/or reasoned cases may be required, including where revised claims are being proposed. Otherwise it may be necessary to remove the affected claims from the label.

In most cases the Annex I listing does not have specific conditions, but there will be a series of identified issues that must be subsequently addressed at the Step 2 stage. It is important to consider whether such issues could have a significant impact on UK approved product uses, particularly those affecting the GAP. There may be various options to address potential changes in label recommendations, including deleting or amending individual claims. There is also an opportunity to generate additional data in the interim period between ‘Step 1’ and ‘Step 2’ to support a revised label. Approval holders are encouraged to discuss with CRD any specific concerns prior to ‘Step 2’ submission.

b) ‘Step 2’

This involves the subsequent submission and evaluation of an Annex III package for each product. The efficacy assessment is largely concerned with this second stage, and involves ‘updating’ the existing COPR evaluation to the standards of 91/414, concentrating on those areas not previously assessed. A standard authorisation will then be issued under PPPR (2011) replacing all existing COPR approvals5.

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4 Control of Pesticides Regulations 1986 (as amended).
5 1107/2009 and 91/414 data requirements are unchanged, the only difference being the data package is judged on its’ relevance to potentially a ‘zonal’ area under 1107/2009 rather than just the individual MS under 91/414.
CRD consider that similar standards have been applied to efficacy evaluations over the period that COPR and ACAS\(^6\) have been in operation, and that evaluations were generally conducted in accordance with Annex VI Uniform Principles (Directive 97/57/EC). Therefore there is no general requirement for the re-submission and re-evaluation of the existing pest control and crop safety data supporting the current COPR approval. However, the applicant should provide a reasoned case for its’ continuing relevance. In particular where there are resistance concerns affecting field performance, the applicant will need to consider if current claims of control are still justified. For example, triazole fungicides have a requirement for data generated from 2006 onwards (Regulatory Update 17/2007 and Efficacy Guideline 617). Appropriate references can be made, and in many cases little or no additional data in these areas will be required. Approval holders should note that previously evaluated data may be relevant in supporting new or expanded areas of the Annex III Efficacy requirements (Directive 93/71/EEC) not previously fully considered under COPR (see ‘Addressing Annex III data requirements’).

There are in essence two types of re-registration application, and the extent of the UK efficacy evaluation will depend on which scenario is the more relevant:

a) The proposed uses and formulation are equivalent to those considered under COPR. As such reference can be made to current COPR approvals, which will support effectiveness and crop safety. The applicant should focus on the additional PPPR requirements, in particular minimum effective dose and resistance (see below).

b) The proposed uses have significantly lower rates; and/or there is a proposed major change in formulation (see below); and/or additional new uses (crop, target) are requested. In these cases the existing data underlying current COPR approvals may be of limited value. New effectiveness (and possibly crop safety) data may be required, alongside addressing the other aspects of PPPR. If the rates have had to be reduced, then the applicant may need to consider removing certain claims or supporting revised control claims (but may still need data to support these lower claims).

The approval holder may choose to support a formulation change at re-registration. This should be addressed in exactly the same way as any other proposed formulation change. A reasoned case may be appropriate for minor changes, but where the change is considered major then a full data package or comparability data may be required. Further guidance on formulation changes is provided in Chapter 8 of the ‘Data requirements Handbook’, available on the CRD web site.

When considering the data submitted, CRD will determine the relevance of the data presented to UK conditions only. As such, the applicant should provide a reasoned case based not only on environmental conditions (including EPPO climate zones), but also relevance of target (biology, pressure, resistance) and crop agronomy. Again, full details on the use of non-UK data are in Chapter 8 of the ‘Data requirements Handbook’. For claims against pests previously approved in the UK there is no requirement to provide any justification of the need for control. For any proposed new pests not currently recognised as economically important in the UK, some demonstration of the benefit of the control measure must be provided from trials undertaken in the UK, or another MS where agronomic conditions and pest pressures are considered comparable. It may also be useful to support with independent information on their emerging importance as pests in the UK.

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\(^6\) Agricultural Chemicals Approval Scheme. This was a voluntary scheme in operation prior to COPR that considered effectiveness and crop safety data. When COPR was introduced in 1986, approval holders could refer to any existing ACAS approvals to address the COPR efficacy requirements.
General Points to Consider

Once an active substance has been included on Annex I the following points may help avoid problems in the re-registration process:

- Consider the whole range of products containing the active substance, including amateur products. Many of the additional Annex III requirements can potentially be addressed for the range of products.
- Review all product labels – are there existing warnings/restrictions that may be removed with appropriate justification? Consider whether warnings/instructions must be followed, or are they actually advisory/best practice? Are doses consistent for similar uses? Are there any potential new uses for the products? The re-registration process presents an opportunity to rationalise labels and ensure consistency between them.
- Review all existing data relating to the range of products. There may be data for one product that can be extrapolated to another or data generated for one purpose that are relevant to another.
- Consider re-formulations of existing products at the same time as the approved formulation.
- Consider re-registering single active products first. For dose justification of co-formulated products where there is no additive activity reference individual active substance documents. Where there is complementary or additive activity or there is a higher dose include reduced doses of the mixture product in trials. Resistance risk will also need to be considered for both single active and co-formulated products.
- Address any outstanding data requirements established under COPR.
- Consider whether there have been shifts in sensitivity that may now affect field performance.

Presentation of the Efficacy Re-registration Submission

The applicant must provide information which clearly explains how the proposed uses relate to their current UK COPR approvals, and product label claims. This should include details of any uses no longer being supported, changes to existing claims, and proposed new uses; as well as details of any Annex I restrictions. This can be presented either in the covering letter, or as an introduction in the draft Registration Report (dRR) or Biological Assessment Dossier (BAD). (NB CRD have introduced a technical sift of applications which will include a check of whether this information has been provided. If it is not clear the application may be rejected at this sift).

7 Rural Payments Agency (RPA) inspectors are responsible for checking cross-compliance, including whether the label instructions have been followed (Regulatory Update 15/2007). It is therefore very important to consider whether label text is a direct instruction/restriction that must be followed (using terms such as ‘must’/’do not’) or a more general advice/good practice (terms such as ‘should’). Older product labels may have been written prior to the introduction of RPA, and may not have fully considered the implications of differentiating between the two.

8 For full details, including Efficacy Sift Criteria, see Regulatory Update 23/2012 ‘Changes to Sift Criteria to Improve Efficiency and Quality: Introduction of a more detailed sift for certain types of applications for Plant Protection Products’
The UK preference is for a BAD to be used where there is a need for a detailed presentation and assessment of large volumes of data. Part B, Section 7 of the dRR can be used to provide an appropriate overview of the data presented, uses being applied for, and as outlined above the relationship to existing COPR approvals. It is acknowledged that applicants are now often summarising much of their data across the EU into one (often large) BAD, and then submitting this to several MS. The key point is if this approach is used, then the dRR could provide a more tailored overview to each MS, highlighting which parts of the BAD are particularly relevant to them. For the UK, this should include a justification of the relevance of non-UK data and consider not only climate but also target relevance, biology, agronomic factors (full details in Chapter 8 of the ‘Data requirements Handbook’). It is also important to relate the resistance risk analysis and particularly management strategies to UK conditions. There is extensive available guidance and information, including any statutory restrictions, from the relevant UK-Resistance Action Groups and CRD Efficacy Guidelines (601, 602, 603 and 611). In addition, for those aspects not previously covered under PPPR (see below), the dRR could usefully highlight those sections of the BAD where this information is contained.

Reference to relevant previously evaluated data should include the application reference (COP number). Each point may be addressed in ways already familiar to applicants and are discussed in more detail under ‘Effectiveness’.

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**Addressing the Annex III Efficacy Data Requirements**

The Annex III submission must address all these areas for each product. A reasoned case or reference to previously submitted data will be appropriate in some cases, but there will be instances where the submission of further data may be necessary. The submission should make clear how each PPPR data point is being supported. Below is a comparison of COPR and PPPR efficacy requirements, with a key highlighting the differences/similarities.

- Preliminary tests *(Annex III, 6.1)*
- Dose justification *(Annex III, 6.2)*
- Effectiveness (Annex III, 6.2)
- Resistance management *(Annex III, 6.3)*
- Yield quality and quality, including transformation processes *(Annex III, 6.4)*
- Phytotoxicity (Annex III, 6.5)
- Adjacent crops (Annex III, 6.6)
- Succeeding crops (Annex III, 6.6)
- Plant parts for propagation (Annex III, 6.6)
- Observations on non-target organisms (Annex III, 6.6)
- The effectiveness of tank-cleaning procedures should also be addressed, especially with reference to safety to crops from subsequent spray operations.

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Key:
Assessed under COPR

May have been considered under COPR, but not always at same level of detail or for all product types

New requirements under PPPR

**Preliminary Tests (Annex III, point 6.1)**

Summaries from preliminary tests will not normally be required as the broad spectrum of activity of the active substance will already have been established. However such data may be used to provide supporting evidence in other areas e.g. dose justification, resistance, adjacent/following crops. In these situations, a case should always be presented to demonstrate the relevance of the tests.

**Effectiveness (Annex III, point 6.2)**

Where approval is to be based on previously evaluated data, full references to the current COPR, PPPR (or ACAS approvals if relevant) are required. These should be accompanied by a brief justification for the continued relevance of previously evaluated data to current conditions, target organisms and commercial practices. This may be a simple statement that conditions have not significantly changed since the data were first evaluated.

Where particular issues have impacted on effectiveness these may need to be addressed, for example accelerated microbial degradation of certain soil applied pesticides. More commonly it may be that there has been a shift in sensitivity by the target to that group of chemistry, resulting in reduced performance or complete resistance and loss of control. Where resistance in the target organisms has developed a justification for the continued effectiveness of the product and associated claims must be produced. In some cases where resistance is known to be widespread recent effectiveness data may need to be submitted to support existing label claims.

In circumstances where additional data are required a variety of approaches may be used:

- Submission of new data, including reference to relevant [EPPO guidelines](https://www.pesticides.gov.uk) and any deviations if appropriate. Any data generated in other countries should be accompanied by a full justification for their relevance. Please also refer to current guidance on Official Recognition of trials conducted after 1998 ([Efficacy Guideline ‘110 - Official recognition of efficacy testing organisation’](https://www.pesticides.gov.uk)). New trials generated in other MS should be accompanied by appropriate OR certificates where such schemes were in place at the time the trial was conducted. The BAD should also provide appropriate details on any non-UK approved standards.
- Extrapolation of data from another formulation, or submission of bridging data, with a case supporting comparability.
- Public domain data or data out of protection, with an appropriate case for their relevance.
- Reference to previously evaluated data, including use in other trials as a standard, where the product was used in accordance with relevant conditions.
- ‘Mutual Recognition’ of an authorisation issued in another Member State, providing that authorisation was issued under the terms of the Directive in accordance with Uniform Principles (i.e. equivalent to a PPPR approval). This should be accompanied by a case demonstrating the comparability of conditions and relevance of data to the UK. As part of this is it necessary to summarise or provide information on the % levels of control, to allow a judgement on the appropriateness of the label claims in relation to the UK system levels of control. For more details, see Regulatory Update 17/2006 ‘Efficacy Issues Relating to Mutual Recognition Applications’, and ‘The Applicant Guide: Mutual Recognition Procedure, Efficacy’.

Further details on the above approaches may be found in Chapter 8 of the ‘Data requirements Handbook’ available on the CRD web site. The web site also includes a number of specific Efficacy guidelines which may be relevant.

**Dose justification**

A justification of why the recommended dose is the minimum necessary to achieve the desired effect must be provided for the major label uses. EPPO guideline ‘PP1/225 - Minimum effective dose’ should be read when addressing this point.

This is one of the new requirements under UK-PPPR, and it is recognised it may be a difficult area because of limited availability of historical data generated at lower doses. The applicant may use any of the above approaches, including reference to previously submitted trials where the product was applied at less than recommended doses. Preliminary studies may also provide supporting evidence, but evidence from field studies will be required. In the case of herbicides it may be possible for older actives to refer to the recommendations for weed control made in the ‘Weed Control Handbook vol. II’ (Ed. Fryer J D; Makepeace R J). This is a peer-reviewed book and CRD accept that the recommended rates are appropriate under UK conditions. (There is no equivalent for insect or disease control).

Applicants are encouraged to consider this aspect at an early stage in the re-registration process, particularly reviewing historical data and identifying where generation of limited data may be of benefit. Where the submission is to be based on data out of protection it is important to remember that COPR did not make an assessment of dose justification, and therefore there may not be any relevant available data.

Where data show lower doses than recommended can give control of certain targets, or targets at earlier growth stages, applicants are encouraged to ensure that the label makes reference to the use of these lower doses.

Co-formulated mixtures containing two or more active substances may also need further dose justification data. This will depend on how the proposed targets and rates of the mixture relate to any existing relevant solo active products. And additionally, whether the active substances have any overlap in their spectra of activity. Chapter 8 of the ‘Data Requirements Handbook’ has further information on requirements on formulation mixtures.

**Information on the occurrence or possible occurrence of the development of resistance (Annex III, point 6.3)**

Resistance is one of the new PPPR requirements which must be addressed for each product. Even where it has been previously considered, a review and update on the resistance status of the active substance should be provided. The requirements for re-registration will depend on the incidence of resistance that prevails at the time. Where resistance has developed the applicant will need to justify the continued use of the product
(see below) and the relevance of any claims for control on the product label. If resistance has not yet developed, the applicant will need to assess the resistance risk. For all products where resistance has either developed or there is considered to be a high risk, details of the resistance management strategy must be provided.

As a first step information should be provided on the resistance history of the active since it was first approved. This should include resistance both to the relevant class of pesticides and target organisms, and be presented as a case history referring not only to the situation in the UK but also resistance patterns elsewhere if relevant. In those situations where resistance is established and the label already has appropriate warnings in line with CRD guidance, the applicant may make simple reference to these.

The EPPO resistance guideline PP 1/213 outlines the criteria for assessing resistance risk. Additional UK guidance is also available in Efficacy Guideline ‘606 - Resistance risk analysis and use of resistance management strategies’. The criteria include the resistance history of the target, and use pattern of the product which may result in high selection pressure on the target. Where there is no reported resistance the applicant should use this information, as well as knowledge of the biology of the target organism, to assess the risk of resistance developing from continuing use of the product. For a new active, sensitivity data are required for those species considered to be at high risk. However, for existing actives exposure to the target has occurred over several years. It therefore may not be practical to determine baseline sensitivity levels, although isolates of known sensitivity may be available. In some cases field trials data conducted over a number of years demonstrating continued effectiveness may be used as a substitute. In such cases it may be possible to provide full references to previously submitted data. Where sensitivity data have not been produced for a high risk target the applicant must give a case for non-submission. This may be based on unchanged use patterns and no reports of resistance. Or an explanation based on circumstances which may mitigate against the production of baseline data including practicality of testing, minor importance of the target, and availability of test methods or reference populations. In addition there may be other target organisms which should be tested to establish baseline responses. These targets may not yet have shown the development of resistance, but are considered to be under high selection pressure because of the use of the product.

If resistance has developed the applicant must make a case based on one of the following principles which, if relevant, would allow the re-registration of the active substance:

- Resistance is sufficiently limited that the active substance still gives acceptable levels of control. If the product no longer gives consistent control then the product label should be amended to reflect this.
- The resistant target is minor and the major pest is still susceptible.
- Even though resistant strains are widespread the active still gives useful, if reduced, levels of control.
- The active substance is needed in a resistance management strategy for a specific pest/situation.

The need for a resistance management strategy must be considered for all products with a history of resistance or where there is a likelihood of resistance developing. The management strategy must be reflected by changes to the label and/or an explanation of how the applicant intends to support the strategy where label phrases are inappropriate. Resistance management strategies should normally follow the most recent advice issued by the relevant UK Resistance Action Group (archive link only) where this exists. CRD has also produced resistance warnings and statutory restrictions for some uses; these must always be
included on the product label. Efficacy Guidelines 601, 602, 603 and 611 provide additional guidance.

Effects on yield of treated plants or plant products in terms of quantity and/or quality (Annex III, point 6.4)

With regard to yield quantity/quality, a reference to previously submitted data is acceptable or information on the long term use of the product.

Where transformation processes are relevant, a case may be made on the presence of the product on any relevant industry approved list (e.g. British Beer and Pub Association (BBPA); Campden BRI), previously considered data, or submission of new data. Taint may also be addressed using these approaches. Full guidance on taint and transformation requirements are in EPO guidelines PP 1/242 and PP 1/243. In the absence of any data, or inclusion of the active on recommended lists, a warning to consult processors will be placed on the label.

Phytotoxicity to target plants or target plant products (Annex III, point 6.5)

A reference to previously submitted data is acceptable. If new crops are requested as part of the re-registration application then further data may be required.

Observations on undesirable or unintended side-effects (Annex III, point 6.6)

This includes succeeding crops, adjacent crops, plant parts used for propagation and effects on beneficial and other non-target organisms. A case may include: previously evaluated data, mode of action and use of the product, observations from trials, and general long term use. Plant parts for propagation may be addressed for fungicides and insecticides by a case based on mode of action. For herbicides the concern is clearly greater and may be addressed by a case and submission of further data depending on the risk. Alternatively advice that ‘treated crops should not be used for propagation’ may be added to the label. For further information consult EPO guideline ‘PP 1/135 - Phytotoxicity Assessment’ which specifies the circumstances under which specific data is required.

The applicant should provide a justification for any existing label claims or statements relating to non target crop species by reference to previously submitted data or information. In addition information on any observed effects which are not reported or addressed by other areas of the data package should also be provided.

The effectiveness of tank cleaning procedures must also be fully investigated using a case, previously evaluated data or submission of new data, especially with reference to the safety to crops from subsequent spray operations. Further information is available in Efficacy Guidelines ‘302 - Cleaning application equipment - efficacy aspects’ and ‘305 - Cleaning application equipment – small scale jar test protocol’.

Summary and evaluation of data (Annex III, point 6.7)

A summary of the data and cases should be provided justifying the relevance of the previous UK approvals to the current conditions under which the product is used. The applicant should review any conditions and restrictions of Annex I listing, including any highlighted short term concerns.