UK GUIDANCE ON PLANT PROTECTION PESTICIDE (PPP) FORMULATION CHANGES – EFFICACY REQUIREMENTS

Introduction and scope of guidance

EU Guidance document SANCO/12638/2011 provides details on what are considered to be significant and non-significant changes in chemical composition of PPP under 1107/2009. (NB this refers only to changes within a formulation type, and not changes to a different formulation type as these are automatically considered to be major).

Applicants should in the first instance refer to this guidance when considering if efficacy data are required to support a change. However, the guidance covers only a very limited type of possible minor changes, and gives no indication on % changes in content that may be acceptable. Most formulation changes are unlikely to fall within the criteria, and the SANCO document notes that future EPPO guidance will cover aspects of phytotoxicity and effectiveness when exchanging co-formulants. At present, the EPPO guidance is under development.

Therefore, applicants are advised that for efficacy, changes not covered by SANCO/12638/2011 are currently subject to any National MS requirements and criteria. The UK guidance is provided below, and remains relevant for those changes not included in the SANCO document, where a UK authorisation is sought.

Comparability of pesticide formulations

Formulation changes have the potential to influence the efficacy of a product as many co-formulants are added to a product to increase effectiveness against the target organism, directly or indirectly. This section is intended to give general guidance on the extent of efficacy testing required when, for the purposes of registration, a formulation is claimed to be comparable with another; and existing data on the ‘old’ formulation’ are used to support approval of the ‘new’ formulation.

When is supporting data required?

Changes to surfactants, such as wetters or spreaders, including to the amount of surfactant, are normally regarded as changes that will require efficacy testing. It should be remembered that a change that improves effectiveness can have the opposite effect on crop safety and vice versa. Similarly changes in solvents or carriers can impact on performance and unless changes are considered minor (e.g. to a chemically very similar solvent) then efficacy testing is required. For granule carriers, the comments under ‘Herbicides used pre-emergence’ apply to other granule formulations e.g. insecticides and nematicides. Note that it is the applicants responsibility to justify the similarity of two formulations where they believe formulation differences are sufficiently similar that efficacy testing is not required. However there are some cases where supporting efficacy evidence is not required to show that the two products have comparable efficacy.
Minor formulation changes.

The following changes to formulations are considered minor and do not usually require supporting efficacy evidence provided the change does not affect the amount of active substance or other co-formulants that are applied.

- Changes in the source of active substance.
- Change in substances added to preserve the formulation in the container or to improve safety to non-targets, e.g. preservatives and anti-freeze - except for vertebrate control bait products.
- Changes in substances used to identify the formulation, e.g. dyes.
- Some changes to the fertiliser content of granular herbicide fertiliser based granules. The nature of the manufacturing process for granular herbicide fertiliser products means that often several different forms of nitrogen, phosphorus, potassium or other elements may be included. It is considered unlikely that variation in fertiliser base will affect the performance of the product. CRD will accept a range of formulation details for the fertiliser base component, for these products alone. Formulation details should include the expected concentration range of all the raw materials used in the production of the fertiliser base, and the minimum specification of the final formulated product. The latter must include the N:P:K ratio, active ingredient content, particle size, density and dust content. CRD must be notified of any additional materials used, and data or information must be provided showing that the change has no adverse effect on the product.
- In general, changes of less than 10% in the amount of any formulation component applied, including the active substance, are considered to be minor and as such require no further data. With respect to efficacy, it is the amount of active substance and co-formulants 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 back to the original formulation for each change and where appropriate request supporting data.

Some products contain two or more co-formulants with the same function, e.g. wetters. Where this is the case, providing the co-formulants concerned are chemically similar, it may be acceptable to change the quantities of them by more than 10% providing the overall content of that group of co-formulants is not changed by more than 10%. A case to justify similarity of the co-formulants concerned should be provided.
**Note of caution:** Many applications submitted to CRD for changes in formulation do not contain any information on the chemical nature of the co-formulants, nor any justification of the similarity between them. In the absence of any further information, CRD will generally err on the side of caution and refuse approval for the revised formulation.

- 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. In particular it is not appropriate to make successive small changes to the active substance content which ultimately result 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.

**Uses/types of products**

For the following uses and types of product, although differences in formulation may exist, these are unlikely to affect efficacy and thus efficacy data are **not** required to show that the two formulations are comparable.

- **Simple salts in water**
  Products that are simple salts in water are taken to be comparable to other products containing the same salt of an active substance. Products containing different salts of the same active substance are taken to be comparable if both salts disassociate equally in water. Examples of active substances which can be formulated in this manner are, arylalkanoic acids (the 'hormone' herbicides), dicamba, and chloromequat.

- **Herbicides used pre-emergence**
  It is generally accepted that once a formulation is present in soil then the co-formulants have no effect on performance. This means that for a product which is used before neither the crop or weeds have emerged, no efficacy data are required to establish comparability. If used pre-emergence of the crop on emerged weeds then only data on effectiveness are required. If used before weeds emerge on an emerged crop then only crop safety data are required. A case may be provided to reduce the data required where the herbicide is only active through the roots.

Exceptions to this are granular and capsule suspension formulations or slow release formulations, for which data may be required. For a change in size of granule or alteration of the material from which release occurs, data are required to show that efficacy is not affected. For the latter this may be based on physical property data, such as active substance release rate.
Other types of products used pre-emergence

For soil-applied/compost incorporated products other than herbicides, a case for a reduced comparability package may be considered, depending on the type of activity and the considerations of release rate and coverage given above for herbicides.

Seed treatments

It may be possible to submit data showing that the loading of the active substance on treated seed is the same for both the old and new formulations rather than carry out field trials. Please consult CRD’s Environment Branch for further advice.

Fumigants

Where the product is a fumigant then provided either; that gas is evolved from the formulations at a similar rate, or gas levels are maintained through monitoring and redosing, the formulation is unlikely to affect efficacy.

Groups of formulations

Companies may have access to existing data which demonstrate that a range of formulations of the same active substance are similarly effective and crop safe. Where this is so, a case may be accepted that it has already been demonstrated that formulations containing this active substance are broadly comparable. If only formulations of a similar type have been shown to have comparable efficacy then the case for comparability may be restricted to that formulation type, e.g. if three suspension concentrate (SC) formulations control a certain target then extrapolation to another SC might be possible but extrapolation to an emulsifiable concentrate might not.

In some cases, one formulation can be recommended at a lower dose of active substance than another formulation containing the same active substance. This could indicate that there is variation in the performance of different formulations containing that active substance, therefore broad comparability has not been established and efficacy comparability work will be required.

Knowledge of previous formulation changes with a particular active substance.

The intended change in formulation from the ‘old’ to the ‘new’ product may be similar to a change which has already taken place with that active substance or one with very similar properties. If the applicant has access to existing data which shows that this change in formulation did not affect efficacy, then comparability testing may not be required.

An applicant may have access to existing data that show that a number of formulation changes have taken place with an active substance and efficacy is always equivalent. In which case, it may be possible to make a case for a reduced level of comparability work when approval is sought for a further ‘new’ formulation.
Please Note: The examples given above are not exhaustive. If you are undertaking another change in formulation that you consider does not require efficacy testing, or where existing knowledge suggests a reduced package would be satisfactory or a case could be made, please consult CRD’s Efficacy Branch.

Extent of efficacy testing required demonstrating comparability

Zonal authorisations under 1107/2009

There is currently no harmonised approach on the requirements for the type and extent of data required to demonstrate comparability of PPP formulations to support a zonal authorisation (across, for example, a number of EPPO regions). Applicants should refer to the principles described in EPPO standard 1/226(2) ‘Number of efficacy trials’, and with particular reference to ‘Similar formulations’ section.

UK-only authorisations under 1107/2009

A UK label will have been established for the authorised product taking into account the acceptability of the levels of pest control achieved and whether any crop effects seen will affect yield. The tests described below are only relevant to establishing comparability of two formulations so that similar label claims can be made for the proposed product.

i) Generally, results from a minimum of five fully supportive trials are required for a UK authorisation. Both effectiveness and crop effects should be assessed in these trials on a selected range of target species and crops claimed on the label. Not all species and crops on the label need to be tested. If the label is very diverse in terms of the claims made then more trials are likely to be required, depending on the type of action of the product. On the other hand, where a particular target or crop can be identified as a good indicator of comparability, all trials may be carried out on this target/crop.

ii) Target organisms for examination in trials should be selected from the list of organisms claimed as controlled on the label. Those selected should include targets that are less well controlled by the product or are known to be more difficult to control with that type of product. Reduced doses can be included to provide a more severe test of comparability of effectiveness.

iii) Crop safety should be examined on crops stated to be acceptable for treatment on the label. Crops selected should include any that are known to be more sensitive to the product and thus most likely to show damage to give the most testing examination of comparability.

iv) Trials carried out in one growing season should be acceptable as long as they are carried out in different conditions and preferably in different situations, to reflect those possible from the label instructions. One seasons testing may also be sufficient where disease or pest challenge in that season has been adequate, or where the product is used under controlled conditions, e.g. glasshouse. Existing data on the extent to which the active substance is affected by varying conditions should be
taken into account. Otherwise trials will need to be carried out over two growing seasons.

v) 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 may need to be assessed.

vi) Where there are differences between results statistical analysis should normally be carried out, unless such analysis can be shown to be not relevant.

Acceptable levels of product performance

Usually, if these tests show that the effectiveness and the crop safety of the two formulations are the same, then no further tests are required to establish comparability. However, if in most trials the formulations are comparable, but due to adverse conditions, the level of efficacy of both formulations at recommended doses is below that considered acceptable, this may not in itself be a sufficient demonstration of comparability. In this case, further trials may be required to assess whether the two formulations are still comparable in trials where conditions are such that the ‘old’ product does give the expected level of efficacy.

Further investigation

Where the trials show that the proposed formulation is less effective or less crop safe than the ‘old’ formulation, data on the ‘new’ formulation should stand alone. In this case a more detailed examination of its efficacy will then be required. This is likely to include a full range of trials, some taken to yield, so that the label claims are supported by evidence where only the ‘new’ formulation has been used.

Formulations where supporting data are out of protection

In order to access data out of protection for another formulation, comparability trials are required which compare the proposed formulation with the one for which data out of protection are available. As a general rule, the formulation to which bridging is proposed should always be the original formulation which was supported by a full data set and not to any subsequent formulation approved as a minor formulation change, or one supported by limited bridging data.

In some situations, that formulation may no longer be available. As such, direct bridging is not possible. However, provided the applicant conducts trials across a broad and representative range of uses, and the proposed product performs as expected for such a product type, then a reduced data package can be accepted on the basis of the out of protection knowledge that the formulated active substance is effective for the uses sought.

This approach may mean that a rather greater number of trials are required than when bridging directly to an out of protection formulation, particularly if wishing to gain approval for all the original label claims, but still enables a reduced data set compared to the full data set required for a new and protected use to be used. The same principle applies if the trials are conducted outside of the UK where an
appropriate non-UK authorised product is being used as the standard instead of the UK authorised product for which data is out of protection.

Note that if the numbers of trials are limited, the label claims may be restricted to the actual situations (i.e. crop/pest combinations) tested in the trials. In this situation, further data would be needed to add additional pests/crops to the label later.

Other efficacy aspects

Data on some other efficacy aspects, for example, following crops and resistance, are generally taken to be related to the active substance. Therefore formulation comparability evidence is not normally needed to make use of existing data. For many other aspects, the fact that formulation comparability has been established should provide the basis to substantiate that existing data can be used for the new formulation, e.g. dose response, biological compatibility, effects on quality, transformation processes, and plants or plant products to be used for propagation.

- 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.