Guidance on requirements for efficacy data for zonal evaluation of a plant protection product in the Northern Zone

Version 6.0

Editing log				
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1.0 (draft)	Jan 2010	The guidance document was circulated for comments to potential applicants in 2010	Per Kudsk	
2.0	Feb 2010	Outcome of the discussions at a NJF workshop on efficacy testing and evaluation held in Norway	Per Kudsk	November 2010
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5.0	May 2016	Annex 1 corrected	Per Kudsk	6 May 2016
6.0	Nov 2017	Major revision to bring the guidance document in line with existing EU guidance and current practice in the Northern zone.	Per Kudsk	11 Jan 2018

Preamble

The present document is based on Regulation 1107/2009 for placing of a plant protection product (PPP) on the market. The document aims to specify the requirements for documentation wherever possible.

For the purpose of this document the Northern zone is defined as follows; Denmark, Estonia, Finland, Latvia, Lithuania, Norway and Sweden. This guidance document describes the requirements for registration of PPPs containing new active ingredients, new uses of existing PPPs registered for other purposes and new formulations of PPPs. New uses include additional target organisms, additional crops and additional countries if registration is asked in a country not covered by the EPPO climatic zone in which the data supporting the previous registration were generated. For re-authorization applicants can refer to the data submitted for previous registrations but data should be made available to the authorities and a draft registration report (dRR) in English should be submitted.

The efficacy evaluation of plant protection products in the zone will be carried out when applications for registration of common uses are submitted to a member state of the zone. Applicants should use the new and updated draft Registration Report (dRR) Part B Section 3 and also submit a Biological Assessment Dossier (BAD) and individual trial reports. One member state in the zone (Zonal Rapporteur Member State = ZRMS) will carry out the efficacy evaluation on behalf of the other member states reviewing and amending the dRR. All member states will have access to the BAD. Data submitted for registration must be generated according to relevant EPPO guidelines. Before finalising the evaluation the dRR will be presented to the concerned Member States (CMS) in the zone for comments (for details on the process see Regulation 1107/2009).

Along with the application for efficacy evaluation the applicant must provide 1) a GAP table including all intended uses in the Northern zone specified for each country together with 2) draft national labels written in the local languages containing detailed information on e.g. crops, harmful organisms and the timing and dosage in each of the countries in which the product will be marketed. The national labels, submitted as part of the zonal evaluation, have to be in line with the GAP table. The national labels will be evaluated by each national authority.

The applicant should explain how the pest challenge might vary across the zone, e.g. including available maps of distribution. Where information is available indicating important differences in pest populations across the zone, which may affect the performance of the plant protection product (e.g. different resistance strains), this should be submitted with the application. In some cases the GAP will be identical for all countries while in other cases the GAPs will be different within the zone reflecting that e.g. pest challenge or length of growing season vary across the region. Due to differences in growing conditions, e.g. day length, phytotoxicity issues may vary within the zone thus the acceptable dose and number of applications may vary between countries. Sufficient data must be supplied to confirm that the directions for use are applicable over all the conditions likely to be encountered in the zone when used according to the label recommendations, including for example regional and seasonal differences.

For a more detailed discussion of the principles to be considered when designing a trials series for the generation of efficacy data to support an authorization of a plant protection product across a substantive area like the Northern zone, i.e. beyond that currently considered by existing standards such as EPPO

Standard PP1/226 *Number of efficacy trials* applicants should consult the EPPO Standard PP 1/278 *Principles of zonal data production and evaluation*.

1. General requirements

1.1 Quality assurance

The trials must be conducted by official or officially approved trial units (GEP) that are subject to requirements and inspection, *cf.* the requirements and inspections mentioned in Commission Regulation (EU) No 284/2013, Annex, Points 3.2 and 3.3.

1.2 Origin

A minimum number of efficacy trials should be carried out within the Northern Zone (see Annex 1 for further details). The number of trials depends on whether the pest is considered a major or a minor target in the Northern zone and whether the active substance is new to one or more of the countries in the Northern zone. As climate in the region differ significantly and the countries within the zone cover two different EPPO climatic zones, the Maritime and the North-east zones, the applicant must make sure that the trials are placed at relevant locations to cover the variation in weather and cropping conditions. When deciding on the location of the trials in the Northern zone also the importance of the relevant pest should be considered. If a pest problem only occurs for example in Sweden and Denmark, the trials should mainly be placed in these countries. On the other hand if a pest problem occurs in the whole region, the trials should be evenly distributed in the zone. The applicant should include a map showing the location of the trials.

Data originating from regions with comparable climate (temperature, precipitation etc.), length of the growing season, soil conditions, agricultural practice, cultivars, yield level etc. can be submitted as supplemental data. Field trials can to a certain extent be supplemented with semi-field trials e.g. small plot cage trials to provide additional data on the performance of the PPP.

1.3 Guidelines

The trials must be conducted according to relevant EPPO standards. For pest and crops where no EPPO standards are available, national guidelines can be applied if they have at least the same level of requirements as the EPPO standards.

1.4 Reference product, untreated control and test product

Trial designs must include an untreated control, a standard /reference product and test products.

A reference product is defined as a product that has proved to be effective on relevant harmful organisms with effects similar to those of the test product. The test and reference products should be tested at the full dose rates. More than one reference product may be required due to different authorizations within the Northern zone. Different maximum doses may be recommended in the zonal countries due to different regulation regarding environmental and/or health concerns.

The test product must be identified by means of product ID and/or batch number, content of active substance(s) and formulation type (for further information see EPPO Standard PP 1/181 *Conduct and reporting of efficacy evaluation trials, including good experimental practice*)

The performance of the tested product should be in line with commercially available standard treatment (s). Lower levels of efficacy may be accepted if the product has particular benefits, such as specific activity against a target, compatibility with biological control or use in anti-resistance strategies.

1.5 Adjustments of trials to GAP

The trials should reflect the GAP. If the GAPs vary between countries in the zone the efficacy trials should encompass these differences. Trials should generally reflect the maximum number of treatments (= maximum dose rates in the GAP). In case the GAP in one country is lower than in the other countries it should be justified that the lower dose provides adequate control.

1.6 Extent of assessments

The duration of the effects of the treatment must be investigated in accordance with existing guidelines. This applies to both the effects on harmful organisms and on the crop. The level of control provided by the plant protection product should be expressed relative to the level of harmful organisms in the untreated control plot.

If more than one application is recommended, it may be necessary to report trials showing the duration of the effects of individual applications, the number of applications necessary and the desired intervals between the applications.

1.7 Harmful organisms

The trials must document the level of control of the test product on the harmful organisms or species considered to be representative of the groups for which claims are made. The trials must include the relevant growth stages and biotypes/pathotypes of the harmful organisms. Trials submitted to demonstrate effectiveness should have a challenging level of infestation in the untreated plots.

When resistance against a plant protection product appears, the trials must include the representative biotypes, strains or races for a common field situation, if these are likely to show different degrees of susceptibility. The efficacy trials must be conducted under conditions where the target group of harmful organisms is present to an extent that causes or is known to cause adverse effects (yield, quality, harvest delays, *etc*.) to untreated crops. Different intensity and pest pressure within the region could lead to a requirement for extra trials in order to verify differences, e.g. concerning relevant intervals between treatments.

1.8 Cultivars and species of the crop and number of trial years

Trials must be conducted on crop species and cultivars that are relevant to the zone and susceptible to the relevant harmful organisms.

Field trials must have been conducted over at least 2 growing seasons for new active substances and 1 growing season for new formulations of registered active substances. In case of the non-presence of the harmful organism or in case of abnormal climatic or agricultural conditions, it may be required that trials are conducted over more years.

1.9 Information on influence of environmental factors on the effect of a product

If data are available that show that the effect of a product was influenced by environmental factors, such as temperature or rain, data must be submitted that show the results that can be expected. These data may originate from tests in semi-field or climate chamber trials. Relevant data on climatic and soil conditions at the time of application must be available (e.g. temperature, relative humidity, wind force, cloud cover, precipitation, soil humidity, irrigation, fertilization, soil type, pH, organic matter content, light intensity and day-length) in the individual trial reports. For the entire test period, data on temperature and precipitation with a registration interval relevant to the type of trial must also be available in the individual trial reports.

2. Number of efficacy trials

The number of trials conducted in the Northern zone should be sufficient to cover the variation of conditions encountered in the zone as well as the main areas where the target is a substantive pest problem on the crop in question. As a general guide, the majority of trials should be conducted in the part of the Northern zone where the crop is most important and/or the pests are most prevalent. The remainder may be placed where conditions are more extreme with greater emphasis of trials in the more challenging conditions and less emphasis in the least challenging.

Only fully supportive trials e.g. in terms of pest infestation level and yield level are accepted as documentation. The lowest number of trials is applicable when pest occurrence is uniform over trials and/or variability in the performance of plant protection products is low. For more information on number of trials for zonal registration see EPPO Standard PP 1/278: *Principles of zonal data production and evaluation* and the specific examples supporting the interpretation of EPPO Standard PP 1/278. For details on the number of recommended trials in the Northern Zone see Annex 1.

2.1 Preliminary trials (3.2.1 in dRR Part B Section 3)

Summary reports from preliminary trials (field, semi-field, climate chamber and laboratory trials) that were conducted to assess the biological activity (target spectrum, climate dependency) and dose range of the product can be submitted. Preliminary trials do not have to be carried out by GEP approved trial units.

Such data can supplement the area of approval with harmful organisms that are rare in the field or assist in clarifying questions of correct timing. Semi-field and laboratory data alone are not in themselves sufficient basis for approval of a product.

2.2 Specifications for trials addressing the effect on the pest (3.2.2 and 3.2.3 in the dRR Part B Section 3)

Sufficient data should be provided to permit an evaluation of the level, duration and consistency of control or protection or intended effects of the plant protection product. As the countries in the Northern zone belong to two EPPO climate zones, the Maritime and the North-east zones, data should be provided for both EPPO zones if authorization is sought for the whole of the Northern zone. In the dRR data should be summarized according to EPPO climate zones. However, some of the submitted data must originate from the Northern zone (see Annex 1 for guidance on minimum number of trials conducted in the Northern zone). If authorization is requested in countries in both EPPO climate zones

applicants are urged to aim for an even distribution between the two zones of the data generated in the Northern zone. The authorities acknowledge that, e.g. the prevalence of crops and the pest in question can make it difficult to fulfill this requirement but this should then be justified in the dRR.

In order to clarify the dose response, doses lower than that recommended should be included in some trials in order to enable an assessment of the minimum dose necessary to achieve the desired effect (see 2.2 and EPPO Standard PP1/225: *Minimum effective dose*).

2.2.1 Products containing new active substances or new uses of authorized active substances

FUNGICIDES AND INSECTICIDES
At least 50% of the trials required from the Northern zone should be dose-response trials. Preferably, two doses lower than the proposed dose (e.g. 1/2 N and 1/4 N) should be included for fungicides and a dose lower the recommended rate (e.g. 1/2 N) for insecticides.

HERBICIDES

The following guideline should be followed:

Competitive crops (e.g. cereals, oilseed rape and pea): At least 50% of the trials required from the Northern zone should include two doses lower than the proposed dose (e.g. 1/2 N and 1/4 N)

Non-competitive crops (e.g. all row crops): At least 50% of the trials required from the Northern zone should include a dose lower than the proposed dose (e.g. 1/2 N).

As a minimum, data from 2-4 trials from each EPPO climate zone must be available for each weed species included on the label.

PLANT GROWTH REGULATORS AND DESSICANTS

At least 50% of the trials required from the Northern zone should include one dose lower than the proposed dose (e.g. 1/2 N).

2.2.2 New formulations of authorized active substances

ALL PLANT PROTECTION PRODUCTS
Some trials should preferably be dose-response trials including at least one dose lower than the maximum dose recommended. An authorized formulation of the active substance should be included as reference product at the same doses as the test product (‘bridging trials’).

Where a formulation change is claimed to increase efficacy then more doses lower than recommended dose should be included.

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

- Changes in the source of active ingredient

- Change in substances added to stabilise 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.
- Replacement of a safener (Note: selectivity trials are always required for safener replacements)

In general, changes of less than 10% in the amount of any formulation component, including the active substance, are considered to be minor and as such require no further data.

Many applications for changes in formulation do not contain any information on the chemical nature of the co-formulants, or any justification of the similarity between them. In the absence of any further information, the authorities will generally err on the side of caution and refuse approval for the revised formulation.

2.2.3 Re-registration of existing products (Article 43)

With regards to efficacy evaluation of products, which has previously been authorized the demand for new data can vary significantly. New data are required:

- if the risk assessment has triggered a lower dose;
- if the applicant would like to harmonize the GAP across EPPO climate zones and data is only available for one zone;
- if there is evidence of changed sensitivity of the target organisms to the product;
- if the efficacy of the product can be questioned compared to new active substances after the previous efficacy evaluation.

Data on existing product should address the same data requirements as for new active substances. Data from old non-GEP trials and practical experiences can be included in these evaluations. For some products there may be a need to adjust the label claims.

2.2.4 Tank mixes and co-formulations of several active substances

If specific claims are made on the label for tank mixes documentation on the effect and phytotoxicity of these must be provided. If the active substances are authorized 1-3 trials are required depending on the importance of the target(s).

As regards co-formulations, trial documentation or argumentation must be submitted that justifies the use of the mixture. Co-formulations containing at least one active substance that is not registered shall be regarded as a product with new active substances. Co-formulations containing only known active substances shall be regarded as new formulations of known active substances.

2.3 Specification for trials addressing phytotoxicity and effects on yield (3.4.1 and 3.4.2 in dRR Part B Section 3)

If damage to the crop is observed in the efficacy trials or if phytotoxic effects can be expected, trials examining this risk are required. For herbicides and plant growth regulators, selectivity trials including

the 2N dose are always required. Differences in growing conditions, e.g., day-length that may influence the risk of phytotoxicity should be considered when locating the trials. For details on the number of recommended trials in the Northern Zone see Annex 1.

If adverse effects are observed but claimed to be temporary or to be unimportant compared with the benefit of using the product evidence supporting this claim is required. If necessary, yield measurements must be submitted. For herbicides and plant growth regulators yield measurements are always required.

It must be shown that a plant protection product can be applied without any risk to the most widely grown crop varieties for which it is recommended. Small-plot variety screens can partly substitute standardised selectivity trials

If the draft label includes recommendations for the use of the plant protection product together with other plant protection product(s) or adjuvant(s), the provisions of the previous paragraphs apply to the mixtures. It is expected that efficacy trials conducted with mixtures should be assessed for phytotoxicity. Only where these trials show damage, trials with a double dose are required.

Although seed treatment is regarded as an inter-zonal and not a zonal issue, applicants are required to provide phytotoxicity data originating from field trials conducted in the Northern zone for new active substances. The reason is that the growing conditions in the Northern zone, e.g. the lower soil temperatures, may result in phytotoxicity not observed under more favourable conditions.

Authorization of plant protection products for glasshouse crops is also an inter-zonal issue. However, as particularly the light conditions in the Northern zone are significantly different from those of the rest of Europe applicants are encouraged to supply phytotoxicity data generated within the zone.

3. Resistance (3.3 in dRR Part B Section 3)

The applicant needs to present a resistance risk analysis as described in EPPO Standard PP 1/213: *Resistance risk analysis*. The resistance risk analysis should include a resistance risk assessment, in which the probability of development of resistance and its likely impact are evaluated, and an analysis of resistance risk management in which possible strategies for avoiding or delaying the appearance of resistance are considered and suitable modifiers are chosen and implemented.

In the resistance risk assessment, the inherent risk is first assessed using the characteristics of the pest and the product (required information is listed in EPPO PP 1/213, part 4.2); the unmodified risk is then evaluated from the inherent risk when the product is applied under unrestricted conditions of use. The resistance risk management part concludes whether the unmodified risk is acceptable; if it is, the process can stop. If the unmodified risk is not acceptable, possible modifiers should be analysed to determine whether they can be used to mitigate the risk. If suitable modifiers exist, the applicant should present a resistance management strategy (comprising one or more modifiers) that can be applied when the product is used commercially and explain how this strategy will be communicated to the user.

Requirements following registration of a plant protection product and to be used for re-registration:

In EPPO standard PP 1/213 it is stressed that sensitivity monitoring, i.e. the continuing observation of field performance and/or evaluation of the sensitivity of target organisms, is imperative to the

management of resistance. Monitoring before the commercial introduction of a new active substance establishes the baseline sensitivity of the target organism. As part of a management strategy for products whose unmodified risk of resistance has been evaluated as being unacceptable, a programme should be designed before release of the product onto the market to monitor the continuing efficacy of the plant protection product on the target pest(s). This programme normally comprises observations of field performance, with reporting to the registration authority of significant changes in efficacy and, depending on the resistance risk and the availability of appropriate test methods, may also include testing of sensitivity by bioassay. The monitoring should be a continuous process, conducted in representative commercial crops with different cultural conditions and in areas of intensive use of the product. A sufficient number of populations should be sampled in order to be able to determine the distribution of practical resistance. The results of the monitoring should indicate whether the management strategies are effective, or whether resistance is developing and management strategies may need to be introduced or modified. The monitoring programme should also note any possible development of resistance in non-target pests. In particular, attention should be paid to non-target pests with a known high risk of resistance. Regulatory authorities should be informed at an early stage about all cases of field failure known to be due to resistance.

4. Quality and transformation processes (3.4.3 and 3.4.4 in the dRR Part B Section 3)

Sufficient information should be provided to permit an evaluation of the possible occurrence of taint or odour or other quality aspects of plant products after treatment with the plant protection product.

When the treated plants or plant products are intended for use in transformation processes such as brewing or bread and wine making and significant residues are present at harvest (>LOQ), the possibility of adverse effect should be investigated if there are indications that product could have an effect on the process involved (see EPPO Standard PP 1/243 for further information).

5. Plant parts for propagation (3.4.5 in dRR Part B Section 3)

The safety of products to propagation material must be addressed, except where the proposed uses preclude application to crops intended for production of seeds, cuttings, runners and tubers for planting, as appropriate. Where there is sufficient interval between application and harvest and no residues or metabolites are found in the plant parts used for propagation it may be possible to address this issue by a case making reference to residues and metabolism studies.

6. Succeeding crops (3.5.1 in the dRR Part B Section 3)

If there is evidence that significant biologically active residues of the active substance, its metabolites or degradation products remain in soil or in plant materials up to sowing or planting time of possible succeeding crops, observation should be submitted on effects on likely succeeding and replacement crops (see EPPO Standard PP 1/207 for further information).

7. Adjacent crops (3.5.2 in the dRR Part B Section 3)

Observations should be submitted on adverse effects on other plants, including the normal range adjacent crops, where there are indications that product could affect these plants via vapour drift.

Consideration should also be given to the effects of spray drift (see EPPO Standard PP 1/256 for further information).

8. Effects on beneficial and other non-target organisms (3.5.3 in the dRR Part B Section 3)

Any effects positive or negative, on the incidence or other harmful organisms, observed in the tests, should be reported. Any observed environmental effects should also be reported, especially effects on wildlife and/or beneficial organisms.

9. Summary and conclusions (3.1 in the dRR Part B Section 3)

A summary of all data and information with a critical assessment and conclusion for each use must be submitted along with the results from single trials. A GAP table including all intended uses in the Northern zone specified for each country must be provided An overview of authorizations including minor use authorizations of the product within the zone should be provided in the GAP table.

For active substances on the list of candidates for substitution the applicant must provide a comparative assessment as part of the national addendum.