Editing log				
Version	**Date**	**Actions**	**Responsible**	**Date of commencement**
1.0 (draft)	Jan 2010	The guidance document was circulated for comments to potential applicants in 2010	Aarhus University	
2.0	Feb 2010	Outcome of the discussions at a NJF workshop on efficacy testing and evaluation held in Norway	NJF workshop Norway 2010	November 2010
3.0	Jun 2011			June 14 2011
4.0	Jul 2014	Guidance paper updated and a new Annex 1 added	NORBARAG Estonia 2013 Latvia 2014	14 July 2014
5.0	Apr 2015	The editing log added as front page to the guidance paper. Minor mainly linguistic corrections in the guidance paper. Annex 1 updated. Number of trials and extrapolations corrected for powdery mildew in cereal crops and number of trials corrected for weed control trials in spring oilseed rape.	NORBARAG Denmark 2015	28 April 2015
5.0	May 2015	Annex 1 corrected	Per Kudsk	6 May 2015

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

Preamble

The present document is based on Directive 93/71/EEC amending the Commission's Directive 91/414/EEC on the marketing of plant protection products and the new regulation 1107/2009 for placing of PPP on the market. The document aims to specify the requirements for documentation wherever possible. The references in the text apply to Annex III to the Directive.

The following specifications on requirements for documentation and number of trials are intended as a guide to the common requirements for documentation in connection with efficacy evaluation in the Northern Zone. *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 on new active ingredients, new uses of active ingredients registered for other purposes and new formulations of active ingredients. 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. The guidance document does not cover re-registrations of products where no new uses are proposed. For re-registration applicants can refer to the data submitted for previous registrations but data should be made available to the authorities and a registration report in English should be submitted.

The document was prepared by a group of evaluators in the Northern zone based on a Danish guidance document. A first draft of the guidance document was circulated for comments to potential applicants in 2010, a second version was published on basis of the outcome of the discussions at a NJF workshop on efficacy testing and evaluation held in Norway in November 2010. This version of the guidance paper is a consolidated version incorporating the outcome of the discussions from the meeting of efficacy evaluators and industry representatives held in conjunction with the NORBARAG meetings in Estonia in 2013, Latvia in 2014 and Denmark in 2015.

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. 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 draft Registration Report (dRR). All member states will have access to the Biological Assessment Dossier (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 a GAP including all intended uses in the Northern zone specified for each country. A master label written in English containing detailed information on crop, harmful organism, timing and dosage must be available along with draft national labels written in the local languages of each of the countries in which the product will be marketed must also be provided. 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, and where relevant and available maps might provide a useful means of illustration. 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*.

A transition period of 3 years, i.e. until June 14, 2014, in which the authorities show flexibility in order to allow the applicants to adopt the new guidelines, was accepted. This transition period guaranteed that the registration of plant protection products developed in the recent years is not unnecessarily delayed. The transition period has now expired.

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 the Northern zone or already registered in one or more countries. As climate in the region differ significantly from south to north 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 distributing the trials in the 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 only 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 conducted in the Northern Zone.

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. Information about countries/regions from where supplemental data are accepted can

be found for each country in the Northern zone in Annex 2. If data are submitted that originates from regions not listed in Annex 2 they should be accompanied by full justification for their relevance to the zone. Field trials can to a certain extent be supplemented with semi-field trials.

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 product/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 comparable dose rates. More than one reference product may be required to accommodate the differences in the plant protection product market 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 GAPs and the label recommendations of the product in the zone. If the GAPs vary between countries in the zone the efficacy trials should reflect these differences. Trials should generally reflect the maximum number of treatments (= max dose rates in the GAP). If a national GAP is lower than the maximum it should be justified that the lower dose is still providing 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.

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 that are attacked by 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. Preliminary trials

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 must 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.

3. Extent of efficacy trials carried out in the Northern zone

The number of trials 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 major growing region of the crop in the Northern Zone. 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.

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. 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 3.1 and 3.2).

For details on the number of trials in the Northern Zone see Annex 1. 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. It is anticipated, in particular for new active substances and new uses of registered active substances but also for new formulations of registered active substances, that data generated in the Northern zone is supplemented by data originating from regions with comparable climate, cropping conditions etc. (see section 1.2). 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.

If a target is rarely found in the Northern zone or only occurs in a minor part of the zone the requirement for data generated in the zone can be reduced.

3.1 Specifications for trials addressing the effect on the pest

3.1.1 Products containing new active substances or new uses of registered active substances

FUNGICIDES AND INSECTICIDES

At least 50% of the minimum required number of trials should be dose-response trials. Normally at least two doses lower than the proposed dose (e.g. 1/2 N and 1/4 N) should be included for fungicides and at least one dose lower the recommended rate (e.g. 1/2 N) for insecticides.

HERBICIDES

The following dose-response trials should be conducted:

Competitive crops (e.g. cereals, oilseed rape and pea): At least 50% of the minimum required number of trials 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 minimum required number of trials should include one dose lower than the proposed dose (e.g. 1/2 N).

As a minimum, data from 2-4 trials must be available for each weed species included on the label (including any supplemental data).

PLANT GROWTH REGULATORS AND DESSICANTS

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

3.1.2 New formulations of registered active substances

ALL PLANT PROTECTION PRODUCTS

Some trials should preferably be dose-response trials including minimum one dose lower than the maximum dose recommended. A registered formulation of the active substance should be included as reference product.

Where a formulation change is considered or is shown to increase efficacy then one or more additional doses, lower than recommended, should be included.

The following changes to formulations 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.

Note of caution: 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.

3.1.3 Re-registration of existing products

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 applicant intends to include new uses or adjusts the recommended doses
- 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 the evaluation. For some products there may be a need to adjust the label claims.

3.1.4 Tank mixes and co-formulations of several active substances

If specific claims are made on the label for tank mixes documentation of the effect and phytotoxicity of these must be provided. If the active substances are well known 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.

3.2 Specification for trials addressing effects on yield

If damage to the crop is observed during the efficacy trials or if there is a reasonable suspicion of phytotoxic effects, trials are required that examine this risk. For herbicides and plant growth regulators, selectivity trials including the 2N dose are always required. Data should cover the whole zone as it is expected that variations in phytotoxicity could occur due to differences in growing conditions, e.g., day-length (see Annex 1 for details on number of trials).

When adverse effects occur, but are claimed to be temporary or to be unimportant compared with the benefit of using the product, evidence in support of 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 proved that a plant protection product can be applied without any risk to the most important varieties of the crops for which it is recommended including effects on crop growth stage and vigour and other factors that may affect the crop tolerance. 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 EU and not a zonal issue, applicants are recommended to provide data originating from the Northern zone as part of an authorisation, as seed treatments are subject to the wide range of soil types and climatic conditions across the zone, as well as to variation in pest pressure and sensitivity. 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.

Similarly, EU is considered one zone for glasshouse crops, i.e. the applicant cannot be asked to generate data in the Northern zone. As particularly the light conditions of the Northern zone are significantly different from those of the rest of Europe applicants are encouraged to supply phytotoxicity data generated within the zone.

4. Resistance

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.

5. Quality and transformation processes

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 wine making, brewing or bread making and significant residues are present at harvest, the possibility of

adverse effect should be investigated if there are indications that product could have an effect on the process involved (see also EPPO Standard PP 1/243).

6. Succeeding crops

Where there is evidence that significant biologically active residues of the active substance, its metabolites or degradation products, which may have an effect on succeeding crops, 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 crops (see also EPPO Standard PP 1/207).

7. Adjacent crops

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 also EPPO Standard PP 1/256).

8. Plant parts for propagation

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.

9. Observations on non-target organisms

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.

10. Summary and evaluation

A summary of all data and information with a critical assessment of the data 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 along with a master label written in English containing detailed information on crop, harmful organism, timing and dosage must be available. Draft labels including instructions for use written in the local languages must also be provided as part of the submission. All other data and information must be presented in English. An overview of authorizations including minor use authorizations of the product within the zone should be provided in the dRR.

Efficacy data submitted for evaluation should be in the form of a BAD and a dRR. It is important that applicants address all the requirements of Regulation 1107/2009. The dRR should contain summary tables of the efficacy trials conducted in the Northern zone, in the EPPO Maritime Zone and in the EPPO North-East Zone, respectively. The summary tables in the dRR should contain mean, minimum and maximum values. The dRR should not contain data from individual trials but the applicant should ensure that the results of the individual trials can easily be tracked in the BAD.