Examples of zonal efficacy evaluations

Clarification of efficacy data requirements for the authorization of a fungicide (protectant applications and curative treatments) for the control of apple scab (*Venturia inaequalis*, VENTIN) on apple (*Malus domestica*, MABSD) in the European Central authorization zone

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This document is intended to assist applicants and evaluators to interpret EPPO Standard PP 1/278 *Principles of zonal data production and evaluation.* Expert judgement should be applied in all cases.

The focus of this paper is in particular on the number and location of trials for the justification of effectiveness, phytotoxicity and resistance issues. There is a need to provide clarification of these areas as part of the zonal authorisation process for plant protection products as defined in EU Regulation 1107/2009 (EC, 2009).

All trials should be carried out under Good Experimental Practice (GEP) and using all relevant general EPPO Standards. Efficacy trials should be performed according to the latest version of the EPPO Standard PP 1/5 *Venturia inaequalis* and *V. pyrina*. (Available at http://pp1.eppo.int/)

All tests should be carried out with the formulation of the product intended for use. If other formulations were used such data may still be used to support the proposed formulation, however bridging data or a sound scientific justification should be supplied to demonstrate comparability of the formulations and allow bridging between formulations. See EPPO Standard PP1/ (in preparation) *Efficacy considerations and data generation when making changes to the chemical composition of plant protection products.*

Trials should be carried out across a range of climatic and environmental conditions likely to be encountered, and over at least two years. Trials submitted to demonstrate effectiveness should contain challenging levels of disease representative of potential disease pressure encountered across the zone. Disease-free or low level disease trials may be used to support crop safety.

General information

The EU Zonal Rapporteur Member State (zRMS) and Concerned Member States (cMS) where a product authorization is sought should be named, together with the relevant EPPO climatic zones and the status of the use (major or minor) in each country.Where the product/formulation is already authorized in countries, information should be provided about the fungicide (e.g. active substance(s), content, type of formulation, authorized dose rate), the current registration situation and the registration history in the zRMS and the cMS. Some information should be provided about the active substance(s) (e.g. approval status, mode of action, uptake and transport in the plant, behaviour in the soil, FRAC classification).

Information on the disease

Apple scab is caused by the fungus *Venturia inaequalis*. It is by far the most important apple disease, causing economic losses in almost all apple production areas. Three-quarters of the pesticide use in apple production is related to control of fungal diseases and 70 % of this use is on apple scab (Working Group Integrated Plant Protection in Fruit Crops, 2011). The fungus overwinters in fallen leaves; in which pseudothecia develop. In early spring, the pseudothecia mature and, under wet conditions, discharge their ascospores. Under suitable conditions of temperature and humidity, the ascospores infect the leaves, causing primary lesions. Conidia formed on these primary lesions 2-3 weeks later will infect further leaves, causing successive secondary lesions and, finally, lesions on the developing fruit. According to the cultivar and the disease incidence of the previous year, hibernating mycelia on leaves still attached to the shoots or on shoots and buds may produce conidia providing an additional source of inoculum in spring. In the absence of control, trees may be completely defoliated. While some damage to leaves can be tolerated, scabby fruits cannot be sold in high-quality grades, and are less suitable for storage, being liable to infection by various secondary pathogens.

Primary infection by ascospores in spring should be prevented, thus minimizing the need for further treatments against secondary infections through the summer. This can be assured by spraying preventative fungicides at regular intervals (7-14 days) or by spraying with curative fungicides according to the infection periods detected by monitoring weather conditions and leaf wetness. In general, in most European countries, advisory services provide a scab warning service on this basis. In addition, commercial devices are available to provide a local warning. Further observations may be made on the presence of ascospore inoculum, on plant growth (susceptible leaves, fungicide cover) and on rainfall (fungicide wash-off). Sometimes it is recommended to adjust the frequency of summer sprays according to the scab susceptibility of the cultivar.
The applicant should provide details of the biology of the pest and the agronomic importance in all countries in the Zone.

Information on apple production in the Central Authorization Zone

Apple is a major crop that is mainly located in the Central and Southern authorization zone of the European Union. Apple production is widely distributed in the Central authorization zone with large production areas in each of the three EPPO climatic zones in the Central authorization zone (174 300 ha in the North-East zone, 104 800 ha in the South-East zone and 80 800 ha in the Maritime zone; mean of the years 2006-2010).
Further information on apple production is available from the Eurostat website[1] and also from a Belgian study on the distribution of crops in Europe on the EPPO zonal webpage[2].
The applicant should always make sure that reliable and recently updated sources of information are used.

Intended Use(s)

[1] http://epp.eurostat.ec.europa.eu/portal/page/portal/agriculture/data/main_tables
[2] http://www.eppo.int/PPPRODUCTS/zonal_efficacy/zonal_efficacy.htm

The applicant should clearly describe the details of the recommended use for each country where registration is sought. (See EPPO Standard PP 1/240, *Harmonized basic information for databases on plant protection products* particularly points 15 - 34).

Number and distribution of trials required for an authorization

Effectiveness (**6.2 under Commission Regulation 284/2013),**

EPPO Standard PP1/226 *Number of efficacy trials* indicates that for authorization in a single country/climatic zone, 6 to 15 fully supportive results are required over 2 years for each intended use. Clearly this requirement is less where pest is a minor pest.

To support an authorization in the Central authorization zone, which encompasses different EPPO climatic zones, more than the EPPO recommended number of trials results (6-15) for a single EPPO zone will be needed. ADD sentence on zones
The Central authorization zone encloses three different EPPO zones of comparable climates: the Maritime zone (Ireland, the United Kingdom, the Netherlands, Belgium, Luxembourg, Germany, the Czech Republic and Austria), the North-East zone (Poland) and the South-East zone (Slovenia, Slovakia, Hungary and Romania).
The climatic variation across the Central authorization zone, particularly with respect to temperature and rainfall during the main period of crop growth is high. Climatic variability may have an impact on the product performance and response. However, the greatest impact of the climate variability is expected to be on development and subsequent severity of the disease. Regions with drier spring/early summer climates (e.g. South-Eastern EPPO countries) are expected to have less severe and shorter epidemics. In these countries the GAP (in terms of the dose and the number of applications) may differ from that required in the more disease prone wetter Maritime countries. Trials should cover the typical variation in climatic conditions. Where data suggest lower required doses in some areas, it may be necessary to conduct further trials to support the proposed doses.

When planning the number and distribution of trials required for an authorization in the central authorization zone, the majority of the trials (**22-28** fully supportive trials) should be carried out in the locations where *Venturia inaequalis* is most severe and in the most important production areas. Apple scab is a major disease in all three climatic zones, but it is expected to be most severe in the Maritime zone. On the other hand apple production in the North-East and South-East climatic zone covers a wider area than the apple production in the Maritime zone.
Taking both into account, it would be wise to spread the effectiveness trials well over all three climatic zones (e.g. **10-12** trials in the Maritime zone, **6-8** trials in the North-East zone and **6-8** trials in the South-East zone (indicated with red spots in Figure 1)). It is important in these trials that disease developed to challenging levels in the untreated plots.
When curative and preventive action of the product is claimed, for both claims a sufficient number of trials should be available
If different doses are proposed for different regions within the Central authorization zone, there should be sufficient trial results provided to support each dose.
Note that it is also possible to perform some of these trials e.g. in the North of France, where this disease can also be important because of its comparable climate (Maritime climatic EPPO zone), although this country does not belong to the central EU registration zone (Figure 1). Also some trials located in countries of the North-East and South-East climatic EPPO zone which do not

belong to the EU Central authorization zone, but with comparable climate may be relevant. For more information on the use of the extra-zonal data see PP 1/278.
Note that there is much variation in crop structure across apple orchards in Europe. To be able to compare results from different regions, doses used should be presented as specified in EPPO standard PP 1/239 *Dose expression for plant protection products*.
Number of trials need to be adapted if there is a significant variation in crop structure (e.g. multiple rows) among apple orchards.

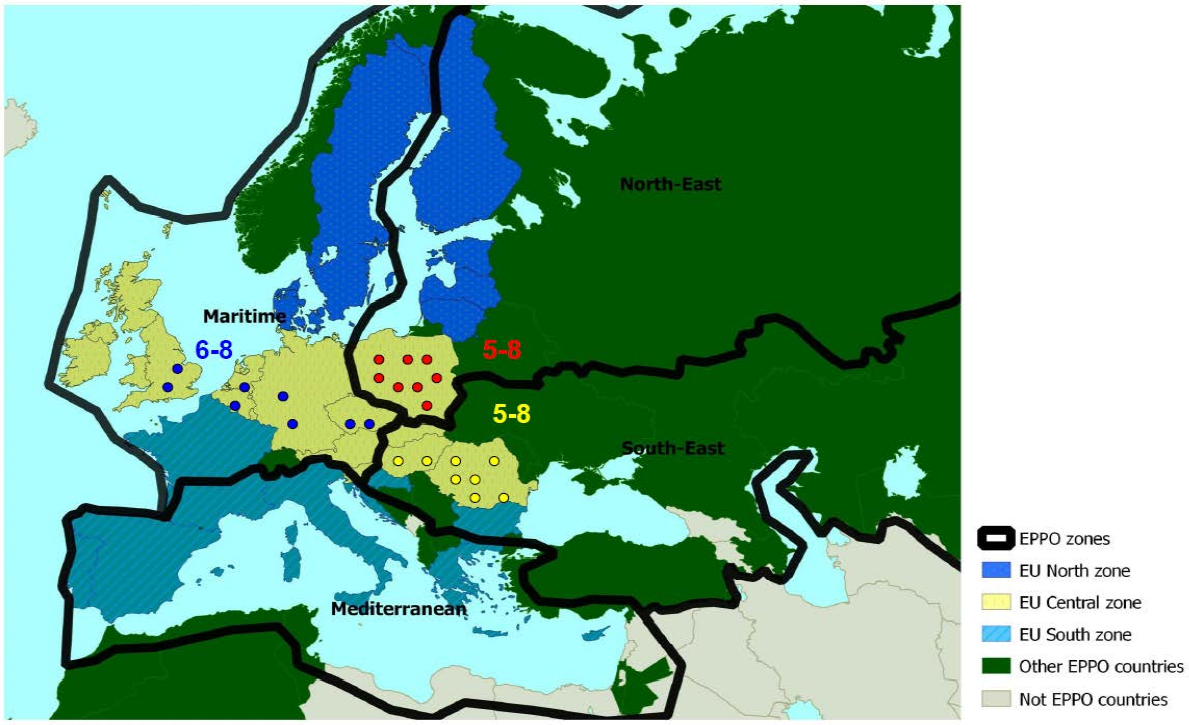

Figure 1: Visualization of the planning of trials for *Venturia inaequalis* in apple. Note that this is a schematic overview of the distribution and does not show exact locations (e.g. instead of a trial in Germany, a trial in the UK or North of France is also possible).
The EPPO climatic zones: please note that the borders are intentionally broad indicating that there is an area of gradual change in climate between the zones proposed (as defined in EPPO Standard PP 1/241 *Guidance on comparable climates*).

Data should be presented separately by EPPO zone to enable a consideration of whether there is any impact of climatic conditions on performance.
Quantitative yield data should be presented as specified in EPPO Standard PP 1/5 *Venturia inaequalis* and *V. pyrina*.

Minimum Effective Dose (6.2)

When data are generated across a range of disease pressures (as described above) it is important to determine whether a single dose is appropriate for the whole Central authorization zone, or whether the proposed dose should be different depending on disease pressure or influence of the climatic conditions on the performance of the product. The claimed dose(s) should be justified by including at least one dose below the recommended one in some trials (for more information see EPPO PP 1/225 *Minimum effective dose*). Some justification of the proposed dose for high disease pressure of the Maritime region and for lower diseases pressure of the North- and South-

East regions should also be provided because the performance of the product may be influenced by climatic conditions.

Resistance (6.3)

For a new active substance (not belonging to an existing mode of action group) the variability in sensitivity (baseline data) should be established from sites in which no previous usage of this active substance has occurred following the principle outlined in EPPO Standard PP1/213 *Resistance risk analysis*. Isolates should be taken from a range of the main apple growing areas within the Central authorization zone. Where the new active substance is from an existing mode of action (MOA), recent sensitivity data should be provided, although it may not be possible to establish true baseline sensitivity. Where shifts in sensitivity have been reported for the MOA it will be necessary to establish the pattern of cross-resistance within the group. It is also important to investigate the cross resistance pattern between the new active substance and other commonly applied fungicides in apple from other MOA particularly where reductions in field performance have been reported.
For *Venturia inaequalis*, where a high resistance risk is predicted (see the website of the Fungicide Resistance Action Committee), a resistance management strategy should be proposed. Detailed resistance management strategies will often need to be country specific. Reference may be made to relevant 'Resistance Action Committee' (RAC) recommendations, but should be tailored to individual country and reflect e.g. number of applications required, availability of other control options etc. In particular any advice from local 'Resistance Action Groups' should be addressed in National Addenda.

Phytotoxicity to target plants (including different cultivars), or to target plant products (6.4.1)

Observations for phytotoxic effects should be made in all effectiveness trials. Trials should be conducted with a range of varieties (main varieties grown in the Central authorization zone). Specific crop safety trials are only required if phytotoxicity is observed in the effectiveness trials. Phytotoxicity may vary depending on climatic conditions and varietal tolerance. Therefore, it is necessary to have phytotoxicity data from all the different EPPO climatic zones of the Central authorization zone and for a range of varieties. For more information about phytotoxicity assessment see EPPO Standard 1/135 *Phytotoxicity assessment.* Yield data are only needed if there were indications of phytotoxicity in efficacy trials.
In preparation of the biological dossier, the applicant should consider whether there is a need for data on possible effects of the test product on transformation processes. For fungicides some intrinsic activity against yeasts may be expected, hence specific tests on cider making may be required. For more information see EPPO Standard PP 1/243 *Effects of plant protection products on transformation processes.*

Impact on treated plants or plant products to be used for propagation (6.4.5)

EPPO Standard PP 1/135 *Phytotoxicity assessment* provides an indication of the circumstances under which data on plant parts for propagation are required.

Impact on other plants, including adjacent crops (6.5.2)

The decision frameworks in EPPO Standards PP 1/207 *Effects on succeeding crops* and PP 1/256 *Effects on adjacent crops* should be followed when addressing these points.

Effects on beneficial and other non-target organisms (6.5.3)

When there are claims on the label for use as part of an Integrated Pest Management Strategy, special trials may be required on a national basis. Relevant data produced for the Ecotoxicology section or existing IOBC classifications for the active substance may be used.

Extrapolation to other crops

This example may be used for *Venturia* spp. in pome fruits, e.g. pear scab (*Venturia pyrina*, VENTPI) in pear (*Pyrus communis*, PYUCO). Where effectiveness to apple scab in apple has been adequately demonstrated and where other pome fruit crops are minor it may be possible to extrapolate similar claims of activity, although a limited number of trials to demonstrate crop safety are likely to be required. More information may be found in PP 1/257 *Efficacy and crop safety extrapolations for minor uses* and the EPPO extrapolation table for effectiveness of fungicide 'Diseases on pome fruit'.
http://www.eppo.int/PPPRODUCTS/minor_uses/minor_uses.htm
Pear production is concentrated in a limited number of countries in the Central authorization zone (mainly Belgium (8 000 ha) and the Netherlands (7 500 ha) and has a total acreage of 158 000 ha in Europe (mean of the years 2006-2010).
Where pear is considered to be a major crop, specific additional data may be required to demonstrate both effectiveness and crop safety.

References

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directive 79/117/EEC and 91/414/EEC. Official Journal of the European Union L 309, 1-50.

Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0085:0152:EN:PDF

Fungicide Resistance Action Committee (www.frac.info)

OECD Guidance Documents for Pesticide Registration
http://www.oecd.org/env/ehs/pesticides-biocides/oecdguidancedocumentsforpesticideregistration.htm

Working Group "Integrated Plant Protection in Fruit Crops", Subgroup "Pome Fruit Diseases". Proceedings of the 9th International IOBC-WPRS Workshop on Pome Fruit Diseases (Hasselt, BE, 29 August – 2 September 2011). Edited by P. Creemers. ISBN 978-92-9067-262-3 [XIII + 336 pp.]. *IOBC-WPRS Bulletin*, Vol. **84**, 2012 (Hinze *et al.;* Creemers *et al.*; Kelderer M & Gramm D; Prodorutti D et al.; Stensvand A *et al.* ; Montesinos *et al.;* de Jong *et al.*; Smets *et al.*; Rancane R, Lace B & Lacis G; Giraud & Bompeix; Vanwalleghem T; Berrie A & Lower K)