Ministero della Salute

DIREZIONE GENERALE PER L'IGIENE E LA SICUREZZA DEGLI ALIMENTI E LA NUTRIZIONE

Ufficio 7 – Sicurezza e Regolamentazione dei Prodotti Fitosanitari

COMPARATIVE ASSESSMENT AND SUBSTITUTION

Guide for applicants of Plant Protection Product and for authorization in Italy

FINAL

15 March 2017

INTRODUCTION

This document provides guidance for comparative assessment (CA), in the authorisation process of a plant protection product (PPP) which contains an active substance that has been identified as a candidate for substitution (Reg. 1107/2009, article 24 and 50) and provides assistance to applicants in collecting the necessary information. It is based on Guidance document on Comparative Assessment and Substitution of PPPs in accordance with Regulation (EC) No 1107/2009 (SANCO/11507/2013 -rev. 12) and EPPO standard PP 1/271(1) *" Guidance on comparable assessment".* It also takes into account the guidance documents already made available by the UK (*Comparative Assessment and substitution: guide for UK applicants for plant protection products authorisation*), Portugal and Greece which were examined and generally agreed in the framework of the South Member States (SMS) Steering Committee.

The aim of the document is to enable both applicants and Ministry of Health (Ministry) to quickly identify those uses of plant protection products where a substitution would not be appropriate, even when a significantly safer alternative exists. A comparative assessment will only be undertaken by Ministry where it is identified that a substitution may be appropriate.

SUMMARY

- Legal requirements
- Procedure:
  - Presentation of information
  - Regulation action at the end of CA
- Instructions for completing Annex 2, the form 'applicant information to support the process of comparative assessment' for Italy (IT-CA)
- Annex 1 - National addenda to the draft Registration Report (dRR): "Applicant conclusion on Comparative assessment and substitution"
- Annex 2 - Form: Applicant information to support the process of comparative assessment

LEGAL REQUIREMENTS

Candidates for substitution are approved active substances meeting one or more of the conditions listed in Annex II point 4 of Regulation 1107/2009 (Regulation). They have all been evaluated and are approved for use in the EU in authorised plant protection products. Uses of plant protection products considered under the CA process have all been previously

evaluated to represent an acceptable risk for human health and the environment in accordance with Regulation.

According the Art. 50 of the (EC) Regulation 1107/2009, CA is carried out on a national basis "*when evaluating an application for authorisation of a plant protection product (PPP) which contains an active substance that has been approved as a candidate for substitution*".
Article 50 clearly explains the need to weigh up the risks and benefits in line with the regulation requirements (Annex IV) in considering whether there is **a significantly safer alternative control or prevention method** that substitute the considered use **without specified adverse consequences** on crop protection. CA includes comparison with alternatives at the level of use, and when a safer and effective alternative is available, substitution should be considered. In case there is a high level of uncertainty regarding the alternative, the CA is stopped and the candidate product remains available on the market.

EU guidance on comparative assessment has come into force on 1 April 2015. The list of Candidates for Substitution comes into force on 1 August 2015. Any submission for registration from the 1st of August 2015 onwards including one or more active substance candidate for substitution (submission date at zonal RMS) should be accompanied by the CA. Since Italy will not be undertaking optional assessments under Article 50(2), information for CA shall be provided by the applicant only for new applications submitted as from 1 August 2015.

CA and substitution cannot be considered appropriately by the zonal Rapporteur Member State: it remains under the responsibility of the individual Member State (MS) and the applicant should follow their advice and procedures. The applicant should include the CA information provided by the present document in his application, irrespectively whether Italy is the Rapporteur Member State (RMS) or a concerned Member State (cMS). For the purposes of this document use is meant as the combination crop/pest.

PROCEDURE

Presentation of information

This guidance only considers the requirements for essential CA and substitution.
CA is performed during the evaluation of an application for authorisation of a PPP containing one or more candidates for substitution, including renewal or amendment. In case of an

application for extending the authorisation to any additional use(s), only the application for the additional use(s) shall be considered. CA information is also required for authorisations carried out via mutual recognition, since this application is regarded as a new authorization. The applicant has to provide information to enable Ministry to fulfil responsibilities under Article 50. The applicant has to prepare Annex 1 and Annex 2 (see below), that will be included as national addendum to dRR-part A. This addendum will be evaluated together with the whole dossier.

Since each MS is individually responsible for the completeness of the CA, the Annex 1 and Annex 2 application forms of this Guidance should be filled in and submitted:

- at the notification of the start of the commenting period, when Italy is RMS;
- at the beginning of national evaluation, when Italy is cMS.

The applicant need~~s~~ to provide the CA information only for applications submitted after 1 August 2015 regarding:

- New products containing one or more active substances approved as a candidate for substitution, including applications via mutual recognition;
- New or additional uses of PPPs containing one or more active substances approved as candidate(s) for substitution;
- Renewals of PPPs containing one or more active substances approved as candidate(s) for substitution;

CA only considers the above listed situations; the previous authorized uses do not require CA. Any relevant conclusions will not be applied to other existing authorizations for PPPs containing the same active substance candidate for substitution.

Only information from the official database can be used. The CA will not consider PPPs containing other active substances candidate for substitution. The CA will be performed with PPPs authorised under uniform principles and **in line with the conditions of authorisation at the moment of submission**.

Regulatory action at the end of CA

If Ministry concludes that a substitution for any of the uses of a product is appropriate, withdrawal or amendment of that use in line with Article 50(5) of the Regulation 1107/2009 will be necessary. This will take effect three years after the decision to withdraw or amend the authorisation, or at the end of the approval period of the substance candidate for substitution, where that period ends earlier. The applicant will have the opportunity to

consider the proposals for an amendment or withdrawal of an authorisation in line with Article 44 of Regulation. This provides an opportunity for the authorisation holder to submit comments or to provide further information. Such comments or further information should be submitted at latest one year before the date for withdrawal or amendment of the decision.

Given that the substitution will be effective three years after the decision, the Ministry could reintroduce the use, by administrative acts, if the reasons of substitution fail during this time window and/or if the use to be reintroduced is just a combination crop/pest and not the complete range of uses on a crop. This in consideration that in any case that use is however covered by the overall risk assessment on that crop.

It has been agreed by Member States from the South Zone that the zRMS will make available, just for information, the CA as an addendum to the part A of the DRR. Hence CA will not undergo to the commenting phase as it is linked to the authorization pattern in Member States.

INSTRUCTIONS FOR COMPLETING ANNEX 2, THE FORM 'APPLICANT INFORMATION TO SUPPORT THE PROCESS OF COMPARATIVE ASSESSMENT' FOR ITALY

The process of CA may be conducted according to the following sequential steps; however, applicants may choose, in line with EU guidance, to start the assessment at the step which they considered more appropriate. If the applicant concludes at any step that substitution would not be appropriate for the uses of the product on a reasoned basis, there is no need to go further in the CA process.

Step 1

Use of the derogation in Article 50(3) for uses where it is necessary to acquire experience by using that PPP in practice.

This occurs for example when applicant may wish to use this derogation to:

- include a new use of an active substance on a specific crop or against a specific pest;
- introduce significant advance in formulation type;
- introduce a new active substance to an agricultural sector, new PPPs containing a new active substance approved under Regulation (EC) No 1107/2009 and a candidate for substitution.

The applicant will need to make the case that there is a need to gain experience, without providing any further information to support a CA.

If the applicant seeks to make use of this derogation, any authorisation will be limited to a shorter period, not exceeding five years or the expiry date of the approval of the active substance in case it ends before, Afterwards a new application containing the CA will be required to renew the authorisation.

Step 2

Minor use as the proposed new/additional use/renewal

Minor uses are defined as in the article 51 of the (EC) Regulation 1107/2009. However for the purposes of the present document, in order to give a more defined framework, they are intended as:

'Use of a plant protection product on:

- any crop other than a major crop (Decree Ministry of Agriculture- 16th September 1999)

or

- a major crop against a minor pest for which no practicable control measures are available'

If the use(s) are minor uses CA is not required', and applicant does not need to provide further information.

Step 3

Major use/s of the product to be considered in a CA

The applicant needs to consider all major uses at renewal, or proposed new/amended uses in other applications.

In line with EU guidance, consideration of alternative control measures in a comparative assessment CAis required for major uses of the product, including control measures other than PPPs. 'Use' means specific crop/pest combinations and the level of control claimed. If it is clear that the applicant can complete an assessment without listing all of the details (e.g. of levels of control) of the individual uses of the product (for example where there are few alternative products authorised for use on the crop), this is acceptable.

Step 4

Other available options to be assessed for the proposed uses

a) Non-chemical alternatives:

The applicant shall indicate non chemical alternatives, if any, only if there is proved evidence of comparable effects on the target and without significant economic and practical disadvantages to the user.

If only few non-chemical alternatives are available and suitable to substitute uses of plant protection products, the applicant does not need to consider them further. In any case an estimate of the overall impact of possible non-chemical alternatives is required.

b) **other authorised PPPs**:

Alternative products can be selected according to the following criteria:

1. Mode of action (eg IRAC; HRAC, FRAC)
2. Same translocation properties (eg systemic)
3. Same application method (eg foliar versus foliar)
4. Same formulation type
5. Authorised and on the market in Italy at the time CA is performed

If many alternative products are available, the applicant should list all them. The applicant may select some of them, based on the effectiveness of the possible alternative active substances. but a reasoned explanation for this selection should be given.

Step 5

Information on how diversity of the active substances in alternative products is adequate to minimize the occurrence of resistance

Information about the chemical mode of action of the active substances in the evaluated product and of the alternative active substances must refer to information published by the relevant resistance action committees and groups.

The Herbicide Resistance Action Committee (HRAC) has produced a list of herbicide resistance groups available at:

http://www.hracglobal.com/Education/ClassificationofHerbicideSiteofAction.aspx

The Insecticide Resistance Action Committee (IRAC) list of modes of action for insecticides at: http://www.irac-online.org/modes-of-action/

The Fungicides Resistance Action Committee (FRAC) list of fungicide modes of action is at: http://www.frac.info/publication/anhang/FRAC%20Code%20List%202013-update%20April-2013.pdf

For each considered use, the applicant shall specify how many different modes of action are available. If less than four modes of action are available, substitution will not be appropriate as the chemical diversity of the active substances is unlikely to be sufficient to minimise the occurrence of resistance. According to the European Plant Protection Organisation (EPPO) guidance at least four modes of action are required to manage a high resistance risk. Whilst lower levels of resistance risk might be managed with fewer modes of action, the impact of the re-registration programme and of other legislation, such as the Water Framework Directive, can, in practice, further reduce the availability of alternatives.
Where more than four modes of action are available, applicant shall provide a further analysis indicating whether the chemical diversity is sufficient to minimize the occurrence of resistance, by using other specific information. For example, information about specific resistance problems for a particular use might represent an additional concern.

Step 6

Potential consequences on minor uses if the major uses are lost in case of substitution.

Italy set the maintenance of all minor uses as a key priority in the CA process. Although minor uses are explicitly excluded from the substitution process, a number of authorised minor uses could be jeopardised if retention of authorisation of major uses through CA leads to reduced market size of the product or even to the termination of the support by the authorisation holder. For this reason all the uses should be maintained (even if the criteria of substitution are fulfilled) in order to safeguard the secure supply of the product.

Applicant shall include a list of the minor uses of the evaluating product.
Applicant shall explain the consequences on minor uses if the uses under consideration were to be replaced by an alternative. If many minor uses are authorised, the applicant may wish

to focus specifically on those for which chemical diversity is enough to minimize the occurrence of resistance.

Step 7

Possibility of the alternative controls to be used with similar effect on the target pest and without significant immediate and long term economic and practical disadvantages to the user.

The EU guidance on CA defines significant disadvantages as 'quantifiable impairment of working practices or business activity leading to an inability to maintain sufficient control of the target organism'. Information that might provide useful evidence includes: i) the need for and availability of specialist application equipment or techniques for some alternative products, where these would result in such a disadvantage; ii) the availability of necessary infrastructure such as specialist storage facilities; iii) restrictions on flexibility in the timing of treatments to respond to environmental and other conditions. Product labels and/or registration certificates often contain information about other aspects of the use of the products such as the application equipment recommended or required, the life stage of the pest that is controlled, and the pre-harvest intervals required following use. The applicant might also hold specific commercial information useful in addressing this consideration that would support his case.

Step 8

CA for health and environment

The information on alternatives should be obtained by documents publicly available. In many cases for PPPs the only available data will be obtained from the corresponding label. Therefore the CA will be mainly based on Hazard properties (reflected in Classification pictograms and phases).

Annex IV of Regulation indicates that a range of criteria are to be used to determine a significant difference among PPP. These include:

- the hazard properties of the active substance and plant protection product;
- the stringency of imposed restrictions on use and DPI prescribed
- the estimate of possible exposure of vulnerable population subgroups directly or indirectly through food, water or the environment;

.The risk mitigation measures required for evaluating product and for the alternative controls must be listed in a table. Information on the properties of the plant protection product and risk mitigation measures such as DPI, buffer zones or restrictions on timing of applications may be included on the product labels and in product authorisations. Most companies provide information from their product labels on their websites and IT product registration certificates are available in the Official-Journal of the Italian Republic .

Some differences in mitigation measures may simply reflect assessment under different guidance. If this is the case, it must be taken into account in CA.

If there are many alternative products, the applicant may select one or two products containing each of the possible alternative active substances to exemplify whether there are any significant differences in risk mitigation. However, a reasoned justification should be provided-

Step 9

Any other relevant information that will enable a comparison of risk?

In this step the applicant can provide any additional information that he considers significant in the CA of the product.

Annex 1

IT National addenda to the draft Registration Report (dRR)

Applicant conclusion on Comparative assessment and substitution

[Product name] contains [Active substance] which is approved as a Candidate for Substitution because [low ADI, ARfD or AOEL; two of PBT; significant proportion of non-active isomers; classified Carcinogen 1A or 1B; classified as toxic for reproduction 1A or 1B; endocrine disruption; other reasons for concern].

The conclusion of the comparative assessment is:
suitable for substitution/not suitable for substitution (delete as appropriate) because (specify conclusion for each use assessed).

Example(s)

Product contains wonder stuff, approved as a candidate for substitution because it is persistent and toxic (PT).

The conclusion of the comparative assessment is that it is not suitable for substitution because there is only one alternative mode of action available amongst alternative products for all of its uses and thus the chemical diversity remaining is not sufficient to minimise the occurrence of resistance.

Or

Product contains wonder stuff, approved as a candidate for substitution because it is persistent and toxic (IT).

The conclusion of the comparative assessment is that it is suitable for substitution because the product 'lovely' is a significantly safer alternative with no significant economic or practical disadvantages. Sufficient alternatives remain available to minimise the occurrence of resistance and there are no adverse consequences for minor use authorisations.

Annex 2

Form:

Applicant information to support the process of comparative assessment

Country:	IT
Product under evaluation:	
Candidate for Substitution (active substance name)	
Reason(s) for approval as candidate for substitution	
Step 1 Does applicant wish to use the derogation in Article 50(3) to gain experience with this product?	If yes, stop CA. If not, go to the next step.

Step 2

Is the applicant applying for additional uses of the product?

If yes, please list the uses and identify whether the use is a major or a minor use.

Crop	Pest	Major or Minor?

If application is for minor use (s), stop CA.

If additional uses are all major, go to the next step.

Step 3

Product Overview

Uses of the product to be considered in comparative assessment (see guidance):

Crop	Pest name (scientific name)	Label claim

Step 4

a) **Non-chemical alternatives**

Do (non-chemical) alternatives exist for controlling the target organism (or regulating plant growth) in the target crops of the candidate for substitution product (substitution is not possible for those uses where there are no alternatives)?

If yes, provide details of non-chemical alternatives.
If not, go to b)

b) **Alternative controls using authorised plant protection products**

Do alternatives exist for controlling the target organism (or regulating plant growth) in the target crops of the candidate for substitution product (substitution is not possible for those uses where there are no alternatives)?

If yes after the application of the aforementioned criteria, provide details of the examples in the table below.
If not, stop CA.

Use	Example Product	Active Substance	Mode of Action	Resistance code	Number of modes of action *

*per use

Step 5

Consideration of adequacy of chemical diversity to minimize the occurrence of resistance (Art 50.1(c)).

Are there more than 4 modes of action available for any of these uses?
If yes, please provide an analysis of whether the chemical diversity is sufficient to minimize the occurrence of resistance for each use with more than 4 modes of action available (Art 50. 1c). Examples of information that may be relevant here include (but are not limited to):

- whether evaluated product provides a unique mode of action;
- information on current resistance status for the crop/pest;
- whether evaluated product has a specific role in resistance management strategies.

If not, stop CA.

Step 6

Consideration of consequences on minor uses (Art 50.1(d)).

Is the evaluated product authorised for any minor uses ?

If yes, please list the minor uses.

Minor Uses (including Extensions of Authorization for Minor Uses) for product:

Crop	Pest name	Date of first authorisation if known

What would the consequences on the minor uses be if your product is replaced by an alternative product for any/some/all of those uses?

Examples of information that may be useful to consider here includes, but is not limited to:

- the minor uses involved and the alternative products available for them;
- significance of the pest to the growing of those minor crops in IT;
- usage data for both major and minor crops;
- marketing/sales/other commercial data of relevance to your product.

If yes, stop CA.

If not, go to the next step.

Step 7

Can any alternative controls be used with similar effect on the target organism and without immediate and long term significant economic and practical disadvantages to the user?

Examples of information that may be relevant and available on authorised labels here are, whether:

- the alternative products provide control at specific life stages of the crops or pests – for example, seed treatments or treatments with short pre-harvest intervals;
- other disadvantages (e.g. windows of application, post-harvest interval) resulting from the use of the alternative if the candidate is no longer available.

If yes, go to the next step.

If not, stop CA.

Step 8

Consider whether any of the alternatives are likely to provide significantly safer options for control. Compare key properties and risk mitigations from the label or authorisation for your product and for potential alternatives. It is not necessary to consider all the possible alternative products; rather, key indications of significantly safer options may be determined by selecting example products containing alternative active substances or by comparing to other alternatives. A reasoned justification for this selection should be given.

When comparing the results of CA, parameters should be obtained by using the same methodology. If this not the case, stop the CA

Risk mitigations measures

Active substance	PPP	Classification	DPI	Environmental mitigations measures

Are there any alternative products that are less hazardous and require significantly lower risk mitigation?

If yes, go to the next step.

If not, stop CA.

Step 9

Do you have any other relevant information that enables a comparison of risk?

If yes, this application may require a specialized CA.