Evaluation Manual for the Authorisation of Plant protection products according to Regulation (EC) No 1107/2009

EU part

Plant protection products

Chapter 3 Analytical Methods

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Board
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Chapter 3 Analytical Methods

Category: Plant protection products

Important changes with the last version of the E.M.

Evaluation manual PPP EU part Chapter 3 Analytical methods Version 2.0; January 2014		**Evaluation manual PPP EU part Chapter 3 Analytical methods Version 2.1; October 2016**	
	Referrals to • SANCO/825/00 rev.7 has been remover		Only SANCO/825/00 rev.8.1 is mentioned.

GENERAL INTRODUCTION

This chapter describes the data requirements for the aspect analytical methods and how these are evaluated for the EU framework Regulation (EC) No 1107/2009.

1. EU FRAMEWORK

In this document, the procedures for the evaluation and re-evaluation of active substances as laid down in the EU are described; the NL procedure for evaluation of a substance is reverted to when no EU procedure has been laid down. This document aims to give procedures for the approval of active substances and inclusion in Commission Implementing Regulation (EU) No 540/2011.

1.1. Introduction

The analytical methods are evaluated to establish whether the analytical methods are suitable for pre- and/or post-registration of plant protection products.

The evaluated analytical methods are –*inter alia*- used for the 5-batch analysis of the technical substance as manufactured (see Chapter 2 Physical and chemical properties, (plant protection)), for analysis of residues in animal and plant products (see Chapter 5 residues, residue dossier (plant protection)) and for analysis of residues in water, air and soil (see Chapter 6 Behaviour and fate in the environment (plant protection)).
Analytical methods that can be used for monitoring and control of the use of plant protection products are evaluated as well.

The main guidance documents for this chapter are:

- SANCO/3030/99 rev. 4, "*Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A section 5) of directive 91/414*". Currently, no updated version of this SANCO document is available. Therefore, under Regulation (EC) No 1107/2009 this version of the document is used until an adapted version is available.
- SANCO/3029/99 rev.4, "*Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, section 4) and Annex III (part A, Section 5) of directive 91/414*". Currently, no updated version of this SANCO document is available. Therefore, under Regulation (EC) No 1107/2009 this version of the document is used until an adapted version is available.
- SANCO/825/00 rev.8.1 "*Guidance document on residue analytical methods*".

Because there is much confusion about terminology such as LOQ or limit of detection the definition of these terms is given in chapter 10 of SANCO/825/00 rev.8.1.

In this chapter no distinction is made between the terms 'accuracy' and 'trueness'; the term is in all cases defined as trueness, whereas the term 'accuracy' is used to keep in line with the text of the law. This has been done to avoid confusion. This may, e.g., be the result of the literal translation of the English terms into Dutch whereas this is in fact impossible.

1.2. Data requirements

In order to qualify for inclusion in Commission Implementing Regulation (EU) No 540/2011. a dossier that meets the provisions laid down in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013 of Regulation (EC) No 1107/2009 must be submitted for the active substance (and where appropriate for relevant degradation products, isomers and impurities of active substances and their additives) as well as for the plant

protection product.

Generally, EU and OECD guidelines for the protocol of experiments are mentioned in Commission Communications 2013/C 95/01 and 2013/C 95/02 (for (EU) No 283/2013 and (EU) No 284/2013 respectively)

If the applicant holds the view that a certain study is not necessary, a relevant scientific justification may be provided for the non-submission of the particular study.
Deviations from the standard validation of analytical methods should always be justified.

Individual readings of the validations should be submitted; summaries and average values are not acceptable.

There should be no doubt about the identity and the purity of the tested substance for each study.

No GLP is required for validation of the analytical methods. Studies carried out after 25 July 1993 using these analytical methods, however, should be carried out under GLP.

It is important to distinguish between the analytical methods required for monitoring and the methods used for residue studies. (Validation) requirements differ because the purpose of the analytical methods is different.

The validated analytical method must be suitable for the determination of the relevant substances (like active substance and/or relevant degradation products, isomers and impurities) for the appropriate matrices.
A summary is given in the following table:

Matrix	**Relevant substance**
In active substance as manufactured*	pure active substance#
	impurities ≥ 0.1% w/w
	relevant impurities
	additives where present
In plant protection product	pure active substance#
	relevant impurities where these can (theoretically) be formed during production or storage of the plant protection product
	relevant co-formulants
In environment (soil, water, air)	the compounds as included in the residue definition for the particular matrix (soil/water/ air)
In plant and animal material	the compounds as included in the residue definition for the particular matrix (type crops/kidneys/milk/etc)

*) This concerns the active substance as manufactured as traded. Where the active substance is not isolated separately during the manufacturing process, but is subjected to further treatment (e.g. dilution or addition of a stabiliser), the result of the treatment is considered as the active substance as manufactured.
#) inactive isomers are considered as impurities

Different terms are used for the analytical methods used for monitoring: monitoring methods, enforcement methods or post-registration methods. The term post-registration methods has been chosen for this chapter because this is also used in the guidance documents.
This includes only the methods used for enforcement.

Validation of these analytical methods should demonstrate that the method is suitable for determination of residues by enforcement bodies. The post-registration methods are included as a separate requirement in Commission Regulation (EU) No 283/2013 under section 4 (active substance); they are described in Commission Regulation (EU) No 284/2013, under section 5. The requirements for post-registration methods are elaborated in guidance document SANCO/825/00 rev 8.1.

Pre-registration methods are the analytical methods that have (possibly only once) been used for (residue) studies required for registration. Validation of these analytical methods should demonstrate that the results produced in the experiments are reliable.

1.2.1 Data requirements active substance

Data requirements analytical methods for the active substance and impurities in the active substance as manufactured ((EU) No 283/2013)

Methods for determination of the pure active substance concentration in the active substance as manufactured are given in Guidance document SANCO/3030/99 rev. 4, for pre- as well as for post-registration methods. The data requirements are, however, the same for both purposes.

Regulation (EC) No 1107/2009 provide the following descriptions for impurities, (relevant) metabolites, as follows:

- 'impurity' means any component other than the pure active substance and/or variant which is present in the technical material (including components originating from the manufacturing process or from degradation during storage).

- 'metabolite' means any metabolite or a degradation product of an active substance, safener or synergist, formed either in organisms or in the environment.

A metabolite is deemed relevant if there is a reason to assume that it has intrinsic properties comparable to the parent substance in terms of its biological target activity, or that it poses a higher or comparable risk to organisms than the parent substance or that it has certain toxicological properties that are considered unacceptable. Such a metabolite is relevant for the overall approval decision or for the definition of risk mitigation measures.

Methods used for the generation of pre-approval data (283/2013; 4.1)

Methods for the analysis of the active substance as manufactured (283/2013; 4.1.1)

For analytical methods used for generation of data as required in Regulation (EC) No 1107/2009 or for other purposes the applicant has to provide a justification for the method used; where necessary separate guidance will be developed for such methods on the basis of the same requirements as defined for methods for post-registration control and monitoring purposes.

Linearity must be determined for the active substance and the significant and relevant impurities in the active substance as manufactured, in the relevant concentration range. Although the Regulation only mentions linearity, other calibration functions are permitted as well. Not all detection systems or analytical methods will have a linear relationship.
Use of a non-linear relationship should be justified. Otherwise, the same requirements apply as for a linear relationship.

According to SANCO/3030/99 rev. 4, determination of the accuracy is not required for

analysis of the active substance in the active substance as manufactured. This accuracy therefore only needs to be determined for the significant and relevant impurities. Where the method for the impurities in the active substance as manufactured includes no separation of the impurities (from the active substance as manufactured) before the analysis, a statement, e.g. an estimation of the precision based on the analytical technique used, is sufficient for accuracy.

CIPAC and AOAC methods can be used without validation. CIPAC methods can be obtained via http://www.cipac.org/.

Methods for risk assessment **(283/2013; 4.1.2)**
The submitted (pre-registration) analytical methods submitted to addess point 4.1.2 of (EU) No 283/2013 are assessed against guidance document SANCO/3029/99 rev.4 "*Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, section 4) and Annex III (part A, Section 5) of directive 91/414*".
Currently, no updated version of this SANCO-document is available. Therefore, under Regulation (EC) No 1107/2009 this version of the document is used until an adapted version is available.

It is in principle not permitted that the method used for production of the results deviates from the method as it has been validated (e.g. as regards the calibration line, fewer points used than for validation) but this may be acceptable where a sound explanation is given.

Validation requirements
An overview of the validation requirements for the residue-analytical methods is given in Appendix 2 to SANCO/3029/99 rev.4.

Methods for post-approval control and monitoring purposes **(283/2013; 4.2)**
The submitted (post-registration) methods for determination of the pure active substance concentration in the active substance as manufactured to address point 4.2 of (EU) No 283/2013 are assessed against guidance document SANCO/3030/99 rev. 4.

The submitted (post-registration) residue analytical methods submitted to address point 4.2 of (EU) No 283/2013 are assessed against guidance document SANCO/825/00 rev.8.1 "*Guidance document on residue analytical methods*".

Isomers
Where the active substance contains isomers, it should be possible to identify each isomer separately (required for risk assessment and identification of the active substance).

Linearity
Regulation (EC) No 1107/2009 does not specifically mention linearity but this aspect should be determined according to SANCO/825/00 rev 8.1 and SANCO/3029/99 rev.4.
Other calibration functions are permitted as well. Not all detection systems or analytical methods will have a linear relationship. Use of a non-linear relationship should be justified; otherwise the same requirements apply as for a linear relationship.

Validation requirements
A review of the validation requirements for the analytical methods of the technical substance as manufactured is given in Appendix 3 to SANCO/3030/99 rev. 4,
An overview of the validation requirements for the residue-analytical methods is given in SANCO/825/00 rev.8.1

Independent laboratory validation, ILV
An ILV is not required where reference can be made to a published and accepted multi residue analytical method validated in the relevant matrices; this was decided in the expert meeting during EPCO 11 2004.

It should be noted that under an ILV for the analytical method for the determination of residues in drinking water is required.

1.2.2 Data requirements plant protection product

Data requirements analytical methods for the active substance and impurities in the plant protection product (284/2013; 5.1.1)

Methods for determination of the active substance concentration in the plant protection product are given in Guidance document SANCO/3030/99 rev. 4, for pre- as well as for post-registration methods. The data requirements are, however, the same for both purposes. No requirements are given in Regulation (EC) No 1107/2009.

CIPAC and AOAC methods can be used without validation in case validation in the requested formulation type has already been carried out by these organisations. CIPAC methods can be obtained via http://www.cipac.org/.

Generally, EU and OECD guidelines for the protocol of experiments are mentioned in Commission Communications 2013/C 95/02

Article 3 of Regulation (EC) No 1107/2009 provide the following descriptions for impurities, relevant metabolites as follows:

- 'impurity' means any component other than the pure active substance and/or variant which is present in the technical material (including components originating from the manufacturing process or from degradation during storage).
- 'metabolite' means any metabolite or a degradation product of an active substance, safener or synergist, formed either in organisms or in the environment.

The relevant impurities in the plant protection product are defined as "impurities that are (eco)toxicologically or environmentally dangerous and which may, on the basis of theoretical considerations, be formed during production or during storage of the plant protection product".
A metabolite is deemed relevant if there is a reason to assume that it has intrinsic properties comparable to the parent substance in terms of its biological target activity, or that it poses a higher or comparable risk to organisms than the parent substance or that it has certain toxicological properties that are considered unacceptable. Such a metabolite is relevant for the overall approval decision or for the definition of risk mitigation measures.

Article 29 f of Regulation (EC) No 1107/2009 states the following requirement: 'the nature and quantity of its active substances, safeners and synergists and, where appropriate, any toxicologically, ecotoxicologically or environmentally relevant impurities and co-formulants can be determined by appropriate methods'

An analytical method for determination of the active substance in the plant protection product must in principle be validated for each type of formulation

Validation requirements
The validation requirements for the analytical methods for the plant protection product are

given in Appendix 3 to SANCO/3030/99.

1.3. Assessment

Each analytical method is assessed separately.

Where as result of an outlier test (Dixons or Grubbs test) the required number of measuring points cannot be met, acceptability will be judged on a case-by-case basis. Only one outlier may be present per series of the same data (e.g. repeatability at 1 concentration level). Judgement is based on aspects such as the cause of the outlier and the extent to which the outlier affects the results.

1.3.1 Analytical methods for active substance and plant protection product

The submitted analytical methods are assessed against the guidance document SANCO/3030/99 rev. 4, "*Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A section 5) of directive 91/414*". Currently, no updated version of this SANCO-document is available. Therefore, under Regulation (EC) No 1107/2009 this version of the document is used until an adapted version is available.

1.3.2 Pre-registration analytical method residues

The submitted analytical methods are assessed against the guidance document SANCO/3029/99 rev.4, "*Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, section 4) and Annex III (part A, Section 5) of directive 91/414*". Currently, no updated version of this SANCO document is available. Therefore, under Regulation (EC) No 1107/2009 this version of the document is used until an adapted version is available.

1.3.3 Post-registration analytical method residues

The submitted analytical methods are assessed against guidance document SANCO/825/00 rev.8.1 "*Guidance document on residue-analytical methods*".

See also SANCO/10232/2006 "Quality control procedures for pesticide residues analysis" for guidelines for the validation of post-registration methods.

Where an analytical method uses chromatographic techniques, representative chromatograms must be provided: blank, standard, sample blank and sample added at the LOQ. The chromatograms should be clearly labelled with at least: sample description, identification of all relevant compounds in the chromatogram and scale, where necessary.

1.4. Approval

For the EU approval procedure of active substances a representative formulation has to be included in the dossier. Therefore section 1.4.1 to 1.4.3 apply. For the zonal applications of plant protection products only section 1.4.2 and 1.4.3 apply.

1.4.1 Approval of the active substance

Regulation (EC) No 1107/2009 Annex II provides the procedure and criteria for the approval of an active substances, substances and synergists. Point 3 of Regulation (EC) No 1107/2009 Annex II gives the criteria for the approval of an active substance. The text specifically applicable to the aspects identity, physical-chemical properties and analytical methods is presented below.

Point 4 of Regulation (EC) No 1107/2009 Annex II gives criteria for substitution. The texts

specifically applicable to the aspect physical-chemical properties and analytical methods are presented below. In the chapter “Generic aspects” of the Evaluation Manual 2.0, more information is provided on criteria for substitution

Point 5 of Regulation (EC) No 1107/2009 Annex II gives information on low risk substances. The texts specifically applicable to the aspect physical-chemical properties and analytical methods are presented below. In the chapter “Generic aspects” of the Evaluation Manual 2.0, more information is provided on low risk substances.

1.4.2 Evaluation of plant protection products

The principles for the evaluation (the Uniform Principles) regarding analytical methods are presented in Commission Regulation (EU) 546/2011. These concern the relevant sections of the introductory principles, the general principles and the specific principles Analytical methods.

1.4.3 Decision making for plant protection products

The principles for decision making as regards analytical methods are presented in Commission Regulation (EU) 546/2011. These concern the relevant sections of the introductory principles, the general principles and the specific principles Analytical methods.

2. APPENDICES

Appendix 1 Definition terms

	Linearity (Lineariteit)	Precision (Precisie)	Trueness (Juistheid)	Selectivity (Selectiviteit)	Limit of Quantification /Quantification (Bepalingsgrens)
Definition	Linear relationship between response and amount (concentration) of the component to be determined	The closeness of agreement in the analytical results of the same sample	Extent of the agreement between the average of a series of measured values and the actual value	The property of a method to distinguish between the component to be determined and other substances (such as exclusion of Interference/interferin g effects)	Lowest concentration of the component in the sample of which the measured value can still be determined with a certain (un)certainty
Other frequently used terms		ruggedness	Accuracy is often used, although not fully correct	The term specificity is often used. An analytical method is specific where it only reacts to the component to be determined. Specificity can be considered as the ultimate selectivity	Limit of determination (not to be confused with limit of detection)
How determined		Repeatability RSD Reproducibility	Trueness can be determined by means of recovery after addition of a standard (standard addition)		