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

EU part

Plant Protection Products

Chapter 2 Physical-chemical properties and analytical methods

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Chapter 2 Physical and chemical properties and analytical methods

Category: plant protection products

General introduction 4
EU FRAMEWORK....4
1. IDENTITY 5
1.1. Identity of the active substance 5
1.2. Identity of the plant protection product 7
2. PHYSICAL AND CHEMICAL PROPERTIES 9
2.1. Physical and chemical properties of the active substance....9
2.2. Physical, chemical and technical properties of the plant protection product 10
3. FURTHER INFORMATION....14
3.1. Further information on the active substance....14
3.2. Further information on the plant protection product 14
4. ANALYTICAL METHODS 15
4.1. Active substance....15
4.2. Methods used for the generation of pre-approval data 16
4.2.1. Methods for the analysis of the active substance as manufactured 16
4.2.2. Methods for risk assessment....17
4.3. Methods for post-approval control and monitoring purposes 18
4.4. Plant protection product 19
4.5. Methods used for the generation of pre-authorisation data 19
4.5.1. Methods for the analysis of the plant protection product....19
4.5.2. Methods for the determination of residues....20
4.6. Methods for post-authorisation control and monitoring purposes 20
5. Other Information....21

Changes in the Evaluation Manual

Evaluation manual PPP EU part Chapter 2 Physical and chemical properties			
Version	**Date**	**Paragraph**	**Changes**
2.0	January 2014	1.2.1 and 1.2.2	DPD classification and labelling was referred to
2.1	October 2016	1.2.1 and 1.2.2	Only CLP classification and labelling is referred to
2.2	January 2020	1.	Sentence included on the administrative EFSA guidance
2.3	April 2022	1.1	Inclusion of the guidance document for chemical and technical properties of plant protection products SANCO/10473/2003 rev. 5 (applicable from 01-11-2021)
2.4	March 2024	all	Complete revision of the evaluation manual regarding the sections relevant for chemistry. All relevant information is updated. Also the evaluation manual part 'Analytical methods' was combined with the physical-chemical properties part.

GENERAL INTRODUCTION

This Evaluation manual describes the data requirements for the relevant chemistry sections identity, physical-chemical properties, further information and analytical methods and how these are evaluated in the EU framework under Reg. (EC)1107/2009. Sections mentioned below are in line with the sections as included in the data requirements regulations Reg. (EU) 283/2013 for active substances and Reg. (EU) 284/2013 for plant protection products.

The identity (composition) and physical-chemical properties of active substances and plant protection products are evaluated to prevent products being placed on the market which:

1. are of insufficient quality, resulting in reduced applicability or reduced efficacy
2. may cause risks to user, public health and environment.

Physical-chemical properties of an active substance and plant protection product are also important from a safety point of view, used for classification under Reg. (EC) 1272/2008.

Under further information, data is presented which are of concern for transport and handling of the active substance or plant protection product, or packaging material used for storage of the plant protection product.

The analytical methods are evaluated to establish whether the analytical methods are suitable for pre- and/or post-registration of active substances and plant protection products. The evaluated analytical methods are –inter alia- used for the 5-batch analysis of the technical substance as manufactured, for analysis of residues in animal and plant products and for analysis of residues in water, air and soil or other matrices in support of studies used by other sections. Analytical methods that can be used for monitoring and control of the use of active substances or plant protection products are evaluated as well.

EU FRAMEWORK

In this document, the procedures for the evaluation and re-evaluation of active substances and plant protection products as laid down in the EU are described; the NL procedure for evaluation is used 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.

Notifiers preparing an assessment report for active substances need to comply with the relevant guidance, instructions and format laid down in the EFSA Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances.

In order to qualify for inclusion of an active substance 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 as well as for the representative plant protection product.

1. IDENTITY

The most important guidance documents can be found on the European Commission site: Guidelines on Active Substances and Plant Protection Products under section Phys-chem analytical methods. The guidance's used for this chapter include:

- SANCO/12638/2011 rev. 2, *"Guidance document on significant and non-significant changes of the chemical composition of authorised plant protection products under Regulation (EC) No 1107/2009 of the EU Parliament and Council on placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC"*
- SANCO/10597/2003 rev. 10.1 *"Guidance document on the assessment of the equivalence of Technical materials of substances regulated under regulation (EC) no 1107/2009."*

Guidelines FAO (Food and Agriculture Organisation of the United Nations): Link

- FAO/WHO March 2016 – first edition - third revision "Manual on Development and Use of FAO and WHO Specifications for Pesticides"

All end-points under 1.1 – 1.11 in Reg. (EU 283/2013) for active substances and 1.1 – 1.6 in Reg. (EU) 284/2013 for plant protection products should be covered either with information, (open) data, a study or a waiver (expert statement).

Confidentiality can be claimed for identity data in line with art. 63 of Reg. (EC) 1107/2009.

In principle when a study is required for a certain end-point (*e.g.* 5-batch data) GLP is required, for studies carried out after 25 July 1993 (Directive 2004/10/EC).

1.1. Identity of the active substance

The data requirements regarding the identity of the active substance (which are considered to be of chemical nature) are described in part A of Commission Regulation (EU) No 283/2013, section 1 (identity of the active substance).

In Commission Communication 2013/C 95/01 no specific test methods are proposed to be used for the identity section, only reference is made to the use of the GD on equivalence (SANCO/10597/2003 rev. 4) and FAO manual.

Any necessary additions to data requirements set in Commission Regulation (EU) No 283/2013 are described below.

Identity of the active substance
Producer (name, address, including location of plant) (283/2013; 1.2)
If the active substance is to be obtained from a different manufacturer or when there is a change of location of the manufacturing plant or manufacturing process of the active substance, this should be notified. For guidance on data requirements related to changes of the producer, refer to the guidance document on the assessment of the equivalence of technical materials, SANCO/10597/2003.

CAS, EC and CIPAC numbers (283/2013; 1.6)
The CIPAC number of a substance can be obtained on the following website: http://www.cipac.org/.
The ESIS database (archived version), containing EC (EINECS and ELINCS) registered compounds has been discontinued 17 November 2014. Alternatively, ECHA has a database

of all REACH registered substances and provisional and final classification and labelling information as included in annex VI of Regulation (EC) 1272/2008.

Method of manufacture (synthesis pathway) of the active substance (283/2013; 1.8)
For guidance on data requirements related to changes of the manufacturer, refer to the guidance document on the assessment of equivalence of technical materials, SANCO/10597/2003 rev. 10.1

Specification of purity of the active substance in g/kg (283/2013; 1.9)
The specification should at least meet the specification laid down by the FAO.
A non-isolated active substance in a solvent, including possible additives, is considered a technical concentrate (TK). This may be because the active substance is not stable in pure form, or for safety reasons. The technical material (TC) is the solvent-free material, including residual impurities, not isolated during manufacture of a TK. Specifications are mostly based on the TC, which is also known as a dry weight specification. Only a minimum specification has been laid down, without an upper limit. When the TC is not isolated, a TK should specification should be proposed, in case the active substance and impurities are determined in the TK, and consequently a TC specification should be derived/calculated, based on the following calculation:

$$\text{content active (TC, dry)} = \frac{\text{measured value active (TK)}}{\text{1000 - measured value of water in the TK}} \times 1000$$

Note: In principal, the conversion of a TK in a TC specification is not necessary when the specification of the TC is derived by the respective TK-batch analysis data. The measured values of the individual batch data are calculated on a dry weight basis. These "dry" measured values are than used to derivate the TC specification as usual. The calculation of the contents for the impurities has to be done according to the same principles by using the individual measured contents.

In some instances the TK can also be dried and used for a TC-specification, which is also an acceptable approach.

Identity and content of additives (such as stabilisers) and impurities (283/2013; 1.10)
The ‘non-active isomers’ of the active substance should according to the guidelines also be considered as impurities.
A detailed composition of the active substance should be provided by submitting a specification that is used for production. All impurities that could potentially exceed 0.1% w/w (or 1 g/kg) should be specified.

Significant impurities (283/2013; 1.10.2)
The specification should at least meet the FAO specification. Where significant impurities are present, these should be included in the specification ≥ 1.0 g/kg (or 0.1 % w/w).
The specification should be a statistically based realistic reflection of the concentrations found in batch analyses (mean value found in the batch analysis+ three times standard deviation) and should be representative for the batches used for toxicological and ecotoxicological testing. According to the FAO manual the content of impurities must be given in g/kg *in comparison with* the active substance content. The absolute as well as the relative presentation of the specification are accepted.

Relevant impurities (283/2013; 1.10.3)

Relevant impurities may, e.g., be formed during the production process or by degradation of the active substance, but can also be process solvents or additives.
Examples of relevant impurities are hexachlorobenzene in chlorothalonil, ETU (ethylene thiourea) in dithiocarbamates, but also impurities that are not directly related to the active substance such as dioxins and nitrosamines. Where on the basis of the production process relevant impurities can be expected, analysis of the active substance for these impurities may be requested.
The applicant should indicate whether relevant impurities are present in the active substance; if this is the case, these should be included in the specification, even below the cut-off criterium of significance of 1 g/kg (or 0.1 % w/w). A list of impurities of known toxicological concern are presented in Appendix III of SANCO/10597/2003.

Analytical profile of batches (283/2013; 1.11)
At least 5 representative batches should be analysed. These batches should be representative of the current production. The impurities content of the batches should meet the specification of the active substance as provided by the manufacturer and the FAO specification where available. The used analytical methods must meet the requirements laid down in Section 'Analytical methods'.
In addition to batch analysis data, quality control (QC) data can be used to support a proposed technical specification.

If quality control data are to be relied on in support of a technical specification what are the minimum requirements for the submission of this data.

- *Only a summary of the data is required, not the raw data, although this should be available on request. At least the minimum purity of the active substance and maximum contents of all impurities per batch should be provided.*
- *The number of batches analysed, the year of their production and the total number of batches produced in the respective years should be provided.*
- *The site of manufacture (source) must be identified.*

1.2. Identity of the plant protection product

The data requirements regarding the identity of the plant protection product are described in part A of Commission Regulation (EU) No 284/2013, points 1 (identity of the plant protection product.

In Commission Communication 2013/C 95/02 no specific test methods are proposed to be used for the identity section, only reference is made to the use of the GD on equivalence (SANCO/10597/2003 rev. 4) and FAO manual.

Any necessary additions to data requirements set in Commission Regulation (EU) No 284/2013 are described below.

Detailed quantitative and qualitative information on the composition of the plant protection product (284/2013; 1.4.1, 284/2013; 1.4.2, 284/2013; 1.4.3)
If the product contains a total of more than 10% 'aliphatic, alicyclic and aromatic hydrocarbons' the hazard statement H304 (1272/2008/EC) should be assigned, depending on viscosity and/or surface tension of the product. The term 'aliphatic, alicyclic and aromatic hydrocarbons' refers to solvents that consist only of carbon and hydrogen atoms.
The active substance is only included in the summation if it falls under this definition (e.g. mineral oils).
In Annex III of Reg. (EC) 1107/2009 a list of co-formulants which are not accepted for

inclusion in plant protection products as referred to in Article 27 is mentioned. This list is amended in Reg. (EU) 2021/383 containing all not acceptable co-formulants to be used in plant protection products. Each co-formulant will be checked on the presence of any of these constituents, which can trigger a request to provide a full composition of the co-formulant (whether or not via a producer directly sent to NL). Furthermore, each co-formulant will be checked on the presence of any constituent which complies with one of the requirements stated in Reg. (EU) 2023/574, to be included on the list of not acceptable co-formulants.

The laws, regulations and administrative provision relating to restrictions on the marketing and use of certain dangerous substances and preparations (and supplements) are set in the REACH Regulation (EC) No 1907/2006.

Safety Data Sheets provided for the plant protection product, active substance(s) and co-formulants should be provided not older than 2 year. In addition they should always comply with Reg. (EC) 1907/2006.

Type and code of the plant protection product (284/2013; 1.5)
See also FAO manual or SANCO/10473/2003 for type and code.

In addition to the requirements described in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013 of Regulation (EC) No 1107/2009, there are supplementary requirements arising from overlap with other European guidelines or from the Uniform Principles Regulation (EU) 546/2011 (2.7.2).

2. PHYSICAL AND CHEMICAL PROPERTIES

The most important guidance documents for this chapter are:

- Guidance document for the generation and evaluation of data on the physical, chemical and technical properties of plant protection products under regulation (EC) no. 1107/2009 SANCO/10473/2003 –rev.5 of 21.10.2021

Guidelines FAO (Food and Agriculture Organisation of the United Nations): Link

- FAO/WHO March 2016 – first edition - third revision "Manual on Development and Use of FAO and WHO Specifications for Pesticides"

In order to qualify for inclusion of an active substance 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 as well as for the representative product.

Generally, EU, UN-MTC (v.7) 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)

When the applicant is of the opinion that a certain study is not necessary, a relevant scientific justification can be provided for the non-submission of the particular study.

Where GLP is required, studies carried out after 25 July 1993 should be performed to GLP.

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

The data requirements and limits for physical properties, and the fact whether or not they are required for specific formulation types and the corresponding guidelines are summarised in the SANCO/10473/2003 –rev.5 of 21.10.2021. FAO manual can be used/consulted in case the specific information is not stated in this GD.

2.1. Physical and chemical properties of the active substance

The data requirements regarding the physical-chemical properties of the active substance are described in part A of Commission Regulation (EU) No 283/2013, 2 (physical and chemical properties of the active substance).

Classification based on the physical and chemical properties need to be done in accordance with Reg. (EC) 1272/2008 part 2 Physical hazards. Reference is also made to UN-MTC (v.7), The Guidance on the application of CLP criteria and Guidance on labelling and packaging in accordance with Regulation (EC) No 1272/2008

Any necessary additions to data requirements set in Commission Regulation (EU) No 283/2013 are described below.

FAO specifications can be obtained via the internet. In addition, OECD test methods are available. A large number of test methods include in Reg. (EC) 440/2008 are available, although in principle, the EEC methods are not valid for CLP labelling. CIPAC methods can be used without validation. The UN-MTC (Recommendations on the Transport of Dangerous

Goods. Manual of tests and criteria) manual contains the testing methods required for classification and labelling. Any waivers for certain CLP end-points are also described in detail, in case no tested is considered not required.

The European guidelines and guidance documents do not clearly state what requirements apply in case a variant (ester, salt) of the active substance is used in the product. In principle, the (physical and chemical) properties of the substance that is applied in the product are required for the risk evaluation.

Melting point and boiling point (283/2013; 2.1)
There are no clear European agreements about the minimum temperature down to which the freezing point should be determined. Testing down to -20°C is generally considered to be adequate.

Spectra (UV/VIS, IR, NMR, MS), molecular extinction at relevant wavelengths, optical purity (283/2013; 2.4)
The spectra should be suitable for identification purposes.

Solubility in organic solvents (283/2013; 2.6)
CIPAC method MT 181 ‘solubility in organic solvents’ can be used where solubility exceeds 10 g/L. CIPAC method MT 157 (water solubility) can be amended and used for lower concentrations.

Partition coefficient n-octanol/water (283/2013; 2.7)
According to the description the EC method (or in fact: the HPLC method as well as shake-flask method as described in EC method A8) cannot be used for surface active compounds (surface tension < 60mN/m tested at the appropriate concentration and temperature). The column elution method cannot be used for surface active compounds”. For surface active compounds the report on the determination of the octanol/water partition coefficient should contain information about a possible phase separation to enable evaluation.

Explosive properties (283/2013 ; 2.11)
In the case a theoretical estimation is insufficient, the requirements for explosive properties as laid down in Regulation (EC) 1272/2008 shall be followed.

Oxidising properties (283/2013; 2.13)
In the case a theoretical estimation is insufficient, the requirements for oxidising properties as laid down in Regulation (EC) 1272/2008 shall be followed.

The principles for the evaluation for decision making as regards physical and chemical properties are presented in Commission Regulation (EU) 546/2011.
These concern the relevant sections of the introductory principles, the general principles and the specific principles Physical and chemical properties.

2.2. Physical, chemical and technical properties of the plant protection product

The data requirements regarding the physical-chemical properties of the plant protection product are described in part A of Commission Regulation (EU) No 284/2013, 2 (physical-chemical and technical properties of the plant protection product).

Generally, EU, CIPAC and OECD guidelines for the protocol of experiments are mentioned

in Commission Communications 2013/C 95/02. Some test methods are also described Reg. (EC) 440/2008 and for CLP-endpoints (related to Reg. (EC)1272/2008) in UN-MTC v.7. Any waivers for certain CLP end-points are also described in detail, in case no tested is considered not required. Furthermore, the link to the OECD methods.

For all parameters in section 2 the guidance document for the generation and evaluation of data on the physical, chemical and technical properties of plant protection products under regulation (EC) no. 1107/2009 SANCO/10473/2003 –rev.5 of 21.10.2021 is applicable.

Any necessary additions to data requirements set in Commission Regulation (EU) No 284/2013 are described below.

CIPAC standard water
The hardness of the water used in the test is relevant for a number of properties. From FAO guideline, revision 5, water types A and D are recommended as standard water, even if the CIPAC methods recommend a different water type. Standard water A and D must be used for the emulsion and dispersion tests because the properties may be affected by soft as well as by hard water. The type of water used must be clearly indicated for all tests.

Explosive and oxidizing properties (284/2013; 2.2)
Extrapolation of the test methods EC A14, EC A17 and EC A21 to the UN tests, as prescribed by Regulation (EC) 1272/2008 is problematic. It is advisable to use the screening procedures as much as possible.

Flammability and self-heating (284/2013; 2.3)
Extrapolation of the test methods EC A10, EC A15 and EC A16 to the UN tests, as prescribed by Regulation (EC) 1272/2008, is problematic. It is advisable to use the screening procedures as much as possible.

Viscosity and surface tension (284/2013; 2.5)
Only the rotational viscometer can be used for determination of the (dynamic) viscosity of non-Newtonian liquids. CIPAC method MT 192, based on OECD114, is the preferred method. CIPAC MT192 requires two shear rates to be reported, covering the range of 20 to 100s^{-1}.
In case the viscosity is required for classification and labelling (assignment of H304), viscosity shall be determined at 40°C.

Storage stability and shelf-life: effects of temperature on technical characteristics of the plant protection product (284/2013; 2.7)
Depending on the formulation type, physical properties need to be tested after storage. The requirements can be found in the guidance document for the generation and evaluation of data on the physical, chemical and technical properties of plant protection products under regulation (EC) no. 1107/2009 SANCO/10473/2003 –rev.5 of 21.10.2021 and the specification guidelines in the Manual on Development and Use of FAO and WHO Specifications for Pesticides.
CropLife Monograph No. 17 can be used as guidance for shelf-life studies, as indicated in Commission Communication 2013/C 95/02, however it is not officially used within the framework of evaluation of shelf-life claims and or extension of shelf-life claims.

If the product shows a decrease of more than 10% of the active substance, it may be necessary to state the shelf-life of the product on the label (e.g. in months) if a shelf life of less than two years can be assigned. For this, the timepoint at which no change (±5%) was

shown should be considered., however only based on actual data measured at this timepoint. This depends on the actual decrease, the fact whether or not the specifications are met after the decrease, and the efficacy of the product after storage.

For aerosols it should be demonstrated that the nozzle is not blocked after storage. No corrosion of the nozzle may be visible after storage. The aerosol must sometimes be opened for determination of the properties of its content.
This can, e.g., be done according to the method described in the guidance document for the generation and evaluation of data on the physical, chemical and technical properties of plant protection products under regulation (EC) no. 1107/2009 SANCO/10473/2003 –rev.5 of 21.10.2021 and the Manual on Development and Use of FAO and WHO Specifications for Pesticides" under 8.11 (aerosol dispensers). More methods for determination of the physical properties of an aerosol can be obtained from the 'European Aerosol Federation'.

The suitability of the trade pack for its content should also be checked in the storage tests (e.g. by checking for: corrosion, leakage, malformation, closure). This means that the test must be carried out with the trade pack or a pack of the same material (or worst case). Where different packaging materials are applied for, these should all be investigated and described in the test, insofar as these show essential mutual differences (to be indicated by the applicant).

Technical characteristics of the plant protection product (284/2013; 2.8)
The requirements for determination of the technical characteristics of the plant protection product are formulation type specific. The guidance document for the generation and evaluation of data on the physical, chemical and technical properties of plant protection products under regulation (EC) no. 1107/2009 SANCO/10473/2003 –rev.5 of 21.10.2021 and the Manual on Development and Use of FAO and WHO Specifications for Pesticides list the specific requirements and preferred testing methods for frequently used formulation types.

FAO specifications are not yet available for new formulation types. In such cases, the criteria are derived from known formulation types, giving an explication of the choices that have been made.

In addition to the requirements described in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013 of Regulation (EC) No 1107/2009, there are supplementary requirements arising from overlap with other European guidelines or from the Uniform Principles Regulation (EU) 546/2011 (2.7.2).

Aerosols
For aerosols, the supplementary requirements as described in Directive (EU) 2008/47/EC are also applicable.

"Free" content active substance
For capsule suspensions (CS) and encapsulated granules intended as slow release formulations the content free, unbound, active substance should according to FAO also be determined. Methods are still under development. Requirements have not yet been laid down, however the applicant may indicate and substantiate what a suitable threshold is for the free content.

Water-soluble packaging
Where the formulation is used in water-soluble packaging, the relevant physical-chemical

tests should be carried out with the water-soluble packaging because this may affect the physical properties.
The test must be carried out with the water-soluble packaging in the same ratio as for the use as proposed.

The principles for the evaluation for decision making as regards physical and chemical properties are presented in Commission Regulation (EU) 546/2011.
These concern the relevant sections of the introductory principles, the general principles and the specific principles Physical and chemical properties.

3. FURTHER INFORMATION

3.1. Further information on the active substance

Methods and precautions concerning handling, storage, transport or fire (283/2013; 3.8)
Safety data sheets must be prepared according to Regulation (EC) No 1907/2006.

3.2. Further information on the plant protection product

Packaging
More information on packaging is given in the UN-MTC (Recommendations on the Transport of Dangerous Goods. Manual of tests and criteria) manual and ADR 2023 (Agreement concerning the International Carriage of Dangerous Goods by Road). Extrapolation of packaging material is described in SANCO/10473/2003.

Controlled incineration (284/2103; 4.5.2.)
More information about incineration of dangerous substances is given in Directive 2010/75/EU.

4. ANALYTICAL METHODS

The main guidance documents for this chapter are:

- SANCO/3030/99 rev. 5, "*Technical Active Substance and Plant protection products: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex (Section 4) of Regulation (EU) No 283/2013 and Annex (Section 5) of Regulation (EU) No 284/2013.*". This is an updated version of the SANCO document into force on 1 October 2019.
- SANTE/12830/2020 rev. 1 *"Guidance Document on Pesticide Analytical Methods for Risk Assessment and Post-approval Control and Monitoring Purposes"*. This is a new guidance, which combines and supersedes Guidance Documents SANCO/3029/99 rev. 4 (validation requirements for pre-registration analytical methods) and SANCO/825/00 rev. 8.1 (validation requirements for post-registration analytical methods).

4.1. Active substance

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/enforcement and the analytical methods used in support of studies used in other sections (fate, efficacy, toxicology, residues, ecotoxicology and physical and chemical properties). (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 SANTE/12830/2020.

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

4.2. Methods used for the generation of pre-approval data

4.2.1. Methods for the analysis of the active substance as manufactured

Methods for determination of the pure active substance concentration in the active substance as manufactured are given in Guidance document SANCO/3030/99 rev. 5, 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. 5 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/.

4.2.2. Methods for risk assessment

The submitted (pre-registration) analytical methods submitted to address point 4.1.2 of (EU) No 283/2013 are assessed against guidance document SANTE/12830/2020 rev. 1 *“Guidance Document on Pesticide Analytical Methods for Risk Assessment and Post-approval Control and Monitoring Purposes”*

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 analytical methods is given in SANTE/12830/2020 paragraph 4 ‘Validation requirements for quantitative methods for risk

assessment'.

4.3. Methods for post-approval control and monitoring purposes

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. 5.

The submitted (post-registration) residue analytical methods submitted to address point 4.2 of (EU) No 283/2013 are assessed against guidance document SANTE/12830/2020 *"Guidance Document on Pesticide Analytical Methods for Risk Assessment and Post-approval Control and Monitoring Purposes".*

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). See also GD on stereoisomers SANTE/12278/2020 of 3 December 2020.

Linearity
Regulation (EC) No 1107/2009 does not specifically mention linearity but this aspect should be determined according to SANTE/12830/2020.
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. 5, see pre-registration.
An overview of the validation requirements for the residue-analytical methods is given in SANTE/12830/2020

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. The ILV should be identical to the primary analytical method, any deviations/changes should be communicated/highlighted in the report and their impact indicated on the final result. An ILV is only required for the determination of residues in plant and animal matrices and drinking water.

4.4. Plant protection product

4.5. Methods used for the generation of pre-authorisation data

4.5.1. Methods for the analysis of the plant protection product

Methods for determination of the active substance concentration in the plant protection product are given in Guidance document SANCO/3030/99 rev. 5 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/.

Article 3 of Regulation (EC) No 1107/2009 provides the following description for impurities andrelevant metabolites:

- '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 rev. 5.

Assessment
Each analytical method is assessed separately.

Whereas 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.

Analytical methods for active substance and plant protection product
The submitted analytical methods are assessed against the guidance document SANCO/3030/99 rev. 5, "*Technical Active Substance and Plant protection products: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex (Section 4) of Regulation (EU) No 283/2013 and Annex (Section 5) of Regulation (EU) No 284/2013.*". This is an updated version of the SANCO document into force on 1 October 2019.

4.5.2. Methods for the determination of residues

The submitted analytical methods are assessed against the guidance document SANTE/12830/2020 *"Guidance Document on Pesticide Analytical Methods for Risk Assessment and Post-approval Control and Monitoring Purposes".*

4.6. Methods for post-authorisation control and monitoring purposes

The submitted analytical methods are assessed against the guidance document SANTE/12830/2020 *"Guidance Document on Pesticide Analytical Methods for Risk Assessment and Post-approval Control and Monitoring Purposes".*

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.

5. OTHER INFORMATION

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 sections identity and analytical methods.

Point 4 of Regulation (EC) No 1107/2009 Annex II gives criteria for substitution. The texts specifically applicable to the sections identity and physical-chemical properties. 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. In the chapter “Generic aspects” of the Evaluation Manual 2.0, more information is provided on low risk substances.

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 and Physical and chemical properties.

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 and Physical and chemical properties.