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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.

Working document

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1 INTRODUCTION

In order to generate Annex II and III data for authorisation and post-registration control and monitoring purposes under Directive 91/414 EEC, robust, accurate and precise analytical methods are required.

Methods are required for the identification and quantification of the active substance in the technical material and formulated product.

1.1 Scope

This document has been prepared to provide guidance to applicants on the requirements for analytical methods supporting all submissions under Directive 91/414/EEC and, for formulated products only, for post-registration control and monitoring purposes. In cases where the requirements of these guidelines cannot be fulfilled, full justification must be submitted. The requirements outlined in this guidance paper are applicable to a core data set for each method. It is not a requirement that the whole validation data set is generated every time a method is used.

Directive 96/46/EC, published in the Official Journal on 23.8.96 (1), amends section 4, Part A of Annex II and section 5, Part A of Annex III of Directive 91/414 EEC. This Directive addresses the development of analytical methods required for post-registration control and monitoring purposes. It is also broadly relevant to the methods of analysis required for authorisation. However, some of the requirements such as 'minimum cost' and 'commonly available' equipment do not apply to methods supporting pre-registration studies.

For the analysis of preparations, where authorisation and post-registration requirements differ, this is clearly stated. The majority of validation data required are common to methods supporting both authorisation and post-registration control and monitoring purposes.

1.2 Content

The document is divided into sections addressing the requirements for methods supporting the generation of data. The following topics are discussed: method description; method validation; confirmatory techniques; derivatisation; and non-specific and common moiety methods. Annexes cover glossary/definitions; statistical consideration of validation results; and a summary of required method validation data.

1.3 GLP

Individual requirements for the validation of methods are described in each section. Full details of all validation studies must be reported. GLP compliance requirements for methods submitted in support of applications made under Directive 91/414 (including minor uses GLP requirements) are detailed in the Commission guideline documents 7109/VI/94 (2) and 7017/VI/95 (3). The development and validation of a method is not subject to GLP, however where the method is used to generate data for safety purposes, for example where the a.s. degrades to toxicologically significant product(s), those studies must be conducted to GLP.

1.4 Sampling and storage

This working document covers laboratory sample preparation, extraction and analysis only.

1.5 Description and reporting of methods

Full descriptions of validated methods[1] must be provided, including details of equipment, materials and conditions used. Where published methods are submitted, validation of the published method when applied to the relevant sample matrix and laboratory conditions is required, unless the published method has been validated by a collaborative study. For example validation is not required for CIPAC methods where the collaborative study included the product(s) and parameters under consideration. However the scope of the method must be appropriate to the matrix under consideration. Full method details are required. In cases where the method deviates from the standard method, additional validation data will be required.

The method description must include the following:

- principle of the method (including scope and method specificity)
- method summary; equipment/reagents (including details of any hazards or precautions required and reagent stability information)
- full details of standard compound purity where relevant
- storage of validation samples prior to analysis (where appropriate, details of conditions and period of storage)
- general sample preparation techniques
- analytical procedure (including extract preparation and analytical instrumentation)
- details of calibration
- where chromatographic technique used, representative chromatograms, including peak assignments, (control blank(s), analytical standard/matrix standard(s), lowest fortification(s))
- calculations
- references

Quantification procedures should be described, including detection system calibration, calculation of analyte concentration and any compliance with statistical parameters required. Supporting chromatograms/spectra or non-chromatographic data should be clearly labelled. Labelling should include sample description, scale, concentration and identification of all relevant components. Statistical analyses are discussed in Appendix 2.

A summary of method validation requirements is shown in Appendix 3.

This guideline document should be used in conjunction with Directive 96/46/EC.

For this paper the definitions discussed in Appendix 1 apply.

[1] Validation data are not necessarily part of an analytical method to determine active ingredients in preparations, as the methods are usually written in general terms. However methods must be validated for individual formulations. Therefore validation data may be submitted separately for each specific formulation.

2 SCOPE AND APPLICABILITY OF METHODS SUPPORTING REGISTRATION

2.1 Sample extraction and purification techniques

Methods supporting registration may employ any suitable analytical techniques for sample preparation, providing the method validation criteria are adequately addressed. The use of novel/complex analytical techniques/ instrumentation or hazardous reagents must be justified.

2.2 Derivatisation

For the analysis of some compounds, such as those of high polarity or with poor chromatographic properties, derivatisation may be necessary. Derivatives may be prepared prior to chromatographic analysis or as part of the chromatographic procedure, either pre-or post-column.

- Where a derivatisation method is used, this must be fully reported and justified.
- The derivative must be stable and must be formed reproducibly.
- Where quantification is based on the determination of a derivative, the calibration should preferably be carried out using standard solutions of that derivative, unless the derivatisation step is an on-line part of the detection system.
- The mean yield and precision of the derivatisation step must be demonstrated, where possible.

The method is considered to remain specific to the analyte of interest if the derivatised species is specific to that analyte. However, where the derivative formed is a common derivative of two or more active substances or impurities or is classed as another active substance, the method should be considered non-specific. A consideration of non-specific methods is given in section 2.3.

2.3 Non-specific and common moiety methods

Common moiety methods are considered non-specific if the moiety is common to two or more active substances or significant or relevant impurities, irrespective of how specific the determination of the common moiety is.

It is recognised that, for some analytes, a specific method may be unavailable or difficult to perform. Some common moieties are to be determined because all components containing that moiety are considered toxicologically important and because one of them is not an adequate marker of analyte concentration. However, where possible to do so, the use of non-specific methods is discouraged. Disadvantages of using non-specific or common moiety methods are:

- Where a non-specific method has been used, the identity of the source of the analyte is likely to be called into question. For example, the method may also detect impurities or breakdown products either containing a moiety common to the intended analyte, or which have been derivatised to a common species, or which cannot be resolved from the target analyte. Such methods may also be subject to interferences from other similarly structured compounds.

- when analysing a.s. content in a product that has undergone storage as part of a storage stability study, degradation may be impossible to determine with a method that is not specific to the a.s.

- Where the method determines a moiety common to two or more distinct active substances with differential toxicities, it is important to identify the origin of the analytes, enabling an evaluation of the toxicologically significant components.

Non-specific and common moiety methods will only be acceptable in exceptional circumstances where there is no other practical means of determining the target analyte, and in these cases, full justification is required. This should include an explanation of why the compound cannot be determined by a specific analytical technique.

3 METHODS OF ANALYSIS FOR TECHNICAL MATERIAL AND PREPARATIONS (*Annex IIA, point 4.1 and Annex IIIA , point 5.1 of Directive 91/414/EEC*)

3.1 Technical material - (determination of the active substance and impurities).

Methods must be appropriate to the technical specification and determine the a.s. and all impurities above 0.1% and all impurities of toxicological / ecotoxicological or environmental significance.

Collaboratively tested standard CIPAC and AOAC methods for the analysis of the a.s. in technical material are regarded as validated, with the possible exception of accuracy (see (3.1.1 and 3.1.2 (iii) below). Therefore no additional validation data are necessary providing it can be demonstrated that there is no interference > 3%. However, unless the scope of the collaborative method also includes the impurities in the technical material, validation data will be required for impurities, as described below.

3.1.1 Method Validation for the active substance

(i) *Specificity* - The degree of interference in the determination of impurities in the technical material should be reported. Interferences from impurities should not contribute more than 3% to the total peak area measured for the target analyte. If the a.s. is specified as being optically pure, the method must support this. Where an a.s. contains more than one isomer, analogue, etc., the method should be capable of determining the individual components present, with the exception that this requirement does not include determination of optical isomers in racemic mixtures, or which are more or less equally active. For details of confirmatory techniques, see section 3.1.3 below.

(ii) *Linearity* - The analytical calibration should extend over a range appropriate to the lowest and highest nominal concentration of the analyte in relevant analytical matrices ± at least 20%. Either duplicate determinations at three or more concentrations or single determinations at 5 or more concentrations must be made. The equation of the calibration line and the correlation coefficient (r) must be reported and a typical calibration plot submitted. The limits of the linear range should be given, e.g. in % w/w. Where a linear correlation coefficient (r) is <0.99, an explanation of how accurate calibration is to be maintained should be submitted. Where a non-linear calibration is used, an explanation (including how calibration accuracy is to be maintained) must be provided.

(iii) *Accuracy* – The determination of accuracy for the a.s. in the technical material, in terms of recovery data, is not required. However an assessment of accuracy, required by Directive 96/46/EC, can be made by the assessment of interference and precision.

(iv) *Precision* (*repeatability*) - Details of the precision of the method are required for the a.s. in the technical material. A minimum of 5 replicate sample determinations must be made and the mean, % RSD and number of determinations reported. The acceptability of the % RSD may be assessed using the modified Horwitz equation, however it must be noted that this is empirically derived and may not be appropriate in all situations. Further details are given in Appendix 2. Where outliers have been identified using appropriate statistical methods this should be made clear and justified. A maximum of 1 outlier may be discarded at each fortification level. Where more than one outlier has been identified, additional determinations must be included.

3.1.2 Method Validation for impurities

(i) *Specificity* - Specificity for the analysis of impurities should be addressed to the extent that the technical material is properly characterised. For details of confirmatory techniques, see section 3.1.3 below.

(ii) *Linearity* - See section 3.1.1 (ii)

(iii) *Accuracy* - The accuracy of the method(s) for significant and/or relevant impurities should be reported as mean recovery ± relative standard deviation (see iv below) in the technical material. At least 2 recovery determinations should be made on representative samples containing a known quantity of the analyte. Standard addition is an acceptable method of determining recoveries of impurities in the technical material. Recoveries should be determined at levels appropriate to the material specification. Where the process of recovery is identical to that used for calibration, for example, if there is no separation of the impurity from the a.s. prior to the determinative step, there is no measure of recovery. In these cases, an estimate of the accuracy of the analytical technique may be made by an assessment of the linearity of matrix calibration by standard addition and by a comparison of accuracy with other techniques.

Further discussion of the measurement of accuracy and statistical treatment of results is given in Appendix 2.

(iv) *Precision* (*repeatability*) - See section 3.1.1 (iv)

(v) *LOQ* - The LOQ must be reported for impurities. In order to support the declared technical specification, the LOQ should be <0.1% w/w of the a.s. technical material. However, where relevant impurities are present, the LOQ must be at an appropriate level.

3.1.3 Confirmation of analyte identification

As part of the development of a method to determine impurities, it is necessary to confirm compound identity. However it is recognised that for subsequent use of the method, compound confirmation is not routinely required. The following requirements relate to the initial confirmation of compound identity.

Confirmatory techniques are required to support identification of the a.s. and significant and/or relevant impurities, when the primary method of determination is not GC-MS or another highly specific method such as HPLC-UV DAD. Confirmation should normally involve using a spectroscopic method. Chromatographic confirmatory methods should be used, where practical, such as GC-MS, LC-MS and HPLC-DAD. Where mass spectrometric analysis is carried out, a minimum of 3 ions (ideally with an m/z ratio of >100) must be used for identification/quantification. These ions should be reported and justified. It may also be possible to use chromatographic peak (fraction) collection followed by spectroscopic analysis (e.g. DAD, IR, NMR).

Where the primary method of determination cannot provide unequivocal identification and quantification of the analyte, confirmation may be possible using different separation systems. Examples are given in references 4 and 5. Where the primary method is not chromatographic, for example titration, a case justifying the specificity of the method must be made.

3.2 Preparation - (determination of the active substance and relevant impurities)

Where collaboratively tested CIPAC or AOAC methods are available, additional validation data are not required providing the method was collaboratively tested on the formulation type under consideration. Methods must be provided to support the determination of all relevant impurities.

3.2.1 Method Validation for the active substance

(i) *Specificity* - Where the preparation contains more than one active substance the method(s) must be capable of determining each in the presence of the other.

The degree of interference should be reported. Interferences from other substances present in the preparation, including other active substances, should not contribute more than 3% to the total peak area measured for each a.s. or the sum of the components of that a.s. If the a.s. is specified as being optically pure, the method must support this. Where more than one isomer, analogue, etc., of an active substance is known to occur, the method(s) should distinguish between individual isomers/ analogues where this is relevant, with the exception that this requirement does not include determination of optical isomers in racemic mixtures.

(ii) *Linearity* - as detailed in section 3.1.1 (ii).

(iii) *Accuracy* - The accuracy of the method should be reported as mean recovery for the pure active substance in the preparation. At least 2 recovery determinations should be made on representative samples containing a known quantity of the analyte. Samples should ideally be laboratory-prepared co-formulant mixes to which a known quantity of analyte is added and the whole sample analysed to reduce sampling error. However, where it is not possible to prepare a sample matrix without the presence of the analyte, or there are difficulties in replicating the sample to be analysed (for example with pellet formulations), the standard addition method may be used. Further discussion of the measurement of accuracy and statistical treatment of results is given in Appendix 2.

Where the analytical matrix is a simple solution of the preparation in a solvent, recovery data for the a.s. are not required for authorisation. However recovery data for the a.s. are required for methods designated for post-registration control.

(iv) *Precision* (*repeatability*) - Details of the precision of the method are required for the active substance in the preparation, as detailed in section 3.1.1 (iv).

3.2.2 Method Validation for relevant impurities

(i) *Specificity* - Where the preparation contains more than one relevant impurity the method(s) must be capable of determining each in the presence of the other and in the presence of the a.s. Where more than one isomer, analogue, etc., of a relevant impurity is known to occur, the method(s) should distinguish between individual isomers/ analogues where this is relevant.

(ii) *Linearity* - as detailed in section 3.1.1 (ii).

(iii) *Accuracy* - The accuracy of the method should be reported as mean recovery for relevant impurities in the preparation. See section 3.2.1.(iii).

(iv) *Precision* (*repeatability*) - Details of the precision of the method are required for relevant impurities in the preparation, as detailed in section 3.1.1 (iv).

(v) *LOQ* - The LOQ must be reported for relevant impurities and must take into account the concentration of analyte which is of toxicological or environmental significance, or the concentration which is formed during storage of the product, where this is relevant.

3.2.3 Confirmation of analyte identification

This is not required for the analysis of the active substance in the preparation. However, the identification of relevant impurities, e.g. N-nitrosamine compounds, in the preparation should be confirmed. For a discussion of confirmatory techniques, see section 3.1.3.

4 REFERENCES

[1] Directive 96/46/EC, published in the Official Journal on 23.8.96. HMSO Publications, London.

[2] Commission document 7109/VI/94 rev. 6 cl, 14.7.95.

[3] Commission document 7017/VI/95 rev. 4, 10.6.96.

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[6] International Standard ISO 5725. *Precision of test methods - Repeatability and reproducibility*. Reference number ISO 5725 - 1986 (E).

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[11] W. J. Dixon. *Ann. Math. Stat*. 1951. 22 68.

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Other useful references

(a) Tomlin C.D.S. (Ed). *The Pesticide Manual, 11th Edition*. 1997. British Crop protection Council. Farnham, UK.

(b) *CIPAC Handbooks*. CIPAC Publications, Black Bear Press, Cambridge, UK.

Appendix 1

1 GENERAL DEFINITIONS

For this paper the following definitions apply, as detailed in Directive 96/46/EC:

Impurities	Any component other than the pure active substance which is present in the active substance as manufactured (including non-active isomers) originating from the manufacturing process or from degradation during storage.
Relevant impurities	Impurities of toxicological and/or ecotoxicological or environmental concern which are known, or can be expected, to occur in the active substance as manufactured. For preparations, impurities are defined as relevant, if the composition of the preparation is such that, on the basis of theoretical consideration, impurities of toxicological and/or ecotoxicological or environmental concern may be formed by the manufacturing process of the preparation or from degradation during storage.
Significant impurities	Impurities with a content of $\geq$ 1 g/kg in the active substance as manufactured.
Specificity	The ability of a method to distinguish between the analyte being measured and other substances, based upon sufficient characteristics of the analyte as to make the results completely specific to the analyte, irrespective of the characteristics of other materials present.
Linearity	The ability of a detection system, within a defined range, to produce an acceptable linear correlation between the test results and the concentration of analyte in the sample. Allowing for any transformation of the data. The analyte concentration to be measured must be within the dynamic range of the analytical instrument.
Accuracy[1] (comprised of 'Trueness' and precision)	The degree to which the determined (observed) value of analyte in a sample corresponds to the accepted "reference" value.
Precision[1]	The closeness of agreement between independent test results obtained under prescribed conditions. A measure of random errors, which may be expressed as repeatability and reproducibility.
Repeatability[1]	The closeness of agreement between mutually independent test results obtained with the same method on identical test material in the same laboratory by the same operator using the same equipment within short intervals of time.
Limit of quantification (LOQ)	Defined as the lowest concentration tested, at which an acceptable mean recovery with an acceptable RSD, is obtained.

Recovery	The amount measured as a percentage of the amount of analyte originally added to a sample of the appropriate matrix which contains either no detectable level of the analyte or a known detectable level (not higher than 30% of the amount added).

1 These terms are defined in ISO 5725 (6)

2 GLOSSARY OF TERMS

AOAC	AOAC International (formerly the Association of Official Analytical Chemists)
a.s.	active substance
C	concentration
CIPAC	Collaborative International Pesticides Analytical Council
C.V.	coefficient of variation
DAD	diode array detector
GC	gas chromatography
GLP	good laboratory practice
HPLC	high performance liquid chromatography
IR	infra-red (spectroscopy)
kg	kilogram
l	litre
LC	liquid chromatography
µg	microgram
m	metre
mg	milligram
MS	mass spectrometry
NMR	nuclear magnetic resonance (spectroscopy)
RSD	relative standard deviation
RSD_R	among-laboratory relative standard deviation
RSD_r	repeatability relative standard deviation
UV	ultra-violet (spectroscopy or detection)

Appendix 2

STATISTICAL CONSIDERATION OF VALIDATION RESULTS

(i) General comments

The following guidelines are appropriate to the analysis of technical material and preparations and also reflect guidance given by CIPAC. It should be noted that the guidelines are not a prescriptive set of rules. Data must be considered in the light of appropriate scientific knowledge.

The statistical method used should be 'fit for purpose'. Therefore consideration should be given to the applicability of the statistical method chosen or indeed whether a statistical consideration of the results is necessary. A useful review of recent publications on the application of statistical methods to analytical methodology is given in (7).

(ii) Accuracy

Accuracy may be measured in different ways (8) and the method should be appropriate to the matrix. Assessment may be made by analysing a sample of known concentration and comparing the measured value to the 'true' value. However a well characterised sample must be used. An example of this would be a reference standard.

Alternatively, determination of accuracy may be based on the recovery of known amounts of analyte from a representative sample matrix. Samples should ideally be laboratory-prepared co-formulant mixes to which a known quantity of analyte is added. Where it is not possible to prepare a sample matrix without the presence of the analyte, or there are difficulties in replicating the sample to be analysed (for example for pellet formulations), the standard addition method may be used.

For example, when comparing the measured values with an expected or 'true' value using the Student's t-test (9), the choice of null hypothesis should be appropriate to the data set. The precision of the data set will affect the interpretation of the statistical result in terms of significance. Data may be found to be precisely skewed in one direction, indicating a systematic difference between the measured and expected values, however if these data are skewed but with a large uncertainty, the result may be a non-significant difference. For example, if recovery data are precise and range between 95-96% in comparison with the 'expected' value of 100%, the t-test may yield a significant difference between measured and expected values, however the degree of accuracy would be acceptable. However if the data were less precise, for example 95-102%, the degree of accuracy would still be acceptable, however the data are less precise and the t-test would yield a non-statistical difference.

Guideline confidence intervals for % mean recovery from preparations, based on consultation with Industry, are as follows.

% active (nominal)	mean % recovery	% impurities(nominal)	mean % recovery
>10	98-102	>1	90-110
1-10	97-103	0.1-1	80-120
<1	95-105	<0.1	75-125
0.01-0.1	90-110		
<0.01	80-120		

A consideration of the measured recovery data in relation to these guideline values is encouraged. The details of any statistical approach used must be reported.

(iii) Precision

A suitable test for outliers may be applied to the precision data, for example the Grubbs or Dixons Tests (10, 11). If outliers are discarded, justification must be given.

Acceptability of the % RSD (coefficient of variation, CV) results for precision may be based on the Horwitz equation, an exponential relationship between the among-laboratory relative standard deviation (RSD_R) and concentration (C):

$$\% RSD_R = 2^{(1-0.5 \log C)}$$

which, for estimation of repeatability (RSD_r), is modified to:

$$\% RSD_r = \% RSD_R \times 0.67$$

The Horwitz curve has been empirically derived and has been shown to be more or less independent of analyte, matrix and method of analysis over the concentration range C=1 (100%) to $C = 10^{-9}$ by the analysis of vast numbers of method precision studies (12). The modified Horwitz values for repeatability CV given below may be used for guidance. If measured repeatability is outside these recommended values, an suggested explanation should be submitted for consideration.

% Analyte	Proposed acceptable RSDr (Horwitz value x 0.67)
100	1.34
50	1.49
20	1.71
10	1.90
5	2.10
2	2.41
1	2.68
0.25	3.30

The unmodified Horwitz equation is used as a criterion of acceptability for methods collaboratively tested by CIPAC.

Appendix 3
SUMMARY OF REQUIRED VALIDATION

Sample/ Purpose	Analyte consideration	Accuracy	Precision (% RSD)	LOQ	Linearity	Interference	Specificity	Confirmatory analysis
Technical material Authorisation	Active substance Significant impurities Relevant impurities	Where collaboratively tested methods are not available: For impurities. Determinations (mean at 2 different fortification levels appropriate to the material specification. 2 controls. Standard addition method is acceptable.	Minimum of 5 replicate sample determinations.	For impurities	Calibration appropriate to the nominal concentration range ± 20% in relevant analytical solutions. • duplicate determinations at 3 concentrations, *or* • single determinations at 5 concentrations.	Interference from impurities in a.s. not >3% of total peak area for target analyte.		Required for a.s. and significant/ relevant impurities unless primary method is highly specific.
Section reference		3.1.1 (iii) 3.1.2 (iii)	3.1.1(iv) 3.1.2 (iv)	3.1.2 (v)	3.1.1 (ii) 3.1.2 (ii)	3.1.1 (i)	3.1.1 (i) 3.1.2 (i)	3.1.3
Preparation Authorisation Post-registration	Active substance Relevant impurities	Where collaboratively tested methods are not available: 2 determinations (mean at fortification levels appropriate to the material specification. 2 controls. Standard addition method is acceptable. Where analytical matrix is a simple solution of the preparation in a solvent, for the a.s., data are only required for post-registration methods.	Minimum of 5 replicate sample determinations.	For relevant impurities	Calibration appropriate to nominal concentration range ± 20% in relevant analytical solutions. • duplicate determinations at 3 concentrations, *or* • single determinations at 5 concentrations.	For a.s. Interference not >3% of total peak area for target analyte		Required for relevant impurities.
Section reference		3.2.1 (iii) 3.2.2 (iii)	3.2.1(iv) 3.2.2 (iv)	3.2.2 (v)	3.2.1 (ii) 3.2.2 (ii)	3.2.1 (i)	3.2.1 (i) 3.2.2 (i)	3.2.3

must be addressed and reported