EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Institute for reference materials and measurements
Community reference laboratory for feed additives

CRL Feed Additives

Explanatory Notes to Applicants

This document aims to provide the applicants with practical instructions concerning chapter ***2.6. Methods of analysis and reference samples*** of Annex II of Regulation (EC) No 429/2008. The document should be understood as an explanatory note, in which scientific and technical aspects are described. The explanatory notes should not be understood as a legally binding text.

Annex II	Explanatory note
The methods of analysis shall be submitted in the standard layout as recommended by ISO (i.e. ISO 78-2).	The use of the standard layout ISO 78-2 is compulsory.
According to Regulation (EC) No 1831/2003 and Regulation (EC) No 378/2005, methods of analysis included in this section shall be evaluated by the CRL. The CRL shall submit to the Authority an evaluation report indicating whether these methods are suitable to be used for official controls of the feed additive that is the object of the application. The CRL evaluation shall focus on the methods specified in sections 2.6.1 and 2.6.2.	The CRL report shall focus on the methods of analysis for the active substance in the feed additive (i.e. the finished product), in premixtures, in feed, and, when applicable in water.
If an MRL has been established for the substance object of the application by Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin, section 2.6.2 will not be subject to evaluation by the CRL. The applicant shall compile section 2.6.2 providing the same method, information and particulars (including relevant updates) for submission to European Medicines Agency (EMEA) in accordance with Annex V of Regulation (EEC) No 2377/90 and in accordance with 'Notice to Applicants and Guidelines', Volume 8 of the series 'Rules governing medicinal products in the European Union'.	The text is self explanatory.
Analytical methods described under 2.6.3 may also be included in the evaluation, if considered necessary by the CRL, the Authority or the Commission.	The text is self explanatory.
In accordance with Regulation (EC) No 378/2005, the applicant shall provide reference samples directly to the CRL prior to the evaluation of the technical dossier, and replacement samples before the expiration date.	Practical details concerning reference samples are provided in the "CRL Guidance for applicants" document available at: http://irmm.jrc.ec.europa.eu/crl-feed-additives.
Applicants shall refer to the detailed guidance provided by the CRL in accordance with Article 12 of Regulation (EC) No 378/2005.	Guidance documents are provided by the CRL at: http://irmm.jrc.ec.europa.eu/crl-feed-additives.

2.6.1. *Methods of analysis for the active substance* Detailed characterisation of the qualitative and, where applicable, quantitative analytical method(s) for determining compliance with maximum or minimum proposed levels of the active substance(s)/agent(s) in the additive, premixtures, feedingstuffs and, when appropriate, water, shall be provided.	The text is self explanatory.		
2.6.1.1. These methods shall meet the same requirements as those for methods of analysis used for official control purpose laid down in Article 11 of Regulation (EC) No 882/2004 In particular they shall meet at least one of the following requirements:	Applying the cascade approach described in Article 11 of Regulation (EC) No 882/2004, the applicant shall propose one of the following (top to bottom):	⇨	Based on documented tests, the applicant should confirm that the method is fit for the intended purpose[1] by testing/validating it and providing the following information:
— comply with relevant Community rules (e.g. Community methods of analysis) where they exist;	— Official Community methods, where available		
— comply with internationally recognised rules or protocols, for example those that the European Committee for Standardisation (CEN) has accepted, or those agreed in national legislation (e.g. CEN Standard methods);	— Standard methods (e.g. CEN, ISO) or Official National methods, where available		Confirmation of trueness, precision, and limit of detection.
— are fit for the intended purpose, developed in accordance with scientific protocols and validated in a ring test in accordance with an internationally recognised protocol on collaborative trials (e.g. ISO 5725 or IUPAC); or	— Ring-trial validated methods, where available		
— are validated in-house according to international harmonised guidelines for the in-house validation of methods of analysis with respect to the characterising parameters mentioned in 2.6.1.2.	— Methods validated in-house by the applicant according to IUPAC harmonised guidelines for single laboratory validation, regardless the origin of the method protocol (e.g. in-house development, literature, etc…)	⇨	Single-laboratory validation report and verification report (2.6.1.3)

[1] Analysis of the active substance at target concentration, in target matrices (feed additive, premixtures, feedingstuffs, and, when applicable water)

2.6.1.2. The detailed characterisation of the method(s) shall include the appropriate characteristics set out in Annex III of Regulation (EC) No 882/2004.	The methods of analysis shall be described according to the standard ISO 78-2 and shall include the appropriate performance characteristics listed in Annex III of Regulation (EC) No 882/2004.
2.6.1.3. Performance characteristics of in-house validated methods shall be verified by testing the method in a second, accredited and independent laboratory. Results of such tests shall be provided together with any other information supporting the transferability of the method to an official control laboratory. For reasons of independence and involvement in the evaluation of the documentation provided by the applicant, where the second laboratory is a laboratory participating in the consortium of National Reference Laboratories (NRLs) assisting the CRL, as laid down in Regulation (EC) No 378/2005, the laboratory shall send a declaration of interests to the CRL, as soon as the application is received by the CRL, describing the work of the laboratory in the application and shall not participate in the evaluation of the application.	Details concerning the requirements for the verification study related documentation to be included in the technical dossier are provided in the document "CRL-FA Technical Guide: Protocol for verification studies of single-laboratory/in-house validated methods" available at: http://irmm.jrc.ec.europa.eu/crl-feed-additives.
2.6.1.4. The CRL may select appropriate characteristics as mentioned under Annex III of Regulation (EC) No 882/2004 in its evaluation report to the Authority.	The text is self explanatory.
2.6.1.5. Performance criteria for methods for specific groups of substances (e.g. enzymes) may be established in the detailed guidance provided by the CRL in accordance with Article 12 of Regulation (EC) No 378/2005.	The text is self explanatory.
2.6.2. *Methods of analysis for the determination of the residues of the additive or of its metabolites in food* Detailed characterisation of the qualitative and quantitative analytical method(s) for determining the marker residues and/or metabolites of the additive in target tissues and animal products shall be provided	The text is self explanatory. The general requirements under point 2.6 apply.

2.6.2.1. These methods shall meet the same requirements as those for methods of analysis used for official control purposes as laid down in Article 11 of Regulation (EC) No 882/2004. In particular, the methods shall meet at least one of the requirements mentioned in 2.6.1.1.	The text is self explanatory. See explanatory note for 2.6.1.1 and 2.6.1.2.
2.6.2.2. The detailed characterisation of the method(s) shall include the appropriate characteristics as set out in Annex III of Regulation (EC) No 882/2004 and shall take into account the requirements set out in Commission Decision 2002/657/EC. The same performance criteria laid down in Commission Decisions laying down analytical methods to be used for detecting certain substances and residues thereof in live animal products according to Council Directive 96/23/EC shall be considered where appropriate. The limit of quantification (LOQ) for each method must not exceed half of the corresponding MRL and must be validated across a range at least from one-half to two times the MRL.	The text is self explanatory.
2.6.2.3. Performance characteristics of in-house validated methods shall be verified by testing the method in a second, accredited and independent laboratory. Results of such tests shall be provided. For reasons of independence and involvement in the evaluation of the documentation provided by the applicant, where the second laboratory is a laboratory participating in the consortium of National Reference Laboratories (NRLs) assisting the CRL, as laid down in Regulation (EC) No 378/2005, the laboratory shall send a declaration of interests to the CRL, as soon as the application is received by the CRL, describing the work of the laboratory in the application and shall not participate in the evaluation of the application.	See explanatory note for 2.6.1.3.
2.6.2.4. The CRL may select appropriate characteristics from the ones mentioned under point 2.6.2.2 in its evaluation report to the Authority.	The text is self explanatory.

2.6.2.5. Performance criteria for methods for specific groups of substances (e.g. enzymes) may be established in the detailed guidance provided by the CRL in accordance with Article 12 of Regulation (EC) No 378/2005.	The text is self explanatory.
2.6.3. *Methods of the analysis relating to the identity and characterisation of the additive* A description of the methods used for the determination of the characteristics listed under points 2.1.3, 2.1.4, 2.1.5, 2.2.2, 2.4.1, 2.4.2, 2.4.3, and 2.4.4 shall be provided by the applicant.	The text is self explanatory.
In accordance with Annex II of Regulation (EC) No 1831/2003 as amended by Regulation (EC) No 378/2005, the methods submitted under this section may also be evaluated if considered relevant by the, the Authority or the Commission for the assessment of the application.	The text is self explanatory.
It is recommended that the methods described under this section are internationally recognised. For those methods that are not internationally recognised, the methods have to be fully described. In those cases, studies shall be performed by accredited and independent laboratories and shall be documented according to appropriate quality standards (e.g. GLP in accordance with Directive 2004/10/EC or ISO standards).	The text is self explanatory.
Methods for the identification and characterisation of the additive shall meet the same requirements as those for methods of analysis used for official control purposes as laid down in Article 11 of Regulation (EC) No 882/ 2004, particularly where legal requirements are established (e.g. impurities, undesirable substances).	See explanatory note for 2.6.1.1 and 2.6.1.2.