European Commission

# Joint Research Centre

## Renewal of authorisations (art 14) – Requirements from the EURL


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5-6 May 2015, Barcelona
Stakeholder meeting

*Serving society*
*Stimulating innovation*
*Supporting legislation*

# Article 14 and EURL evaluation

- Fitness for purpose criteria: Review of 10 years
- Work of CEN: standardisation of methods
- Other aspects

European Commission

# Analytical methods and details of the authorisation

| Identification number of the additive | Name of the holder of authorisation | Additive (Trade name) | Composition, chemical formula, description, analytical method | Species or category of animal | Maximum age | Minimum content | Maximum content | Other provisions | End of period of authorisation | Maximum Residue Limits (MRLs) in the relevant foodstuffs of animal origin |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | mg of active substance/kg of complete feedingstuff with a moisture content of 12 % | | | | |
| **Coccidiostats and histomonostats** | | | | | | | | | | |
| 5 1 771 | Janssen Pharmaceutica N.V. | Diclazuril 0,5 g/100 g (Clinacox 0,5 %) | *Additive composition*<br>Diclazuril: 0,50 g/100 g.<br>Protein-poor soybean meal: 99,25 g/100 g<br>Polyvidone K 30: 0,20 g/100 g<br>Sodium hydroxide: 0,05 g/100 g<br><br>*Characterisation of the active substance*<br>Diclazuril, $C_{17}H_9Cl_3N_4O_2$, (±)-4-chlorophenyl[2,6-dichloro4-(2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-2-yl)phenyl]acetonitrile,<br>CAS number: 101831-37-2<br>Related impurities:<br>Degradation compound (R064318): ≤ 0,1 %<br>Other related impurities (T001434, R066891, R068610, R070156, R070016): ≤ 0,5 % individually<br>Total impurities: ≤ 1,5 %<br><br>*Analytical method* (1)<br>For determination of diclazuril in feed: reversed-phase high performance liquid chromatography (HPLC) using Ultraviolet detection at 280 nm (Regulation (EC) No 152/2009)<br>For determination of diclazuril in poultry tissues: HPLC coupled to triple quadrupole mass spectrometer (MS/MS) using one precursor ion and two product ions | Guinea fowls | — | 1 | 1 | 1. The additive shall be incorporated in compound feed in form of a premixture.<br>2. Diclazuril shall not be mixed with other coccidiostats.<br>3. For safety: breathing protection, glasses and gloves shall be used during handling.<br>4. The holder of the authorisation shall carry out a post-market monitoring programme on the resistance to bacteria and *Eimeria* spp. | 16 March 2021 | 1 500 µg diclazuril/kg of wet liver<br>1 000 µg diclazuril/kg of wet kidney<br>500 µg diclazuril/kg of wet muscle<br>500 µg diclazuril/kg of wet skin/fat |

(1) Details of the analytical methods are available at the following address of the Community Reference Laboratory: www.irmm.jrc.be/crl-feed-additives

# Target of analytical methods evaluated by the EURL I

- Regulation (EC) No 1831/2003 applied from 2004
- Until 2008 applicants had to follow Commission Directive 2001/79/EC, also specifying criteria for analytical methods
  - Chapter 2.5 …. *routine control* of the active substance in premixtures and feedingstuffs with a list of some method performance characteristics

# Target of analytical methods evaluated by the EURL II

- Since 2005: Regulation (EC) No 378/2005 specifies the tasks of the EURL
- Art 5 (2). The evaluation report provided for in paragraph 1 shall include in particular:
- (a) an evaluation indicating if the methods of analysis in the data
- submitted in the application are suitable to be used for **official controls**;

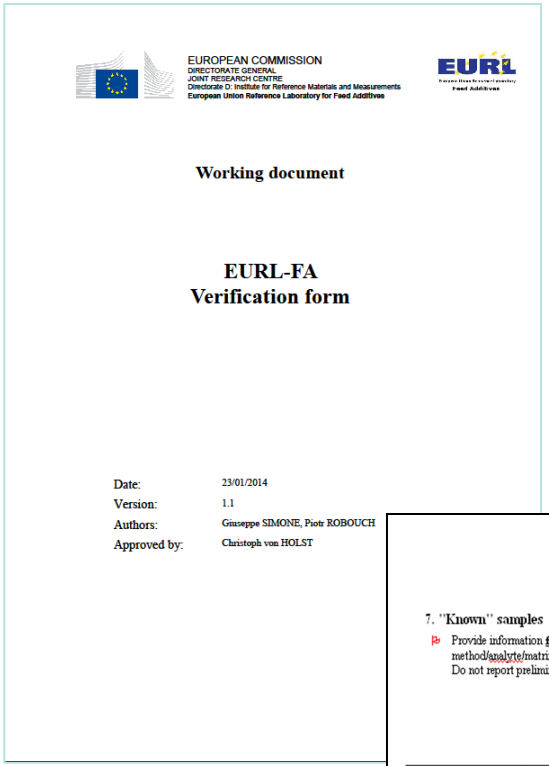
- (b) an indication if testing of a method of analysis is considered necessary;
- (c) an indication if a validation of a method of analysis by an intercomparison study is considered necessary.

# Commission Regulation (EC) No 429/2008

- Dossier guideline applies from 2008
- Takes into account requirement of the methods for official control
- Concept of verification: New requirement
- Response to option for testing/validation by intercomparison study

# Single laboratory validated methods fit for official control?

- First: single laboratory validation
- But the method needs to work also in an official laboratory?
- Check for transferability
- Prior to submitting the dossier, the method need to be tested in a second lab?
  - Is the protocol clearly written?
  - Results of verification experiments need to be comparable with those from the validation study!
- Transferability is an important prerequisite for fitness for purpose



EUROPEAN COMMISSION
DIRECTORATE GENERAL
JOINT RESEARCH CENTRE
Directorate D: Institute for Reference Materials and Measurements
European Union Reference Laboratory for Feed Additives

EURL

**Working document**

**EURL-FA**
**Verification form**

Date: 23/01/2014
Version: 1.1
Authors: Giuseppe SIMONE, Piotr ROBOUCH
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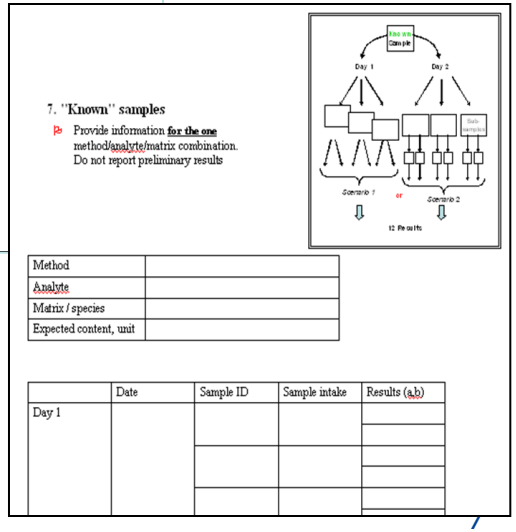

7. "Known" samples

Provide information **for the one** method/analyte/matrix combination.
Do not report preliminary results



| | |
|---|---|
| Method | |
| Analyte | |
| Matrix / species | |
| Expected content, unit | |

| | Date | Sample ID | Sample intake | Results (a,b) |
|---|---|---|---|---|
| Day 1 | | | | |

# The verification concept

## Two types of verification experiments:

- Single-laboratory validated methods
- Extension of scope of ring trial validated methods
- Example from EURL report

**Table 1:** Performance characteristics of analytical methods for the determination of *phytase* in *feed additive* (FA), *premixtures* (PM) and *feedingstuffs* (FS)

| Matrix | Activity | $RSD_r$ (%) | $RSD_{ip}$ (%) | $RSD_R$ (%) | $R_{rec}$ (%) | Reference |
|---|---|---|---|---|---|---|
| FA | 24000 U/g | 4.6 | 9.2 | - | 100.3 | Val. [10] |
| FA | 7060 U/g | 3.7 | 5.2 | - | 102.1 | Ver. [11] |
| PM | 200 U/g | 7.8 | 10.4 | - | - | Val. [8] |
| FS | 500-1500 U/kg | 6-8.3 | 10.4-12.7 | 8-15 | - | EN ISO, [4] |

$RSD_r$, $RSD_{ip}$ and $RSD_R$ : relative standard deviation for *repeatability*, *intermediate precision* and *reproducibility*.

# Consequence from this progress: Inconsistency in respect to fitness for purpose criterion

- Before 2008: Single laboratory validated method recommended for official control without verfication
- After 2008:  Single laboratory validated methods need vertfication

# Criteria for method for *official* control: The method cascade

Regulation EC (No) 882/2004

1. Community methods

COMMISSION REGULATION (EC) No 152/2009

of 27 January 2009

laying down the methods of sampling and analysis for the official control of feed

(Text with EEA relevance)

2. CEN/ISO methods/National methods/ European Pharmacopoeia

NEN-EN 15781:2009

EUROPEAN STANDARD **EN 15781**

NORME EUROPÉENNE

EUROPÄISCHE NORM August 2009

ICS 65.120

English Version

Animal feeding stuffs - Determination of maduramicin-ammonium by reversed-phase HPLC using post-column derivatisation

3. Single laboratory methods, validated against IUPAC protocol

# Method cascade and CEN method

- Analytical methods for feed additives are – and will be - standardised after validation by intercomparison study und a CEN mandate. Examples:
  - Phytase
  - Organic acids
  - Carotenoids
  - Coccidiostats
  - ….
- CEN methods are compulsory and need to be included in the Regulation authorising the additive

# Why involvement of EURL in evaluation of methods also for art 14 applications?

- Application of the verification concept to all single laboratory validated methods
- Considering scientific progress of analytical methods
- CEN methods
- Harmonisation of methods and method description

# Thank you for your attention!