Human and veterinary pharmaceuticals regulation

Towards EU accession: Serbia's regulatory challenges, expectations and opportunities

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Republika Srbija
Ministarstvo zdravlja
Ministarstvo poljoprivrede, šumarstva i vodoprivrede,
Uprava za veterinu

Republic of Serbia
Ministry of Health
Ministry of Agriculture, Forestry and Water Management,
Veterinary Directorate

alims
Agencija za lekove i medicinska sredstva Srbije
Medicines and Medical Devices Agency of Serbia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Control of Veterinary Drug Residue in European Union

anses
alimentation, environnement, travail

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Outline

Legal framework

Laboratory organisation

Analytical methods

Conclusion

Legal Framework : Council Regulation 470/2009

Veterinary drugs, Biocides

- Maximum residue limit (MRL)

Table 1 :Substances for which MRLs have been established.

- Animal Species, use

Table 2 : Substances for which no MRL could be established because of an uncertainty about the risk.

- The administration of substances listed in this table to food-producing species is prohibited.

Reference Point of Action

- EU-RL and EFSA

Legal Framework : Directive 96/23/CE

Regulation of residue control

Group of compounds

- Compounds group A : **Substances with anabolic effect and unauthorized substances (A6 : Table 2 Reg 470/2009)**
- Compounds group B : **Veterinary drugs residue and contaminants**

Legal Framework : Directive 96/23/CE

Competent authority tasks

- Annual control programme
- Inspection

Laboratories tasks

- European Union Reference Laboratory
- National Reference Laboratory
- Routine Laboratory

Methods validated according decision 2002/657

Quality assurance system : ISO17025

Species	Number of controlled animals (% of annual production)	Group A		Group B
Bovine	0.4%	0.25%	50% live animal	0.15% (30% for groups B1)
			50% slaughterhouse	
Porcine	0.05 %	0.02%		0.03% (30% for group B1)
Sheep and Goat	0.05 %	0.01%		0.04%
Equine	In relation to the problems identififed			
Poultry (broiler chicken, turkeys)	1 per 200 tons of annual production (minimum : 100)	50% of samples		50% of samples (30% for group B1)
Aquaculture products	1 per 100 tons of annual production	33% of samples		67%
Milk except sheep and goat milk	1 per 15000 tons of annual production	70% for veterinary medicament and 30% for B3		
Eggs	1 per 1000 tons (equivalent ton)	70% for groups A6, B1, B2b and 30% in relation to the problems identififed (B3a)		
Honey	10/300 tons (3000 tons) + 1/300 tons	50% for groups B1 and B2c and 40% for groups B3a, B3b, B3c		

Directive 96/23 : Annex I
GROUP A6

Aristolochia spp. and preparations thereof

Chloramphenicol

Chloroform

Chlorpromazine

Colchicine

Dapsone

Dimetridazole

Metronidazole

Nitrofurans (including furazolidone)

Ronidazole

Directive 96/23 : Annex I

Group B : Veterinary drugs & contaminants

(1) Antibacterial substances, including sulphonamides, quinolones

(2) Other veterinary drugs

- **(a) Anthelmintics**
- **(b) Anticoccidials, including nitroimidazoles**
- **(c) Carbamates and pyrethroids**
- **(d) Sedatives**
- **(e) Non-steroidal anti-inflammatory drugs (NSAIDs)**
- **(f) Other pharmacologically active substances**

(3) Other substances and environmental contaminants

- (a) Organochlorine compounds including PCBs
- (b) Organophosphorus compounds
- (c) Chemical elements
- (d) Mycotoxins
- **(e) Dyes**
- (f) Others

Laboratory network

EU-RLs

Anses Fougères :
B1+ B3e + A6

BVL Berlin
B2 a,b,c + A6

RIVM Wageningen
B2 d + A6

NRLs : 1 or more/MS

Routine laboratories

Legal Framework : Decision 2002/657

COMMISSION DECISION of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results.

- **MRL or MRPL (Minimum required performance level)**
- **Use of validated methods**
  - Performance criteria for analytical methods
    - Decision limit (CC α) : limit at and above which it can be concluded with an error probability of α that a sample is **non-compliant**.
    - Detection capability (CCβ) : smallest content of the substance that may be **detected**, **identified and/or quantified** in a sample with an error probability of β.
  - Criteria to confirm presence of a compound in a matrix..
- **Definition of « compliant sample »**

Screening Methods

False compliant rate of < 5 % (β-error) at the level of interest.

	CCβ	Precision	Selectivity Specificity	Applicability Ruggedness
Qualitative	+	-	+	+
Quantitative	+	+	+	+

	Biological methods	Biochemical Methods	Chemical Methods
Qualitative	Tube test	Snap test	HPTLC spot
Quantitative	Bacterial Growth inhibition zone	ELISA Receptor test	HPLC HPLC/MSMS

Confirmatory methods

	Group A	Group B
LC or GC with mass-spectrometric detection	X	X
LC or GC with IR spectrometric detection	X	X
LC-full-scan DAD		X
LC –fluorescence		X
2-D TLC - full-scan UV/VIS		X
GC-Electron capture detection		*
LC-immunogram		*
LC-UV/VIS (single wavelength)		*

Confirmatory method validation

	Qualitative	Quantitative
Detection limit CCβ	+	+
Decision limit CCα	+	+
Trueness/recovery	-	+
Precision	-	+
Selectivity/specificity	+	+
Applicability	+	+
Ruggedness/Stability	+	+

Major class of veterinary drugs : Examples

	Screening	Confirmatory
Betalactams	Growth inhibition, Receptor test	LC/UV, LC/MSMS
Tetracyclins	Receptor test	LC/UV, LC/MSMS
Fluoroquinolones	LC/Fluo	LC/Fluo, LC/MSMS
Avermectines	HPTLC, LC/UV	LC/UV, LC/MSMS
Benzimidazoles	HPTLC,LC/UV	LC/UV, LC/MSMS
Sedatives	LC/UV	LC/UV, LC/MSMS
Coccidiostats	HPTLC, ELISA, LC	LC/MSMS

Interlaboratory studies

Three different objectives

- Interlaboratory validation of methods
  - Reproducibility & repeatability
- Production of certified reference material (CRM)
  - Cooperation with Joint Research Center
- Proficiency test
  - Performance of laboratory network
  - Improvement of quality assurance

Conclusion

Twenty years of analytical progress

- Technological progress
- Development of laboratory performance

Quality assurance / Proficiency test

Revision of Directive 96/23 planned

- Targeted control vs exposure monitoring
- Food law requirements
- Responsibility at all stages by food business operators

Thank you for your attention