Ecotoxicology studies
Return of experience from Veterinary pharmacy

R. Magnier - BioBridges 2018

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Legal and regulatory background

Legal background

Directive 2001/82/EC
-Amended by Directive 2004/28/EC,
- In application since November 2005

All studies are conducted according to GPL requirement

Regulatory Background / Guidelines

VICH Topic GL6

- Phase I : CVMP/VICH/592/98-Final

VICH Topic GL38

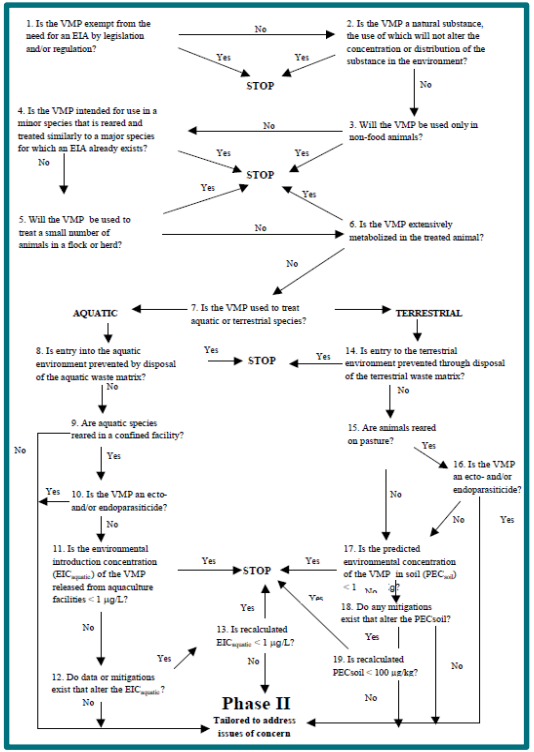
- Phase II: CVMP/VICH/790/03-Final




VICH Guideline – Step by Step Assessment

Environmental Risk Assessmsent (ERA) in Vet Medicine

PHASE I - Decision tree



Question on the product to decide on the need of an experimental risk assessment:

Q3: Non-food animals?
Q7: Use to treat aquatic or terrestrial species?
Q16: Ecto-or endoparasiticide for pasture animals?
Q17: Predicted concentration in soil ≤ 100 µg/kg?
Q18: Do any mitigation exists that alter the PECsoil ?

Major concern : endocrine potential?

PHASE I - Exposure scenarios

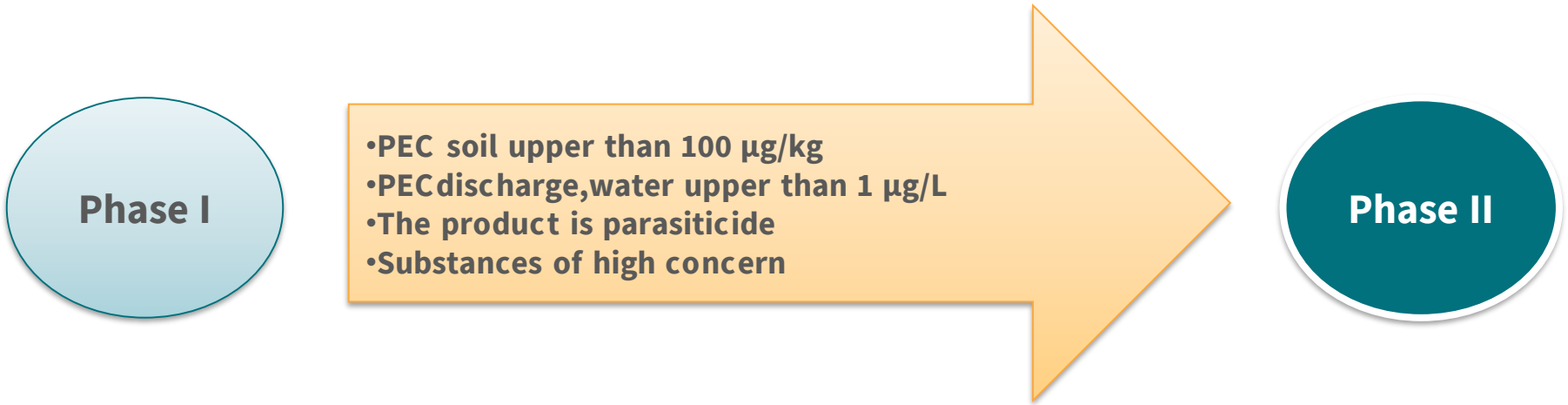
Non-food animals

Intensively reared animals

Aquaculture

Pasture animals

Phase I: conclusion



PEC: predicted environmental concentration

Phase II – Tier A - Testing

- Physical-Chemical Properties Studies

- Environmental Fate Studies
  PEC calculation

- Effects Testing (acute exposure)
  Aquatic Effect Studies
  Terrestrial Effect Studies





Phase II – Tier A – Risk quotient approach

Risk Quotient (RQ) = PEC/PNEC

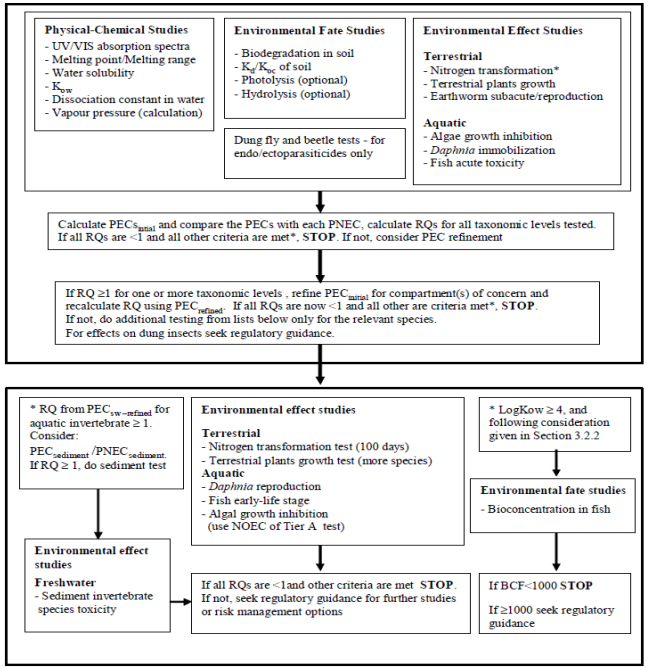
PEC: predicted environmental concentration

PNEC: predicted no effect concentration

Endpoint for unacceptable risk:

- RQ ≥ 1 or effect ≥ 25 % soil microorganism
- RQ for aquatic invertebrates ≥ 1
- Log K ≥ 4
- PECgroundwater ≥ 0.1 µg/L

Figure 3. Decision tree/Flow diagram for VMPs used for pasture animals



Phase II – Tier B - Testing

Environmental Fate Studies

- Bioconcentration in fish study
- PBT substances
- Risk assessment of secondary poisoning

Effects Testing: Chronic exposure

- Aquatic: Reproduction/full life cycle Test/behaviour/growth inhibition
- Sediment: Reproduction
- Terrestrial: Reproduction

Conclusion: Risk Mitigation Measures

Mitigate exposure of the veterinary medicinal product to the environment

- Be in line with agricultural practice

- Be in agreement with the legislation of the EU and its Member States

- Be possible to demonstrate the effect of the proposed risk mitigation measure by re-evaluating the exposure assessment with the proposed risk mitigation measure included

Source: (EMA/CVMP/ERA/418282/2005-rv1)

Summary of main concerns observed

Parasiticides:
dung insects, aquatic invertebrates, protozoa, worms in soil, and surface water, PBT (persistent, bioaccumulate and toxic).

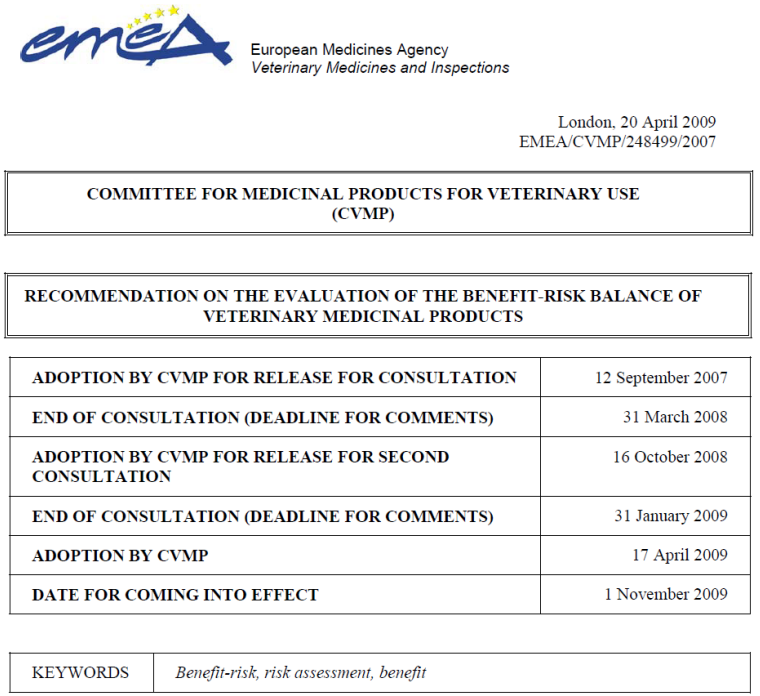
Antibiotics:
algae and plants, potential accumulation in soil, groundwater, microbial antibiotic resistance.

Hormones:
fish, molluscs, invertebrates and birds, reproduction, behaviour and intersex

Veterinary Medicine Product (VMP): Benefice-Risk Balance

Legal documentation

CVMP decision on market authorization following benefit risk analysis.



European Medicines Agency
Veterinary Medicines and Inspections

London, 20 April 2009
EMEA/CVMP/248499/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

RECOMMENDATION ON THE EVALUATION OF THE BENEFIT-RISK BALANCE OF VETERINARY MEDICINAL PRODUCTS

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	12 September 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2008
ADOPTION BY CVMP FOR RELEASE FOR SECOND CONSULTATION	16 October 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2009
ADOPTION BY CVMP	17 April 2009
DATE FOR COMING INTO EFFECT	1 November 2009

KEYWORDS	*Benefit-risk, risk assessment, benefit*

Benefice-Risk Balance

name of product	active substance	year of referral	divergent opinions on	decision on overall (environmental) risk benefit profile
Artide 33(4) referrals[a]				
Ecomectin oral paste	ivermectin	2008	ERA incomplete	positive
Enro-K, Unisol 10% oral solution	enrofloxacin	2009	risk for aquatic and terrestrial compartment	positive
Fenflor, Shotaflor 300 mg ml^{-1}	florfenicol	2009	different opinions regarding exposure assessment	positive
Cevazuril 50 mg ml^{-1} oral suspension	toltrazuril	2010	ERA incomplete	positive
Pharmasin 100% w/w water soluble granules	tylosin	2010	risk for aquatic and terrestrial compartment, ERA incomplete	negative owing to lack of data
Prontax	doramectin	2012	ERA incomplete	positive
Deltanil	deltamethrin	2013	ERA incomplete	positive
Strenzen 500/125 mg g^{-1} powder	amoxicillin + clavularic acid	2013	ERA incomplete	positive
Suifertil 4 mg ml^{-1} oral solution	altrenogest	2013	ERA incomplete	positive
Artide 35 referrals[b]				
	toltrazuril	2008	risk for terrestrial compartment and for groundwater	positive
	doramectin	2013	risk for aquatic compartment, dung fauna, PBT assessment incomplete	positive

[a]Artide 33(4) of Directive 2001/82/EC, as amended ('referral following disagreement at the coordination group on a mutual recognition and decentralized procedure').
[b]Article 35 of Directive 2001/82/EC, as amended ('referral of issues raised with regard to a product or a class of products which is of community interest').

Kuster A, Adler N. 2014 , Phil. Trans. R. Soc. B 369: 20130587

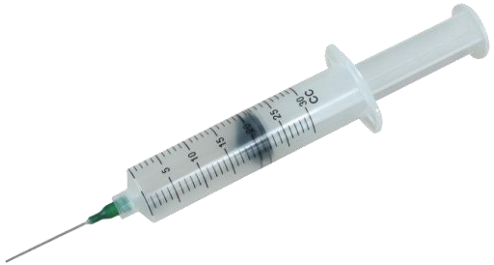
C670: Review of an ERA

Description of our product

- Injectable solution for cattle, dairy cow

- Subcutaneous injection at a dose of 0.2 mg/kg bw

- Endo and ecto-parasiticide



Phase I

Q3: Non-food animals?

- NO (cattle, dairy cow)

Q16: Ecto-or endoparasiticide for pasture animals?

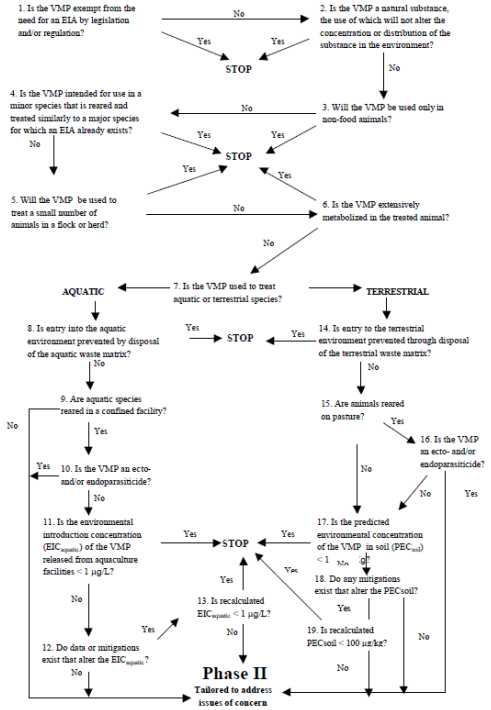
- YES

Q17: Predicted concentration in soil ≤ 100 µg/kg?

- Highest PEC: 1.17 µg/kg

Major concern: endocrine potential?

- NO



Phase II - Tier A – Summary of available data

Physical-Chemical Properties

Fate and behaviour

Metabolism and excretion,

Degradation in soil, Adsorption in soil

Toxicity:

Soil organisms: plants, Earthworm, Dung organisms

Aquatic organisms: Rainbow trout, Daphnia flea, algae (Pseudokirchneriella subcapitata)

Phase II – Tier A – Results

LogK = 5.7

Compartment	Non-target organism	PEC	PNEC	RQ Value	Conclusion
Intensively reared animals – Dairy cow					
Soil	Micro-organisms	0.642 µg/kg	-	-	No unacceptable risk
	Earthworms		4.664 µg/kg	0.138	No unacceptable risk
	Plants		0.5247 µg/kg	1.22	Tier B refinement
Pasture – Dairy cow					
Soil	Micro-organisms	0.56 µg/kg	-	-	No unacceptable risk
	Earthworms		4.664 µg/kg	0.12	No unacceptable risk
Groundwater	-	0.000618 µg/L	-	-	No unacceptable risk
Surface water (run-off scenario)	Algae	0.000206 µg/L	89.9 µg/L	2.29E-06	No unacceptable risk
	Invertebrates		2.66E-04 µg/L	0.77	No unacceptable risk
	Fish		0.566 µg/L	3.64E-04	No unacceptable risk
Dung	Dung Fly	3.33 mg/kg wwt	9.41E-05 mg/kg	35407	Tier B refinement
	Dung Beetle		5.12E-03 mg/kg	651	Tier B refinement
Surface water (direct excretion scenario)	Algae	0.14 µg/L	89.9 µg/L	1.56E-03	No unacceptable risk
	Invertebrates	0.001032 µg/L	2.66E-04 µg/L	3.88	Excretion data refinement
	Fish	0.14 µg/L	0.566 µg/L	0.25	No unacceptable risk
Sediment (direct excretion scenario)	Invertebrates	0.664 µg/kg dwt	0.171 µg/kg dwt	3.88	Excretion data refinement

Phase II – Tier B - Summary of available data

Bioaccumulation in fish

- PBT assessment
- Risk from secondary poisonning

Soil:

- PNEC plants, Dung dweilling organisms

Aquatic:

- Chronic exposure of Chironomus riparius
- Chronic exposure of Daphnia magna

Phase II – Tier B – Results

C670 is not a PBT substance

C670 have not unacceptable risk

- For secondary poisonning
- For plants
- For aquatic invertebrates

Compartment	Non-target organism	PEC	PNEC	RQ Value
Intensively reared animals – Dairy cow				
Soil	Micro-organisms	0.642 µg/kg	-	No unacceptable risk
	Earthworms		4.664 µg/kg	0.14
	Plants*		**1.749 µg/kg**	**0.37**
Pasture – Dairy cow				
Soil	Micro-organisms	0.56 µg/kg	-	No unacceptable risk
	Earthworms		4.664 µg/kg	0.12
Groundwater	-	0.000618 µg/L	-	No unacceptable risk
Surface water (run-off scenario)	Algae	0.000206 µg/L	89.9 µg/L	2.29E-06
	Invertebrates	0.000206	2.66E-04 µg/L	0.77
	Fish	0.000206 µg/L	0.566 µg/L	3.64E-04
Dung	Dung Fly	**0.154 mg/kg wwt**	**9.41E-05 mg/kg**	**1632# (4.61% dose excreted on day 7)**
	Dung Beetle		**5.12E-03 mg/kg**	**30# (4.61% dose excreted on day 7)**
Surface water (direct excretion scenario)	Algae	0.14 µg/L	89.9 µg/L	1.56E-03
	Invertebrates	**0.000245 µg/L**	**2.66E-04 µg/L**	**0.92 (based on maximum daily PEC_{dung})**
	Fish	0.14 µg/L	0.566 µg/L	0.25
Sediment (direct excretion scenario)	Invertebrates*	**0.158 µg/kg dwt**	**0.092 µg/kg dwt**	**1.72 (based on maximum daily PEC_{dung})**

Risk Mitigation Measures proposed

A risk mitigation measure is to keep treated animals away from in-field water bodies for up to 7 days.

The mitigation plan proposed is:

In line with agriculture practice,

In line with le legislation of Europe and its member states

Possible to demonstrate effect by re-evaluation of exposure assessment.

Human Medicine Product and Veterinary Medicine Product

Scope and legal basis

Directive 2001/83/EC

Guideline EMEA/CHMP/SWP/4447/00 corr 2

Question-and-answer document EMA/CHMP/SWP/44609/2010 Rev. 1

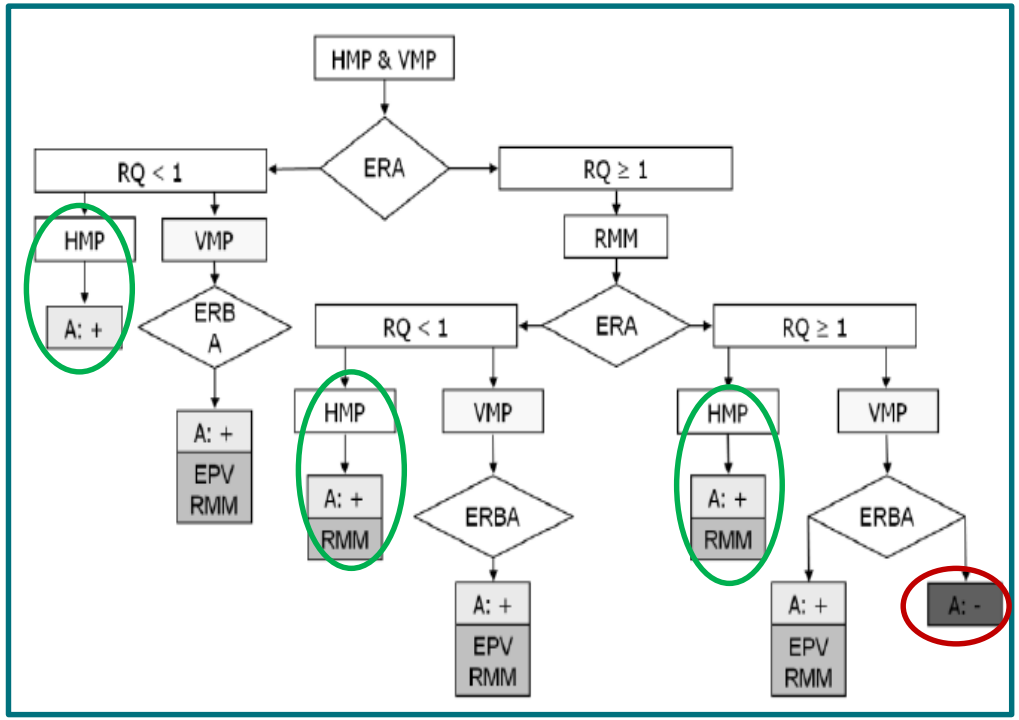
Concept paper EMA/CHMP/SWP/65429/2016

Class of medicines and potential Risk

Human Medicinal Product	Veterinary Medicinal Product
Hormones, Antibiotics, Analgesics, Antidepressants, Antineoplasics	Hormones, Antibiotics, Parasiticides

Kuster A, Adler N. 2014 , Phil. Trans. R. Soc. B 369: 20130587

Market authorization



ERA: environmental risk assessment
A: authorization: (+) granted; (-) refused
ERBA: environment risk-benefit assessment
EPV: eco-pharmacovigilance
RMM: risk mitigation measure

Toxics **2014**, *2*, 35-49; doi:10.3390/toxics2010035

Conclusions

The environmental risk assessment is quite similar between veterinary medicine and Human medicine

Risk–benefit analysis in Human medicine doesn't take into account environmental risk.

Environment exposure is more complex in vet medicine but the application of mitigation plan allow to control it. Implementation of new technical solutions could be applied in sewage plant to control the environment exposure with human medicine product.

Thank a lot for your attention