For prevention of environmental pollution from veterinary medicinal products (VMPs)
-regulation and present situation-

15th June 2016
National Veterinary Assay Laboratory (NVAL)
1. Fate of VMPs after excretion
2. Regulation of VMP
3. Regulation about environmental affair for VMP
4. Guideline of Environmental Impact Assessment (EIAs) FOR VMPs
1. Fate of VMPs after excretion
Discharge route to environment and Fate of VMP (Livestock)

VMP

Dispersal

Administration

Falling down

Metabolism・Excretion

Distribution Absorption Degradation
Discharge route to environment and Fate of VMP (Aquaculture)

- Animals
  - Excretion
    - Fishpond
      - Sea
    - River, Pond
- Aquarium
  - Excretion
  - Treatment plant
- Metabolism • Excretion
  - Distribution
    - Absorption
    - Degradation
2. Regulation for VMP
### The law concerning chemicals for agriculture / stock farming/ aquaculture

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<th>Chemicals</th>
<th>Law</th>
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<td>VMPs</td>
<td>The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (LPMD)</td>
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<td>Feed additives</td>
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<td>The Law Concerning Safety Assurance and Quality Improvement of Feeds</td>
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<td>Residue of agricultural chemicals in feed</td>
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<td>The Law Concerning Safety Assurance and Quality Improvement of Feeds</td>
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<td>Crops</td>
<td>Agricultural chemicals (pesticide)</td>
<td>Agricultural Chemicals Regulation Law</td>
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Flow for approval

- Application
- Data check on NVAL
- Pharmaceutical Affairs and Food Sanitation Council
- Approval
- Ministry of Health, Labour and Welfare
- MAFF
- Food Safety Commission
- Consultation and report (for food animal)

Generic drugs
Required data of application

- Origin or discovery of drug, condition of use in foreign countries, etc.
- Physical and chemical properties
- Production
- Stability
- Toxicity
- Safety for target animal
- Pharmacological action
- Absorption, distribution, metabolism and excretion
- Clinical trials
- Residue study

Where is the data of environmental safety in?
3. Regulation about environmental affair for VMP
How about Japanese laws to protect environment?

The basic environmental law

- It define the basic idea for environmental protection and several laws and acts

Drugs (include for human) are OUT OF THE SCOPE

- Regulation for VMP about environmental safety is self regulation among VMP industries (Japan Veterinary Products Association; JVPA)

- The self regulation is based on VICH guideline

- Ecotoxicity is not defined as subject to reject approval in LPMD

  - Related data is not required at application
VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products)

“VICH is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirement for veterinary product registration. “
(VICH official homepage : http://vichsec.org)

VICH Outreach Forum

“The VICH Outreach Forum is a VICH initiative with the main objective of providing a basis for wider international harmonisation of technical requirements, improve information exchange and raise awareness of VICH and VICH guideline with non-VICH countries/regions.”

18 countries/regions are invited.
4. Guideline of Environmental Impact Assessment (EIAs) for VMPs
Typical EIA method

Ecotoxicity assessment

Toxicity test using some species

estimate

PNEC (Predicted no effect concentration)

PEC/PNEC ≥ 1

It need risk management

Exposure assessment

Surveillance of production / waste volume

estimate

PEC (Predicted environmental concentration)

PEC/PNEC < 1

No problem
PNEC Calculation

1. OECD work on investigation of high production volume (HPV) chemicals
   - Basic dataset is (1) Fish, Acute Toxicity Test (2) Algal Growth Inhibition Test (3) Daphnia sp. Acute Immobilisation Test
   - Calculate PNEC of whole aquatic ecosystem
   - \[ \text{PNEC} = \text{Minimum of } (1) \text{ to } (3) \frac{\text{LC}_{50} \cdot \text{EC}_{50}}{\text{AF}} \] (Application factor, ex. 100 ~ 1000)

2. VICH EIA guidelines
   - Clarify the study subject and method
   - Calculate PNEC of each species in aquatic and/or terrestrial ecosystem
   - AFs are defined to each study in the guidelines.
     ex. Fish acute toxicity test (Ph. I St. A) : 1,000
     Fish chronic toxicity test (Ph. II St. B) : 10
The scope of VICH EIA guidelines

- **Target**: VMP except Biological products (ex. Vaccine)
- “Environment to save” is
  - All place except livestock /aquaculture facility
- “Harmful to environment” is
  1. Toxic to species in environment
  2. Hard to degrade
  3. Bioconcentratable
- **Harmonisable subject is**
  - Evaluation methods (include criteria), Test method
- **Unharmonisable subject is**
  - Regional factor (ex. PEC, Exposure route to environment)
- **Out of Scope**
  - Biological products, Antimicrobial Resistance, Endocrine disruptor
Overview of VICH EIA guidelines

**Ph. I**

Estimation of exposure volume and route to environment based on VMP using volume

- **Criteria**
  1. The VMP enter into environment directly.
  - Using at pasture or fishpond -
  2. Large amount of the VMP is discharged

**Ph. II**

**Tier A**: Physical/Chemical/Environmental effect studies (acute) and Environmental fate studies

- **Criteria**
  1. PEC/PNEC ≥ 1 or Effectable to soil microbe
  2. Risk of bioaccumulation \( \log K_{ow} \geq 4 \)
  3. Risk of toxicity for sediment species

**Tier B**: for criteria 1 → Environmental effect studies (chronic or reproduction) for criteria 2 → Bioconcentration study for criteria 3 → Toxicity studies for sediment species

- **Criteria**
  1. PEC/PNEC ≥ 1
  2. Risk of bioaccumulation \( BCF \geq 1000 \)

Further assessment & Risk management: Out of harmonisation
Phase I

Decision tree
19 Questions
No study (Only calculation)
Criteria for considering to proceed to (Phase II) assessment

The VMP such as
1. used in quantity in the region
2. discharged into environment directly
is assumed to have higher risk to environment

The rationale for the trigger value

EICaquatic (environmental introduction concentration of aquatic environment: 1μg/L): Retrospective review of ecotoxicity data for human drug (CDER/FDA)

PECsoil (predicted environmental concentration of the VMP in soil: 100μg/kg): Retrospective review of ecotoxicity data from environmental assessments for veterinary drug (CVM/FDA)
Phase II

(Step-by-Step evaluation)

Tier A → Tier B

Stop → Stop

Out of scope of the guideline

(3 branches)

Aquaculture

Intensively reared terrestrial animals

Pasture animals

Phase II decision tree
Tier A

Usage of VMP -> Ecotoxicity test

PEC Calculation

Ecotoxicity test -> PNEC Calculation

PEC/PNEC ≥ 1

PEC/PNEC ≥ 1

Re-calculation of PEC

Test for environmental fate

Physical/Chemical test

logKow ≥ 4

PEC/PNEC ≥ 1

Considering metabolism, excretion in target animals and degradation in ecosystem

Tier B

Ecotoxicity test meeting to the problems in step A

Re-calculation of PNEC

PEC/PNEC ≥ 1

Further assessment & Risk management: Out of the scope

Bioconcentration test using fish

BCF ≥ 1000
Studies in VICH EIAs guideline Phase II

Physical/Chemical

- UV/VIS absorption spectra
- Melting point/Melting range
- Water solubility
- Kow
- Dissociation constant in water
- Vapour pressure (calculation)

Environmental fate

Tier A:
- Biodegradation in soil
- Degradation in aquatic systems
- Photolysis (optional)
- Hydrolysis (optional)
- Kd/Koc of soil/sediment

Tier B:
- Bioconcentration in fish

Environmental effects

Tier A:
(Aquatic environment)
- Algal growth inhibition (freshwater/saltwater)
  - Daphnia immobilization
  - Crustacean acute toxicity
  - Fish acute toxicity (freshwater/saltwater)
(Terrestrial environment)
  - Nitrogen transformation test (28 days)
  - Terrestrial plants growth
  - Earthworm subacute/reproduction
  - Dung fly and beetle tests

Tier B:
(Aquatic environment)
- Algal growth inhibition (freshwater/saltwater)
  (use NOEC of Tier A test)
  - Daphnia reproduction
  - Fish early-life stage
  - Crustacean chronic toxicity
  - Fish chronic toxicity or reproduction
  - Sediment invertebrate species toxicity
(Terrestrial environment)
  - Nitrogen transformation test (100 days)
  - Terrestrial plants growth (more species)
- Phase I guideline document: GL6 (established in June 2000)
- Pnase II guideline document: GL38 (established in October 2004)
  (http://vichsec.org/guidelines/pharmaceuticals/pharma-safety/environmental-safety.html)
  EU and USA: Enforced as each guidelines
  Japan: Published as self regulation of JVPA
  Commentary of VICH guideline was published by NVAL
  (January 2012)
- Evaluation to result of EIA and risk management in Japan

At new drug evaluation

- Evaluate the attached result
- If need, accurate risk managements are considered (ex. precaution)
- The degrability/stability data are required at application of fluorquinolones and aquaculture VMP
- Approved VMP are evaluated in reexamination (2〜6 years after approval) and reevaluation (periodically and in case of necessity)