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

15th June 2016

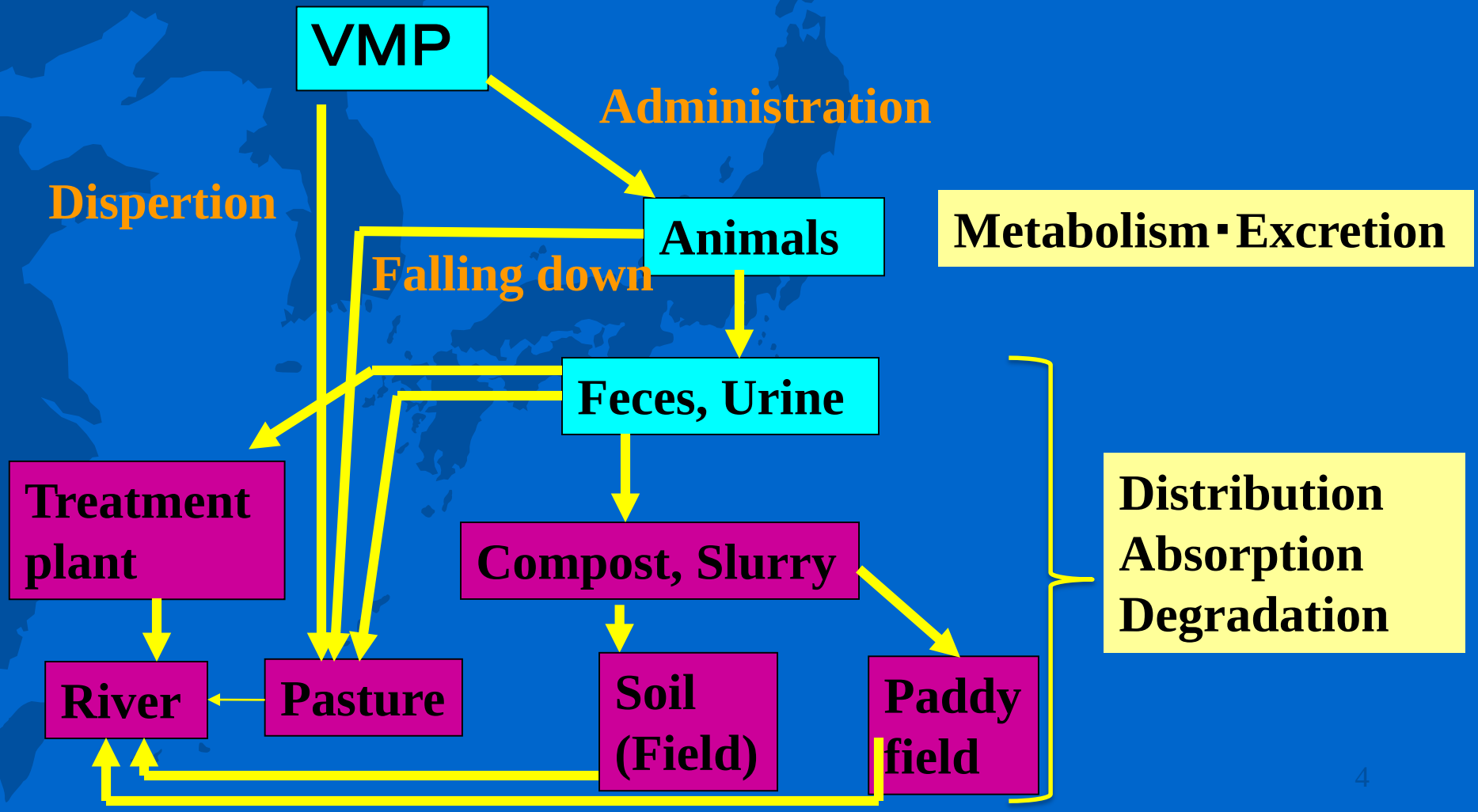
National Veterinary Assay Laboratory (NVAL)

Agenda

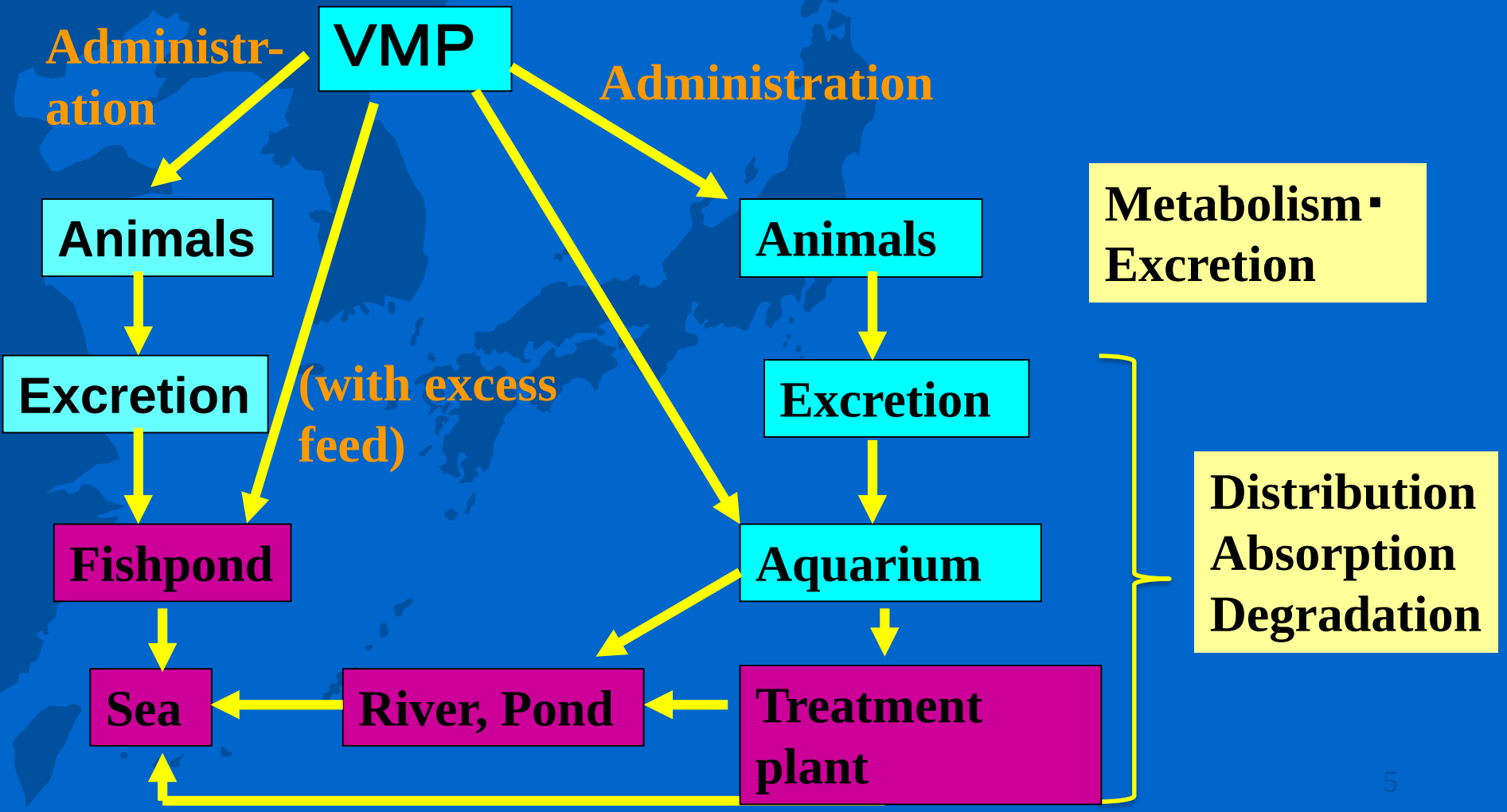
1. Fate of VMPs after excretion
2. Regulation of VMP
3. Regulation about environmental affair for VMP
4. Guideline of Environmental Impact Assessment (EIAs) FOR VMPs

1. Fate of VMPs after excretion

Discharge route to environment and Fate of VMP（Livestock）



Discharge route to environment and Fate of VMP（Aquaculture）

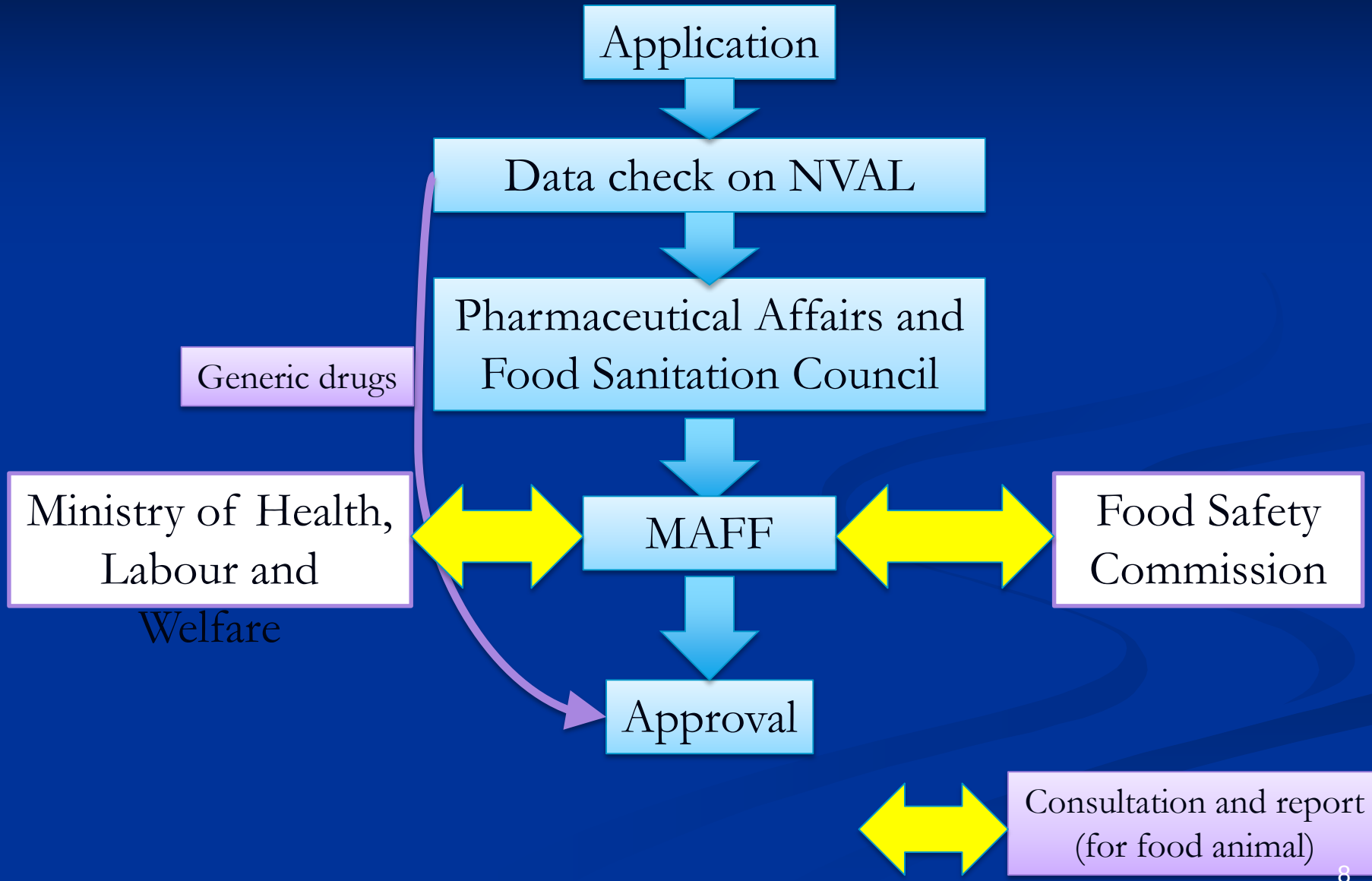


2. Regulation for VMP

The law concerning chemicals for agriculture / stock farming/ aquaculture

Products	Chemicals	Law
Stock farm / aquaculture products	VMPs	The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (LPMD)
	Feed additives	The Law Concerning Safety Assurance and Quality Improvement of Feeds
	Residue of agricultural chemicals in feed	The Law Concerning Safety Assurance and Quality Improvement of Feeds
Crops	Agricultural chemicals (pesticide)	Agricultural Chemicals Regulation Law

Flow for approval



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

- Ecotoxicity is not defined as subject to reject approval in LPMD
  - Related data is not required at application

→ **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

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)

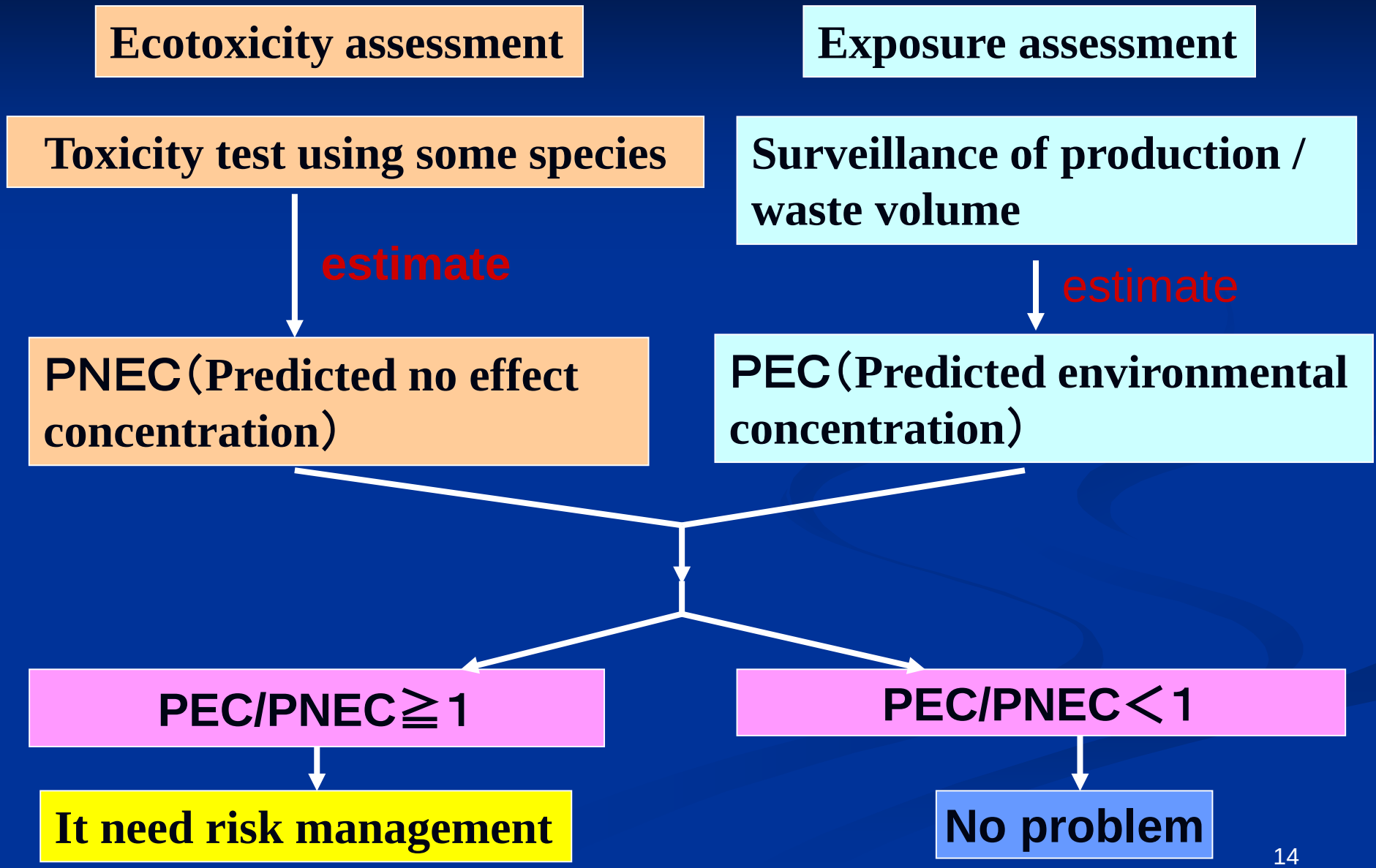
VICH Outreach Forum

"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



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
   - PNEC＝Minimum of (1)to(3) LC_{50}・EC_{50}／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（logKow≧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≧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

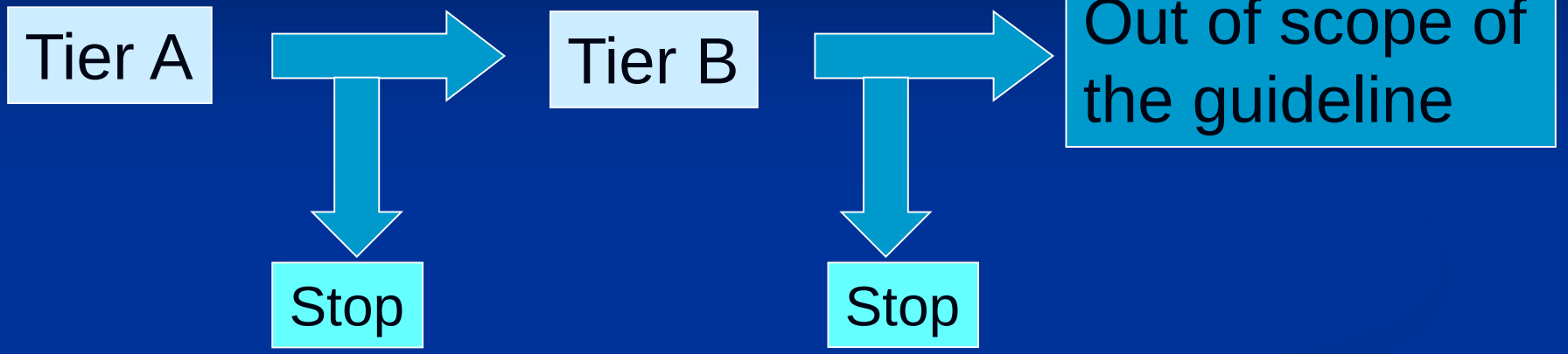
The rationale for the trigger value

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

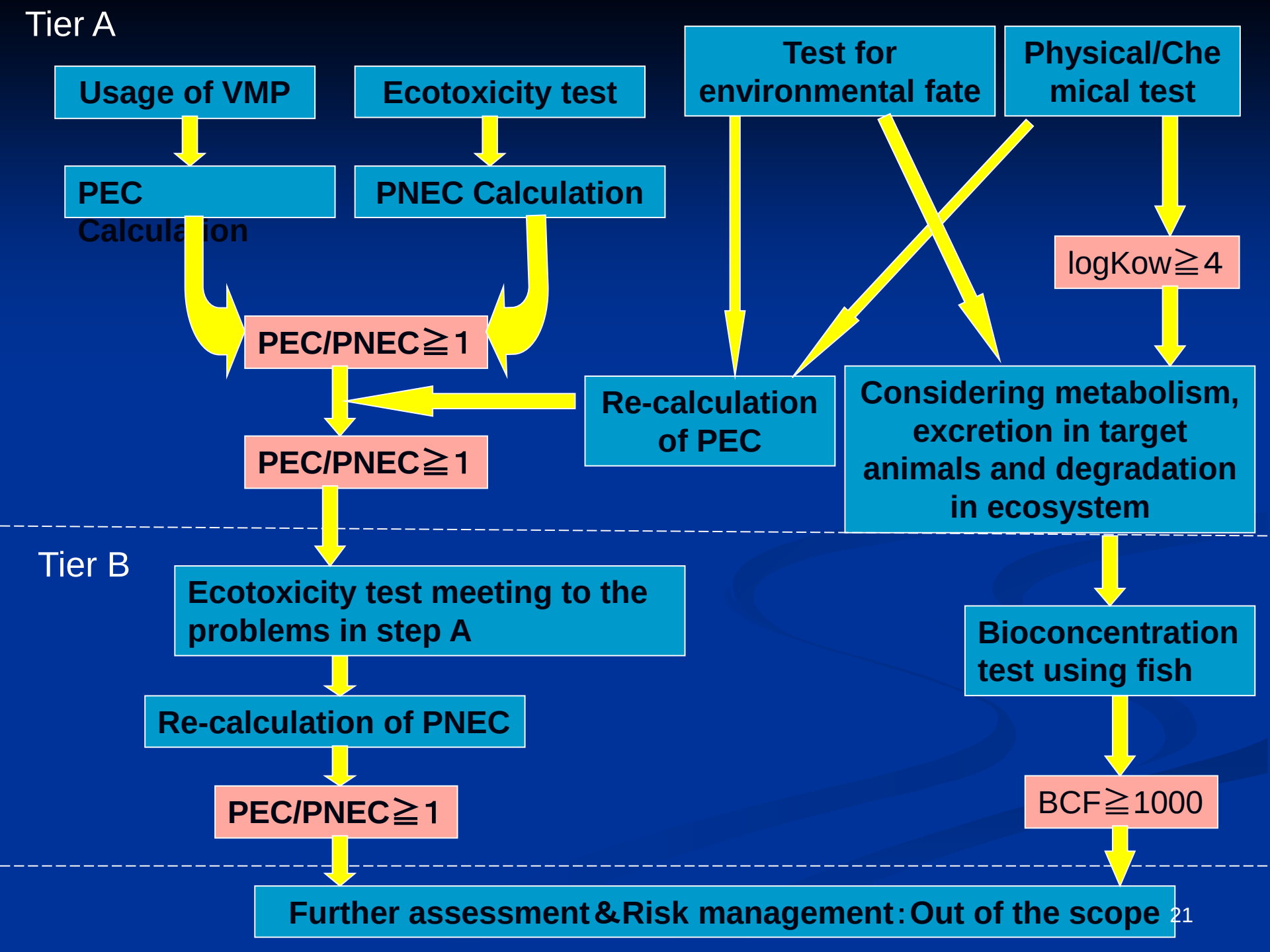
（Step-by-Step evaluation）



（3 branches）

- **Aquaculture**
- **Intensively reared terrestrial animals**
- **Pasture animals**

→ Phase Ⅱ decision tree


Tier A
Usage of VMP
Ecotoxicity test
Test for environmental fate
Physical/Chemical test
PEC Calculation
PNEC Calculation
logKow≧4
PEC/PNEC≧1
Re-calculation of PEC
Considering metabolism, excretion in target animals and degradation in ecosystem
PEC/PNEC≧1
Tier B
Ecotoxicity test meeting to the problems in step A
Bioconcentration test using fish
Re-calculation of PNEC
BCF≧1000
PEC/PNEC≧1
Further assessment＆Risk management：Out of the scope

Studies in VICH EIAs guideline Phase Ⅱ

Physical/Chemical

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

Tier B:
None

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 fluoroquinolones and aquaculture VMP
- Approved VMP are evaluated in reexamination (2～6 years after approval) and reevaluation (periodically and in case of necessity)