OIE PVS Evaluation

National Veterinary Assay Laboratory, 24th October 2016

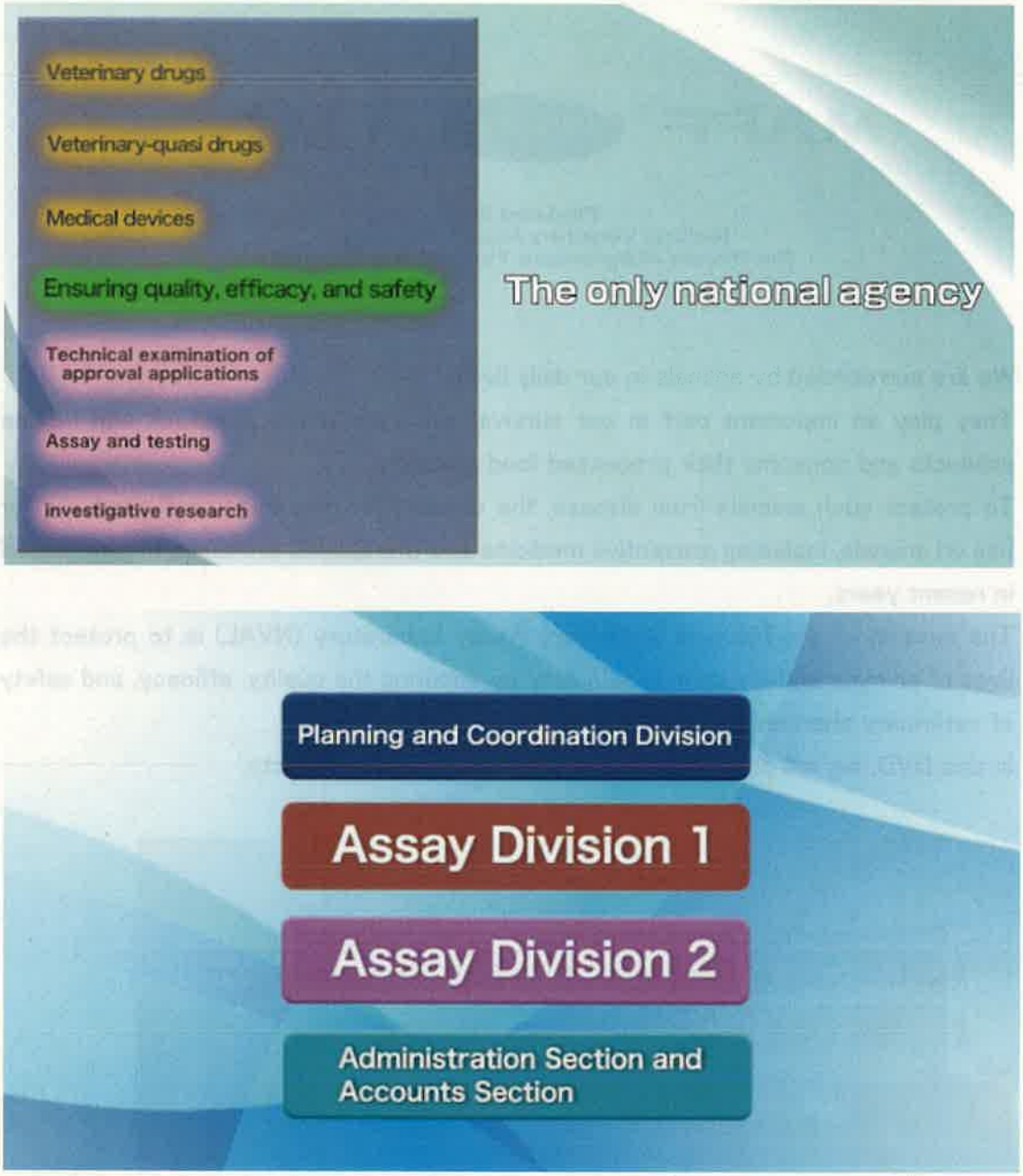
From		To	Content
10:00	-	10:05	**Welcome remarks** (Dr. Yamamoto)
10:05	-	10:30	**NVAL overview** (DVD)
10:30	-	11:00	**Presentation** ➢ Organization (Dr. Ogikubo) ➢ Main activities (Dr. Ogikubo)
11:00	-	11:40	**Lab. Tour** ➢ Antibiotic laboratory (Dr. Kijima) ➢ Fish vaccine test building (Dr. Oishi) ➢ Integrated assay building (Dr. Oishi)
11:40	-	11:45	**Break**
11:45	-	12:20	**Discussion- Closing**

MAFF NVAL OIE

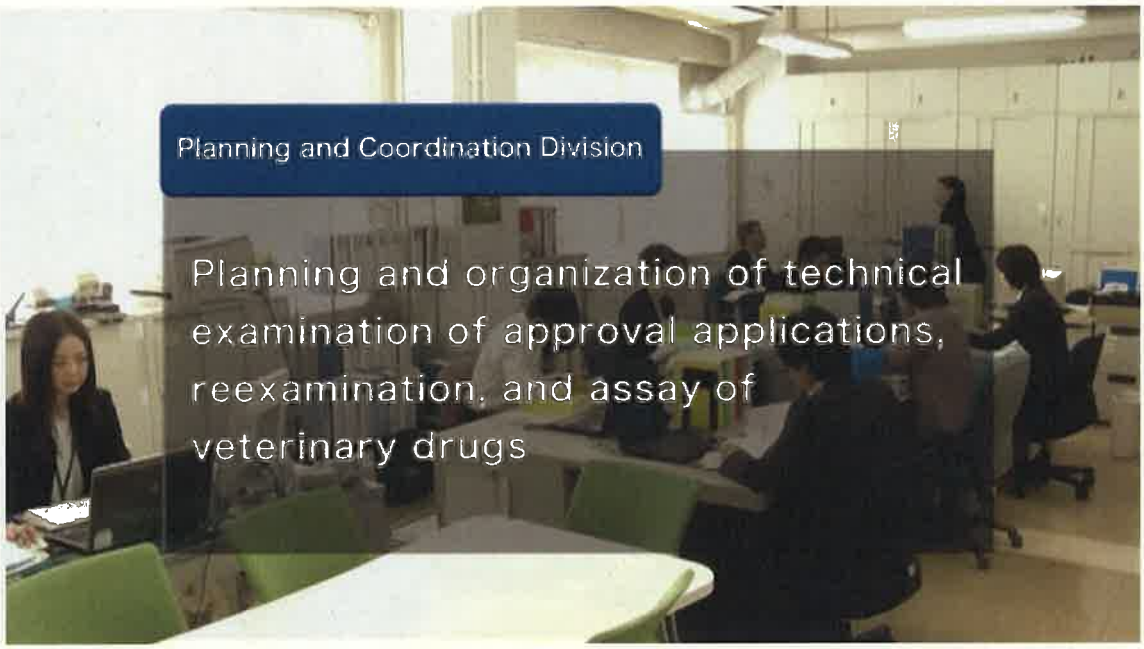
Produced by
National Veterinary Assay Laboratory,
The Ministry of Agriculture, Forestry, and Fisheries

We are surrounded by animals in our daily lives.
They play an important part in our survival since we utilize livestock and marine products and consume their processed food products.
To protect such animals from disease, the demand for pharmaceutical products for use on animals, including preventive medicine and therapeutic products, has increased in recent years.
The mission of the National Veterinary Assay Laboratory (NVAL) is to protect the lives of animals and maintain food safety by ensuring the quality, efficacy, and safety of veterinary pharmaceutical products.
In this DVD, we will present NVAL and the activities it conducts.

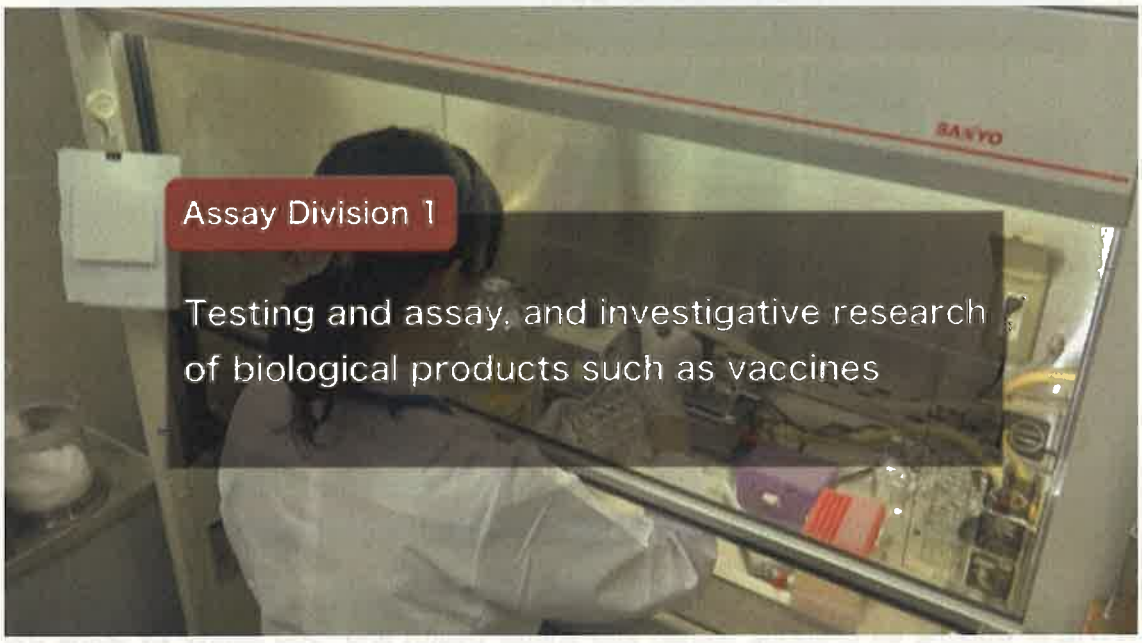
NVAL was established in 1956 as an institution affiliated with the Japanese Ministry of Agriculture, Forestry, and Fisheries.
It is the only national agency engaged in the technical examination of application approval, assay and testing, and investigative research for ensuring the quality, efficacy, and safety of veterinary medicinal products, veterinary quasi-drugs, regenerative and cellular therapy, gene therapy products and veterinary medical devices, based on the Pharmaceutical and Medical Device Act.



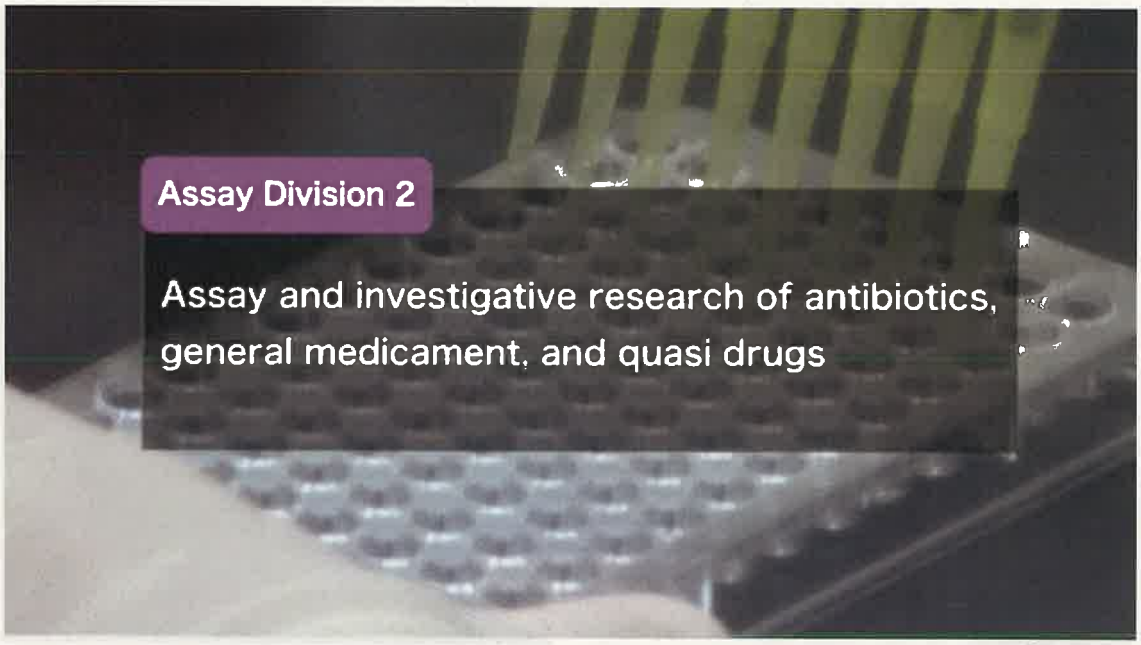
NVAL comprises four main divisions.



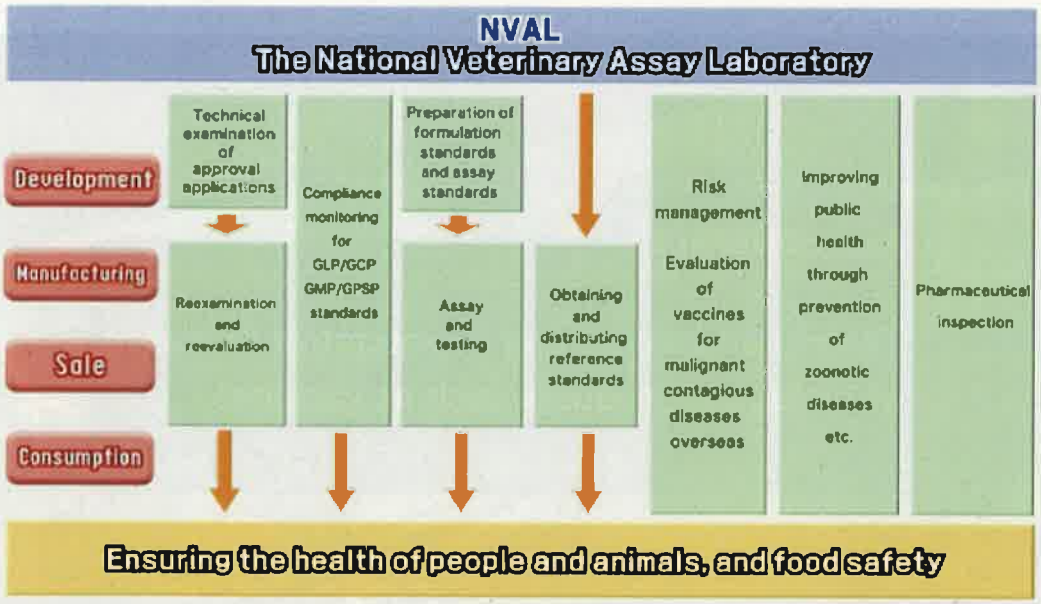
The "Planning and Coordination Division" is responsible for organizing the technical examination of approval applications, reexamination, and assay of veterinary medicinal products.



"Assay Division 1" is responsible for testing and assay and investigative research of biological products such as vaccines, regenerative and cellular therapy products, and gene therapy products.

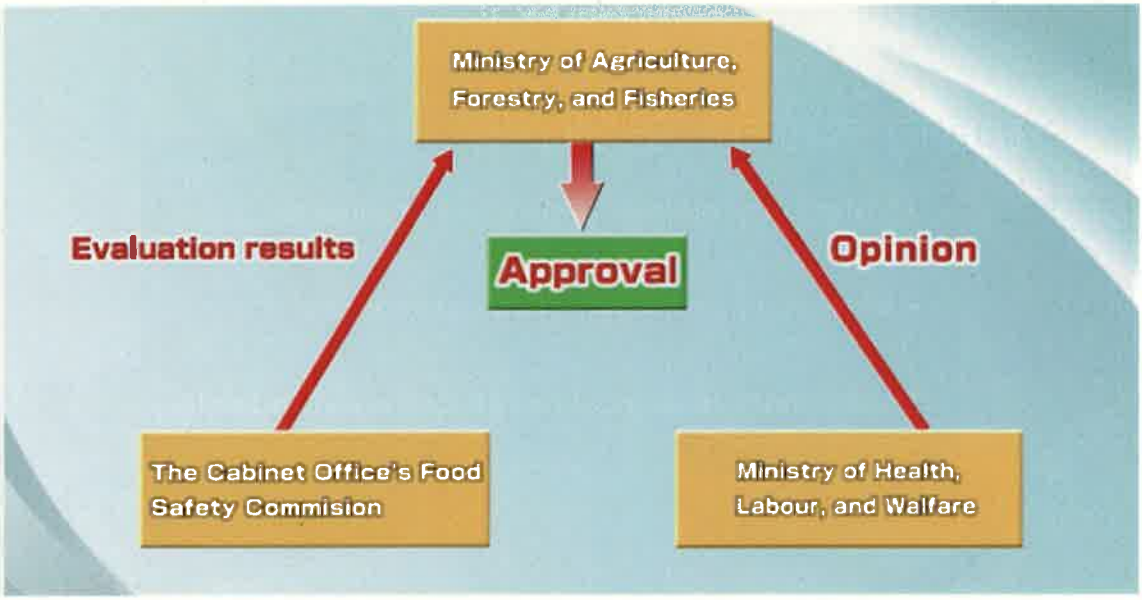


"Assay Division 2" is responsible for assay and investigative research of antibiotics, general medicines, quasi-drugs.
Finally, there is the "Administration Section and Accounts Section".



NVAL is working on ensuring human and animal health and food safety by doing the following: undertaking technical examination of application approval, compliance review for GLP/GCP standards, preparation of formulation standards and assay standards, assay and testing; obtaining and distributing reference standards required for assay; conducting crisis management for malignant contagious diseases overseas, as well as

for improving public health through the prevention of zoonotic diseases such as rabies; and conducting pharmaceutical inspection of veterinary medicinal products at each stage of development—manufacturing, sales, and consumption.

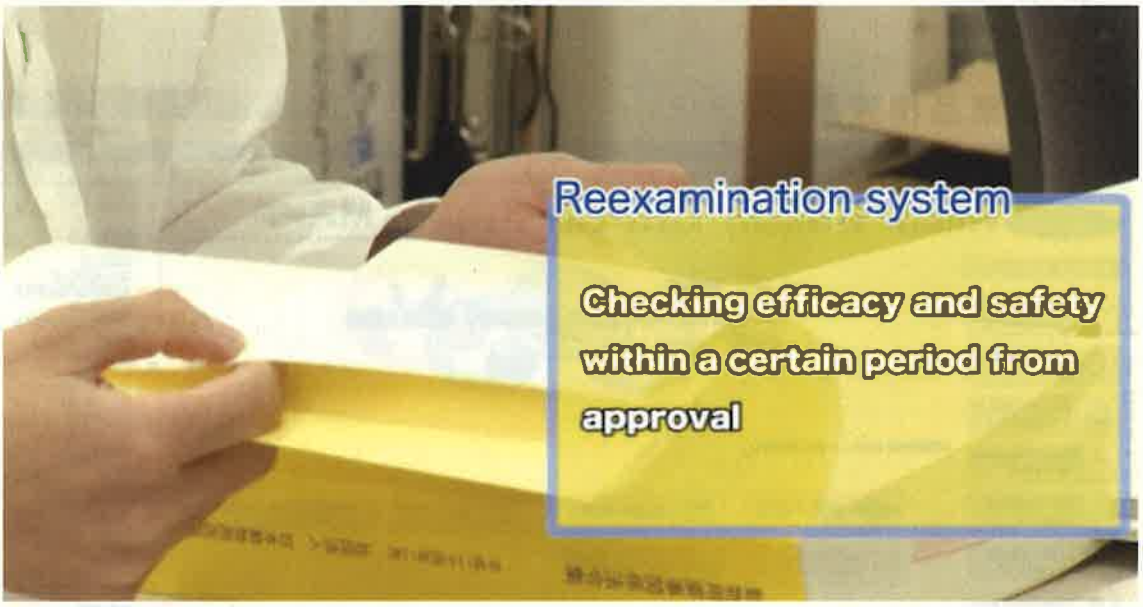


To market and release veterinary medicinal products, each item must be approved by the Minister of Agriculture, Forestry and Fisheries.
Based on documentation submitted by an applicant, NVAL will first examine the application in terms of quality, efficacy, and safety.

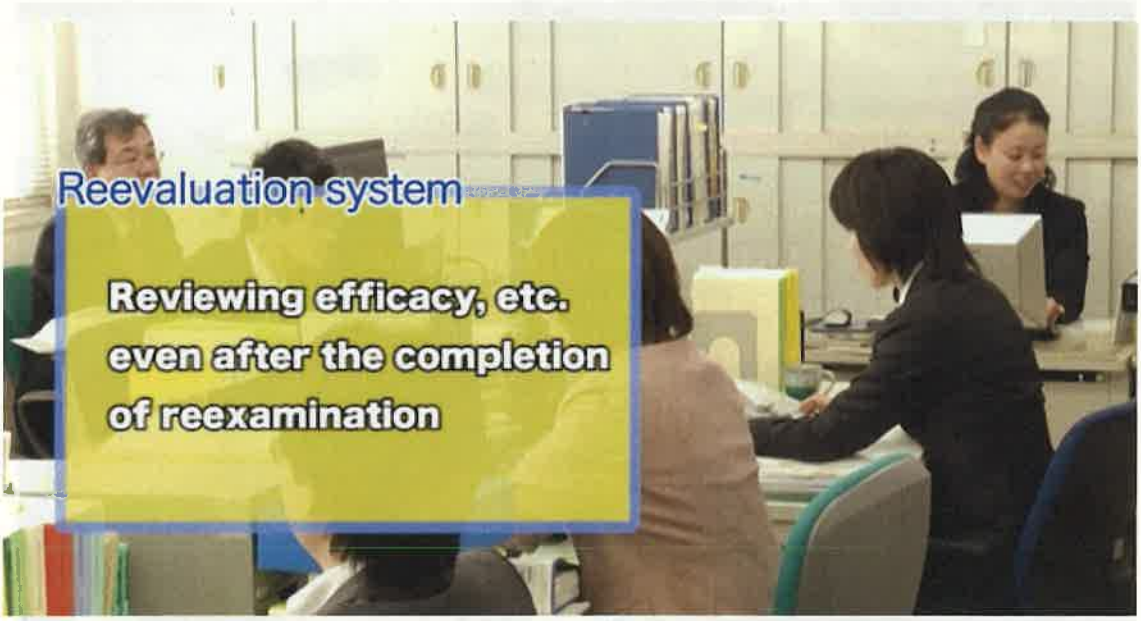
The assessment, including confirmation of the evaluation policy by the responsible officer, begins after the application has been submitted.
When the verification is complete, the responsible officer will review the quality, efficacy, and safety of the application on a scientific basis while conducting a face-to-face interview with the applicant.
After that, the application will be considered by subcommittees of the Pharmaceutical Affairs and Food Sanitation Council (PASC).
Once a decision has been made by subcommittees, further examination is conducted by the Committee on Veterinary Drugs of the PASC and then by the Executive Committee of the PASC.
Furthermore, pharmaceuticals destined to be used on food-producing animals will be subject to risk assessments regarding human safety.
This will be in relation to marine and livestock food products as outlined by The Cabinet Office's Food Safety Commission and the Ministry of Health, Labour, and Welfare in addition to the Ministry of Agriculture, Forestry and Fisheries.
If no problems are found during these examinations and evaluations, the product is approved as a veterinary medicinal product by the Minister of Agriculture, Forestry and Fisheries.

In addition, standards concerning the quality of veterinary medicinal products are established on the basis of the Pharmaceutical and Medical Device Act, and veterinary medicinal products that are manufactured must comply with these standards.

Furthermore, standards required for national assay of vaccines and so on are determined this way.
To ensure the efficacy and safety of veterinary medicinal products, NVAL conducts assay and testing based on these standards and is constantly revising the standards in line with the latest technology.

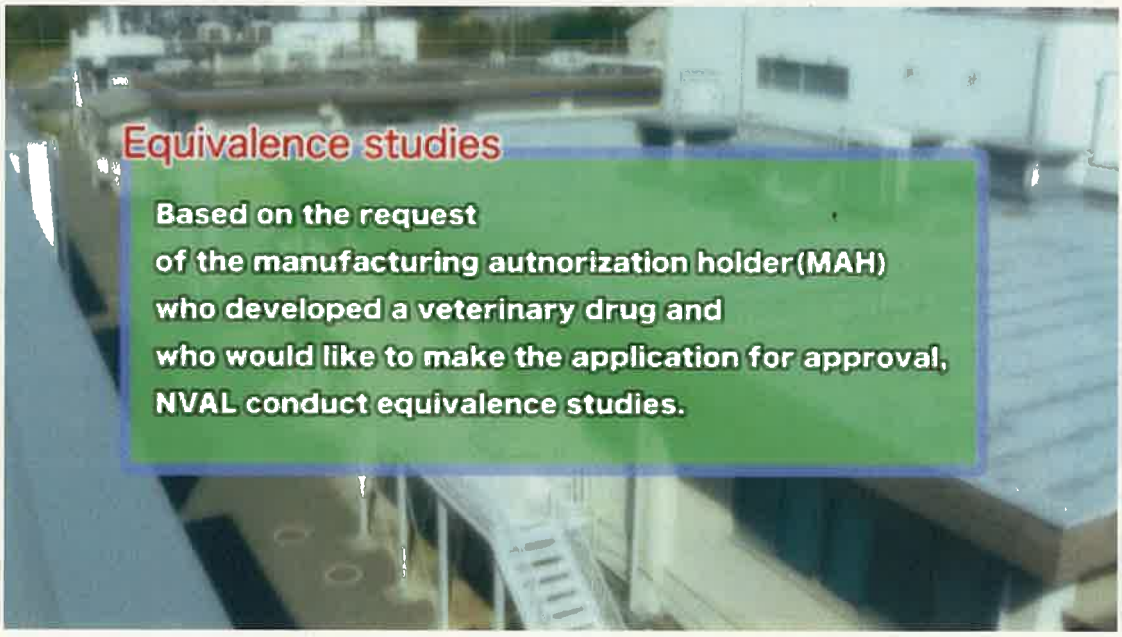


When approving a new veterinary medicinal product, the Act sets a reexamination system for evaluation of efficacy and safety within a certain period of time after the pharmaceutical's initial approval.



Moreover, with regard to veterinary medicinal products designated by the Minister of Agriculture, Forestry, and Fisheries, even after the completion of reexamination, there is a re-evaluation system for reviewing safety and efficacy.
NVAL collects literature and documentation required for re-examination and re-evaluation.

This includes information on adverse effects and prevailing pathogens.
After conducting research based on this information, a database is produced and is published on our website.



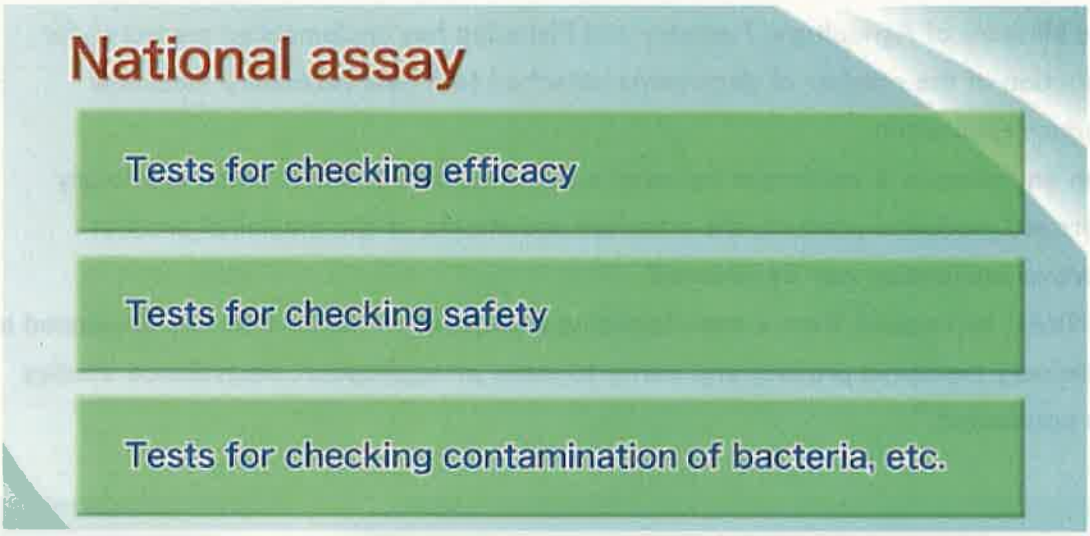
The Ministry of Agriculture, Forestry and Fisheries has implemented measures for reduction of the number of documents attached to a new veterinary medicinal product application.

If an equivalence is confirmed between a new medicinal product and a previously approved medicinal product, the attached documents of the medicinal product approval application can be reduced.

At NVAL, by request from a manufacturing authorization holder that has developed a veterinary medicinal product and wants to make an application, equivalence studies are conducted.

It is mandatory to submit a GCP and GLP compliance report and a GMP compliance investigation application when applying for the approval of a veterinary medicinal product.

This is to ensure the reliability of the application data for approval.



Among veterinary medicinal products, some biological products such as vaccines are manufactured by using microorganisms such as viruses, and therefore ensuring stable quality and passing the assay might be difficult.

Therefore, these biological products cannot be sold unless they undergo and pass the assay for quality assurance.

NVAL is a designated agency for conducting national assay based on the Pharmaceutical and Medical Device Act and undertakes testing to check efficacy and safety for each production lot of vaccine.

Broadly speaking, the national assay includes, among others, tests for checking efficacy, safety, and contamination by bacteria, yeast, and viruses.

To confirm the efficacy of a vaccine, after inoculating the target animals, for instance, cows or laboratory animals, blood serum is collected, and the antibody titer is measured by an immunological test such as agglutination reaction, neutralization reaction, and the ELISA reaction.

Challenge test is also conducted to directly confirm the vaccine's efficacy by challenge with a virus and bacteria that actually cause disease.

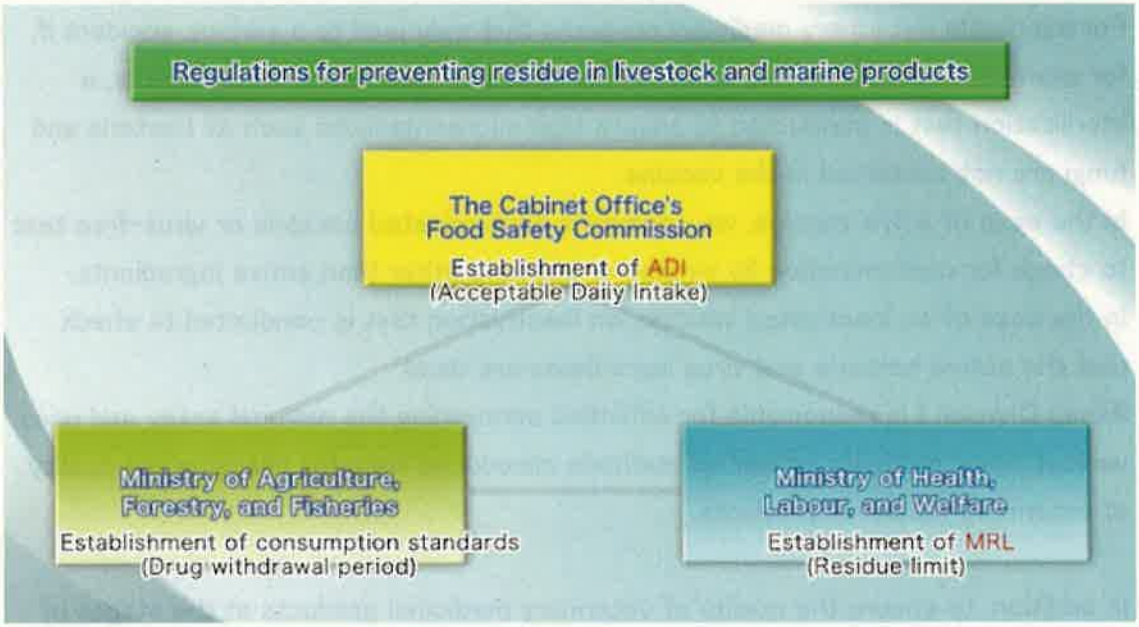
In addition, in the case of a live vaccine that contains a live virus or bacteria as active ingredients, the vaccine's efficacy is checked by measuring the amount of the virus or bacteria in the vaccine.

In safety tests, an average amount or higher than average amount of vaccine is administered to cows, pigs, chickens, fish, etc., and abnormalities in weight, temperature, and the body are monitored.

Because conducting safety tests on horses, dogs, and cats is difficult, tests for checking the absence of abnormal toxicity are conducted by using laboratory animals such as mice and guinea pigs.

For injectable veterinary medicinal products that may lead to a serious accident if, for example, the vaccine has been contaminated by bacteria or other agents, a sterilization test is conducted to ensure that microorganisms such as bacteria and fungi are not contained in the vaccine.
In the case of a live vaccine, we conduct a contaminated bacteria or virus-free test to check for contamination by viruses or bacteria other than active ingredients.
In the case of an inactivated vaccine, an inactivation test is conducted to check that the active bacteria and virus ingredients are dead.
Assay Division I is responsible for activities concerning the national assay and uses various other methods as well as methods introduced here for checking the quality of veterinary medicinal products.

In addition, to ensure the quality of veterinary medicinal products at the stages of manufacturing and distribution and to eliminate adulterated medicinal products. NVAL conducts quality control tests on pharmaceutical samples collected from manufacturers or dealers in the country, which are removed by pharmaceutical inspectors. Sampling tests are conducted on biological products, general pharmaceuticals, or antibiotic preparations that are not the target of national assay. For example, with regard to general pharmaceuticals such as disinfectants, labels, properties such as color, moisture content, and content of the active ingredients are inspected. As a result of the inspection, for noncompliant veterinary pharmaceuticals, guidance is given to manufacturers and retailers for making improvements.



Apart from the national assay and sampling test conducted to ensure the quality of veterinary medicinal products, various activities are conducted for ensuring food safety in Japan.

To ensure food safety, The Cabinet Office's Food Safety Commission, the Ministry of Health, Labour, and Welfare, and the Ministry of Agriculture, Forestry, and Fisheries are responsible for related activities.

The Food Safety Commission establishes ADI, while the Ministry of Health, Labour, and Welfare establishes MRL, and the Ministry of Agriculture, Forestry, and Fisheries defines consumption standards such that residue of veterinary medicinal production livestock and marine food products does not exceed MRL.

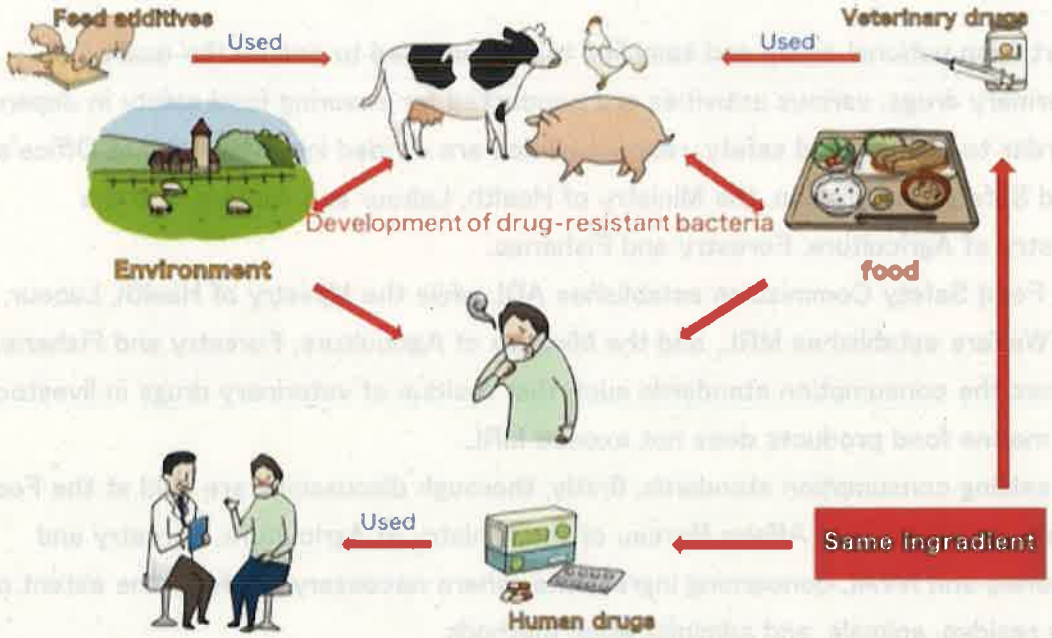
For setting consumption standards, thorough discussions are first held between the Food Safety and Consumer Affairs Bureau of the Ministry of Agriculture, Forestry and Fisheries and NVAL concerning ingredients when it is necessary to check the extent of pharmaceuticals residue, animals, and administration methods.

To check the extent of residue in a veterinary medicinal product, NVAL administers the pharmaceuticals to the target animal and measures the residual concentration of the pharmaceuticals in an organ.

Consumption standards are defined by comparing the residual concentration with MRL.

In the test for checking the extent of residue, because the pharmaceuticals concentration to be measured in the organ is a very minute amount such as 1 gram per 1 billion, suitable analytical techniques are reviewed and developed.

Apart from national assay and sampling test conducted to ensure the quality of veterinary drugs, various activities are conducted for ensuring food safety in Japan.
In order to ensure food safety, responsibilities are divided into The Cabinet Office's Food Safety Commission, the Ministry of Health, Labour and Welfare, and the Ministry of Agriculture, Forestry and Fisheries.
The Food Safety Commission establishes ADI, while the Ministry of Health, Labour, and Welfare establishes MRL, and the Ministry of Agriculture, Forestry and Fisheries defines the consumption standards such that residue of veterinary drugs in livestock and marine food products does not exceed MRL.
For setting consumption standards, firstly, thorough discussions are held at the Food Safety and Consumer Affairs Bureau of the Ministry of Agriculture, Forestry and Fisheries and NVAL concerning ingredients, where necessary to check the extent of drug residue, animals, and administration methods.
For veterinary drugs where the extent of residue needs to be checked, NVAL actually administers the drugs on livestock, and measures the residual concentration in their organs.
Consumption standards are defined by comparing this residual concentration with MRL.
In the test for checking the extent of residue, as concentration of the drug to be measured in the organ is in a very minute amount of 1 gram per 1 billion parts, suitable analytical techniques are studied and developed.



Due to wide use of antibiotics on food-producing animals such as cows, emergence of drug-resistant bacteria can be increasing. There is ongoing international discussion about the potential risk of drug-resistant bacteria that can be transmitted to humans through food, eventually making it difficult to treat bacterial infections in humans.
To respond to the background of this international trend, the JVARM initiative was launched, which is a nationwide survey system concerning drug-resistant bacteria. With JVARM, joint surveys and studies are conducted by NVAL and livestock hygiene service centers of prefectural governments. Obtained information is utilized for risk assessment and risk management, and it is also published on our website.

In Japan, where the economy and the movement of people is increasingly becoming globalized, attention must be paid to virulent diseases from abroad, such as foot-and-mouth disease and the highly pathogenic avian influenza.

In advanced containment facilities at NVAL, microorganisms are kept under strict control, and assay is conducted for vaccines of virulent diseases from abroad that have been stockpiled by Japan.

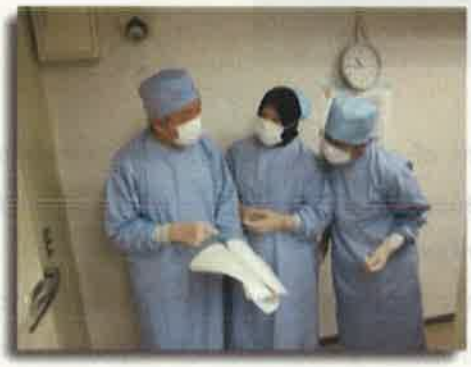
These are required for risk management in the case of an epidemic of infectious diseases such as foot-and-mouth disease.

Office International des Epizooties

OIE

Intergovernmental organization founded in 1924 in Paris, France with the objective of improving animal health all over the world

Member countries: 180 (as of November 2015)



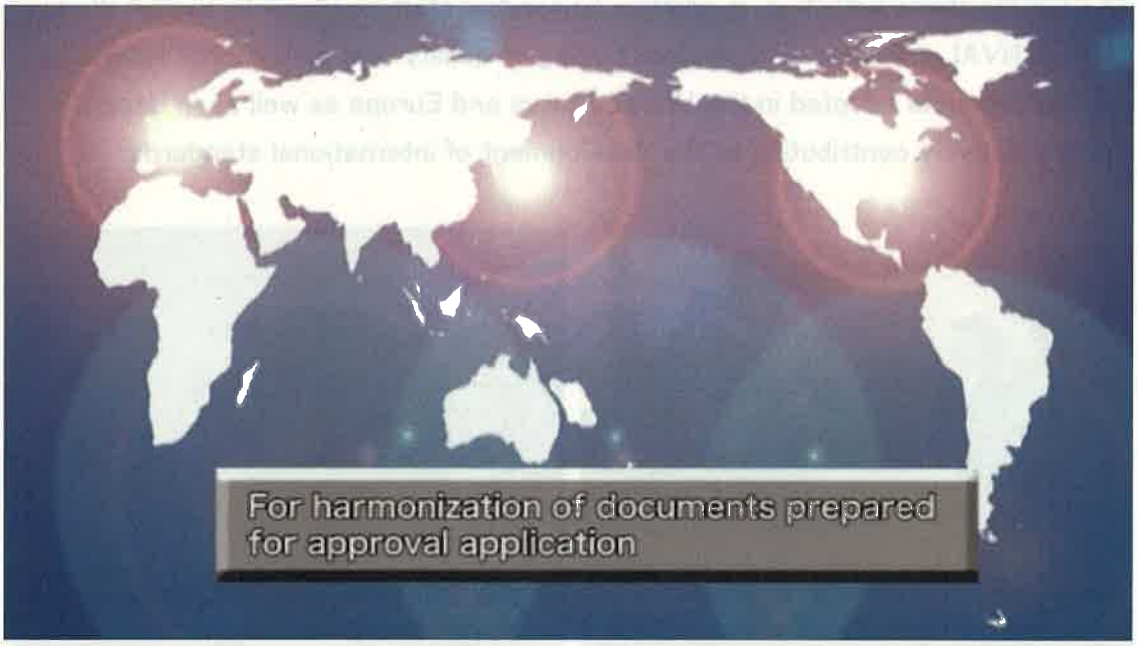
Collaborating Centers

Centres of expertise in a specific designated sphere of competence relating to the management of general questions on animal health issues. In its designated specialty, they must provide their expertise internationally.

Varying expertise, experiences, and skills accumulated at NVAL on a daily basis also plays an important role in international cooperation.

In May 2010, the National Institute of Animal Health and NVAL were approved as the collaborating center of the Office International des Epizooties (OIE), which is an organization that defines international standards.

In the future, we will continue to make international contributions by offering scientific knowledge and testing techniques in the fields of Diagnosis and Control of Animal Diseases and Related Veterinary Products Assessment in Asia.



Furthermore, regulatory authorities and industry for veterinary medicinal products of Japan, the United States, and the European Union are playing a central role in setting up guidelines for preparing documents required for the approval of veterinary medical products.

To promote these activities, in addition to sending staff members to Expert Working Groups, NVAL conducts comparative testing of quality test methods of veterinary medical products adopted in the United States and Europe as well as in Japan, thereby actively contributing to the development of international standards.

To maintain and improve assay techniques concerning veterinary medicinal products, technical training is provided for pharmaceutical inspectors of prefectural and city governments, manufacturers, or distributers.

Furthermore, NVAL staff who have professional expertise have been visiting various countries for transfer of skills to foreign government agencies.

Through these types of activities, we attempt to improve technology related to veterinary medicinal products, both domestically and internationally.

In the coming years, our lifestyle will grow increasingly diverse along with this, our environment, and dietary habits will change at a very fast pace.

It is natural that our lives will become more diverse and our environment and dietary habits will change on a daily basis. However, protecting ourselves from infectious diseases that pose a threat to life and more importantly continuing to safeguard our environment and our diet should not and must not change.

NVAL will continue to secure food safety and protect the lives of animals to fulfill the wishes of the public.

National Veterinary Assay Laboratory

National Veterinary Assay Laboratory

NVAL

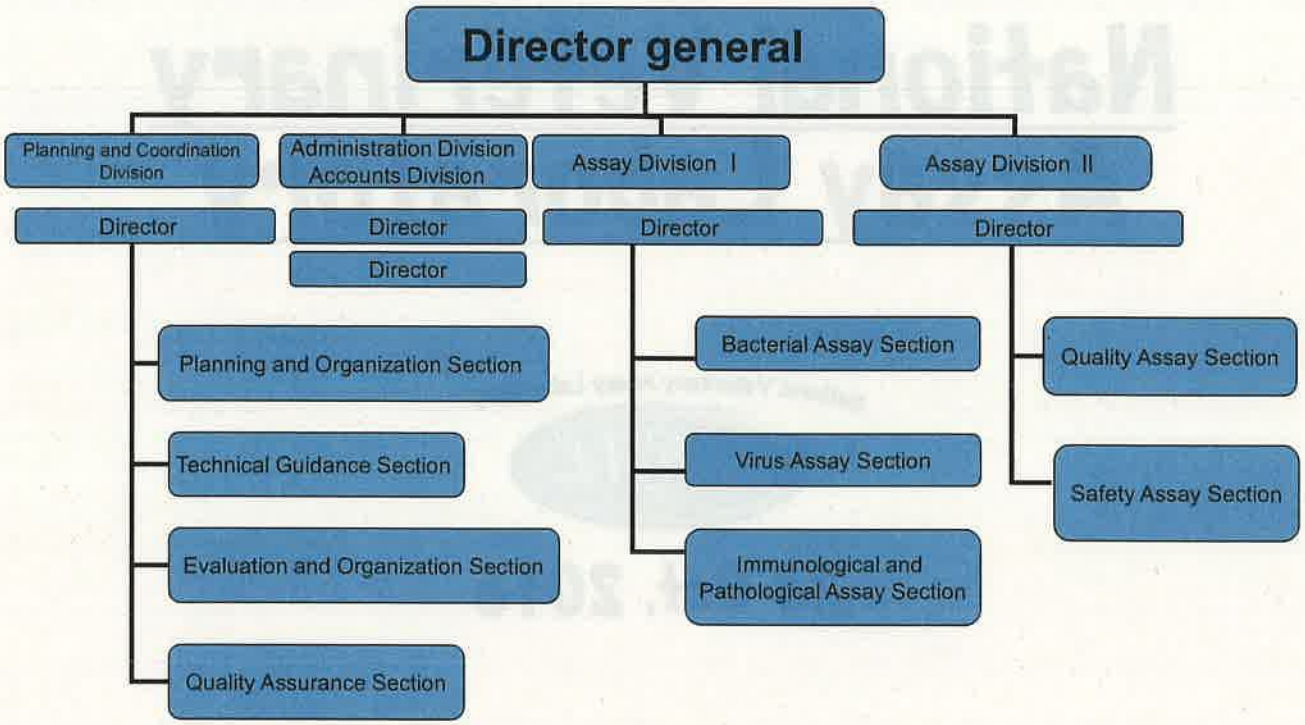
24 Oct. 2016

Mission

- Veterinary medical products (VMPs) are used to diagnose, prevent, and treat animal diseases, contributing not only to the maintenance and improvement of safe animal products, but also to the health of dogs, cats and other companion animals. Moreover, they play an important roles in the improvement of public health through the prevention and control of zoonosis.

- NVAL contributes to improvement of animal hygiene and public health by researching and regulating at the each stage of the development, producing (import), distribution and application of animal medicine, biologics, quasi-drugs, regenerative and cellular therapy, gene therapy products and medical devices. NVAL assures that VMPs are effective and safe as well as performing its roles conclusively.

Organization



Personal Organization

Staff 102 (as of Oct. 1)

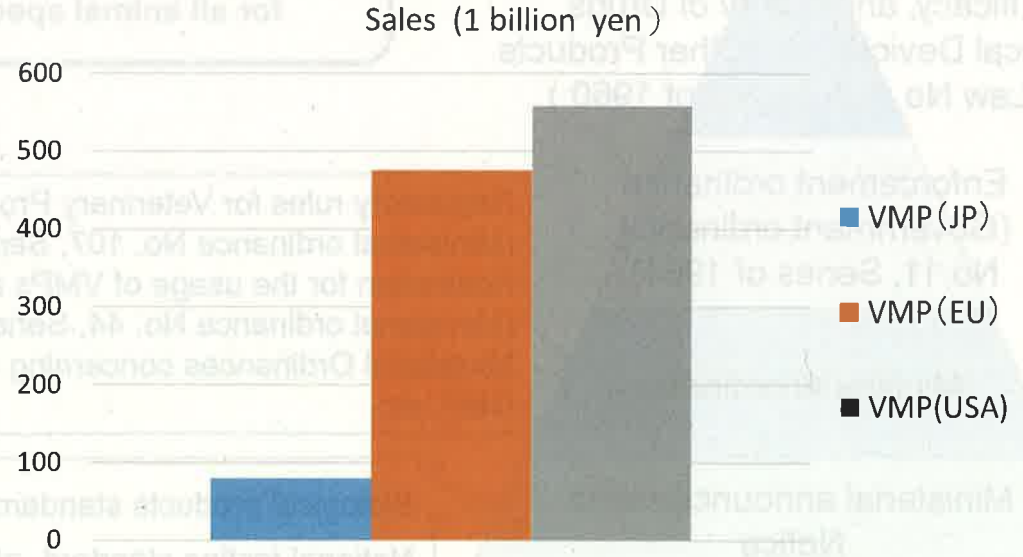
- Veterinarians 38
- Pharmacists 6
- Technical Staff 38
- Others 20

Pharmaceutical affairs inspector

- NVAL 49
- MAFF About 20
- Prefectural government About 2000

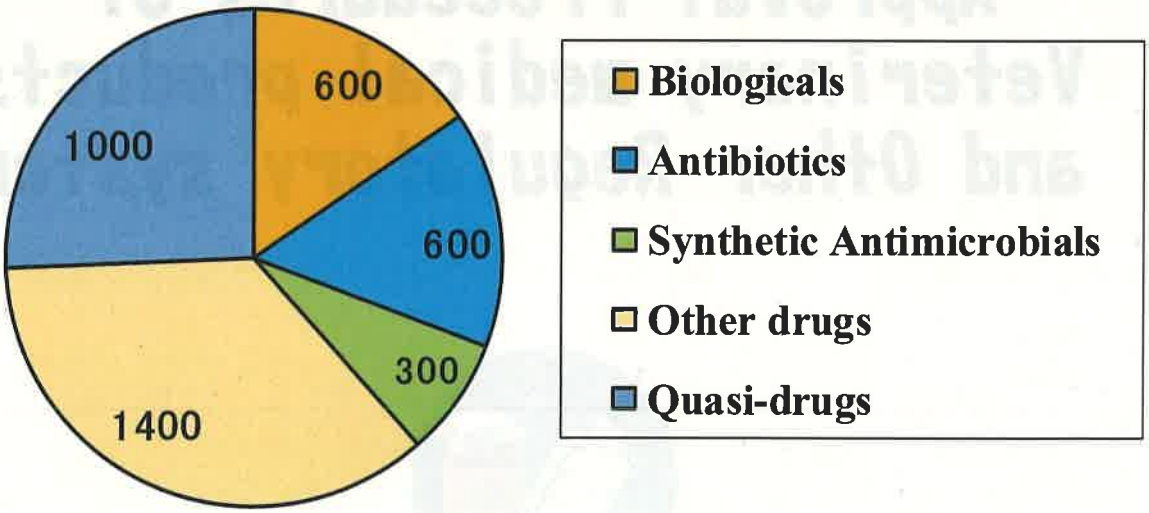
Veterinary Drugs sold in Japan

Sales amount: 80 billion yen/year
≒ 0.8 billion US$/year



Human Medical Products: 11 trillion yen ≒ 110 billion US$/year

Veterinary Drugs Approved in Japan



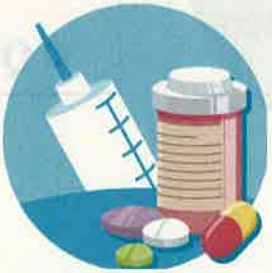
Law hierarchy of Pharmaceutical Affairs in Japan

They cover veterinary medical products (VMPs) for all animal species

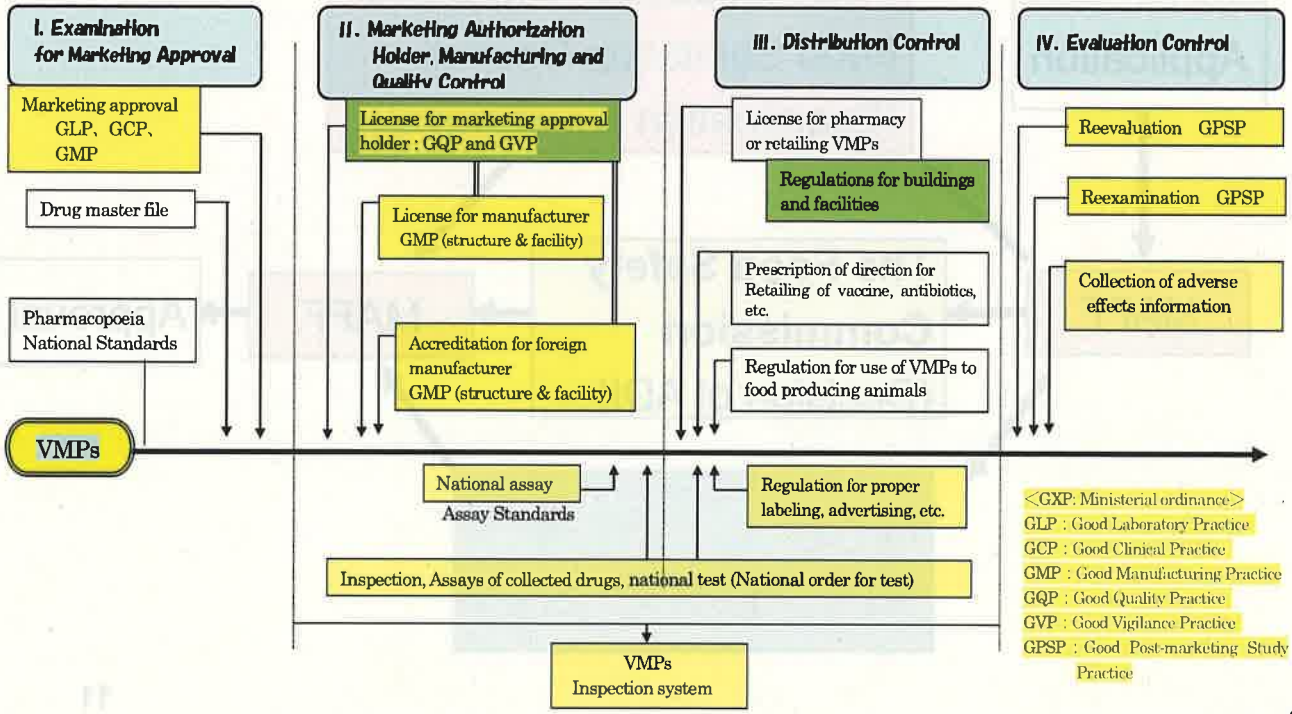
Regulatory rules for Veterinary Products (Ministerial ordinance No. 107, Series of 2004)
Restriction for the usage of VMPs and MPs (Ministerial ordinance No. 44, Series of 2013)
Ministerial Ordinances concerning GLP, GCP, GMP, etc.

Biological products standard,
National testing standard, etc.

Approval Procedures of Veterinary medical products and Other Regulatory system



Regulation Flow of Vet. Medicinal Products (VMPs) from Development to Post-marketing Stage



Council for Veterinary medical products

Pharmaceutical Affairs and Food Sanitation Council (**PAFSC**)

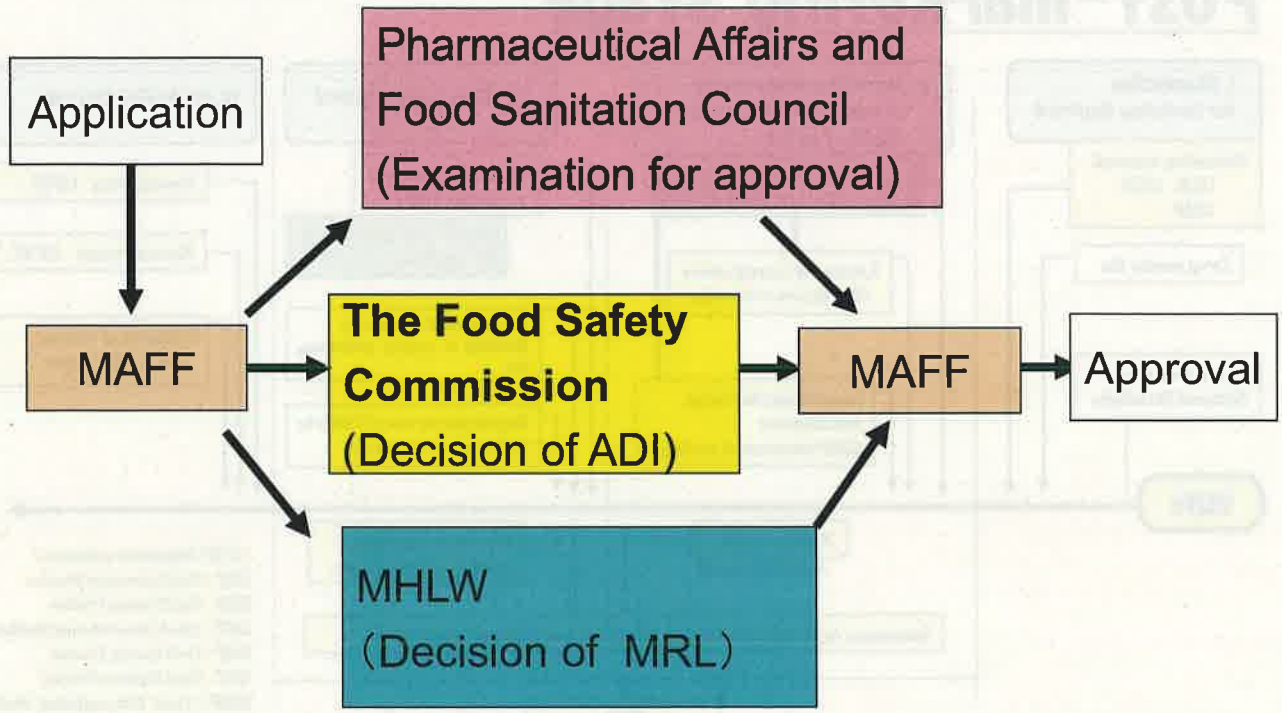
<Sub-Council>
(1)Biological products
(2)Antibacterial Preparations
(3)General Animal Medicaments
(4)Aquatic Products
(5)Re-evaluation of Animal Medicaments
(6)Residue Problem of Animal Medicaments

Request for evaluation

MAFF

-Investigation of VMPs;
(approval of new VMPs, reexamination or reevaluation of approved VMPs)
-Establishment of standards for VMPs

Flow from the application to the approval



Reliability Standard Compliance Assessment (GLP)

- For non-clinical study (toxicity test, safety test, etc.)
- Defined by ministerial ordinance for Good Laboratory Practice (GLP)
- Target VMPs : VMPs fulfilled under the all condition;
  ①new component VMPs
  ②new administration route
  ③new VMPs for cattle, horse, pig, poultry, quail, honey bee, farm-raised fish, dog and cat

※ Accepts data of toxicity, target animal safety or residue according to OECD GLP guidelines or VICH guidelines.

Reliability Standard Compliance Assessment (GCP)

- For clinical study
- Defined by ministerial ordinance for Good Clinical Practice (GCP)
- Target VMPs：VMPs fulfilled under the all condition;
  - ①new component VMPs
  - ②new administration route
  - ③new VMPs for cattle, horse, pig, poultry, dog and cat

※ GCP has been harmonized to the VICH GCP guideline.

Reliability Standard Compliance Assessment (GPSP)

- For Post Marketing Surveillance
- Defined by ministerial ordinance for Good Post-marketing Study Practice (GPSP)
- Target VMPs：VMPs fulfilled under the condition;
  - ①Reexamination; same as approval (GLP or GCP)
  - ②Reevaluation; VMPs designated as a target of reevaluation by PASC

National assay of veterinary vaccines

Veterinary biologics cannot distribute or sell unless pass the assay of NVAL.

Manufacturer Distributer

NVAL National Assay

Distribution

2008.10～
Introduction of seed-lot system

Manufacturer Distributer

Non-seed

Vaccine produced by seed lot system

※

NVAL National Assay

Distribution

※ New vaccine before aproval of re-examination, vaccine for an domestic animal infectious diseases designated by Act on Domestic Animal infectious diseases control and Zoonosis.

Seed lot biologicals number 248 (as of March 2016)
National Assay number 356 (2015)

Assay of collected drugs

Assays are performed randomly for VMPs which collected without notice.
Sampling number : 69 VMPs (2015)

Manufacturer Distributor

①On-site inspection

NVAL Prefecture (Pharmaceutical inspector)

②Sampling of products

NVAL
Receiving process → Test → Determination of result

Manufacturer Distributor

③Notice of result

④if the result is unsatisfactory, product must be collected and disposed

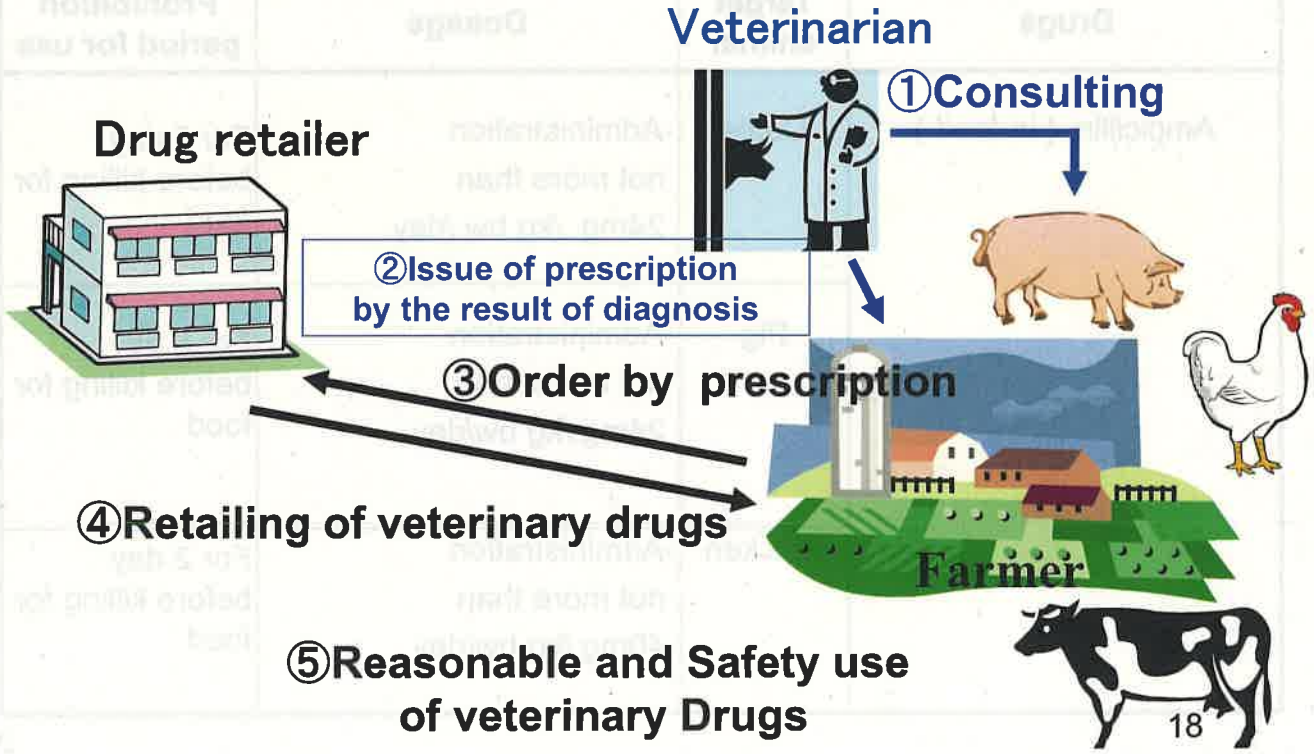
Drugs requiring Veterinary Consultation (The Veterinary license Law)

Any Veterinarian shall not provide or prescribe poisonous and powerful drugs etc. without whose consultation.

1. Poisonous drug
2. Active drug
3. Biologics（vaccine、serum）
4. Prescription drug (antibiotics, hormones, etc.)
5. Drug regulated on the use for animal

Prescription System

Prescription drugs are drugs for bovine, equine, ovine, swine, canine, feline and poultry.



Restriction for usage of Veterinary drugs

Restriction for usage of veterinary drug used for food producing animals,

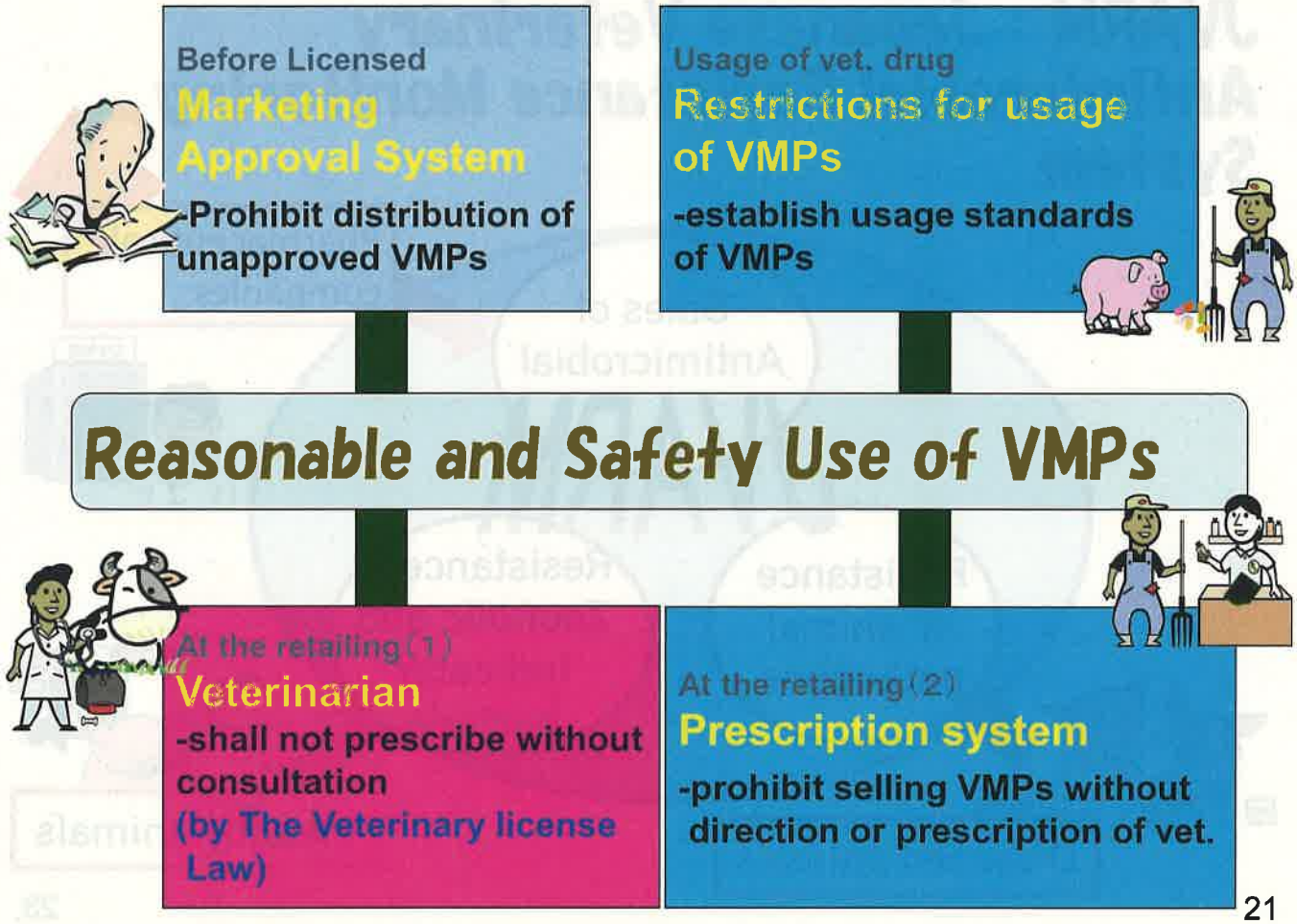
-meat or milk-producing animals, poultry, fish or bees ,

- to assure the public health safety in administration of anti microbial preparations, etc.

-to specify drugs that can be used, and its administration, dosages, and prohibition periods for use to subject animals.

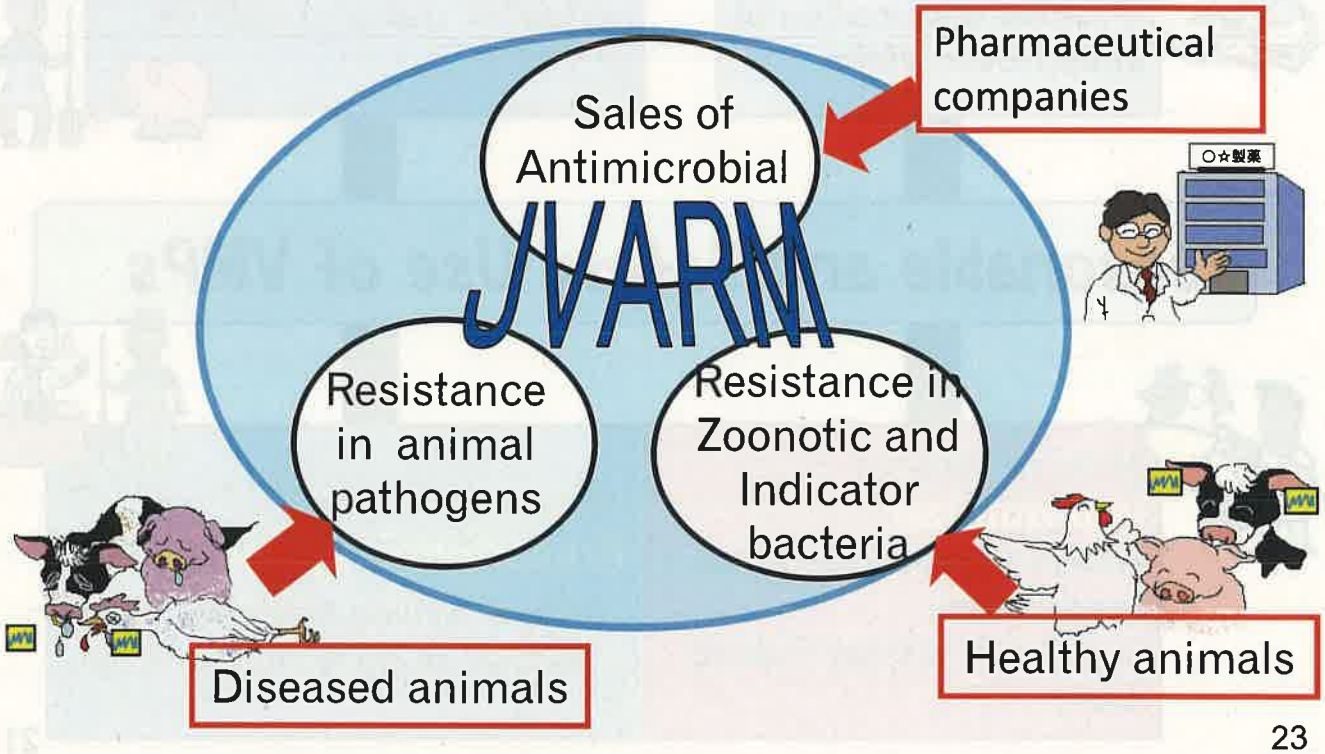
Example of Restriction for usage of Veterinary drugs

Drugs	Target animal	Dosage	Prohibition period for use
Ampicillin (in feed)	Cattle	-Administration not more than 24mg /kg bw /day	For 5 day before killing for food
	Pig	-Administration not more than 24mg /kg bw/day	For 5 day before killing for food
	Chicken	-Administration not more than 40mg /kg bw/day	For 2 day before killing for food

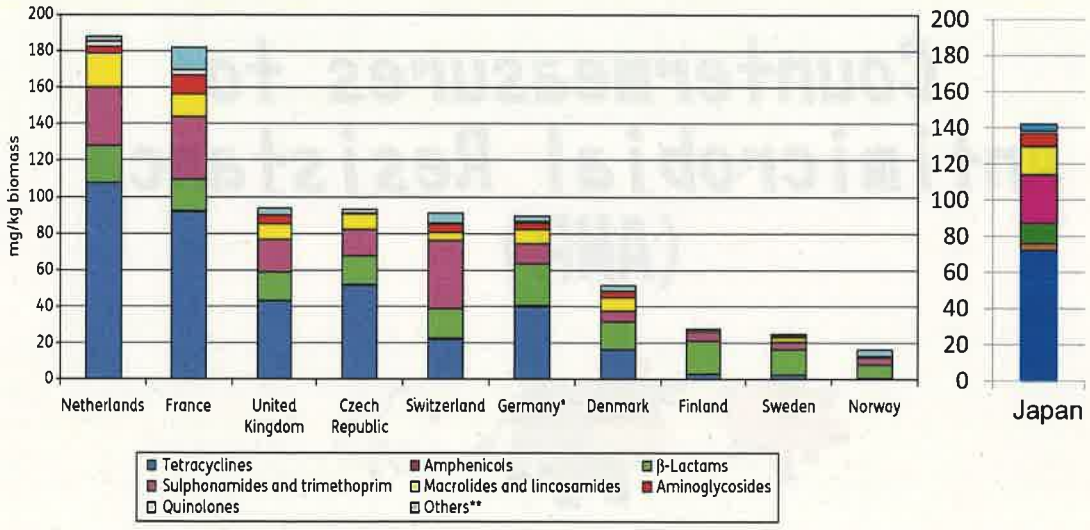


Countermeasures to Antimicrobial Resistance (AMR)

JVARM : Japanese Veterinary Antimicrobial Resistance Monitoring System



Comparison of veterinary antimicrobial use in 2007 in EU countries and Japan (per kg biomass meats)

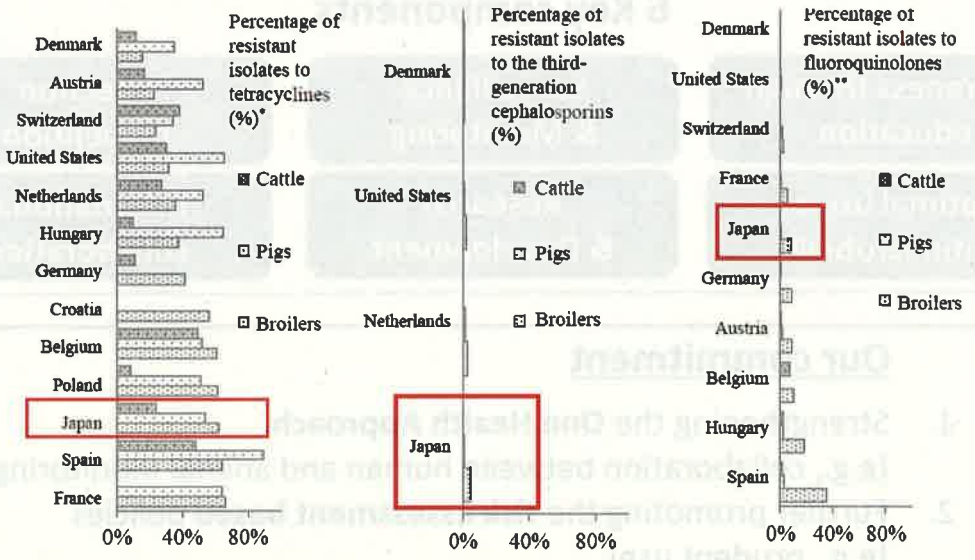


Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.

Kari Grave et al. J. Antimicrob. Chemother. 2010;65:2037-2040

Hosoi et al. Int J Antimicrob Agents. 41:489-90, 2013

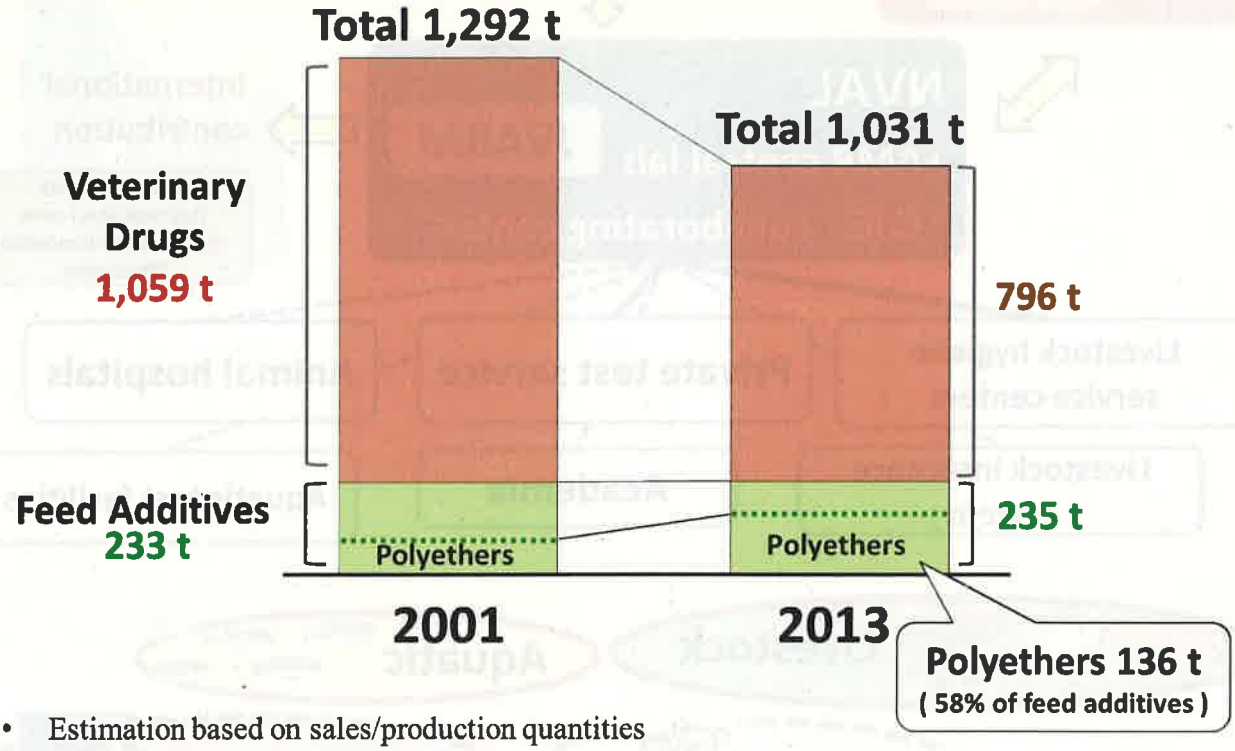
International comparison of antimicrobial resistance in *Escherichia coli* of livestock animal origin (2013)



* No data on pigs in Germany, cattle and pigs in Croatia, and cattle in France
** No data on cattle in Denmark, Switzerland and France, and pigs in Germany and Denmark

the percentages of isolates resistant to tetracyclines, the third-generation cephalosporins, and fluoroquinolones in Japan are at comparable levels to those in EU and USA

Use of Antimicrobials for animals



- Estimation based on sales/production quantities
- Includes companion animals

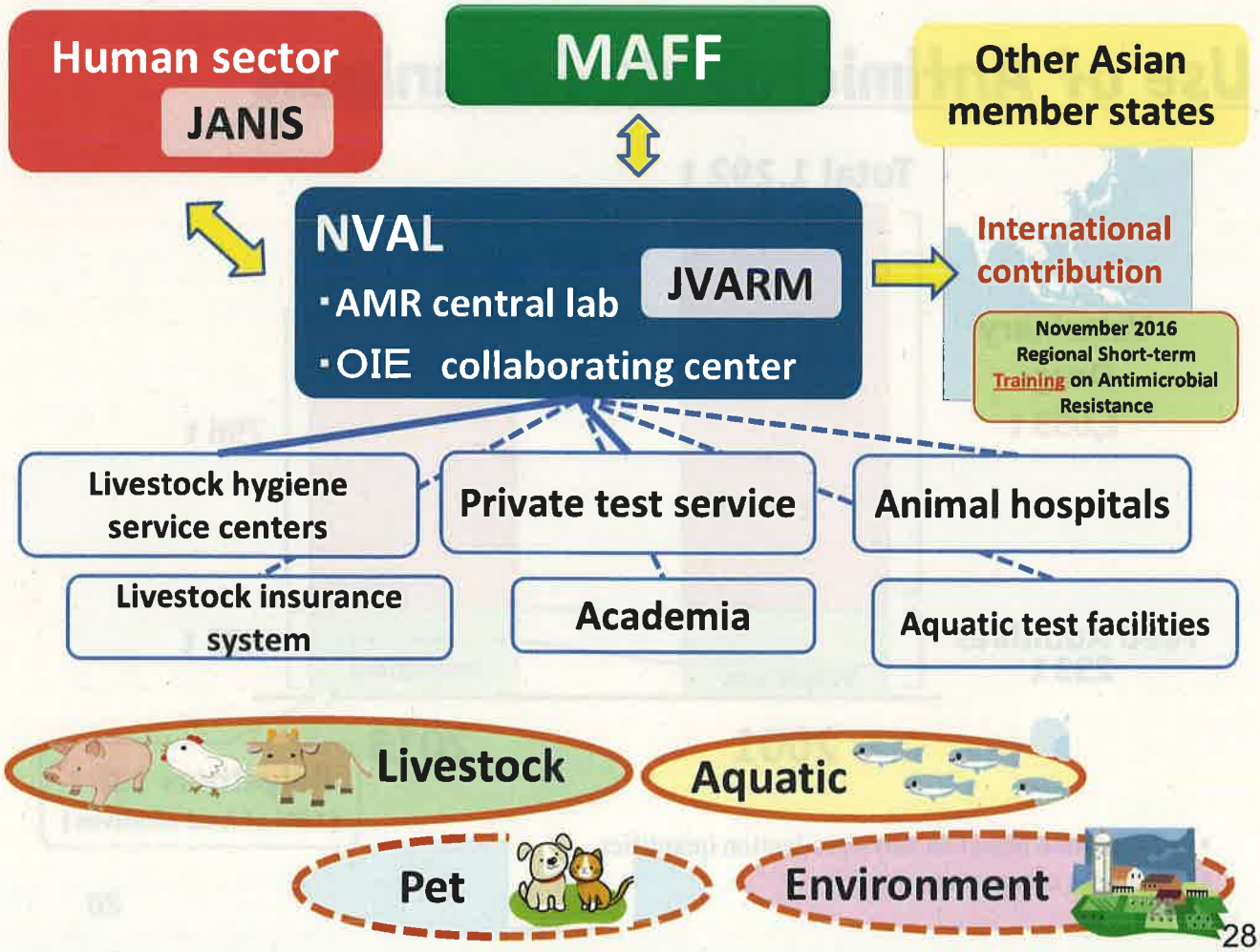
Current Efforts
- AMR National Action Plan -

6 Key components

Awareness through education	Surveillance & Monitoring	Infection prevention
Optimal use of antimicrobials	Research & Development	International collaboration

Our commitment

1. Strengthening the **One Health Approach** (e.g., collaboration between human and animal monitoring)
2. Further promoting the **risk assessment based** policies (e.g., prudent use)
3. **Working with OIE and other international organizations** to contribute to the Asian region

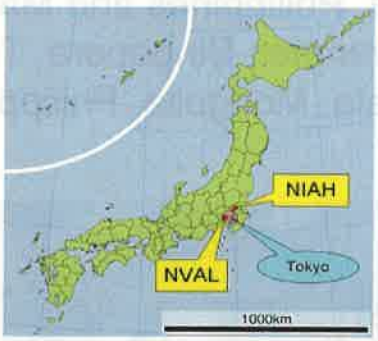


Activities of OIE Collaborating Centre

OIE Collaborating Centre (2010～)
"Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia"

National Veterinary Assay Laboratory

http://www.maff.go.jp/nval/english/



National Institute of Animal Health

http://niah.naro.affrc.go.jp/index.html

Record of activities in the sphere of Veterinary Medicinal Products

- Held OIE regional Workshop in NVAL, Tokyo, 1-3 March 2011 (15 countries participated + speakers from 5 countries participated)
- Participated as speakers in OIE National Focal Point Workshop in Siem Reap, Cambodia, 29 June -1 July 2011
- Participated in OIE-VICH contact meeting on WIH of VICH GL, Tokyo, 15 November 2011
- Participated as speakers/facilitators in OIE National Focal Point Workshop in Bangkok, Thailand, 10-13 July 2012
- Participated as speakers/facilitators in Regional Seminar for OIE National Focal Points for Veterinary Products in Tokyo, 3-5 December 2014



Record of activities in the sphere of Veterinary Medicinal Products (contd.)

- Held OIE-CC Regional Short-term Training on Veterinary Vaccine Assessment in NVAL, Tokyo
  - 6-10 February 2012*1, 12-16 November 2012*2, 7-11 October 2013*3 and 6-10 October 2014*4
  - *1 China, Indonesia, Thailand and Vietnam
  - *2 Taiwan, Korea, Philippines and Malaysia
  - *3 Indonesia, Myanmar, Singapore, Thailand and Vietnam
  - *4 Korea, Malaysia, Mongolia, Philippines and Taipei China



Activities in VICH

VICH =

International Cooperation
on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products (VMPs)

OIE : Associate Member, HealthforAnimals : Secretariat

Output

1 . Making VICH guidelines for the approval (registration) of veterinary medicinal products

→**VICH guidelines are implemented in VICH countries/regions. (Full member of VICH have an obligation to implement the VICH guidelines.)**

→**More than 50 VICH guidelines have been made.**

→Once adopted, the VICH guidelines replace corresponding regional guideline in principle.

Studies according to VICH guidelines are used for application of approval
Reduction of the time to prepare application
Reduction of the time for examination of the studies
Reduction of studies using animals (Viewpoint of animal protection)

2 . VICH Outreach Forum (VOF)

→Dissemination of the VICH guidelines to non-VICH countries/regions

Output

3. Public Conference

VICH Steering Committee meetings are held in Europe, Japan and USA by turns in principle. The meetings were held every 6 months till the 18th meeting in May, 2006, then they were held every 9 months from the 19th meeting.

VICH Public Conference have been held in conjunction with the Steering Committee meeting in order to help information disclosure to the world every 5 years at present, every 3 years at the beginning of the VICH.

4. Others

The VICH hold OIE-training seminars for regulators of veterinary medicinal products.

The participant from countries are the OIE National Focal Points of the countries. The subjects of the seminar are discussed in the VOF meetings.

Legal Status of Regenerative Medicinal Products and the Use of Stem Cell Technology

Definition of Regenerative Medicinal Products

Act on Ensuring quality, safety and efficacy of Pharmaceuticals, Medical Equipment etc.
Article No. 2 (Excerpt)

"Regenerative medicinal products" are;

- To be used in human medicine or veterinary medicine,
- For reconstruction of the structure or function of the body, formation or repair; treatment or prevention of disease
- Has been subjected to cell culture or other processing

Revision of Pharmaceutical Affairs Act

	Before	After
Title	Pharmaceutical Affairs Act	Act on Ensuring quality, safety and efficacy of Pharmaceuticals, Medical Equipment etc.
Chapters on Production and Sales, etc.	Pharmaceuticals, etc. (Pharmaceuticals, quasi-drugs, Cosmetics and medical equipment)	Pharmaceuticals, quasi-drugs and cosmetics
		Medical devices and In vitro diagnostics
		Regenerative medicinal products

- To provide safe pharmaceutical products, medical devices and regenerative medicinal products in a timely manner,
- To establish novel measure i.e., conditioning and/or limited-time approval system for regenerative medicinal products.

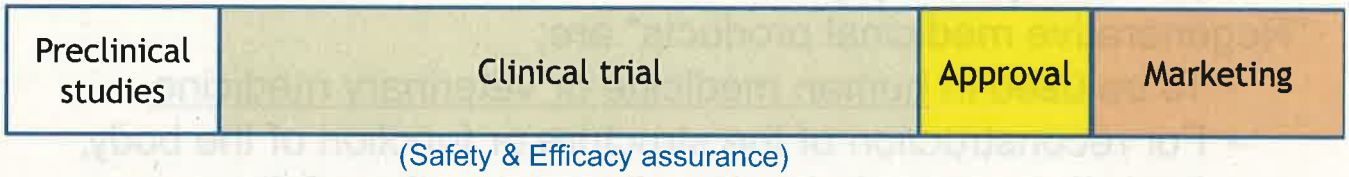
Conditional and/or limited-time approval for regenerative medicinal products

Article No. 23-26(excerpt)

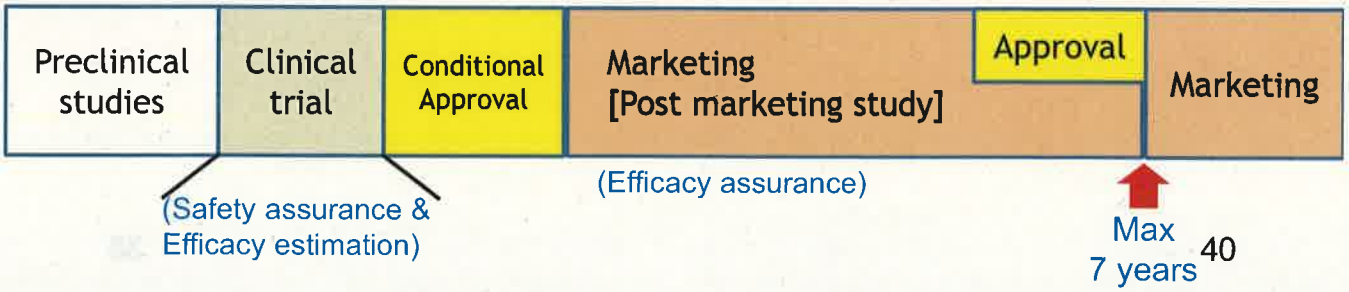
The minister can provide authorization to the applicant by attaching a condition required and/or a period of not exceeding seven years to the products which is;

- Estimated to have an indicated efficacy,
- Have no significant adverse effects.

•[Current track]



[Track for regenerative products]



Clinical application of stem cell technology

A) Cytokine treatment

treatment by biological modulator secreted from stem cells

B) Tissue complement therapy

transplant stem cell-derived artificial tissue

C) Blood cell therapy

Transfusion blood from stem cells

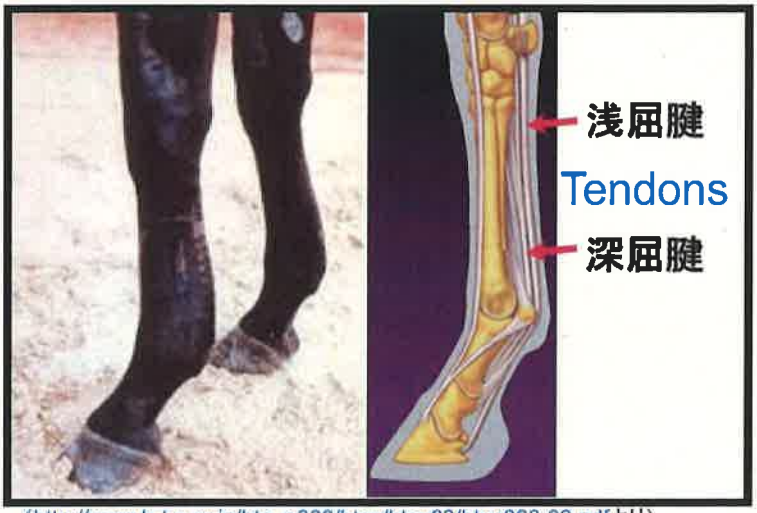
Strengthen immune cells

Case A) Cytokine treatment for tendonitis (JRA)

Cytokines from bone marrow derived mesenchymal stem cells heal injured tendon. Recovered to 10% of patient.

Pathogenesis

(http://blog.jra.jp/onsen/2010/09/より)



(http://www.b-t-c.or.jp/btc_p300/btcn/btcn63/btcn063-02.pdfより)

Veterinary regenerative medicine in Japan

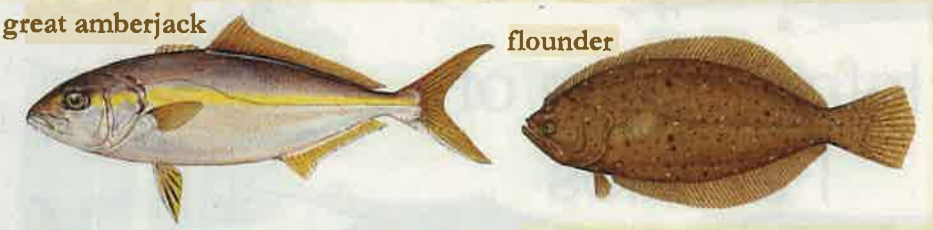
Cell type/therapy	Basic research	Clinical practice	Product development
ES cells	University etc. (Produce ES cells (Dog and Cat)	ND	ND
iPS cells	University etc. (Produce iPS cells (Dog and Cat)	ND	ND
Mesenchymal stem cell Adult stem cell	Univ. Clinic, Private sector (Motor System (Cattle, Horse, Dog and Cat), Hepatic and Renal insufficiency (Dog and Cat)	University, Private clinics (Tendons (Horse), Spinal cord injury (Dog and Cat)	Clinical trial in progress, University hospital, private sector (Spinal cord injury (Dog), Serious hepatic insufficiency
Immunocyte therapy	Univ. Clinic, Private sector (Immunostimulation (Cattle), Tumor (Dog))	University, Private clinics (Tumor (Dog and Cat))	ND
Concentrated platelet	Univ. Clinic (Tissue Regeneration (Cattle and Horse))	Private clinics (Skin regeneration (Dog and Cat)	ND
Bone marrow transplantation	Univ. Clinic (Bone marrow transplantation (Dog))	Private clinics (Bone marrow transplantation (Cat))	ND

Fish Facilities

Subject Fishes of Fish Vaccines

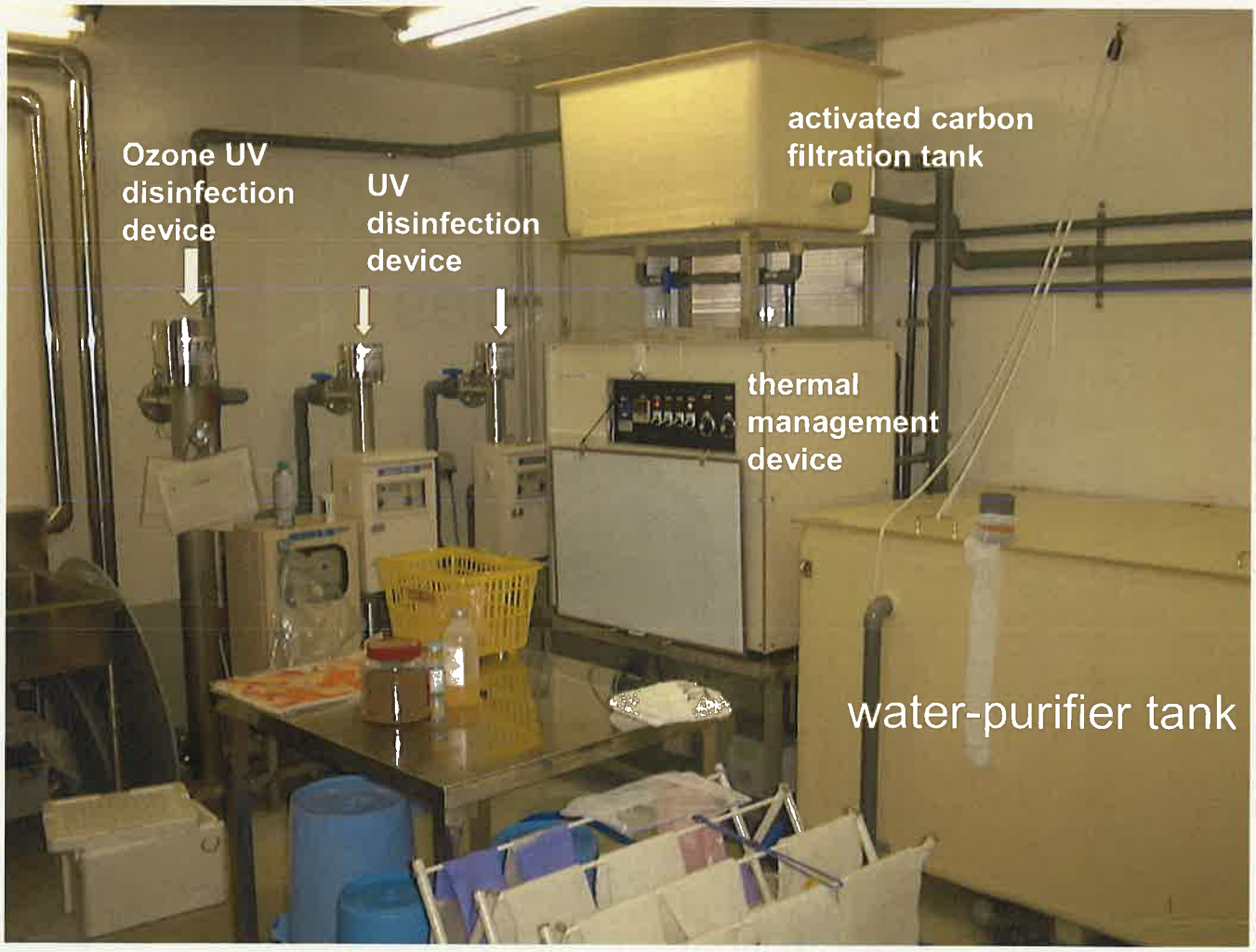
Sea Fish

Freshwater Fish



Seriola fishes

(From : original color fish book, ***Hokuryu-kan***)

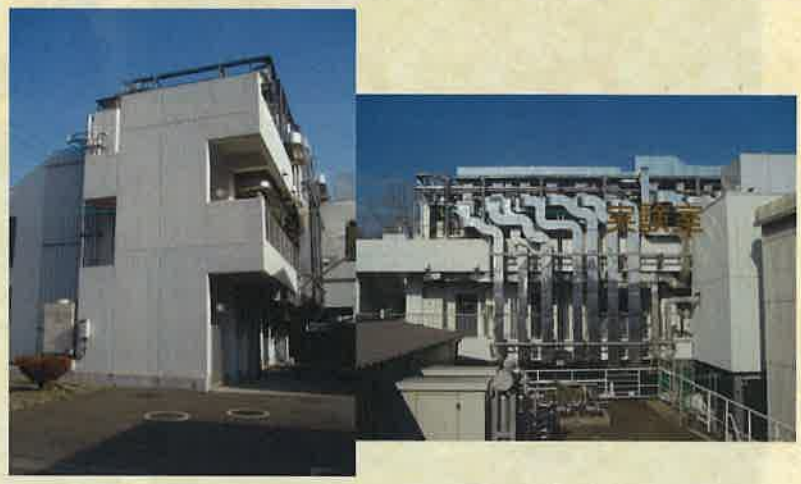


Integrated Assay Building

Integrated Assay Building

Built as BSL-3 facility for safety control plan against exotic infectious diseases and their target pathogen

- Built in March, 2002
- Ground Floor Animal room
- 2nd Floor Experimental room
- Basement Utility room
  Sewage room
  Filter room



Main equipment and function

- Damper air lock keeps inside low-pressure
- Showering is required when exit floor (each floor)
- Differential pressure : adjust 3-9millimeter of mercury
- Sewage water is discharged after autoclaved
- Equipment or carcass is carried out after autoclaved

- Kind of air filter
  - ◎Pre Filter
  - ◎High-efficiency filter
  - ◎Activated carbon filter
  - ◎HEPA filter
  - ◎ULTRA・HEPA filter

- private electric generator is set up in case of power outage

Ground Floor : Animal Room

Animal room
(Cattle, Swine)

Negative Pressure Isolator
System (Poultry)

Second Floor : Laboratory

Safety Cabinet
CO_2 Incubator
Freezer(−30℃)

Examination room

Basement

Sterilization Tank（2 tanks）

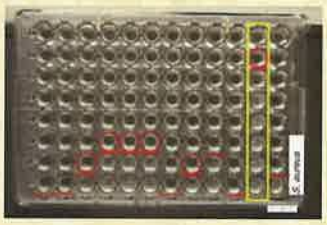
Filter Room

NVAL
Assay Division II
Safety Assay
Section1
(JVARM section)

Determination of minimum inhibitory concentrations (MICs)

Semi-automatic Inoculator
(Inoculator β Eiken)

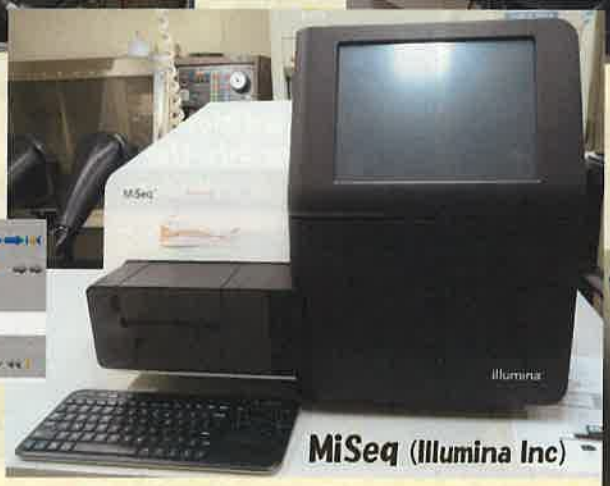
Broth microdilution method



Characterization of resistant bacteria -Whole genome sequence-

PFGE

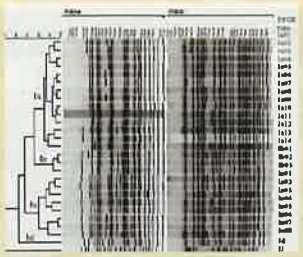
PCR



MiSeq (Illumina Inc)

QIAcube
(Purification of DNA)

Characterization of resistant bacteria
-Pulsed-field gel electrophoresis (PFGE)-



Microbiological potency test of veterinary antibiotics

Antibiotic potency is estimated by comparing the inhibition of growth of sensitive micro-organisms produced by known concentrations of the antibiotic (standard solutions)

Laboratory

Room requirement

- For veterinary biologics
- For chemicals

- Incubator
- Freezer
- Safety cabinet
- refrigerator
- Microscope
- chromatograph
- etc

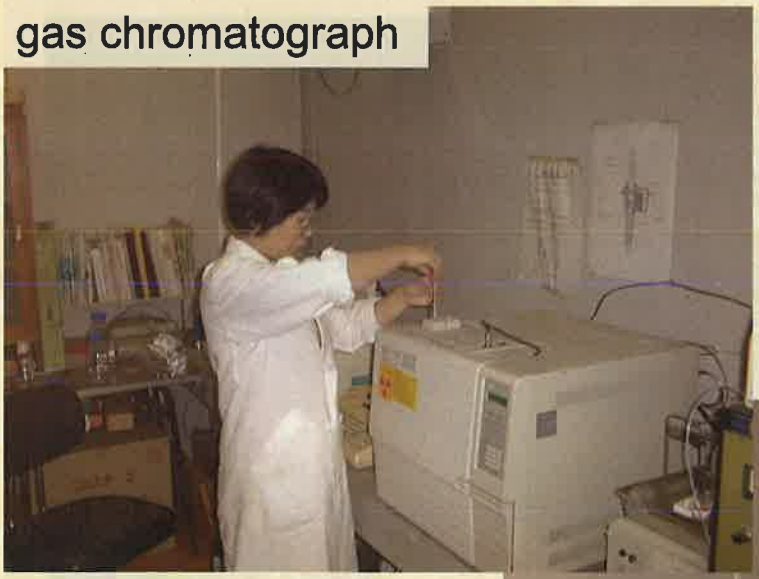
Equipments for Quality Testing on Veterinary Medicinal Products

humidity measurement : Vacuum dryer

Titrimetry

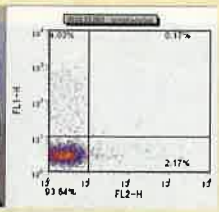
Water measurement: Karl Fischer aquameter

gas chromatograph



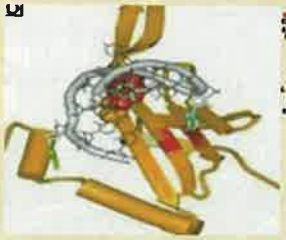
high performance liquid chromatograph

Equipments supporting Technologies①

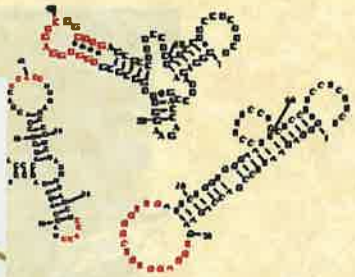


Flow cytometry

•animal testing alternative
•cell immunity assessment technic



Frame format of aptamer
: Science Vol.287



Prion-specific RNA aptamer developed by BDSII

Aptamer

• Alternative antigen-specific probe development technic

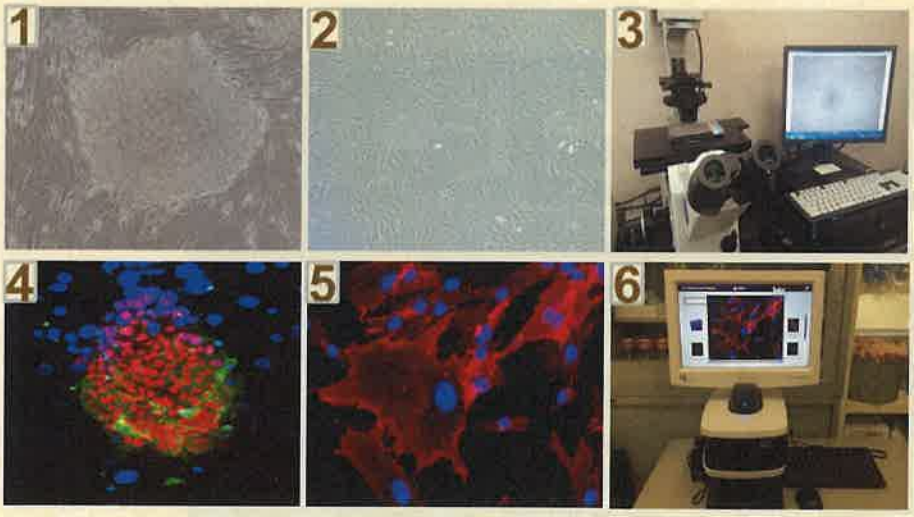
Real- Time PCR

•Alternative diagnostic method
•Test for the detection of Mycoplasma contamination

recombinant DNA techniques

•recombinant pathogenic agent
•recombinant protein

Equipments supporting Technologies②

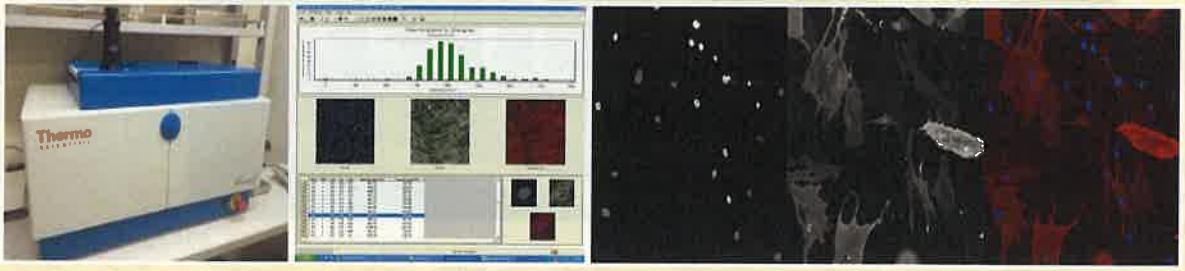


1: iPS cell
(optical microscope)

2: MSC
(optical microscope)

3: iPS cell
(fluorescence microscope)

4: iPS cell
(fluorescence microscope)



Cell Image Analyzer : marker added MSC

Animal Room

Small Animal Room

Negative Pressure Isolator（chicken）

Earthquake-resistant storage Building

Earthquake-resistant Storage Building : Ground Floor

Earthquake-resistant Storage Building : 2nd Floor

Supply Center

Supply Center

- Cleaning, sterilization and preparation of glassware, apparatus and materials
- Management of distilled or purified water
- Preparation of media, buffer for NVAL section

Sewage Facility & Incinerator

Sewage Facility

Incinerator

Vehicle Disinfection Wheel bath

Incinerator

Vehicle Disinfection Wheel bath