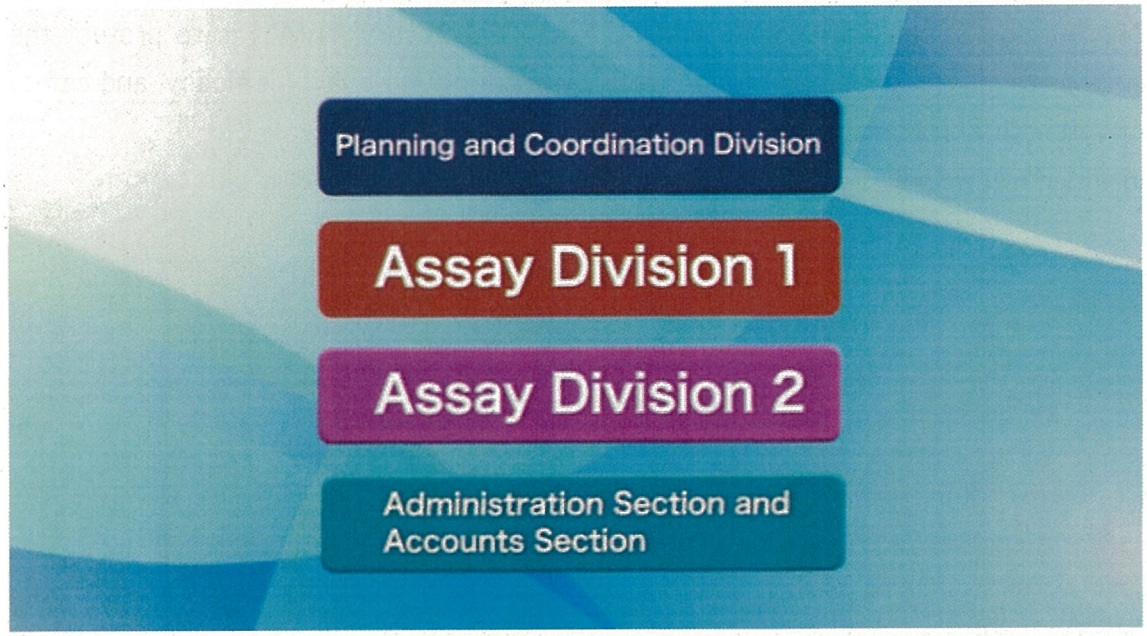
MAFF NVAL OIE

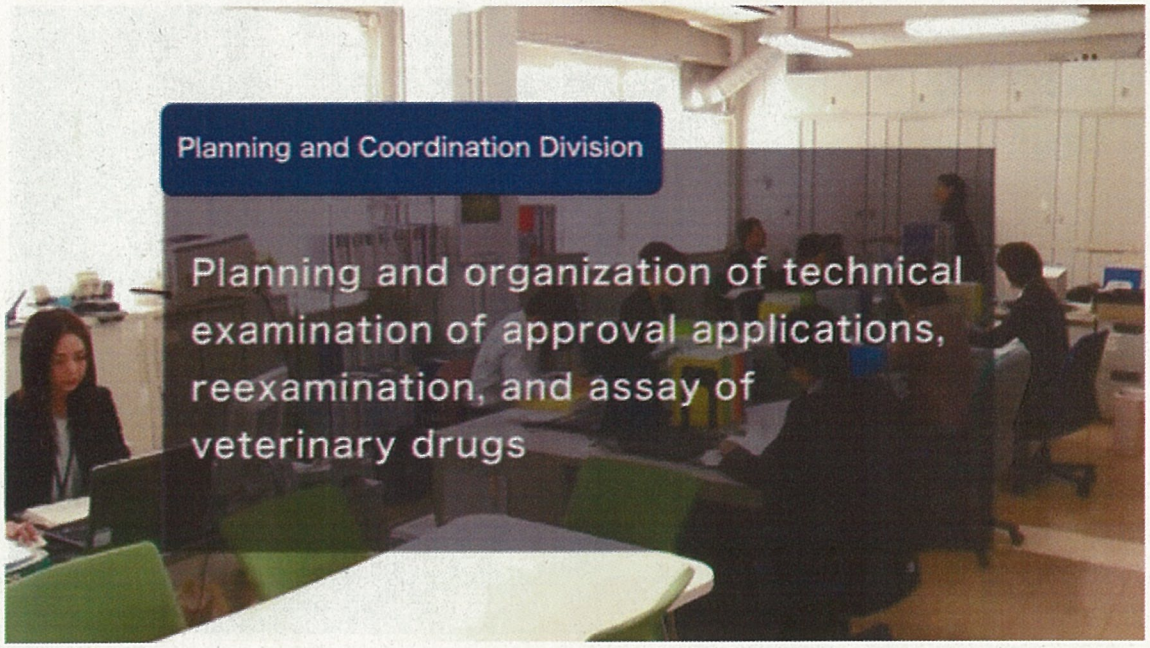
Produced by
National Veterinary Assay Laboratory,
The Ministry of Agriculture, Forestry, and Fisheries

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.

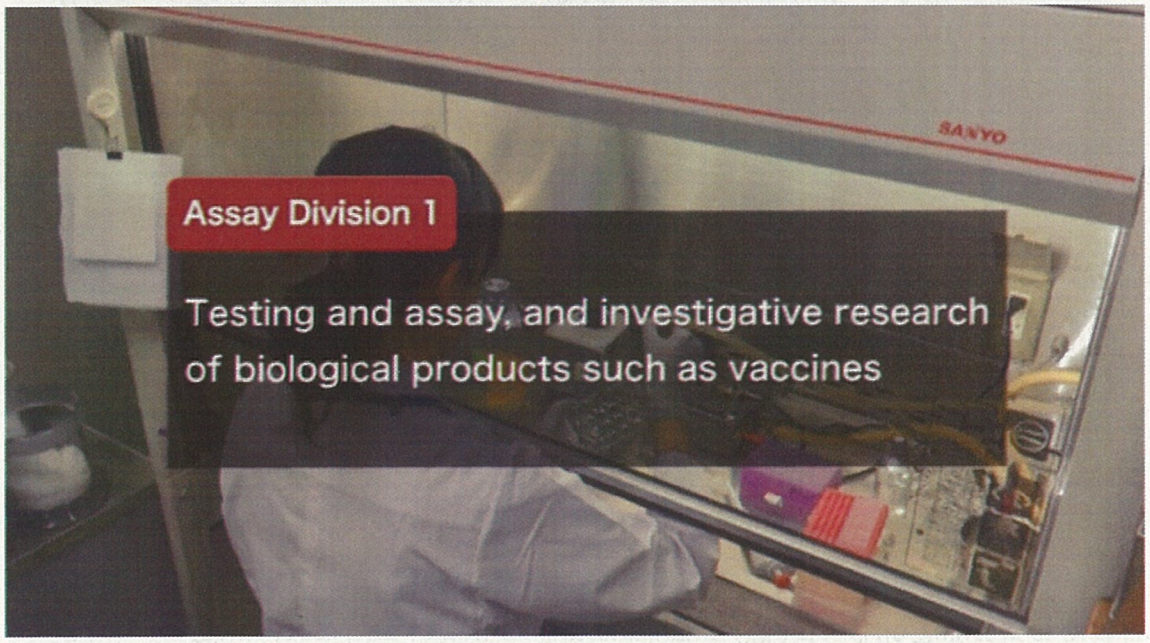
NVAL was established in 1956 as an institution affiliated with the Japanese Ministry of Agriculture, Forestry, and Fisheries.
It is the only national agency engaged in the technical examination of application approval, assay and testing, and investigative research for ensuring the quality, efficacy, 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.

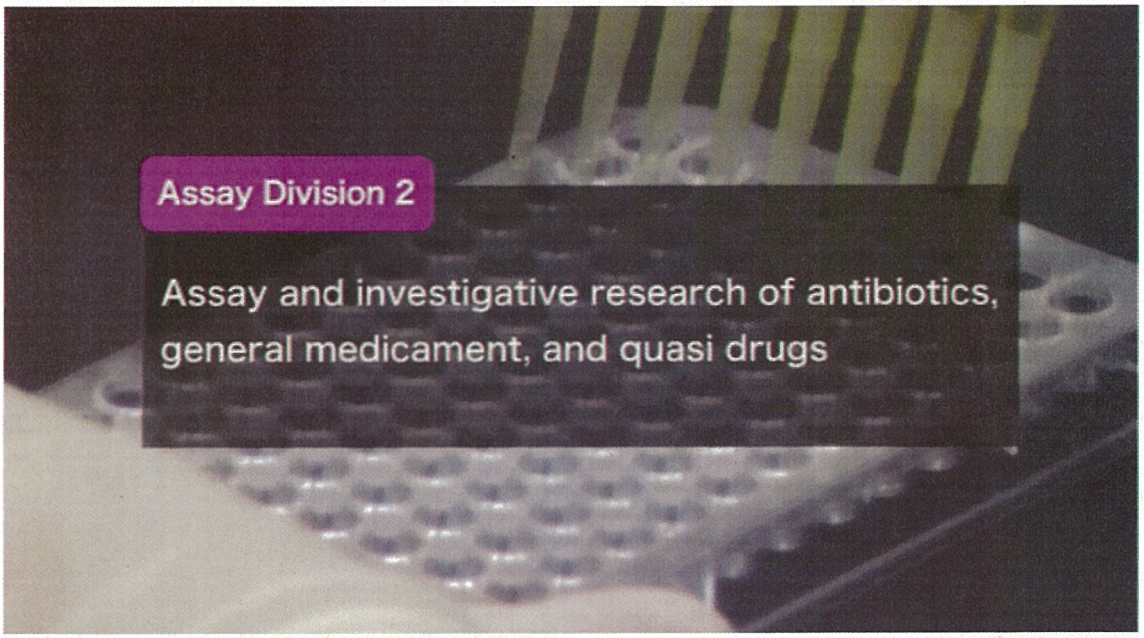

NVAL comprises four main divisions.



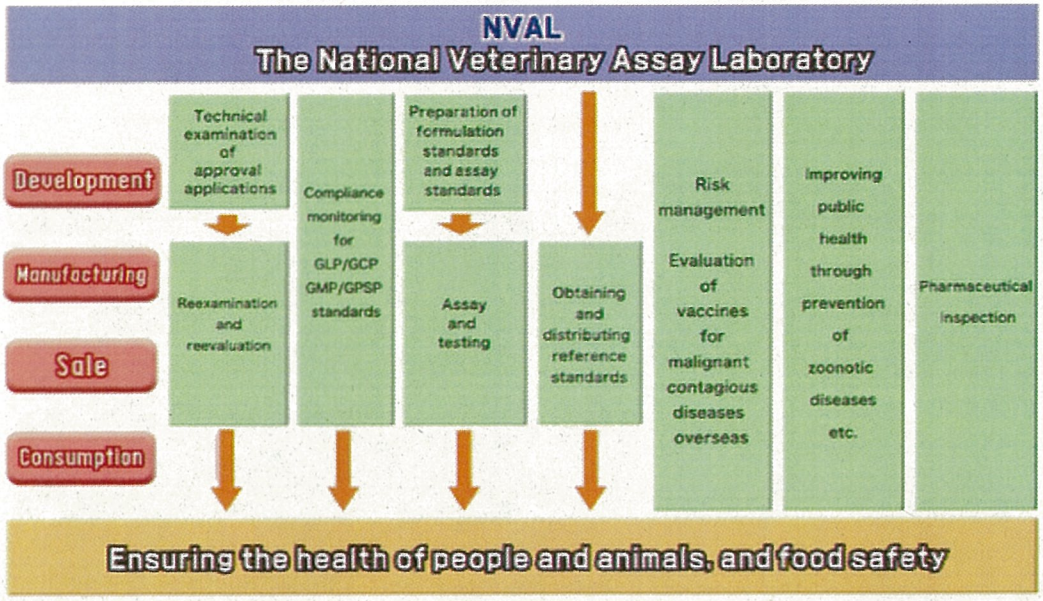

The "Planning and Coordination Division" is responsible for organizing the technical examination of approval applications, reexamination, and assay of veterinary medicinal products.




"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.

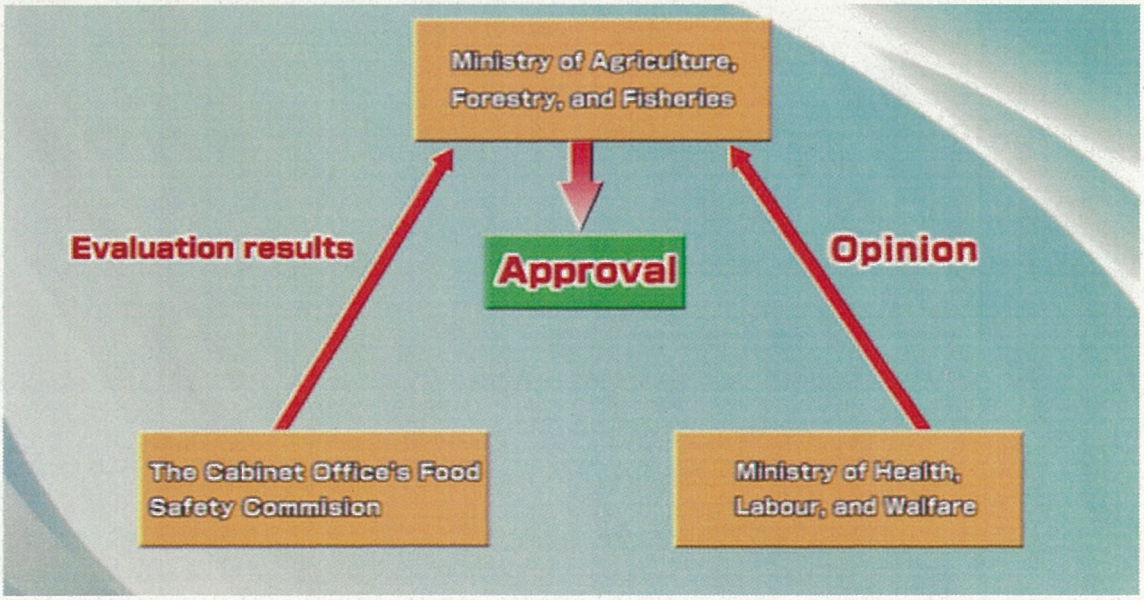



"Assay Division 2" is responsible for assay and investigative research of antibiotics, general medicines, quasi-drugs.
Finally, there is the "Administration Section and Accounts Section".




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.

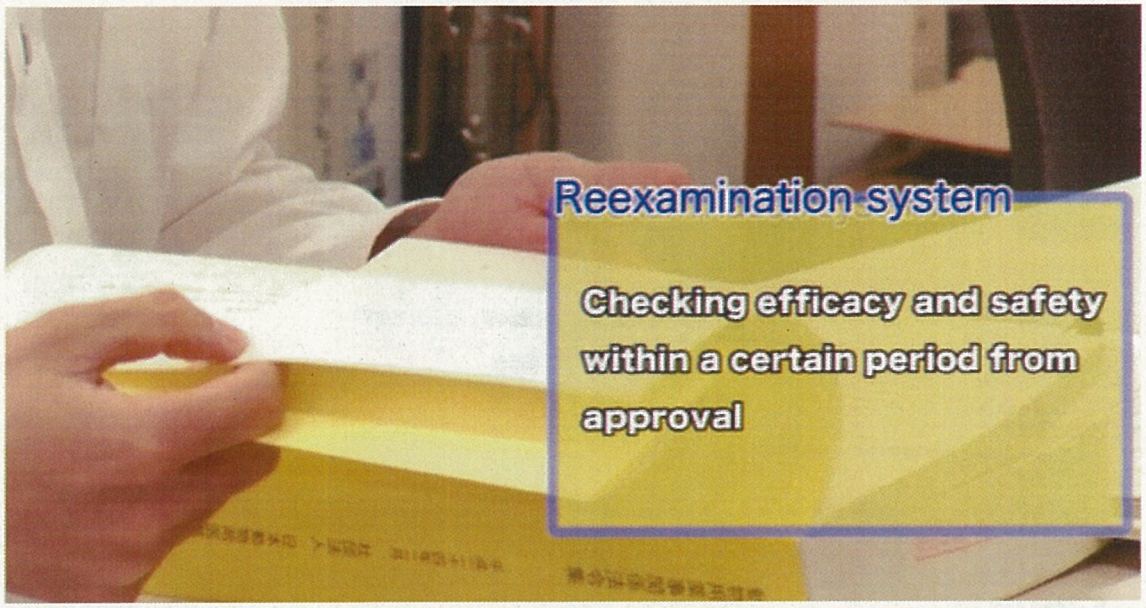




To market and release veterinary medicinal products, each item must be approved by the Minister of Agriculture, Forestry and Fisheries.
Based on documentation submitted by an applicant, NVAL will first examine the application in terms of quality, efficacy, and safety.

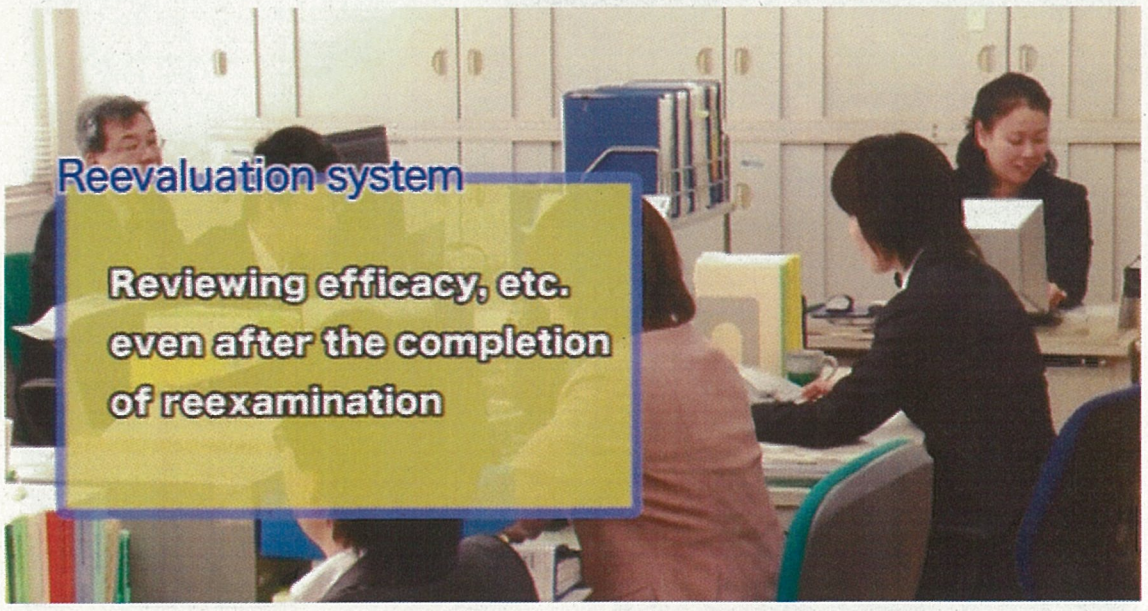
The assessment, including confirmation of the evaluation policy by the responsible officer, begins after the application has been submitted.
When the verification is complete, the responsible officer will review the quality, efficacy, and safety of the application on a scientific basis while conducting 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.

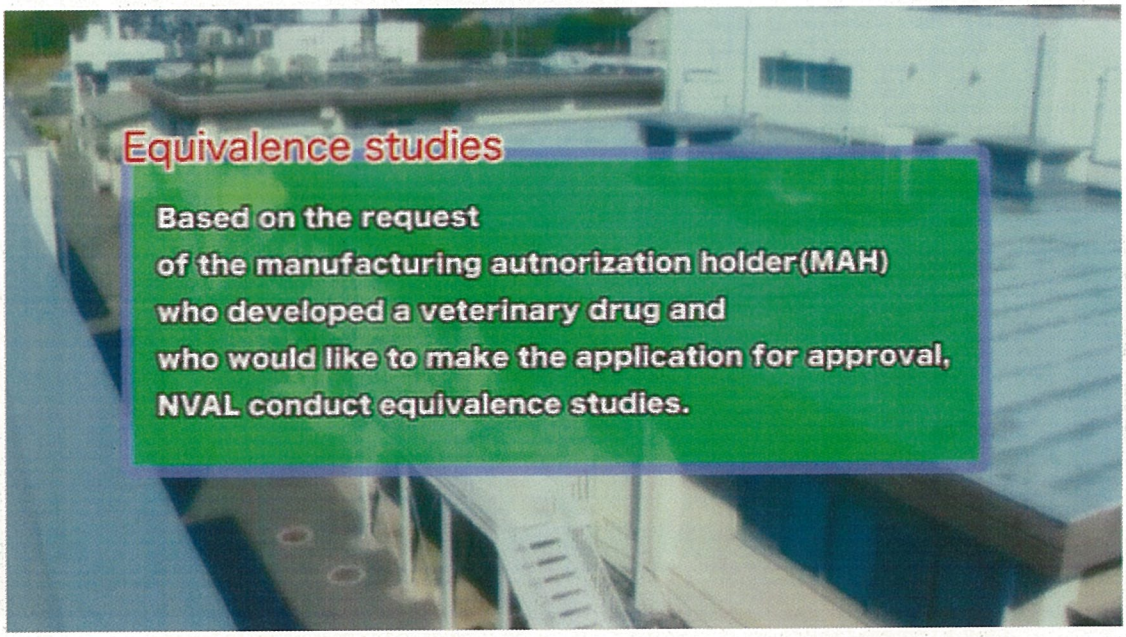



When approving a new veterinary medicinal product, the Act sets a reexamination system for evaluation of efficacy and safety within a certain period of time after the pharmaceutical's initial approval.



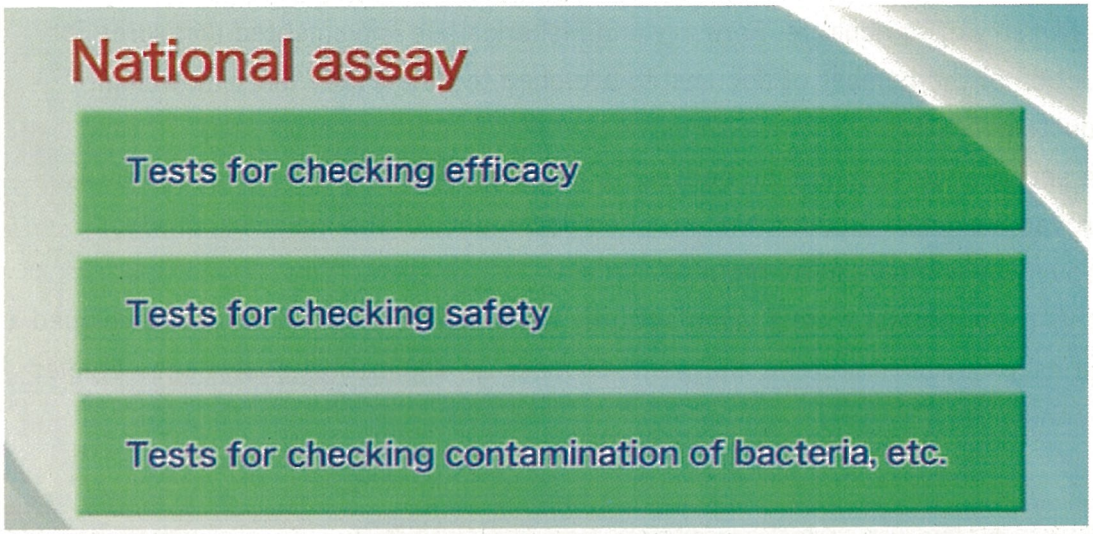
Moreover, with regard to veterinary medicinal products designated by the Minister of Agriculture, Forestry, and Fisheries, even after the completion of reexamination, there is a re-evaluation system for reviewing safety and efficacy.
NVAL collects literature and documentation required for re-examination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

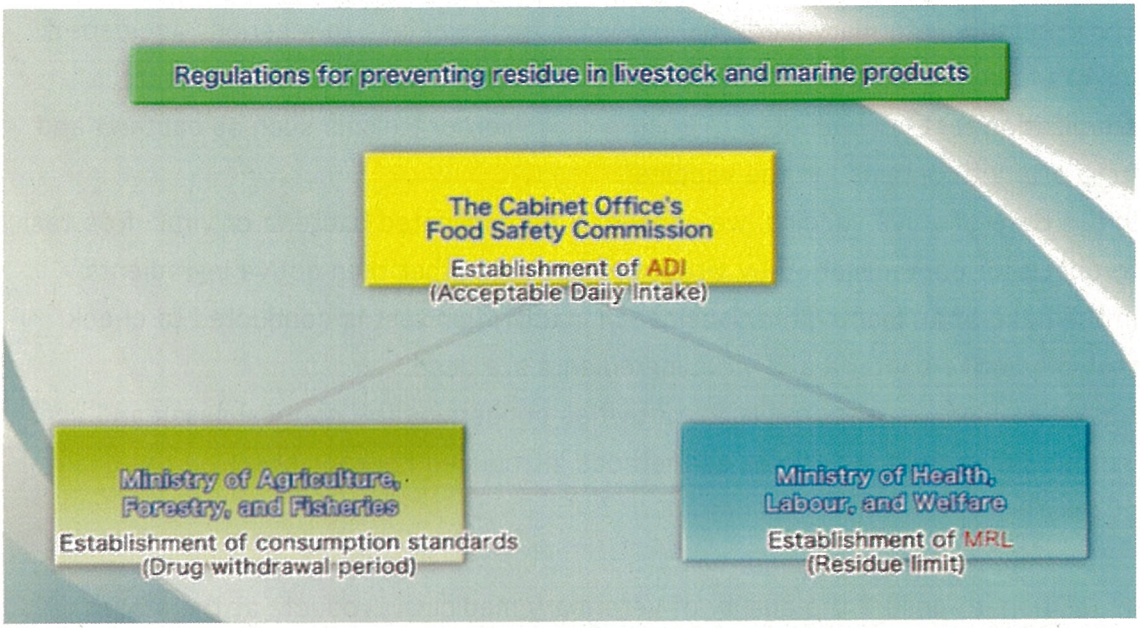
In addition, in the case of a live vaccine that contains a live virus or bacteria as active ingredients, the vaccine's efficacy is checked by measuring the amount of the virus or bacteria in the vaccine.

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.

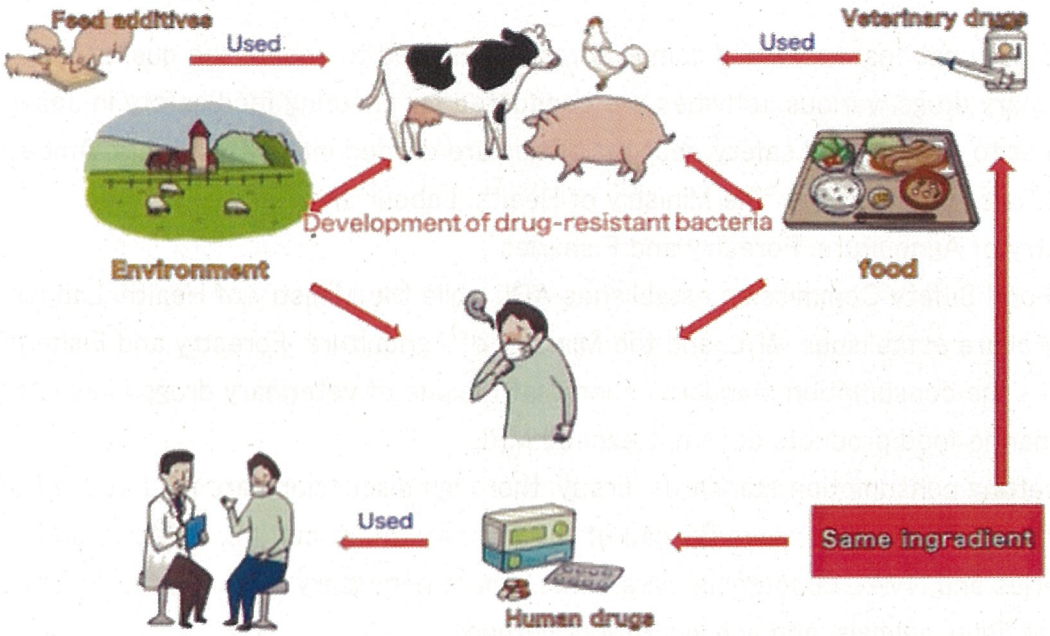
The Food Safety Commission establishes ADI, while the Ministry of Health, Labour, and Welfare establishes MRL, and the Ministry of Agriculture, Forestry and Fisheries defines the consumption standards such that residue of veterinary drugs in livestock and marine food products does not exceed MRL.

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.

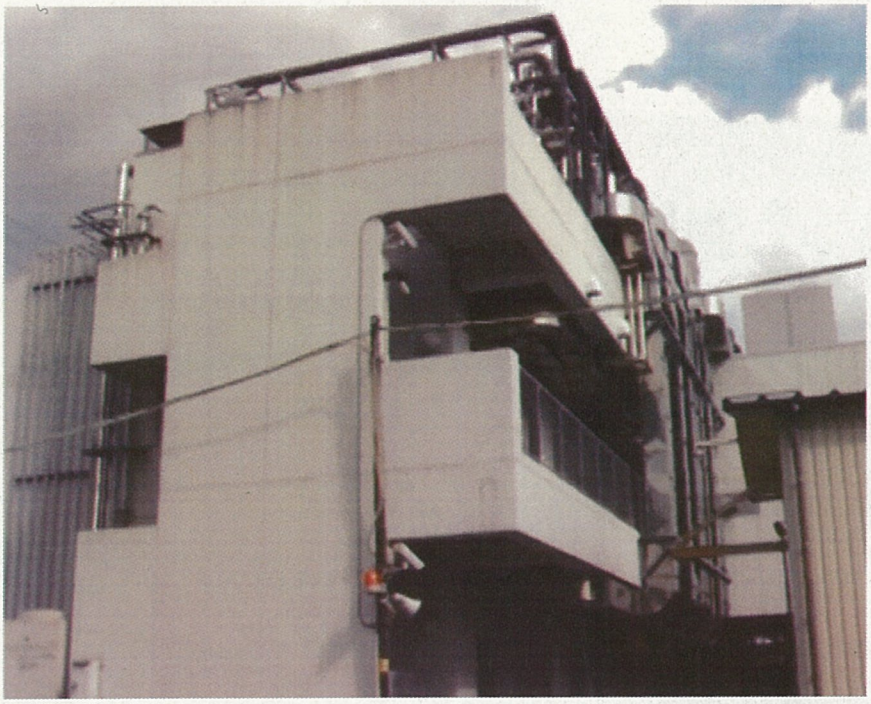
For veterinary drugs where the extent of residue needs to be checked, NVAL actually administers the drugs on livestock, and measures the residual concentration in their organs.

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.

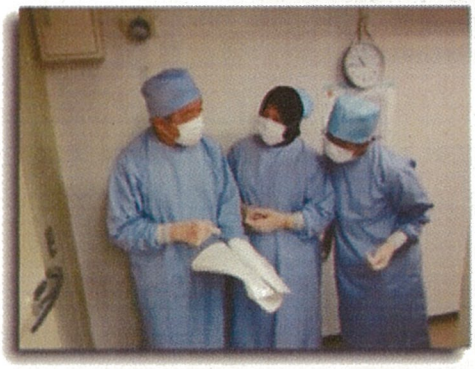
These are required for risk management in the case of an epidemic of infectious diseases such as foot-and-mouth disease.

## 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.