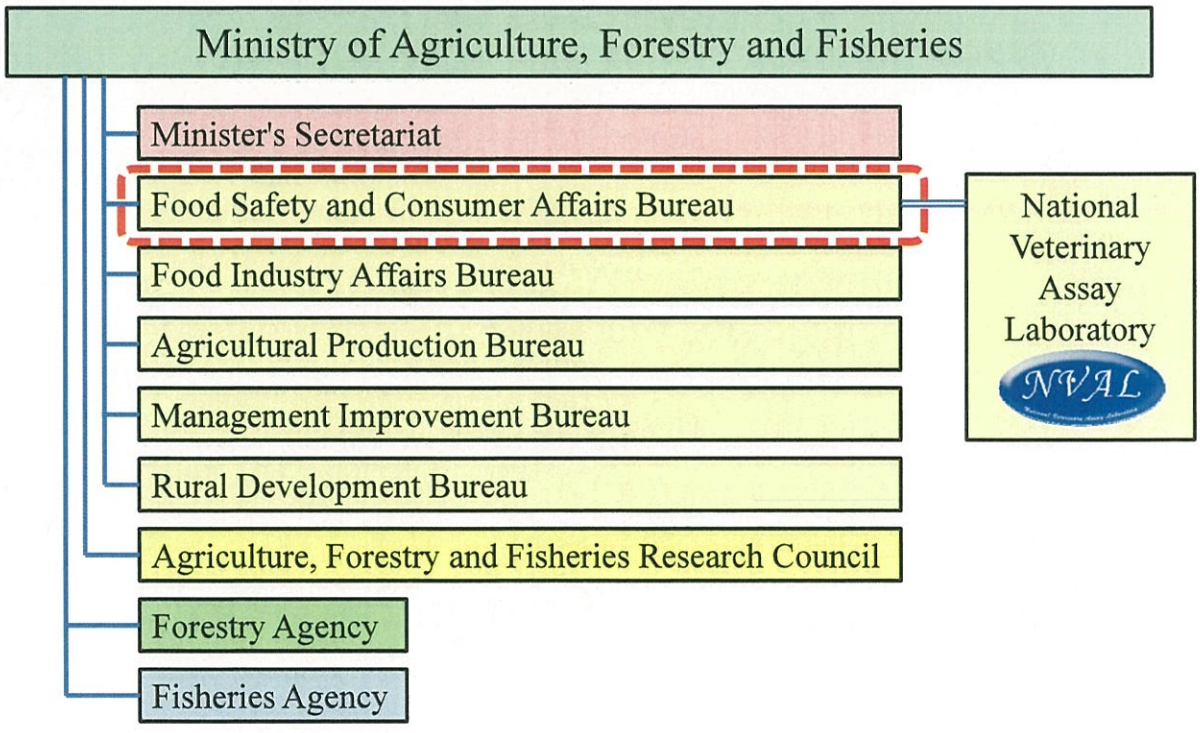
Herbal Medicine for Animal Use in JAPAN

Quality Assay Section,
Assay Division Ⅱ,
National Veterinary Assay Laboratory

21 Dec. 2016

Organization of MAFF in 2016



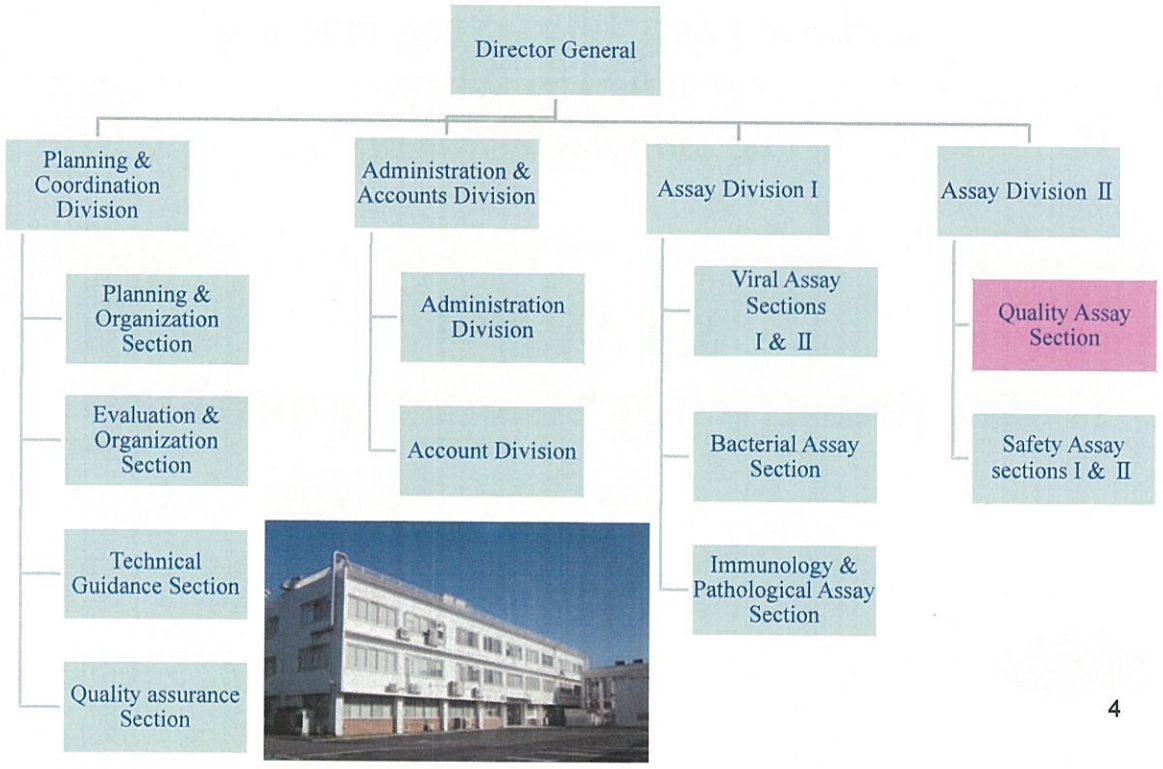
Organization of MAFF in 2016

National Veterinary Assay Laboratory

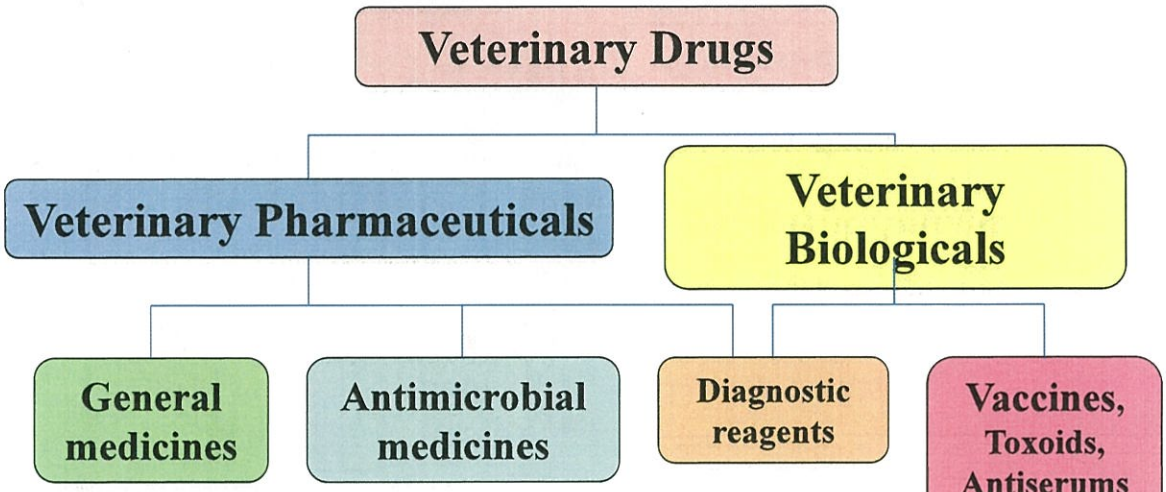
- National assays
- Review of applications for approval
- National tests, spot sampling tests, etc.
- Reviews of reliability standard compliance
- Inspections (GLP, GCP, GMP)
- Consultation on the development of veterinary drugs

HOME PAGE http://www.maff.go.jp/nval/
E-mail nval@nval.maff.go.jp
1-15-1 TOKURA, KOKUBUNJI, TOKYO
185-8511,JAPAN
TEL +81-42-321-1841
FAX +81-42-321-1769

Organization of NVAL in 2016



Veterinary Drugs



- Herbal medicines
- Vitamins
- Hormones
- Digestive medicines
- Anti-inflammatory agents
- Disinfectants / Antiseptics
- Pesticides for animal etc.

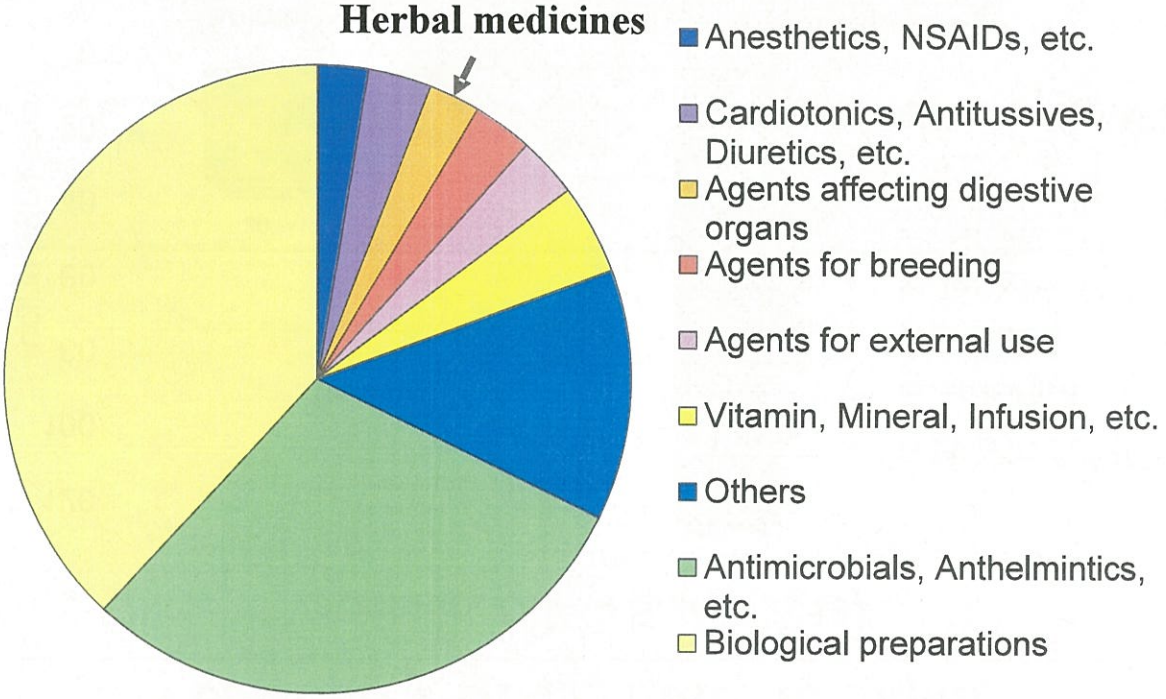
Veterinary Drugs Sales in Japan

(Animal Health Industry Global Market Review 2015)

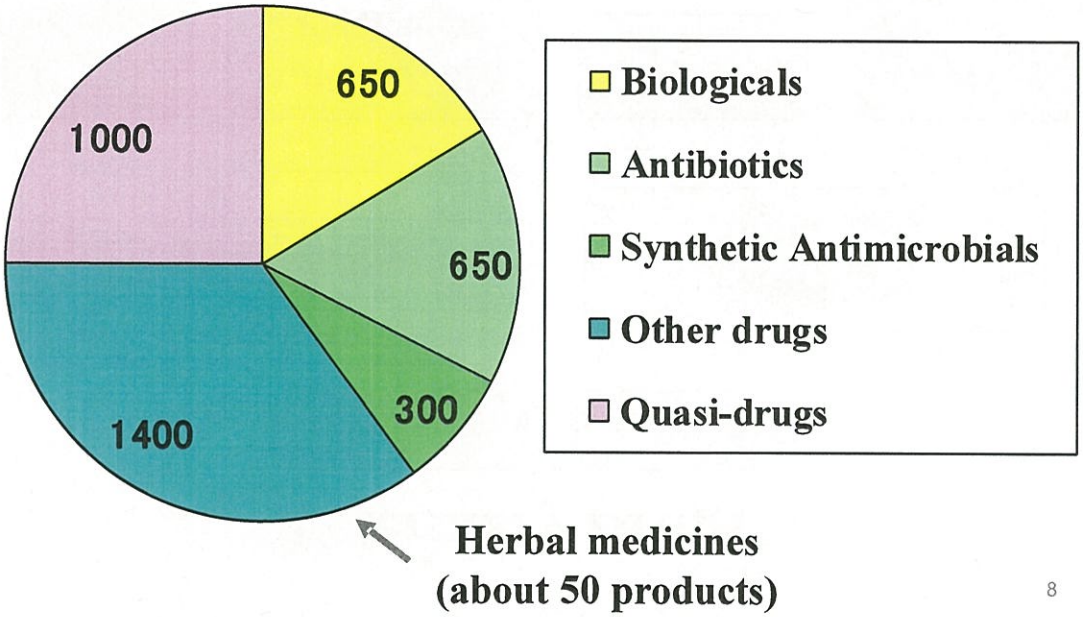
Sales in Japan : 0.8 billion (0.8×10^9) US$/year

Veterinary Drugs Sales in Japan (2014)

Classification by Pharmacological Action



Veterinary Drugs Approved in Japan



Risk Management of Veterinary Drugs

Pre Marketing
- Marketing Approval System

Post Marketing.

Manufacturing & Quality Control
- License of the Manufacturer
- License of the Marketing Authorization Holders

Distribution Control
- License of the Retailer
- System for Drugs Requiring Veterinary Consultation
- Prescription system

Use Control
- Restrictions on the Usage of Veterinary Drugs

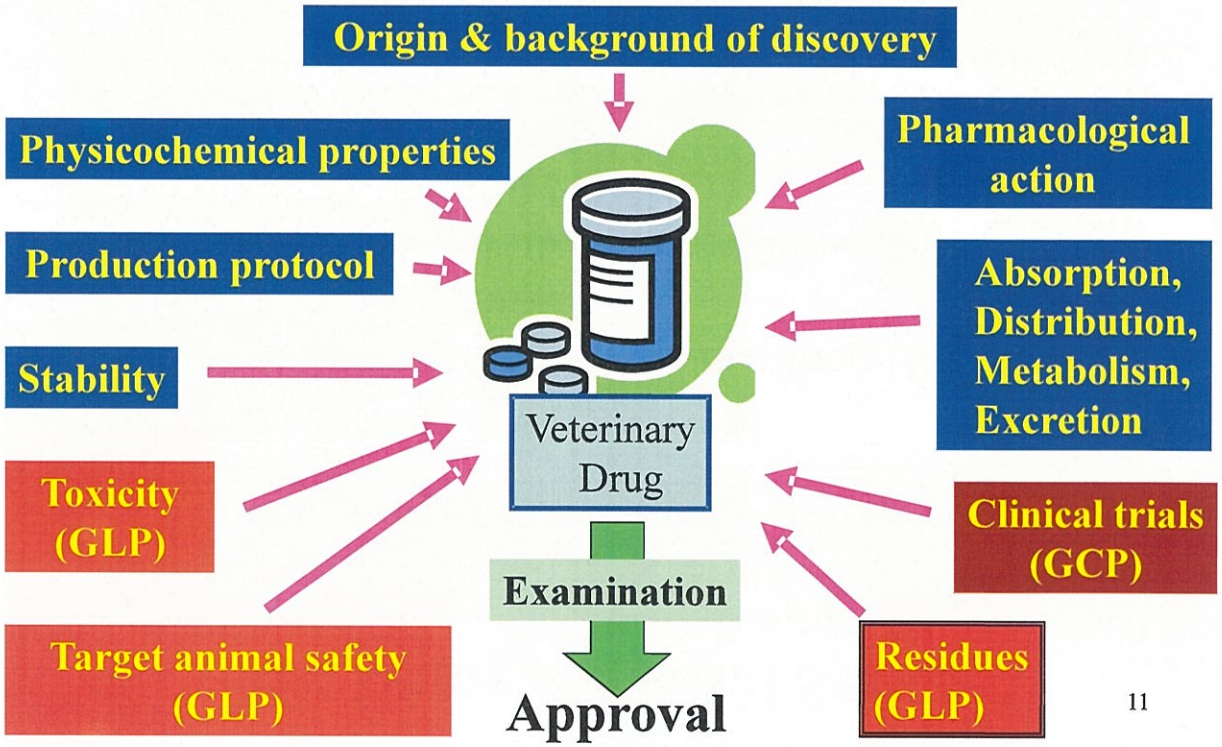
Review of Marketing Approval
- Reexamination & Reevaluation
- Reporting Adverse Reactions

Marketing Approval System

Nobody can sell veterinary drugs without Marketing Approval.

Requirements of the approval
- ✓ License of the Marketing Authorization Holders
- ✓ License of the Manufacturer
- ✓ Management of manufacture conformed to GMP (Good Manufacturing Practice)
- ✓ Data for Marketing Approval
  - Data conformed to GLP(Good Laboratory Practice)
  - Data conformed to GCP(Good Clinical Practice)

Data Required for Marketing Approval of a Veterinary Drug in Japan



Data No.	Data category		(A) New herbal medicine	(B) New compositions	(C)New administration route	(D)New dosage/indications	(E) Generic
1	Origin & background of discovery		○	○	○	○	×
2	Physicochemical properties		○	○	△	△	○
3	Production protocol		△	△	△	△	△
5	Stability		○	○	△	△	○
6	Toxicity	Acute	△	×	×	×	×
7		Repeat (Chronic etc.)	△	×	×	×	×
8		Specific	△	△	△	×	×
9	Target animal safety		△	△	△	△	×
10	Pharmacological action	Efficacy	△	×	×	×	×
11		General	△	×	×	×	×
12	Absorption, distribution, metabolism & excretion		△	△	△	△	×
14	Clinical trial		○	○	○	○	×
15	Residue		△	△	△	△	×

(note) ○: Data must be attached
△: It shall not be necessary to attach the data
×: Data shall not be necessary to attach

Distribution Control

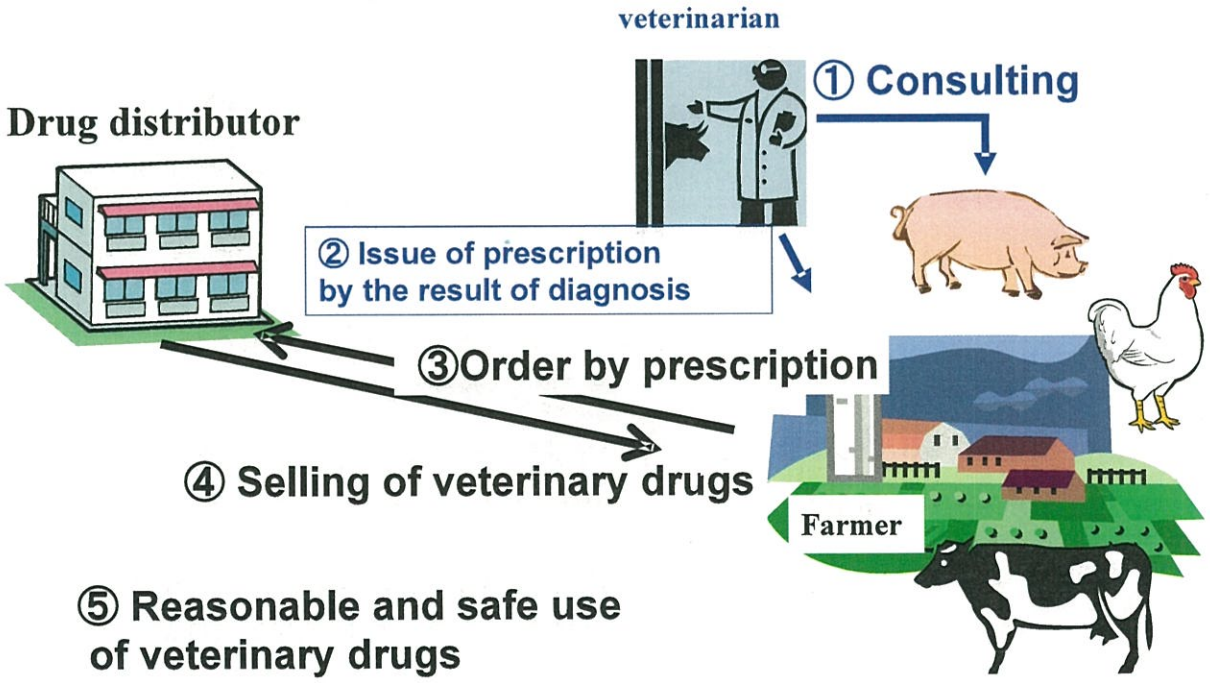
System for Drugs Requiring Veterinary Consultation

No veterinarian should provide or prescribe poisonous or powerful drugs, etc., without providing consultation by themselves.

① Poisonous drugs
② Powerful drugs
③ Biologics（vaccines, serums)
④ Prescription drugs
(Vaccines, Antimicrobial medicines, Hormonal products, etc.)
⑤ Drugs regulated for use on animals
(Antimicrobial medicines, Hormonal products)

Veterinary drugs used for fish is not included in this system.

Prescription System



Veterinary drugs used for fish is not included in this system.

Use Control

Restrictions on the Usage of Veterinary Drugs

Standards governing restrictions on the usage of veterinary drugs used for food-producing animals

to assure public health safety in administration of antimicrobial preparations, etc.

to meat or milk-producing animals, poultry, fish/crustacea or bees,

to specify drugs that can be used, and their administration, dosages, and prohibition periods for use in the animals concerned.

Example of Standards of Restriction for Usage of Veterinary Drugs

Drugs	Target animal	Dosage	Prohibition period for use
Ampicillin (in feed)	Cattle (not more than 6 months old))	- Administrate not more than 24 mg/kg bw /day	5 days before slaughter
	Pigs		ys before ghter
	Chickens	- Administrate not more than 40 mg/kg bw/day	2 days before slaughter

Ampicillin level in beef should not exceed its MRL!

16

Regulation of Veterinary drug Residues in Food

Marketing Approval System

- FSC : ADI (Risk assessment)
- MHLW : MRL
- MAFF : Withdrawal Period

→ **Establishment of Appropriate Withdrawal Period**

Distribution Control

- System for Drugs Requiring Veterinary Consultation
- Prescription System

→ **Appropriate Use of Drugs under the veterinarian's control.**

Use Control

- Restrictions on the Usage of Veterinary Drugs

→ **These regulations will prevent the veterinary drug over MRL from remaining in food**

Countermeasures against Antimicrobial Resistance (AMR)

Marketing Approval System

- FSC : Risk Assessment of AMR
- MAFF : Approval (included specifying method of administration, dose, precautions for use)

Distribution Control

- System for Drugs Requiring Veterinary Consultation
- Prescription System

Use Control

- Restrictions on the Usage of Veterinary Drugs

Other

- Second Choice Drug System
- Enlightenment of Prudent Use

→ **These regulations will manage AMR**

Appendix

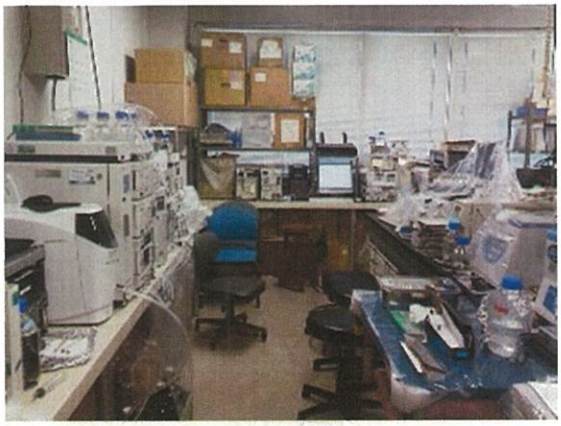
Activities of Quality Assay Section

Members of Quality Assay Section

Permanent employees (2)

- Pharmacist (1)
- Veterinarian (1)

Temporary employee (1)



Main Activities of Quality Assay Section

1. Quality Tests
2. Examination and consultation for approval applications
3. Investigation and Research

   of

   Pharmaceuticals & Quasi drugs for animals

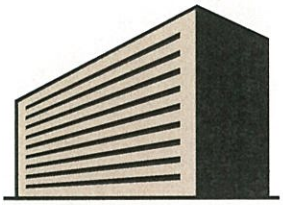
4. Technical support in VICH & Codex to develop international guidelines & standards

Activity 1.
Quality Tests

(1) Sampling tests for veterinary drugs on the market

(2) Tests requested from a license marketing approval holder

Sampling Test



- Marketing License holder
- Retailer

①Inspection

MAFF (NVAL)
Prefecture Government
(Pharmaceutical Inspectors)

② Sampling of Drugs

NVAL

Receive
→ Implementation of Test
→ Decision of test
(1)Passing or
(2)Rejection of test

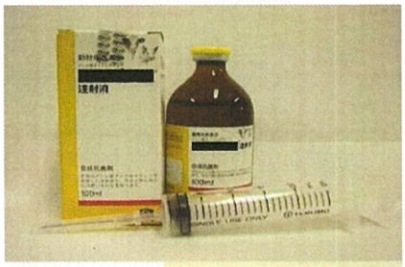
Marketing License holder

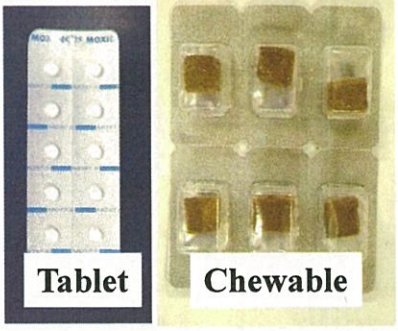
③ Notice of result

④ Rejected products by the test are discarded

Example of Approved Drugs

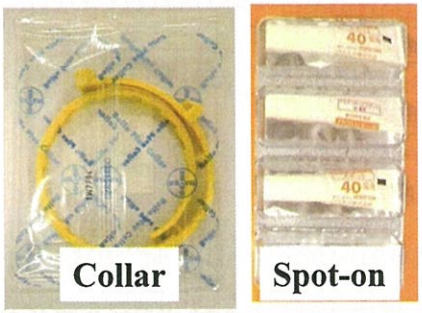
Antibiotic Preparation for therapy





Preparation for Prevention against Filariasis

Preparation for disinfection of goldfish



Preparation for Extermination of flea on dog and cat

Product Label & Package Insert of Drugs

(Restricted by the Pharmaceuticals and Medical Devices Act)

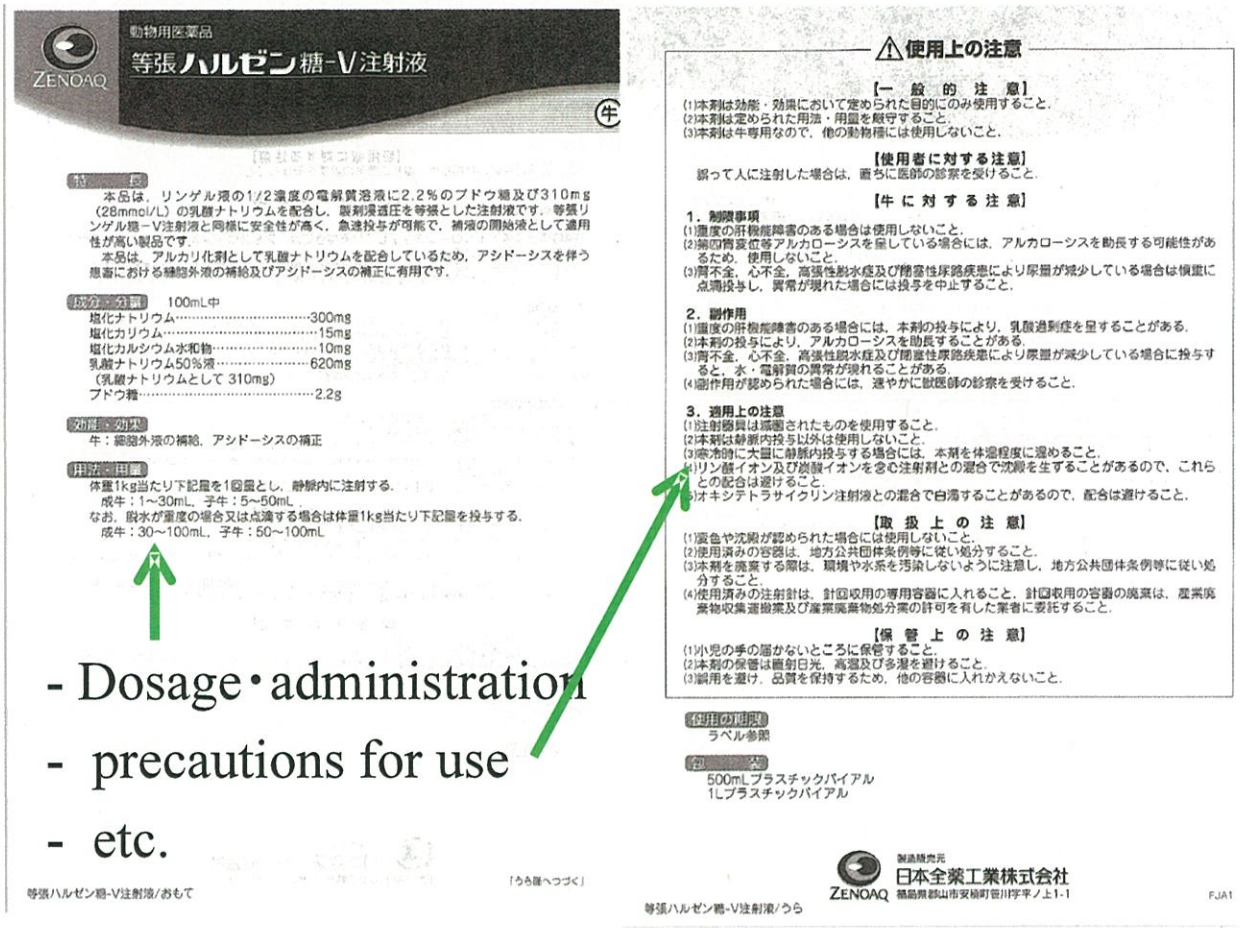
A. Items of Product Label

- "動物用医薬品 (Drug for Animals)"
- Product name, manufacturing number/code
- Weight/content of the drug
- Name and address of the Marketing License Holder
- "毒 (poison)", or "劇 (powerful)"
- etc.

B. Items of Package Insert

- Dosage, administration, precautions for use etc.[4-1]

- "動物用医薬品 (Drug for Animals)"
- Product name, manufacturing number/code
- Weight/content of the drug
- Name and address of the Marketing License Holder
- "毒 (poison)", or "劇 (powerful)"
- etc.



動物用医薬品

等張ハルゼン糖-V注射液

牛

特　長

本品は，リンゲル液の1/2濃度の電解質溶液に2.2％のブドウ糖及び310mg（28mmol/L）の乳酸ナトリウムを配合し，脱刺激酒石を等張とした注射液です．等張リンゲル糖－V注射液と同様に安全性が高く，急速投与が可能で，補液の開始液として適用性が高い製品です．

本品は，アルカリ化剤として乳酸ナトリウムを配合しているため，アシドーシスを伴う患畜における細胞外液の補給及びアシドーシスの補正に有用です．

成分・分量　100mL中

塩化ナトリウム……300mg
塩化カリウム……15mg
塩化カルシウム水和物……10mg
乳酸ナトリウム50％液……620mg
（乳酸ナトリウムとして 310mg）
ブドウ糖……2.2g

効能・効果

牛：細胞外液の補給，アシドーシスの補正

用法・用量

体重1kg当たり下記量を1回量とし，静脈内に注射する．
成牛：1～30mL，子牛：5～50mL
なお，脱水が重度の場合又は点滴する場合は体重1kg当たり下記量を投与する．
成牛：30～100mL，子牛：50～100mL

- Dosage・administration
- precautions for use
- etc.

「うら面へつづく」

等張ハルゼン糖-V注射液/おもて

⚠使用上の注意

【一　般　的　注　意】

(1)本剤は効能・効果において定められた目的にのみ使用すること．
(2)本剤は定められた用法・用量を厳守すること．
(3)本剤は牛専用なので，他の動物種には使用しないこと．

【使用者に対する注意】

誤って人に注射した場合は，直ちに医師の診察を受けること．

【牛　に　対　す　る　注　意】

1．禁忌事項
(1)重度の肝機能障害のある場合には，本剤の投与により，乳酸過剰症を呈することがある．
(2)代謝性アルカローシスを呈している場合には，アルカローシスを助長する可能性があるため，使用しないこと．
(3)腎不全，心不全，高張性脱水症及び閉塞性尿路疾患により尿量が減少している場合は慎重に点滴投与し，異常が現れた場合には投与を中止すること．

2．副作用
(1)重度の肝機能障害のある場合には，本剤の投与により，乳酸過剰症を呈することがある．
(2)本剤の投与により，アルカローシスを助長することがある．
(3)腎不全，心不全，高張性脱水症及び閉塞性尿路疾患により尿量が減少している場合に投与すると，水・電解質の異常が現れることがある．
(4)副作用が認められた場合には，速やかに獣医師の診察を受けること．

3．適用上の注意
(1)注射器具は滅菌されたものを使用すること．
(2)本剤は静脈内投与以外は使用しないこと．
(3)急速に大量に静脈内投与する場合には，本剤を体温程度に温めること．
(4)リン酸イオン及び炭酸イオンを含む注射剤との混合で沈殿を生ずることがあるので，これらとの配合は避けること．
(5)オキシテトラサイクリン注射液との混合で白濁することがあるので，配合は避けること．

【取　扱　上　の　注　意】

(1)変色や沈殿が認められた場合には使用しないこと．
(2)使用済みの容器は，地方公共団体条例等に従い処分すること．
(3)本剤を廃棄する際は，環境や水系を汚染しないように注意し，地方公共団体条例等に従い処分すること．
(4)使用済みの注射針は，針回収用の専用容器に入れること．針回収用の容器の廃棄は，産業廃棄物収集運搬業及び産業廃棄物処分業の許可を有した業者に委託すること．

【保　管　上　の　注　意】

(1)小児の手の届かないところに保管すること．
(2)本剤の保管は直射日光，高温及び多湿を避けること．
(3)誤用を避け，品質を保持するため，他の容器に入れかえないこと．

使用の期限
ラベル参照

包　装
500mLプラスチックバイアル
1Lプラスチックバイアル

製造販売元
ZENOAQ 日本全薬工業株式会社
福島県郡山市安積町笹川字半ノ上1-1

FJA1

等張ハルゼン糖-V注射液/うら

Specification of Chemical Veterinary Drugs

- Content
- Description
- Identification
- Assay
- Specific Tests (depend on individual VMP)

  Loss of drying, Specific Gravity and Density, pH, Sterility, Extractable Volume of Parenteral Preparations, Uniformity of Dosage Units, Foreign Insoluble Matter Test for Injections, etc.

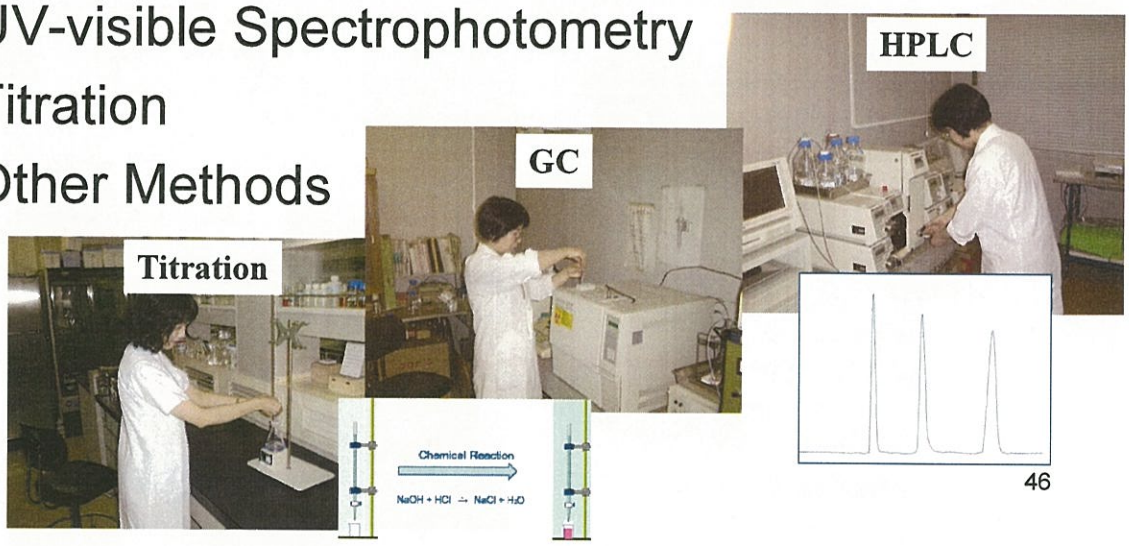
(Based upon Japanese Pharmacopoeia in principle)

Identification

- Qualitative Tests
  -Chloride
  -Calcium
  -etc.
- Thin-Layer Chromatography
- UV-visible Spectrophotometry
- Other Methods

Assay

- Liquid Chromatography（HPLC）
- Gas Chromatography (GC)
- UV-visible Spectrophotometry
- Titration
- Other Methods



Analytical Equipment in NVAL

- HPLC
- LC/MS/MS
- GC
- Spectrophotometer
- ICP (Inductively Coupled Plasma)
- Polarimeter
- Karl Fischer Titration Equipment


HPLC


ICP

47

Activity 2.
Examination and consultation for approval applications

(1) Approval applications of drugs & quasi-drugs

(2) Re-examination & re-evaluation of approved drugs

(3) Clinical trial notifications for new drugs

(4) Consultation on approval of drugs under development

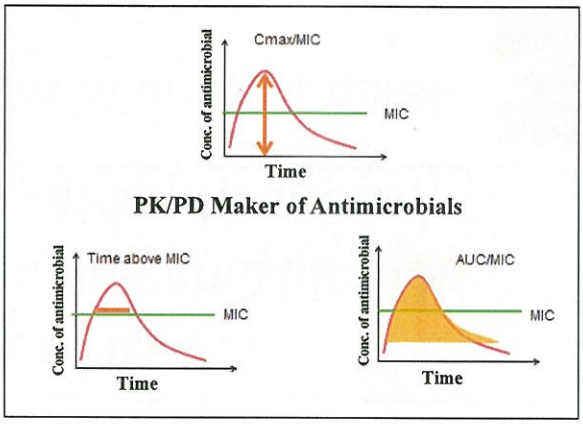
(5) Inspection of GLP, GCP & GMP

48

Activity 3. Investigation and Research

(1) Investigation of effective methods for collection of information on approval review of drugs

(2) Development of guidelines for clinical studies of Bovine Mastitis



Activity 4. Technical support in VICH & Codex to develop international guidelines & standards

VICH

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

Codex

The Codex Alimentarius international food standards, guidelines and codes of practice contribute to the safety, quality and fairness of this international food trade.

VICH Activities

1. A huge money & long time are needed for veterinary drug registration.

2. There are differences in the requirements among the EU, the US and Japan.

3. VICH activities are continuing with a focus on using common data for applications in EU, the US and Japan
   →To reduce developmental costs and time

4. Main VICH activity is making guidelines for the study methods used in the data for approval of veterinary drugs.
   - 53 final guidelines and 3 draft guidelines at present.
   - You can download guidelines from VICH website (http://www.vichsec.org/)