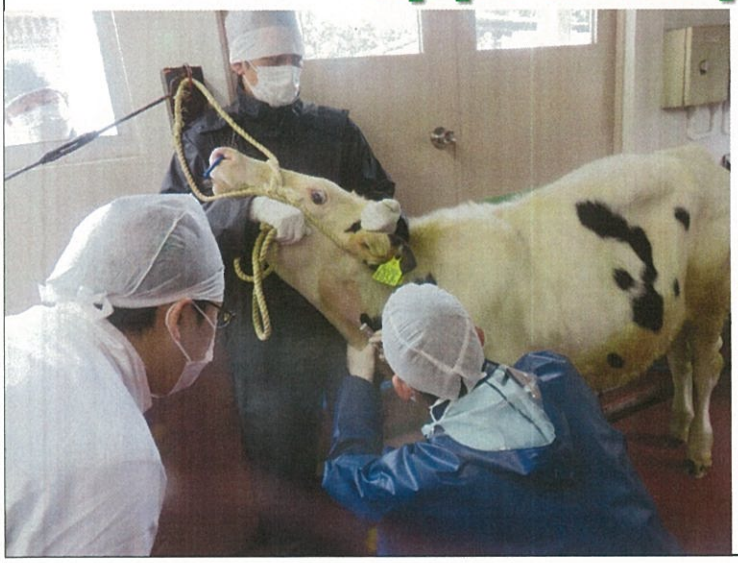
Japanese Veterinary Drug approval procedure



Traning Program in NVAL

2016.12.19～12.22

HOSODA Yuko

細田　裕子

Todays Topic

- Topic 1

Overview of The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices.

- Topic 2

Approval Procedures for Veterinary Drugs

- Topic 3

Approval application for veterinary Drugs

- Topic 4

The Standard for veterinary biological products

- Topic 5

Seed-lot System

Topic 1

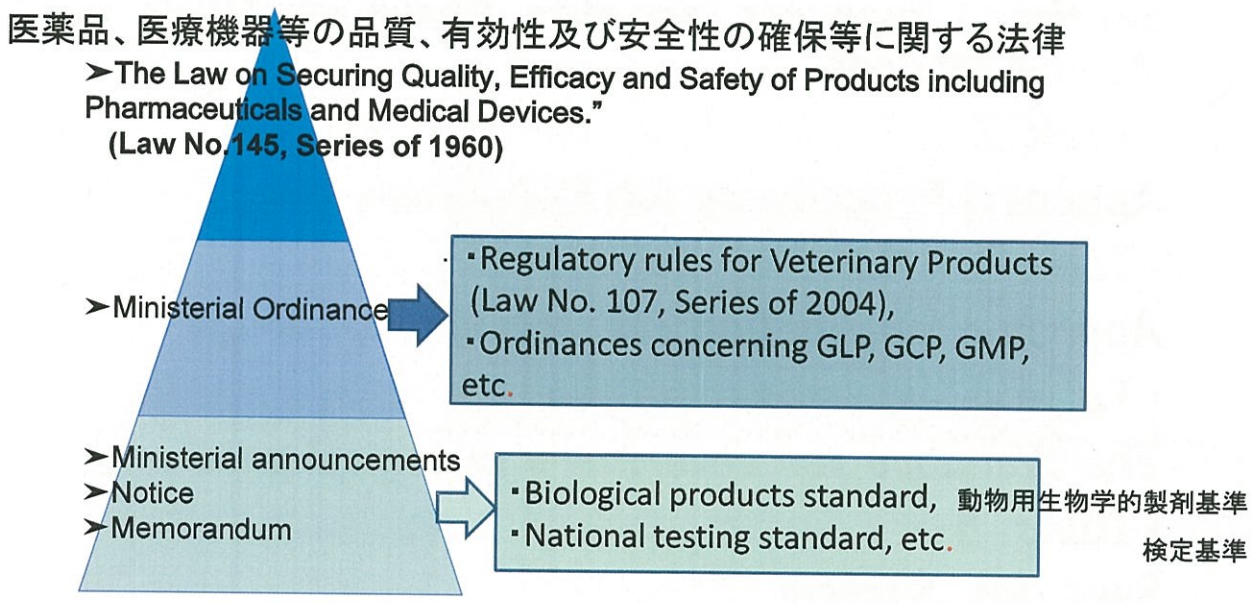
Overview of

The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices."

医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律

The title of the 'Pharmaceutical Affairs Law' was revised at 25, Nov., 2014

Legal Hierarchy



Organizations and functions of the veterinary pharmaceutical administration

Government in Charge of Products

The Ministry of Agriculture, Forestry and Fisheries (**MAFF**) 農林水産省 → Veterinary Medicinal Products (exclusively used for animals) — 動物

The Ministry of Health, Labor and Welfare (**MHLW**) 厚生労働省 → Pharmaceuticals and Medical Devices for human use — 人

What is a Veterinary Drug ?

- Veterinary Medicinal devices
- Veterinary Drugs
  - Quaci-drugs
  - Veterinary Medicine
    - General products
      - ・Vitamins,
      - ・Hormones
      - ・Digestive medicines
      - ・Anti-inflammatory agents
    - Antimicrobial substances
    - Diagnostic reagents
  - Veterinary Biologics
    - **Vaccines**, Toxoids, Antiserums
- Veterinary regenerative medical products

Facility for veterinary drugs

MAFF (Ministry of Agriculture, Forestry and Fisheries) 農林水産省

FSCAB (Food Safety and Consumer Affaires Bureau) 消費安全局

APSD (Animal Products Safety Division) 畜水産安全管理課

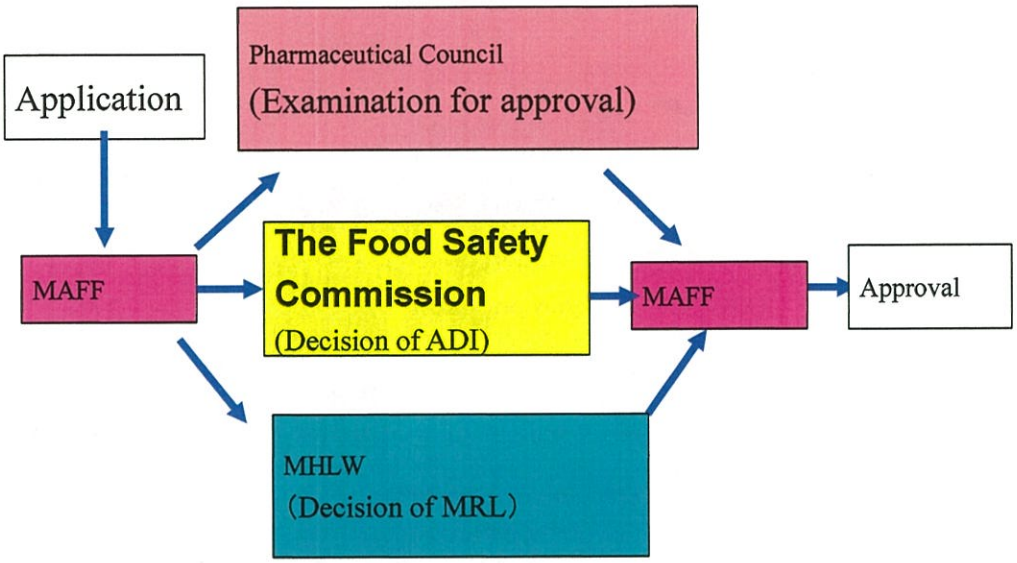
NVAL (National Veterinary Assay Laboratory) 動物医薬品検査所

- National assay of veterinary biologics 国家検定
- Review of application for approval 承認審査
- Spot sampling test of veterinary medicines, etc
- Review of reliability standard compliance
- Inspection (GLP,GCP,GMP)
- Consultation of veterinary drugs development

Topic 2

Approval Procedures for Veterinary Drugs
動物用医薬品の承認手続

Flowchart of Application to Approval



Council for Veterinary Drugs

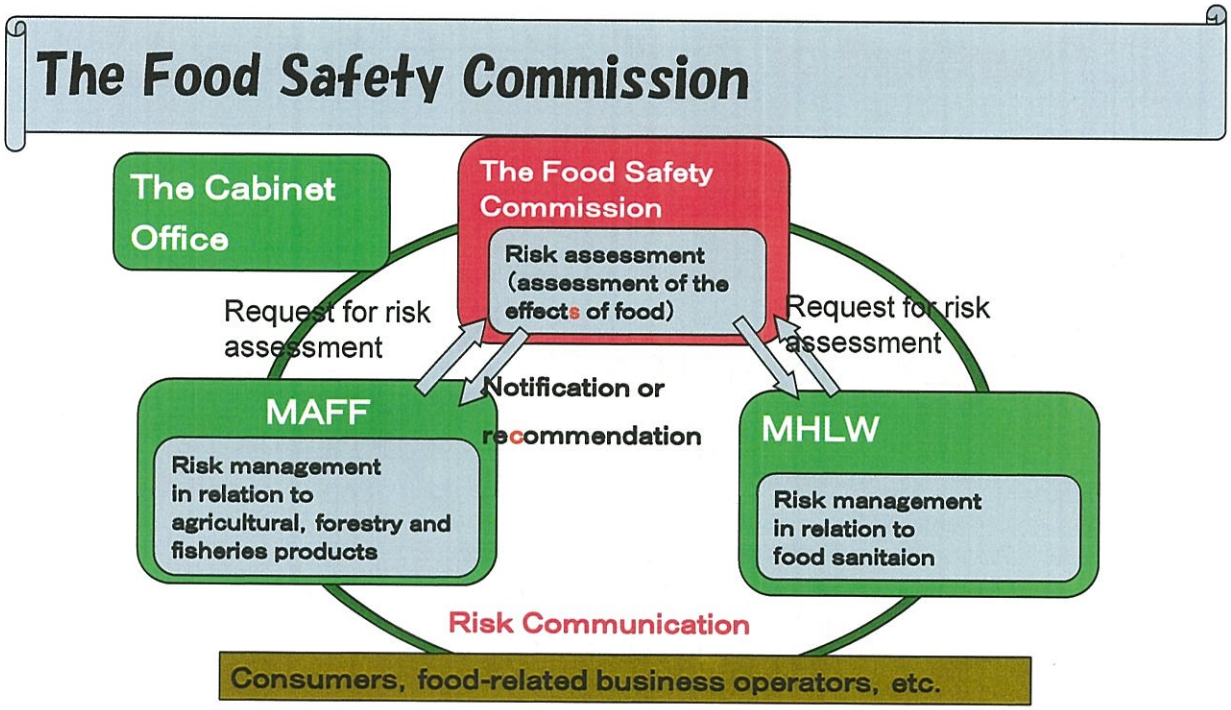
Pharmaceutical Affairs and Food Sanitation Council (**PAFSC**)

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 veterinary drugs: (approval of new drugs, reexamination or reevaluation of approved drugs)
- Establishment of standards for veterinary drugs



Topic 3

Approval application for veterinary medicinal products

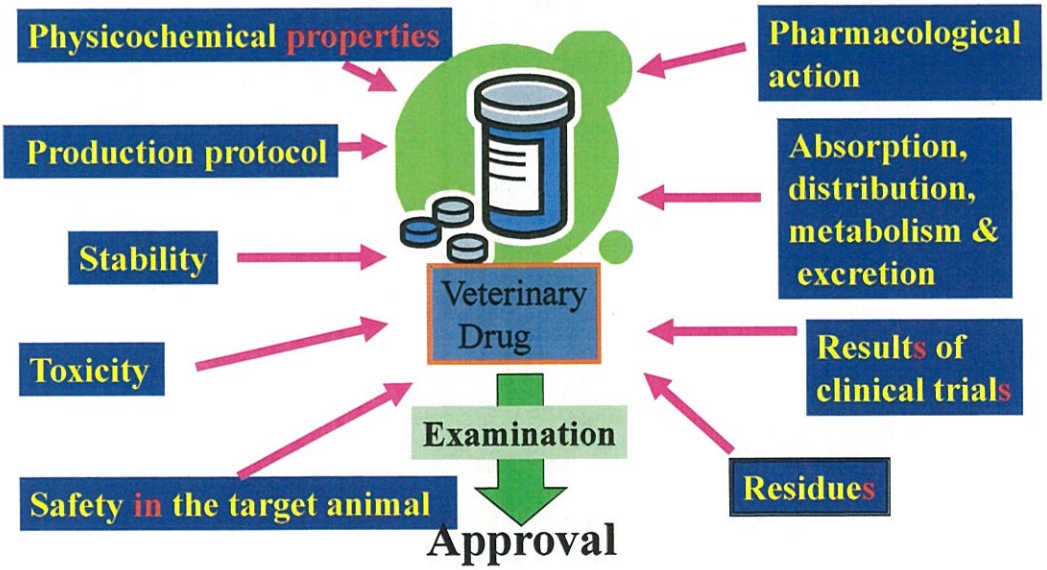
（動物用医薬品等の承認申請）

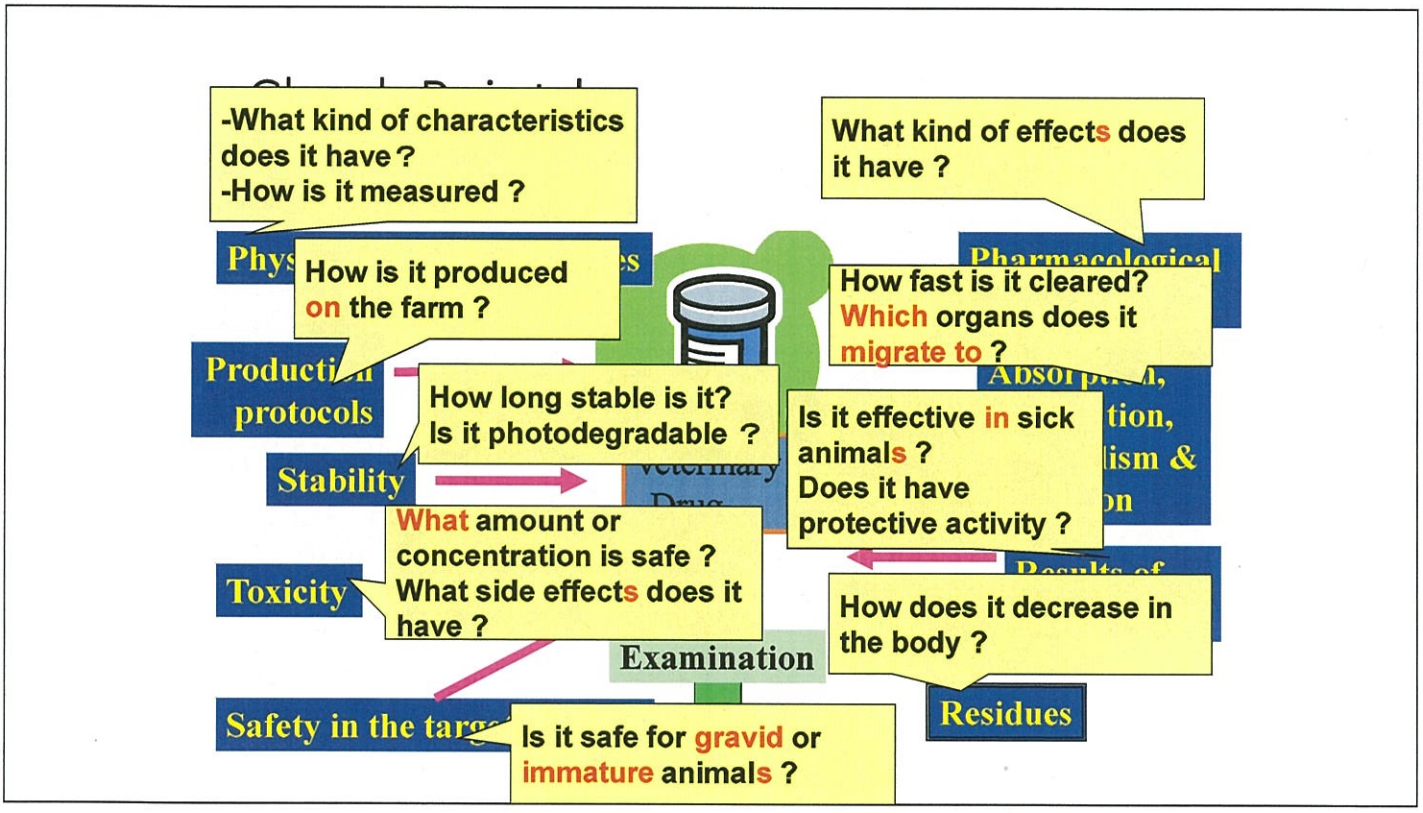
Form for Approval application

Application for Marketing Approval

1 Name and Address of Company
2 License No. & Address of Marketing Approval Holder
3 Type of License
4 Name of Drug Product
5 Ingredients and Quantities
6 Manufacturing Method
7 Administration and dosage
8 Indications and effects
9 Condition for storage
10 Period of validity
11 Standards and Test Methods
12 Reference

Data Required for Marketing Approval of a Veterinary Drug





Appendixes

App. 1: Origin and background of the discovery 起源又は開発の経緯
App. 2: Physicochemical properties 物理化学的性状
App. 3: Production protocol 製造工程
App. 5: Stability 安定性
App. 6: Toxicity (acute toxicity) 毒性(急性毒性)
App. 7: Toxicity (sub acute and chronic toxicity) 毒性(亜急性及び慢性毒性)
App. 8: Toxicity (special toxicity (e.g. mutagenicity, local irritation, etc.) 毒性(特殊毒性(e.g.変異原性、局所刺激、etc.)

* App. 4 is only for Medical Device.

Appendixes

App. 9: Target Animal Safety　対象動物の安全性試験
App.10: Pharmacology related to efficacy
有効性に関する薬理試験
App.11: General pharmacology　一般薬理試験
App.12: ADME (absorption, distribution, metabolism and excretion)
吸収、分布、代謝及び排泄に関する試験
App.14: Clinical trial　臨床試験
App.15: Residue for food producing animals　残留性に関する試験

* App. 13 is only for Medical Device.

Application for Marketing Approval

1 Name and Address of Company
2 License No. & Address of Marketing Approval Holder
3 Type of License
4 Name of Drug
5 Ingredients and Quantities
6 Manufacturing Method
7 Administration and dosage
8 Indications and effects
9 Condition for storage
10 Period of validity
11 Standards and Test Methods
12 Reference

Must be attached　Appendixes

For Example

Approval application
for veterinary biological products

Approval application for veterinary biological products
Appendixes

Appendix 1: Origin and background of the discovery　起源又は発見の経緯
Appendix 2: Physicochemical properties 物理化学的性状
Appendix 3: Production protocol　製造工程
Appendix 5: Stability　安全性
Appendix 9: Target Animal Safety　対象動物を用いた安全試験
Appendix 10: Efficacy　薬理学的試験
Appendix 14: Clinical trial　臨床試験

Application for Marketing Approval

1 Name and Address of Company
2 License No. & Address of Marketing Approval Holder
3 Type of License
4 Name of Drug
5 Ingredients and Quantities
6 Manufacturing Method
7 Administration and dosage
8 Indications and effects
9 Condition for storage
10 Period of validity
11 Standards and Test Methods
12 Reference

Must be attached !

App.1: Origin and background
App.2: Physicochemical properties
App.3: Production protocol
App.5: Stability
App.9: Target Animal Safety
App.10: Efficacy
App.14: Clinical trial

Appendix 1

The origin and background of the development

- **Origin and background of development**
- **Condition of outbreaks in Japan**
- **Condition of use in foreign country**
- **Component comparison of other vaccines**

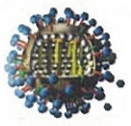
VICH

- International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
- Trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration
- To minimize the need to perform separate studies for regulatory authorities of different countries
- Guideline (GL) 1-51
- http://www.vichsec.org/index.htm

Appendix 2

Physicochemical property of virus strain

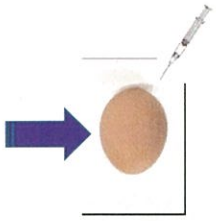
- Origin and creation process
- Attenuation, strain marker and stability (live vaccine)
- Excretion and cohabitation infection (live vaccine)
- Immunogenicity
- Absence of reversion to virulent form (VICH GL41)
- Safety in target animal of master Seed
- Standard and test methods for final product



Appendix 3

Protocol of production

1 Inoculate production seed virus in eggs



Incubate for XXX days at 37 ˚C

2 Gather, filter and centrifuge virus fluid

3 Add diluent and stabilizer

4 Place aliquots in vials and freeze-dry

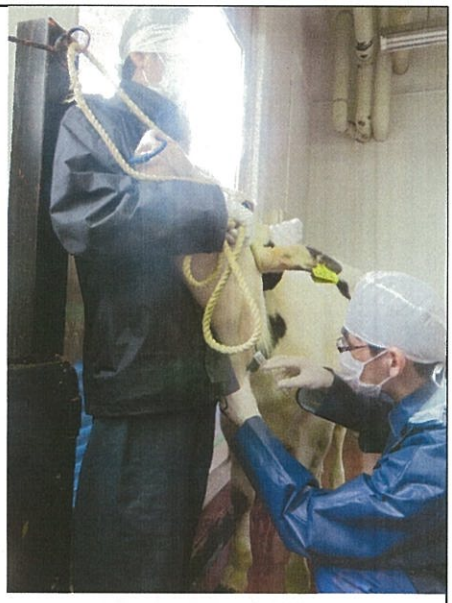
Appendix 5

Stability of Final product

- Method: Long-term stability test (VICH GL3)
- Sample: Final products
- Number of sample: 3 batches
- Test interval : every 3 (6, 12) months
- Test items: All items of the final products

Appendix 9

Target animal Safety test (TAS)



- Method: VICH GL44
- Material: final products
- Number of Animals: 8 animals in each group
- Administration dose:
  - Live vaccine given at 10 doses / animal
  - Inactivated vaccine given at 1 dose / animal
- Data Collection:
  - General clinical observations (vitality, diarrhea, respiration, b.w.)
  - Other relevant criteria such as rectal temperature
  - Injection site (histopathologically after euthanasia)

Appendix 10

Efficacy

- Minimum effective dose
- Minimum effective antibody titer
- Comparative study on sensitivity by age, breed and administration route
- Influence of maternal antibody on vaccination

Appendix 14

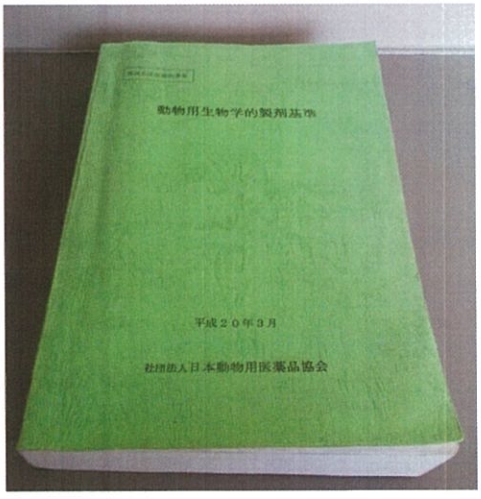
Clinical trial

- Objective :
  - To evaluate the safety and efficacy of the vaccine in the field
- Samples: Final products
- Number of test sites: More than 2 sites
- Number of Animals:
  - ≥ 200 chickens
  - ≥ 60 head for mammals
- Test period:
  - Adequate period for evaluation of safety and efficacy of the vaccine in field

Topic4

The standard for veterinary biological products

(動物用生物学的製剤基準)



http://www.maff.go.jp/nval/kijyun/index.html

動物医薬品検査所

農林水産省トップへ　ホームへ

分野別情報　動物医薬品等データベース　副作用情報データベース

文字の大きさ・色を変えるには　このサイトの使い方　サイトマップ　検索

ホーム > 検定・検査情報 > 動物用生物学的製剤基準名等・手数料・抜取数・標準処理期間の一覧

動物用生物学的製剤基準名等・手数料・抜取数・標準処理期間の一覧

平成23年12月8日現在

番号	基準名等	Internet		手数料		試験品の抜取数（単位本、包、組又は箱）			保存用品の抜取数（単位本、包、組又は箱）	標準処理期間
		製剤基準ファイル名	検定基準ファイル名	（単位円）		最終小分容器1本の内容量が5mL未満の場合	最終小分容器1本の内容量が5mL以上20mL未満の場合	最終小分容器1本の内容量が20mL以上の場合		
				ロット	分注区分					
1	通則	stusoku-e.pdf	ktusoku.pdf	－	－	－	－	－	－	－
（血清類）										
1	牛ロタウイルス感染症弱毒抗体	－	KS00100.pdf	270,000	22,100	－	－	6	2	60

広報資料
関係法令
- 法令データ
- 告示・通知データ
- 動物用医薬品等に関する法令・通知等

分野別情報
- 承認・審査情報
- 検定・検査情報
- 医薬品等情報
- 調査研究情報
- 広報資料
- その他

申請・お問い合わせ
- ご意見・お問い合わせ
- 調達情報
- 申請・届出

動物医薬品検査所案内

Legal basis

Article 42

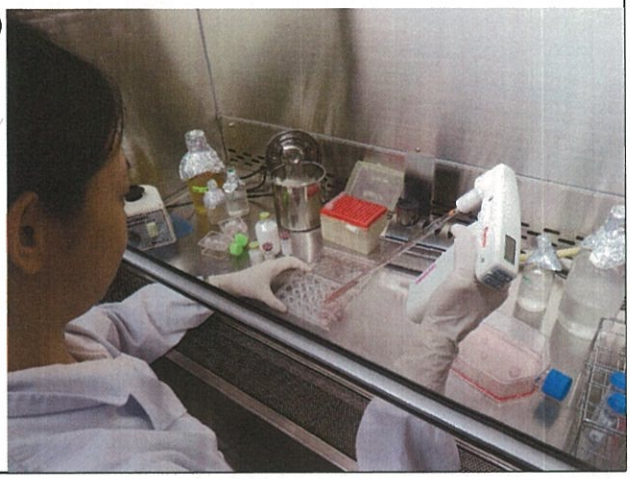
- With respect to drugs requiring special attention to the public health and hygiene, the Minister may, after seeking the opinion of PAFSC, establish necessary standards for the manufacturing methods, properties, quality, storage, etc. of these drugs.

Article 56

- No drug which falls under anyone of the following items shall be retailed, handed over, or manufactured, imported, stored or exhibited for the purpose of retail or hand-over.
- (4) A drug for which the standards are specified under Article 42, Paragraph 1 and which does not comply with the standards (excluding the standards specified under Article 50, Paragraph 6: and Article 52, Item 3)

Table of contents

- General rule
- Variety of serums (10 articles)
- Vaccine (262 articles)
- Vaccine (seed-lot formulation) (71 article)
- Diagnostic product (23 articles)
- General test procedure
- Reagent
- Specifications



General Testing Method 一般試験法

- Property test 特性試験法
- pH determination pH測定試験法
- Vacuum measurement 真空度試験法
- Determination of moisture content 含湿度試験法
- Sterility test 無菌試験法
- Mycoplasma detection test マイコプラズマ否定試験法
- Salmonella detection test サルモネラ否定試験法
- Limit test for viable bacteria count 生菌数限度試験法
- Viral contamination detection test 迷入ウイルス否定試験法
- Thimerosal determination チメロサール定量法
- Phenol determination フェノール定量法
- Formalin determination ホルマリン定量法
- Determination of aluminum アルミニウム定量法
- Determination of carboxymethyl-cellulose sodium カルボキシメチルセルロースナトリウム定量法
- Determination of macrogol マクロゴール定量法
- Total protein nitrogen assay 蛋白窒素定量法
- Abnormal toxicity test 異常毒性否定試験法
- Toxicity limit test 毒性限度確認試験法
- Non-endogenous virus test 外来性ウイルス否定試験法
- Immunogenic test using target animals 対象動物を用いた安全性確認試験法
- Target animal safety 対象動物を用いた安全性確認試験法
- Reversion to virulence 病原性復帰確認試験法

Specifications 規格

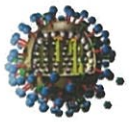
- Material for manufacturing live vaccines
- Seed lot products
- Specific pathogen-free (SPF) animals

Framework of Each Article
- In case of avian influenza vaccine -

- Definition
- Manufacturing process
  - Strain for manufacturing
  - Material for manufacturing
  - Undiluted solution
  - Final bulk
  - Product release after putting vaccine into vials or syringes
- Test methods
  - Test on embryonated egg
  - Test on viral suspension
  - Test on inactivated virus fluid
  - Test on undiluted solution
  - Test on vials or syringes
- Storage and expiration date
- Others
  - Descriptions in appended papers and so on

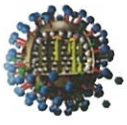
Strain for manufacturing

- The Standard for veterinary biological products
  - Name of the strain
    - Avian influenza virus A-type strains which are separately specified in the notification.



Strain for manufacturing

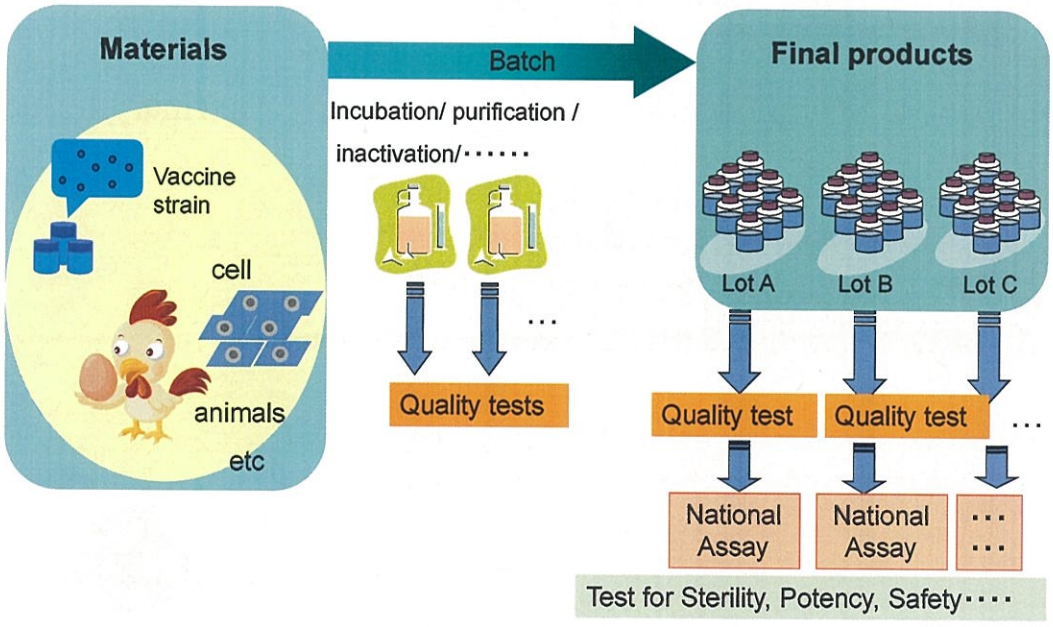
- Notification: Specified strains for manufacturing veterinary influenza vaccines
  - A/Duck/Hokkaido/Vac-1/04 (H5N1)
  - A/Duck/Hokkaido/Vac-2/04 (H7N7)
  - A/Chicken/Mexico/232/94 (H5N2)
  - A/Turkey/Wisconsin/68 (H5N9) (another name: TW68 Bio strain)



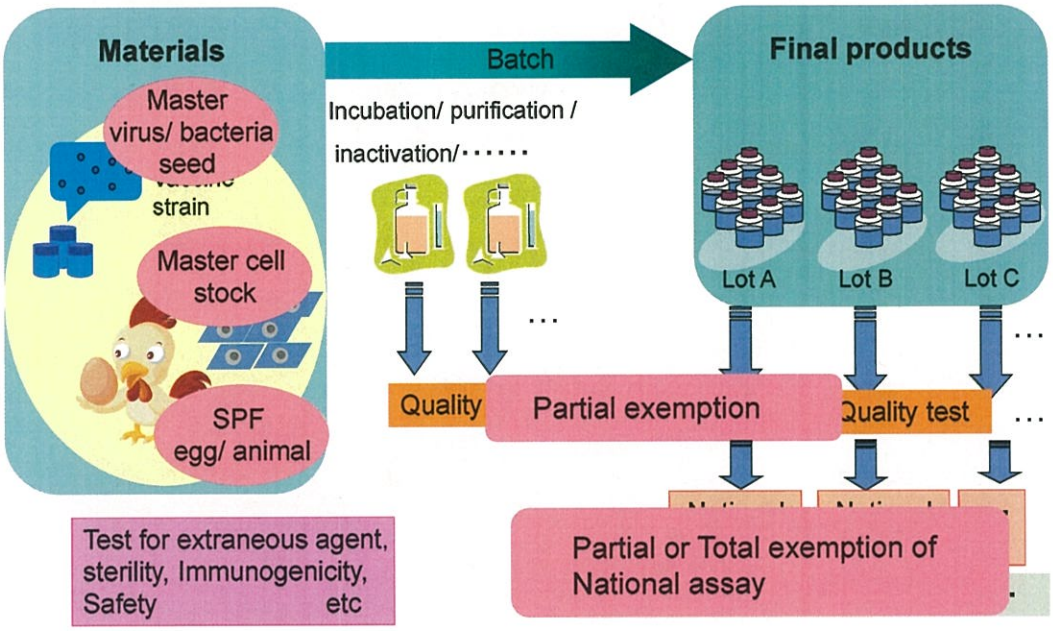
Topic 5

Seed-lot System
シードロットシステム

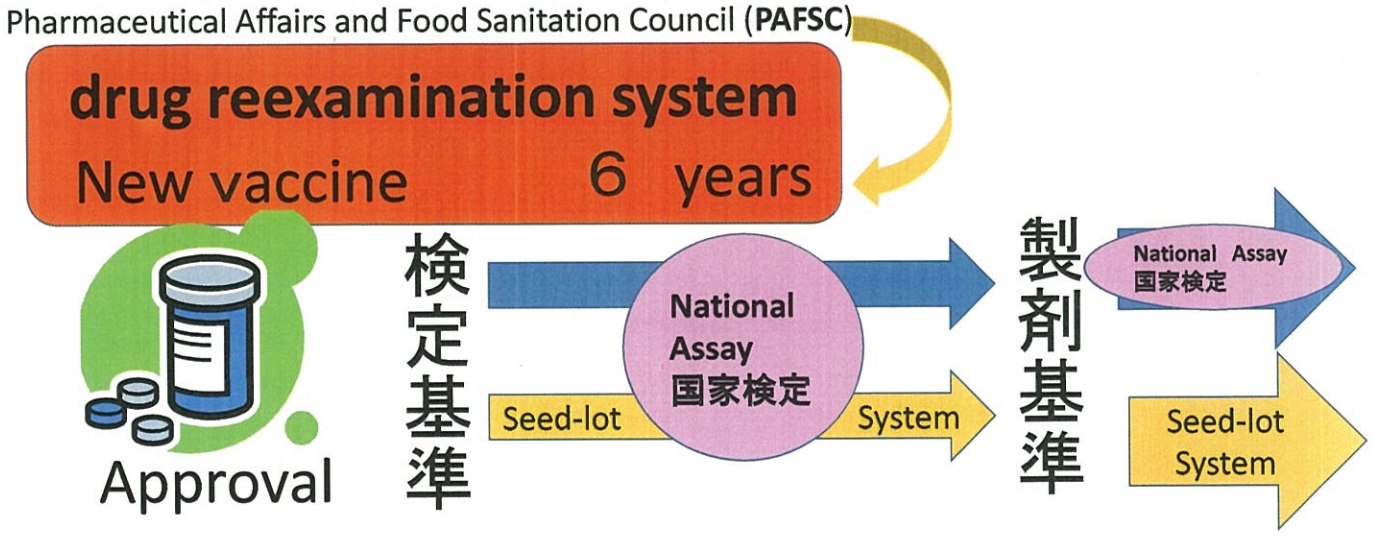
Quality control by seed lot system



Quality control by seed lot system



Difference between製剤基準 and 検定基準




Thank you !