

# Laboratory Outline



**SAFETY RESEARCH INSTITUTE FOR CHEMICAL  
COMPOUNDS CO., LTD.**

# **HISTORICAL BACKGROUND**

## **I. PREDECESSOR CONCERN (SAFETY STUDY ASSOCIATION)**

- The origin of our company is a group of researchers, Safety Study Association, which was established in 1969, comprising researchers from Hokkaido University and Sapporo Medical University.
- This group was formed with a mission assigned by the Hokkaido Government to start a wide range of safety studies of pharmaceuticals.

## **II. ESTABLISHMENT AND DEVELOPMENT OF SAFETY RESEARCH INSTITUTE FOR CHEMICAL COMPOUNDS CO., LTD.**

- Since re-organization in 1970, our company had the 46th anniversary of the foundation.
- Ever since establishment, we have conducted various fields of non-clinical safety studies under the theme of “comprehensive safety evaluation” of pharmaceuticals, medical devices, chemical substances, agricultural chemicals, and food additives and others.

# LABORATORY PROFILE

## ❑ LOCATION

### Head Office & Laboratory

363-24 Shin-ei, Kiyota-ku, Sapporo, Hokkaido, Japan

### Tokyo Office

Aioi Nissei Douwasonpo Kinsityou Bldg. 6F, 4-29-12  
Kotobashi, Sumida-Ku, Tokyo, Japan

### Kansai Office

2-7 Shin-Senri-Higashi-Machi, Toyonaka, Osaka, Japan

## ❑ REPRESENTATIVE

Masao Matsuura, President

## ❑ ESTABLISHMENT

September 1970

## ❑ CAPITAL

250,400,000 yen

## ❑ EMPLOYEES      80



# BUSINESS DESCRIPTION

## □ Non-clinical studies

- Pharmaceuticals
- Medical Devices
- Regenerative Medicine Products
- Agricultural Chemicals
- Chemical Substances
- Quasi-drugs
- Cosmetic ingredients
- Foods for specified health use
- Food Additives
- Animal Drugs
- Efficacy pharmacology
- Others

## □ Business of Contract Research Organization

- Bioequivalence study of generic drugs
- Clinical study of health foods (including foods for specified health use)
- Others

# GLP COMPLIANCE ACHIEVEMENT

## ❑ **Pharmaceuticals GLP**

February 18, 2014

Evaluation result: A

## ❑ **Medical Devices GLP**

February 18, 2014

Evaluation result: A

## ❑ **Regenerative Medicine Products GLP**

April 11, 2016

Complies with the standards

## ❑ **Agricultural Chemicals GLP**

January 28, 2016

Complies with the standards

## ❑ **Chemical Substances GLP**

March 24, 2014

Complies with the standards

## ❑ **Feed Additives GLP**

October 25, 1994

Evaluation result: A

## ❑ **Veterinary Drugs GLP**

November 12, 1999

Evaluation result: A

# NON-CLINICAL STUDY CAPABILITIES

## □ Pharmaceuticals

### Toxicity Studies

- Single dose toxicity studies
- Repeated dose toxicity studies
- Reproduction and developmental toxicity studies
- Antigenicity tests
- Genotoxicity tests
- Carcinogenicity studies
- Local irritation tests
- Sensitization tests

### Others

- Efficacy pharmacology
- Screening toxicity tests

# NON-CLINICAL STUDY CAPABILITIES

## □ Medical devices

- Cytotoxicity test
- Skin irritation/  
intradermal reactivity test
- Sensitization tests
- Acute systemic toxicity study
- Subacute toxicity study
- Chronic toxicity study
- Reproduction and  
developmental toxicity studies
- Pyrogenicity test
- Blood compatibility test
- Genotoxicity tests
- Implantation tests
- Usage simulation test

# **NON-CLINICAL STUDY CAPABILITIES**

## **□ Regenerative Medical Products**

- **Systemic toxicity study**
- **Implantation tests**
- **Efficacy study**
- **Oncogenicity study**

**Karyotype analysis**

**Soft-agar colony formation test**

**Oncogenicity study in immunodeficient animals**





# NON-CLINICAL STUDY CAPABILITIES

## □ Agricultural chemicals

- Acute oral toxicity study
- Acute percutaneous toxicity study
- Twenty-one-day repeated dose percutaneous toxicity study
- Ninety-day repeated dose oral toxicity study
- One-year repeated dose oral toxicity study
- Carcinogenicity study
- Combined chronic toxicity and carcinogenicity study
- Prenatal developmental toxicity study
- Reproduction toxicity study
- Mutagenicity tests
- Irritation tests
- Skin sensitization test
- Neurotoxicity studies
- Study of effects on biological function

# **NON-CLINICAL STUDY CAPABILITIES**

## **□ Chemical substances**

- **Studies under the jurisdiction of the Ministry of Health, Labour and Welfare**
- **Screening toxicity tests**
- **Studies of long-term toxicity, etc.**
- **Studies under the jurisdiction of the Ministry of the Economy, Trade and Industry (Secondary contract)**
- **Studies under the jurisdiction of the Ministry of the Environment (Secondary contract)**

# NON-CLINICAL STUDY CAPABILITIES

## □ Food additives

- Twenty-eight-day repeated dose toxicity study
- Ninety-day repeated dose toxicity study
- One-year repeated dose toxicity study
- Reproduction study
- Prenatal developmental toxicity study
- Carcinogenicity study
- Combined one-year repeated dose toxicity and carcinogenicity study
- Antigenicity tests
- Genotoxicity tests

# NON-CLINICAL STUDY CAPABILITIES

## □ Animal drugs

- Acute toxicity study
- Subacute toxicity study
- Chronic toxicity study
- Reproduction and developmental toxicity studies
- Mutagenicity tests
- Carcinogenicity study

## □ Feed additives

- Single dose toxicity study
- Repeated dose toxicity studies
- Multigeneration reproductive study
- Prenatal developmental toxicity study
- Oncogenicity study
- Mutagenicity tests

# NON-CLINICAL STUDY CAPABILITIES

## □ **Cosmetic ingredients**

- Single dose oral toxicity study
- Percutaneous dose toxicity study
- Genotoxicity tests
- Specific toxicity tests
- Human patch test

## □ **Foods for specified health use**

- Acute toxicity study
- Subacute toxicity study
- Subchronic toxicity study
- Reverse mutation test

## □ **SDS**

- Acute toxicity test
- Irritation test
- Mutagenicity test
- Sensitization test

# **NON-CLINICAL STUDY CAPABILITIES**

## **□ Pharmacokinetics studies**

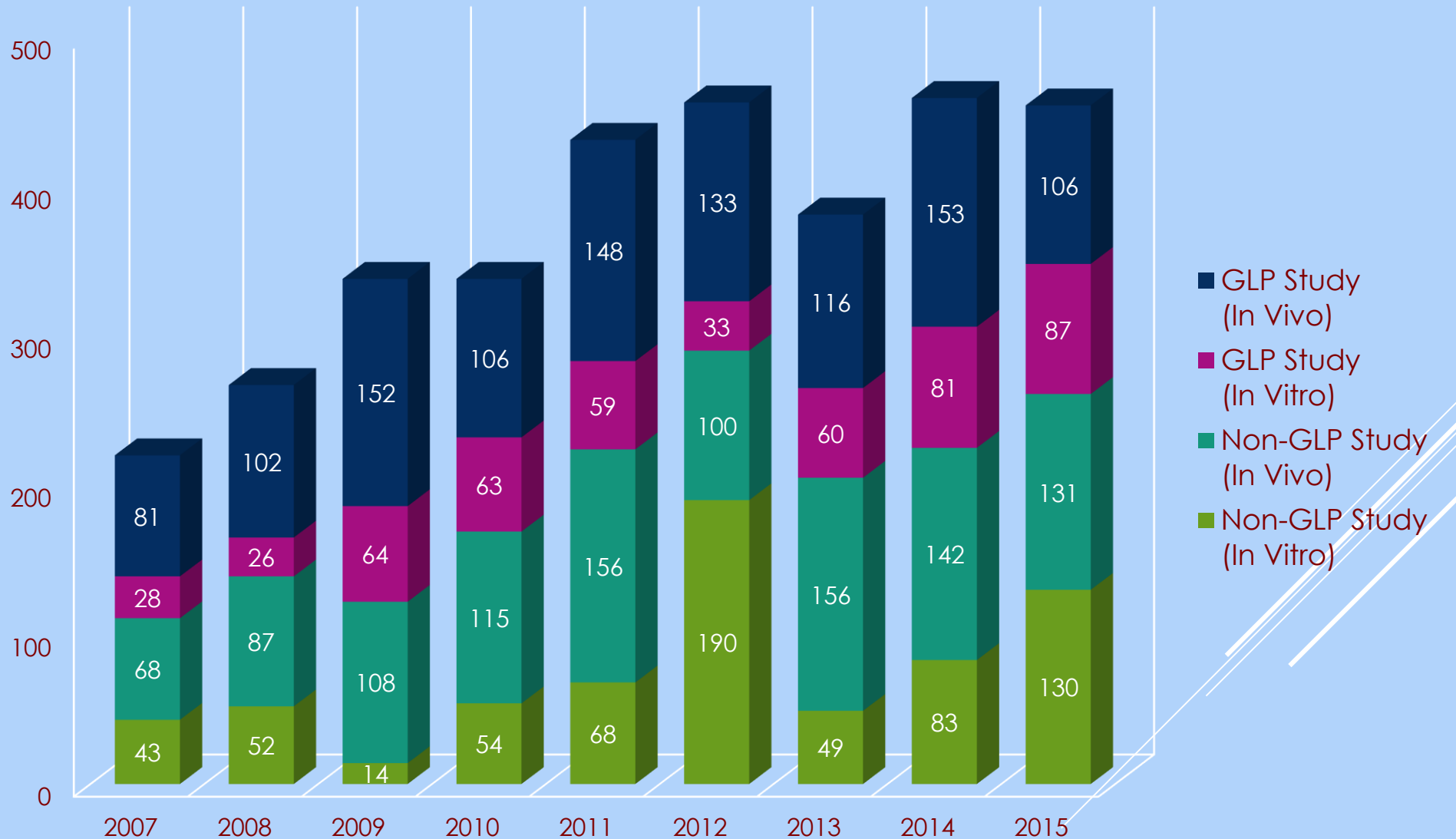
- **Measurement of plasma concentration of the test substance**
- **In vitro metabolism test**

## **□ Steroid hormone measurement by liquid chromatograph-mass spectrometry-mass spectrometry (LC-MS/MS)**

## **□ Preparation and evaluation of histopathological specimens**

## **□ Translation (English-Japanese/Japanese-English)**

# NUMBER OF STUDIES DURING THE LAST DECADE



# ANIMAL HOUSING CAPACITY

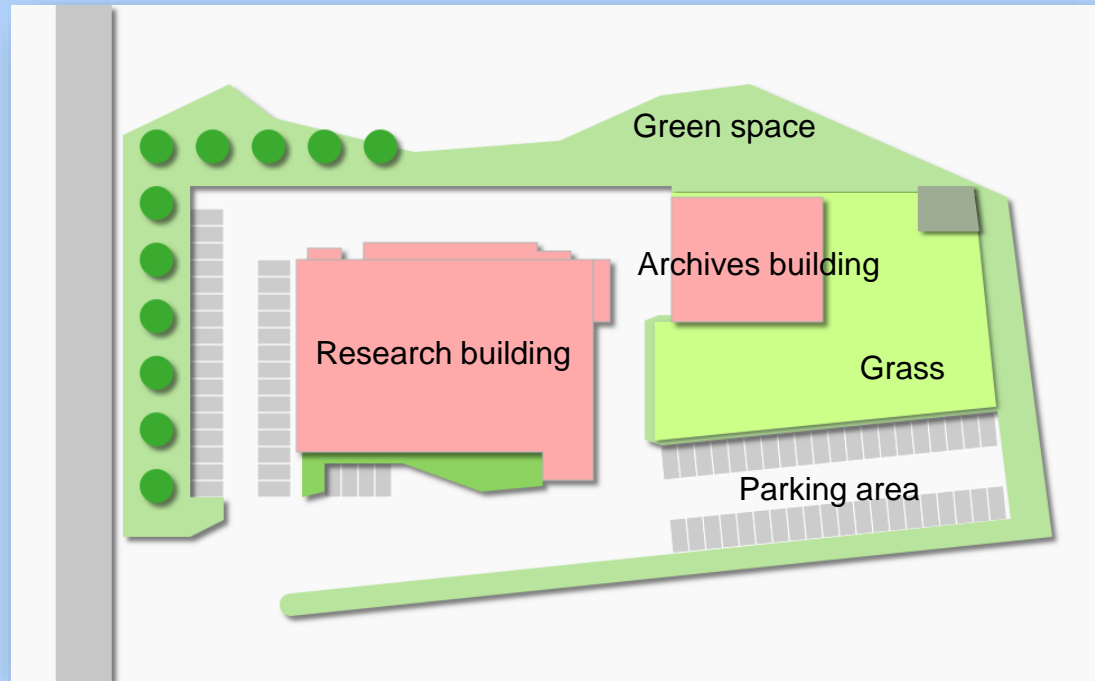
- **SPF Animal rooms**  
20 rooms

- **Conventional Animal rooms**  
15 rooms

- **In-vitro study rooms**

- **Analytical equipment such as LC/MS/MS**

- **Study director**  
More than 20



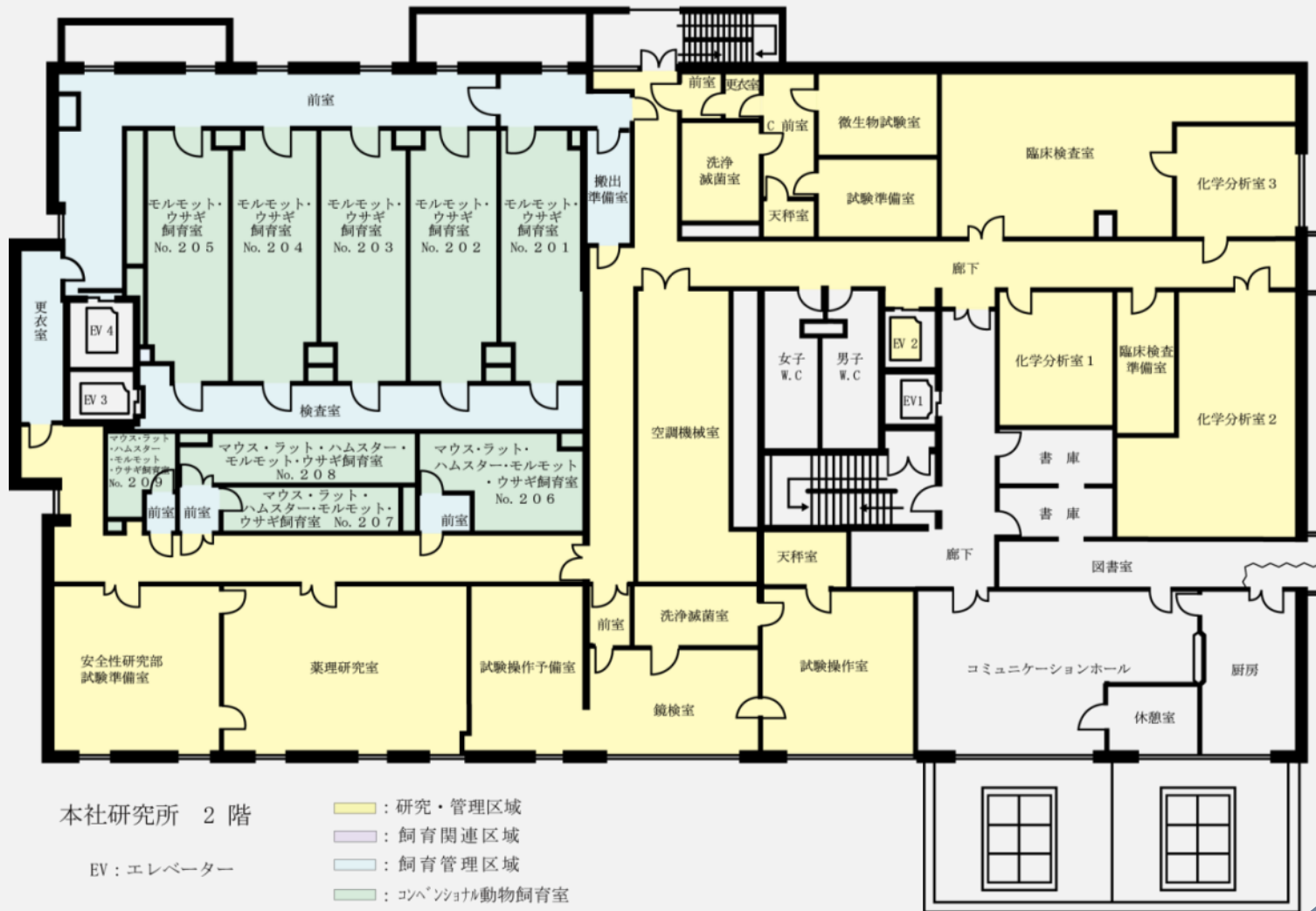


本社研究所 1階

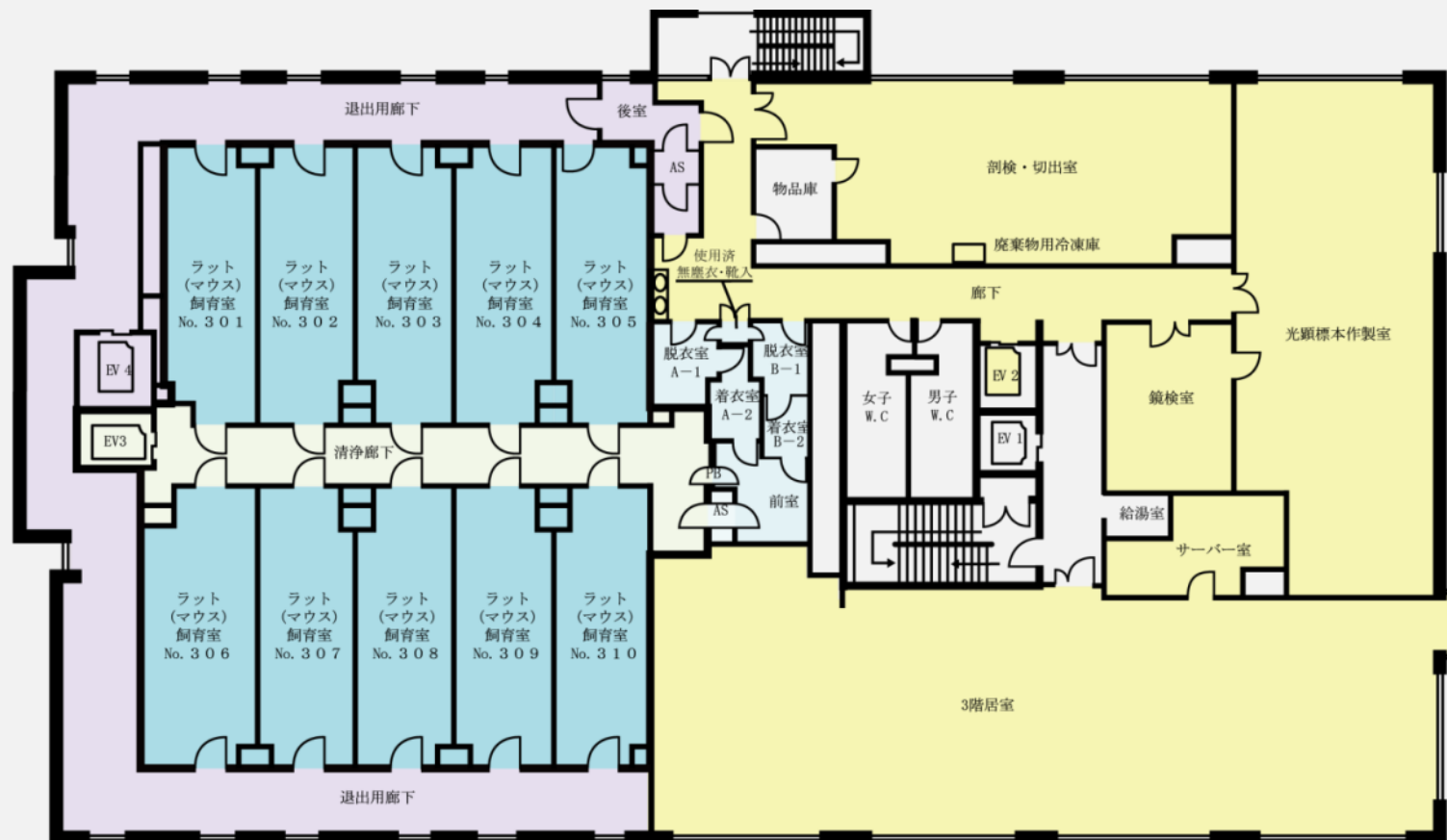
AC: オートクレーブ  
PR: パスルーム  
PB: パスボックス  
EV: エレベーター

研究・管理区域  
飼育管理区域  
飼育関連区域  
ペット動物飼育管理区域  
コンパニオン動物飼育室

## 2nd Floor



# 3rd Floor



## 本社研究所 3 階

AS : エアシャワー

PB : パスボックス

EV : エレベーター

黄色 : 研究・管理区域

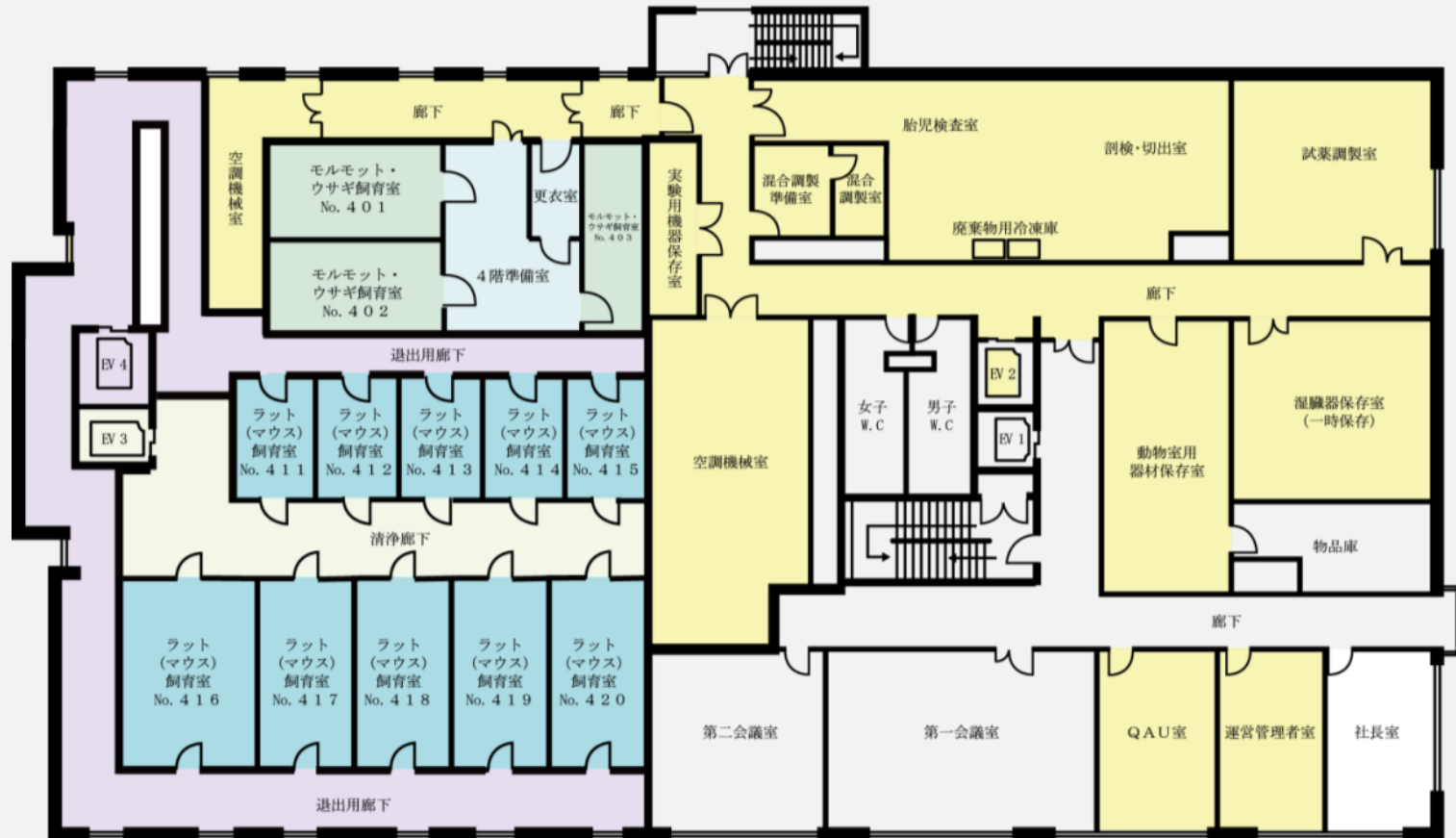
水色 : 飼育管理区域

紫色 : 飼育関連区域

薄緑色 : ハリマ動物飼育管理区域

青色 : ハリマ動物飼育室

# 4th Floor



本社研究所 4 階

EV : エレベーター

- : 研究・管理区域
- : 飼育管理区域
- : 飼育関連区域
- : ハ<sup>®</sup>リア動物飼育管理区域
- : ハ<sup>®</sup>リア動物飼育室
- : コンベンショナル動物飼育室

# LABORATORY ANIMAL WELFARE

## □ **Accreditation of Laboratory Animal Care and Use** **Japan Health Sciences Foundation (JHSF)**

October 1, 2013

Complies with the standards

- **The center for the Accreditation of  
Laboratory Animal Care and Use of JHSF**
  - Independent certification organization in Japan
  - Providing a third-party assessment of animal testing facility

LAB

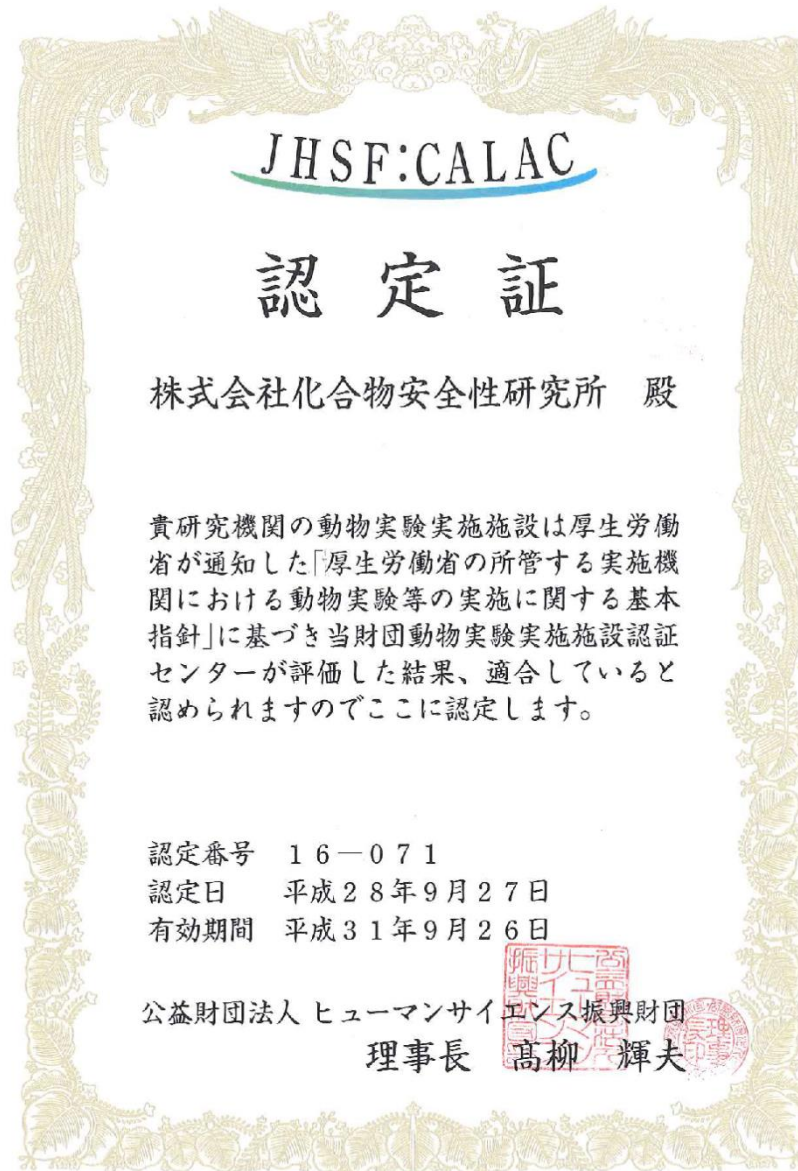
## □ Accreditation

Japan H

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Japan

mal testing facility

# LABORATORY ANIMAL WELFARE

## □ AAALAC International

We are also aiming to acquire accreditation  
from AAALAC International in the near future.



# RECENT TOPICS

**AHEAD OF OTHER COMPANIES,  
WE HAVE ADDED SEVERAL NEW FIELDS.**

- ❑ Regenerative Medicine Products**
- ❑ Bovine Corneal Opacity and Permeability Test (BCOP test)**
- ❑ Determination of steroid hormones by liquid chromatograph-mass spectrometry-mass spectrometry (LC/MS/MS)**
- ❑ Respiratory Sensitization test**



# REGENERATIVE MEDICINE PRODUCTS

## □ Regenerative Medicine Products

- Biological safety evaluation on
  - regenerative medicine for nerve damage
  - regenerative medicine for cerebral infraction
  - cell therapy
  - bone regeneration
  - others
- Collaborating with some universities and companies in Japan.
- Conducting largest number of studies of regenerative medicine products in Japan.
- Immunodeficient animals such as SCID mice and NOG mice.

# BOVINE CORNEAL OPACITY AND PERMEABILITY TEST

## □ BCOP test

- An alternative to the Draize eye irritation test using rabbits
- We are the first to introduce this method into business in Japan
- Adopted as OECD Test Guideline No.437 in 2009 as an in-vitro test method for identifying ocular severe irritants and corrosives in isolated bovine corneas
- Using a by-product of cattle, it is one of useful methods on reducing number of animals used and pain.

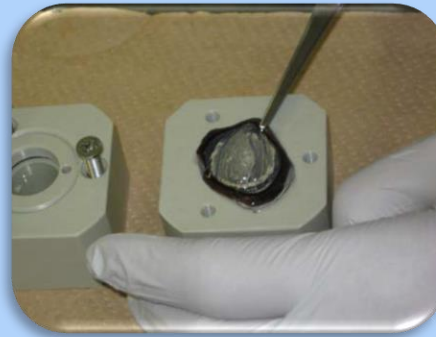
# BOVINE CORNEAL OPACITY AND PERMEABILITY TEST

## □ Procedure of BCOP test

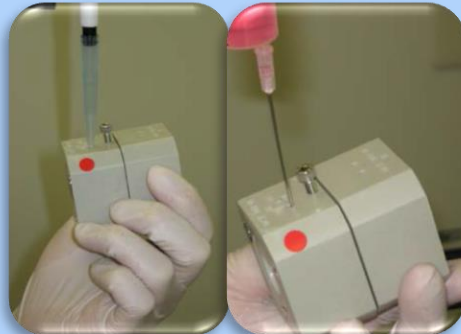
### 1. Excising a cornea



### 2. Mounting to the holder



### 3. Test substance dosing



### 4. Measurement of opacity and permeability



# BOVINE CORNEAL OPACITY AND PERMEABILITY TEST

## □ Procedure of BCOP test

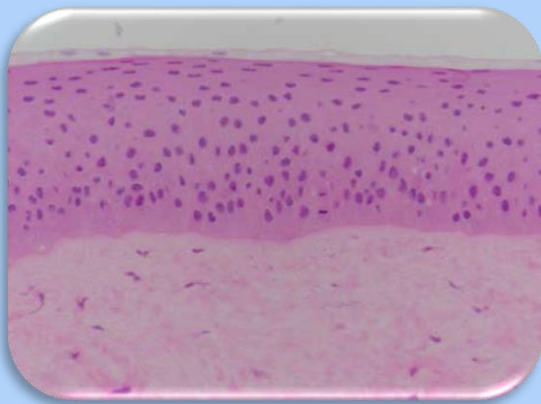
### Calculations

$$\text{IVIS} = \text{opacity} + (15 \times \text{permeability (OD 490)})$$

The histopathological specimens are prepared as needed.

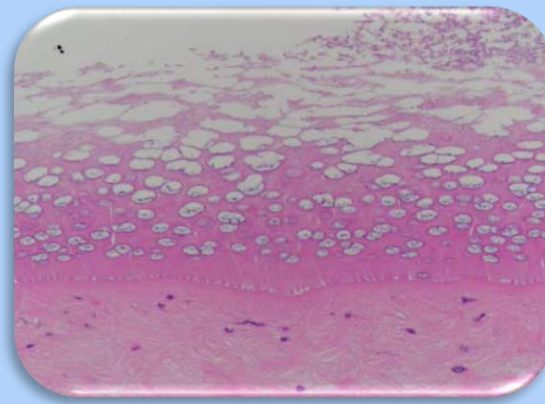
Distilled water

Normal



1% sodium hydroxide solution

Severe irritation



# ACCURATE DETERMINATION OF STEROID HORMONES BY LIQUID CHROMATOGRAPH-MASS SPECTROMETRY-MASS SPECTROMETRY (LC-MS/MS)

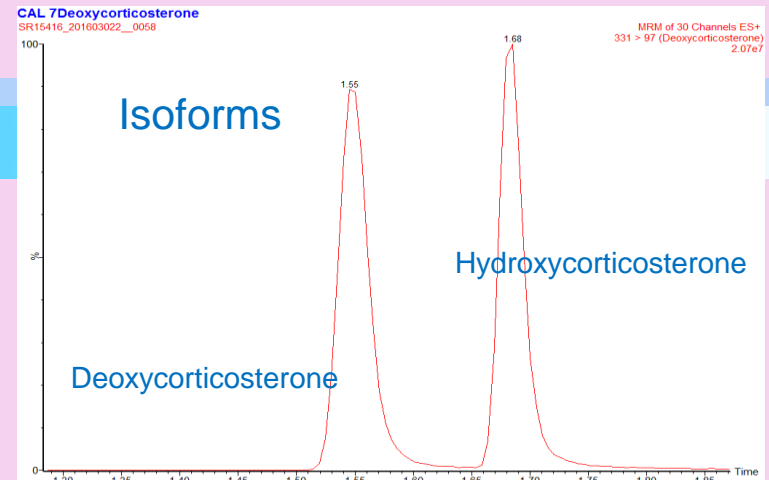
## 1. Samples

Sample: Serum, Plasma, Tissue

Species: Rat, Mice, Rabbit, Dog and others

## 2. Advantage of LC-MS/MS

- 1500-fold sensitivity compared to RIA
- Accurate determination of steroid levels
- High throughput analysis (2.8 min.)
- Complete separation of isoforms



## 3. Detectable items

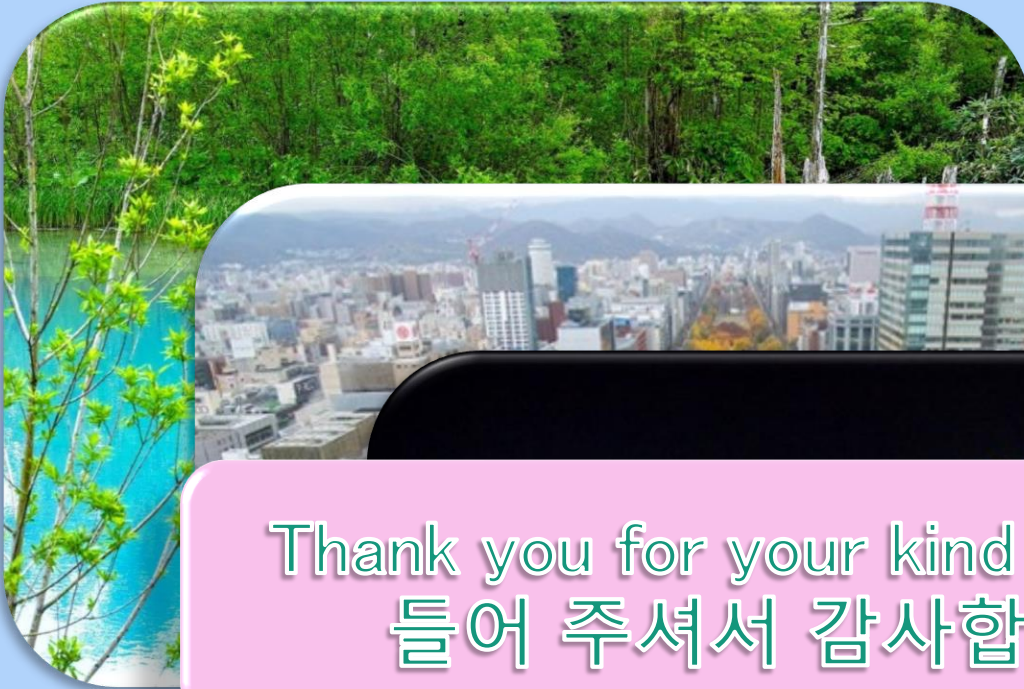
Testosterone	Androstenedione
Progesterone	Hydroxyprogesterone
Cortisol	Hydrocorticosterone
Corticosterone	Hydroxypregnenolone
Aldosterone	Pregnenolone
Deoxycorticosterone	Dehydroepiandrosterone
Deoxycortisol	Estradiol
Dehydrocorticosterone	etc.

## 4. Papers

- **Maeda et al. J. Biochem. 2013;153(1):63–71.**
- **Maeda et al. Environ Toxicol. 2014;29(12):1452-9.**
- **Maeda et al. PLoS One. 2015;10(2):e0117795.**
- **Haeno, Maeda et al. J Endocrinol. 2014; 221(2):261-72.**
- **Haeno, Maeda et al. Endocrine. 2016 Apr;52(1):148-56.**
- **Yamaguchi, Maeda et al. FEBS open Bio, 1 July 2016 accept.**







Thank you for your kind attention.  
들어 주셔서 감사합니다 .

