Japanese Regulatory and Industry perspective

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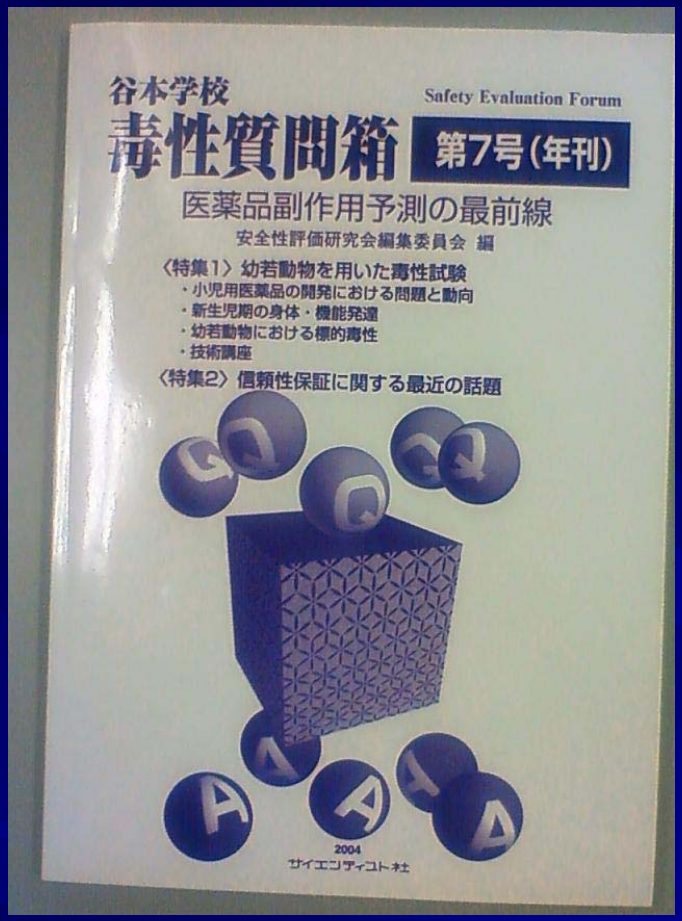
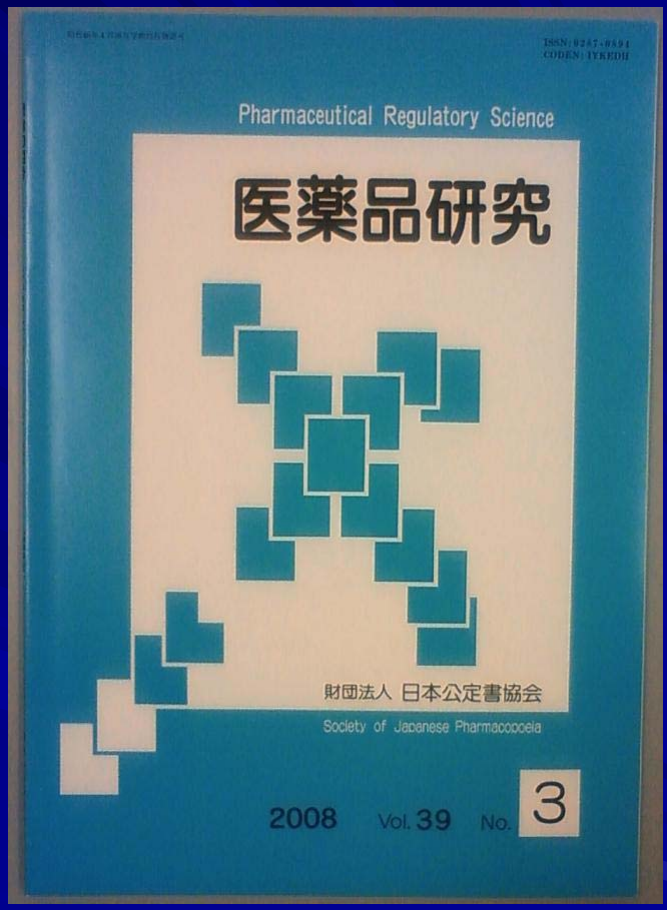
Activities for Juvenile Study in Japan

2004.2	Repro. Tox. Tokyo Seminar
2004.12	Tanigaku Winter Seminar
2005.6	Japanese Society of Toxicology
2005.7	Japanese Teratology Society
2006.4	Repro. Tox. Kansai Forum
2006.7	Japanese Society of Toxicology
2007.8	Tanigaku Nagawa Forum
2008.6	Japanese Society of Toxicology
2009.9	Drug Evaluation Forum

Featuring Articles



Tanigaku Q&A Box on TOX
Vol. 7 (2004)



Pharmaceutical
Regulatory Science
Vol. 36 No.7 (2005)

Taskforce in JPMA

2005.4 ~ 2007.3

Taskforce Team for Non-clinical Juvenile Animal Studies for Pediatric Drugs

Japan Pharmaceutical Manufacturers Association

- **Investigation of NDA documents and assessment reports in Japan**
- **Questionnaire survey**
- **JPMA Guidance**

Investigation of NDA documents and assessment reports in Japan

(1) Timing of pediatric submission

Pediatric only ……. 2

Same timing as adult …… 14

After adult approval …… 15

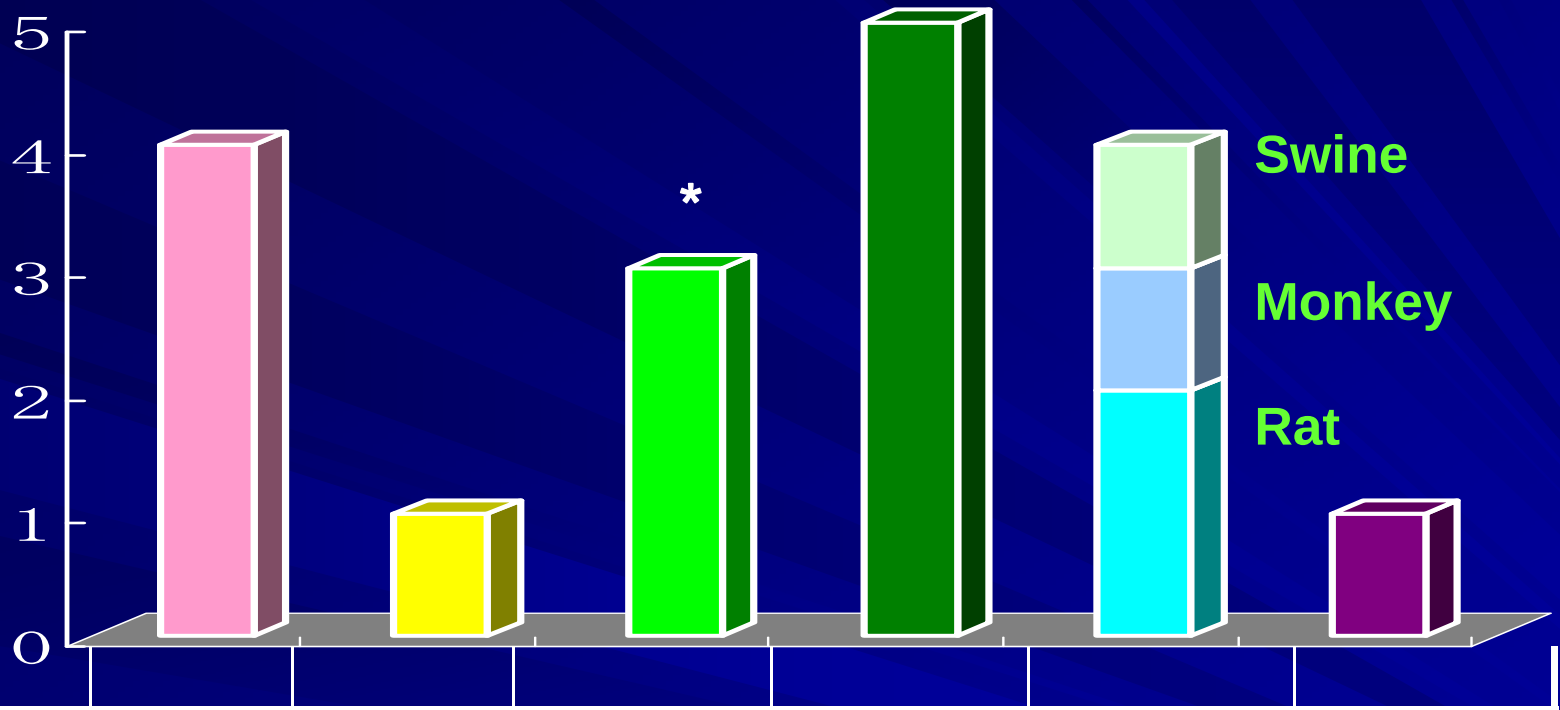
(2) Juvenile study

Conduct …… 18

Not conduct …… 13

31 drugs (1999-2005)

Study type and species

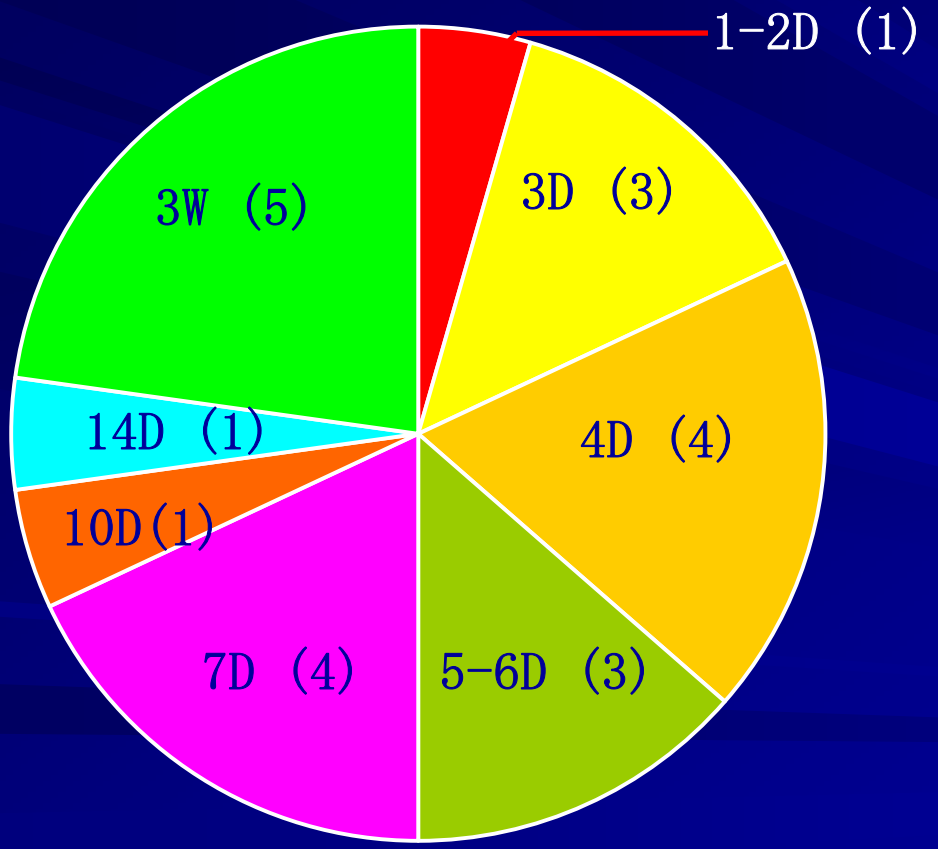


Single	Rat	Rat	Rat, Dog	Rat, Dog	No	Mouse, Rat, Dog
Repeated	Rat	Monkey	Rat, Dog	Dog	Rat, Monkey, Swine	Dog

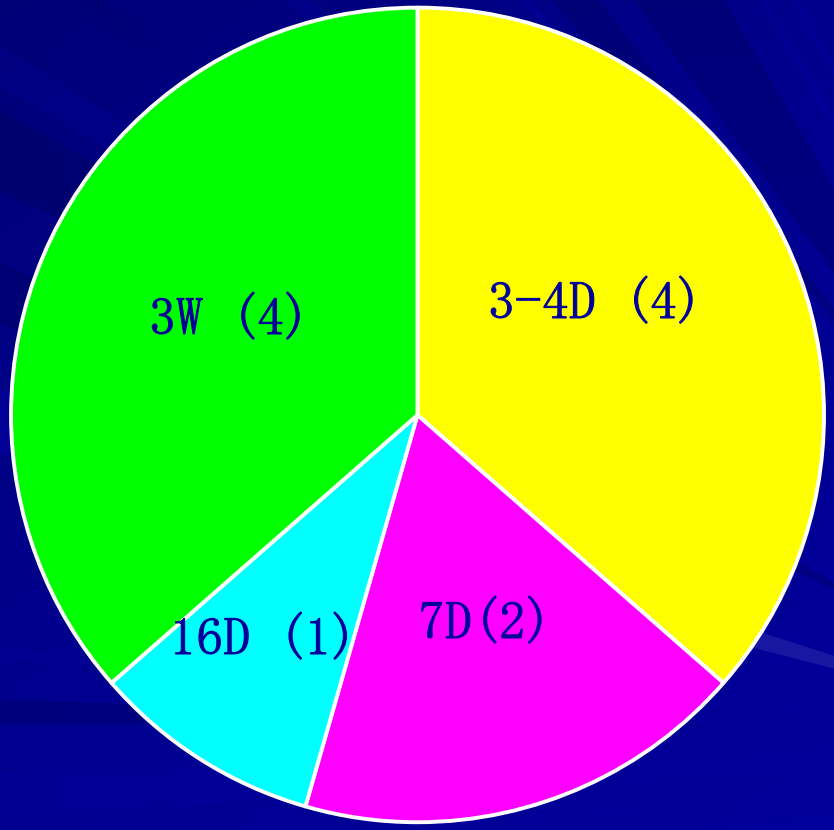
***: 1/3 Repeated dose study of metabolite in rats**
Repeated dose studies were conducted in all compounds.

Age at start dosing in rats

Single Dose Study (22 studies)

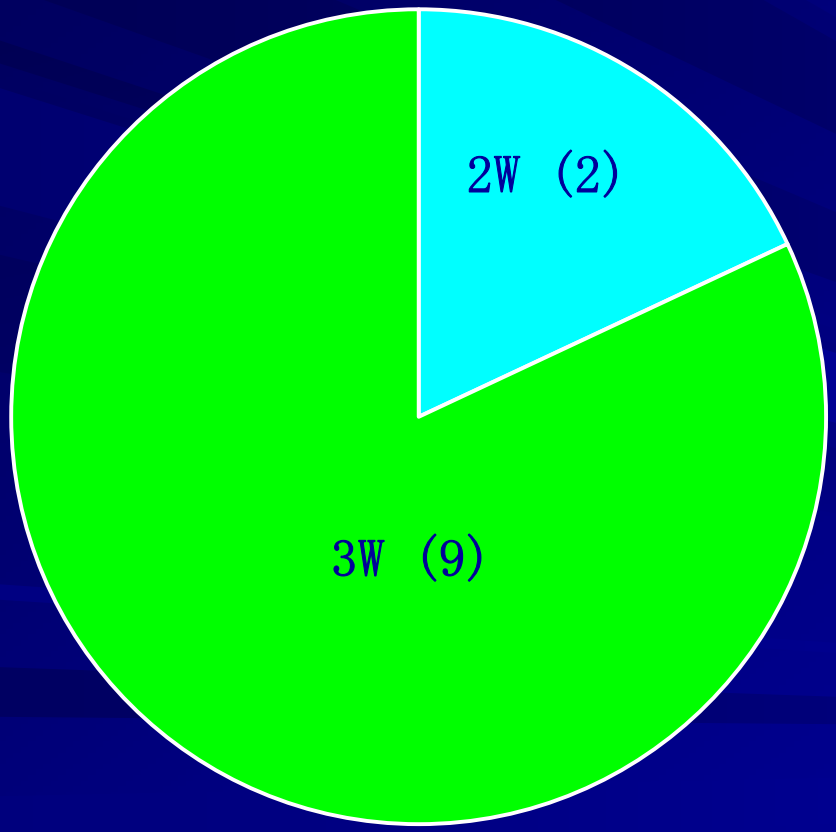


Repeated dose study (11 studies)

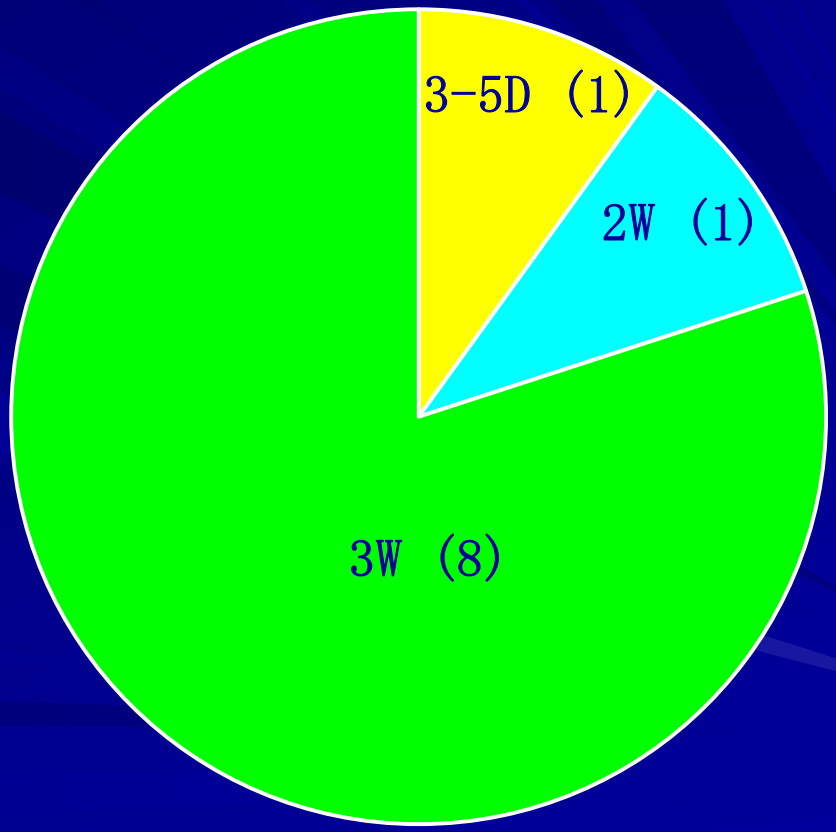


Age at start dosing in dogs

Single Dose Study (11 studies)



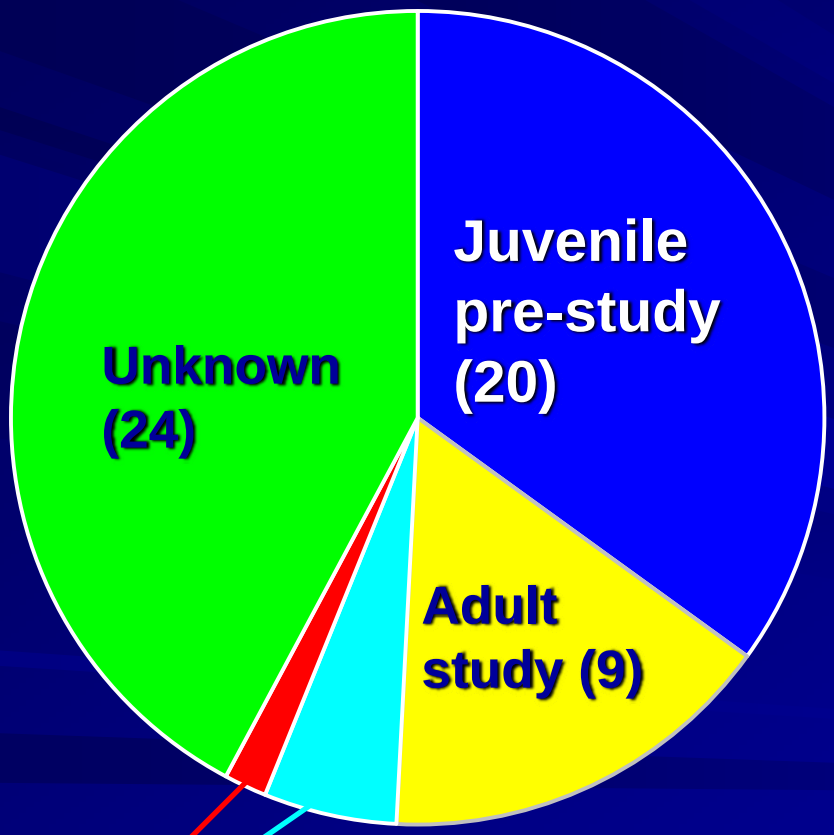
Repeated dose study (10 studies)



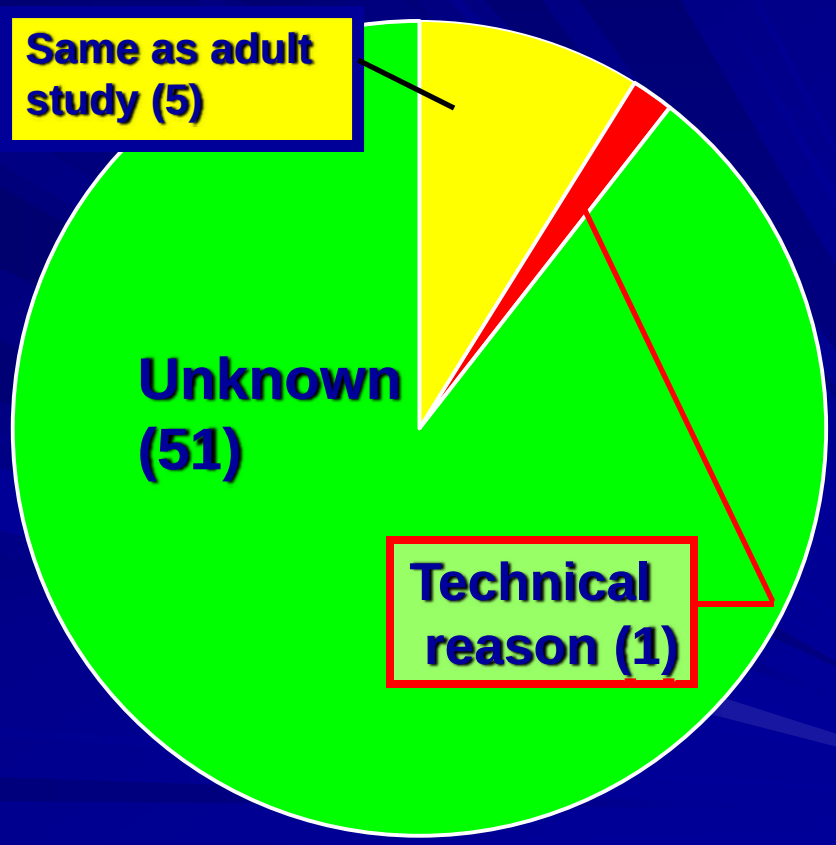
Dosing was started before weanling in all studies

Rational for dose and species selection

Dose



Species



Questionnaire survey (36 companies)

Preclinical study

Inhouse	1 (company)
Outsource	4
Inhouse+Outsource	31

Experience of pediatric drug development

Yes	22
No	14

Experience of juvenile animal study

Toxicity Study

Yes	25
No	11

TK Study

Yes	18
No	18

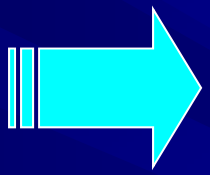
Safety Pharmacology Study

Yes	1
No	35

2001	
Juvenile study type	
Single dose	13
Repeated dose	27
DART	1
Others	1

Species	
Mouse	2
Rat	19
Rabbit	0
Dog	9
Monkey	-
Unknown	1

Age at start dosing in rats	
- 4D	14
5-7D	8
10-14D	1
21D -	4



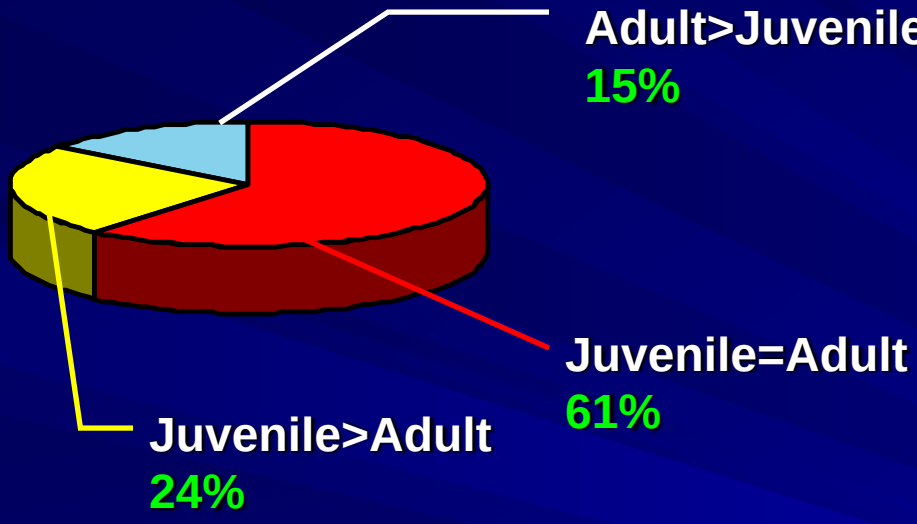
2006	
Juvenile study type	
Single dose	6
Repeated dose	17
DART	2
Others	1

Species	
Mouse	1
Rat	25
Rabbit	0
Dog	18
Monkey	2
Guinea pig	1

Age at start dosing in rats	
- 4D	8
5-7D	10
10-14D	2
21D -	5

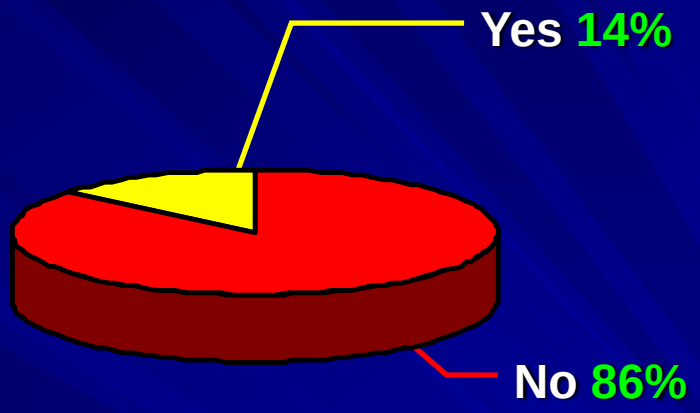
Results of juvenile studies

Comparison of toxicity*

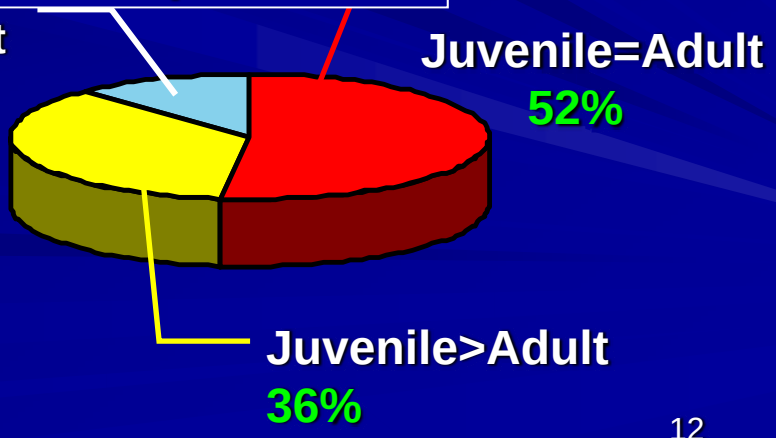


*: Including following case
Rat: Juvenile>Adult
Dog: Adult>Juvenile

Juvenile specific toxicity

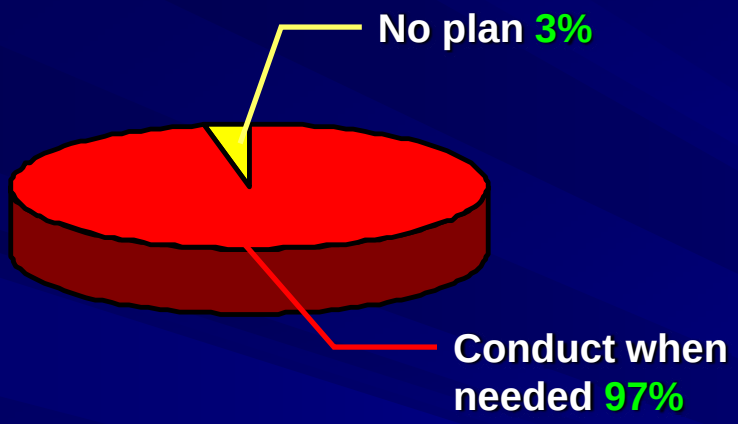


Comparison of exposure

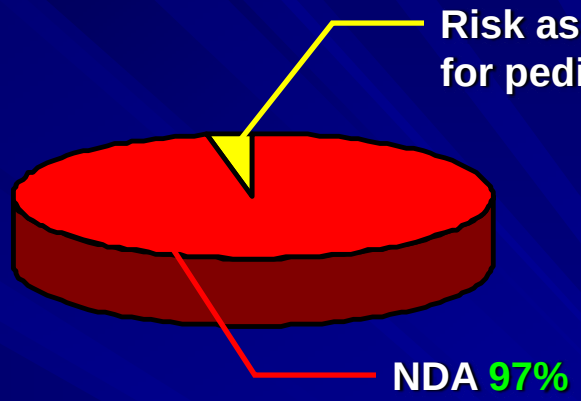


Future prospects (1)

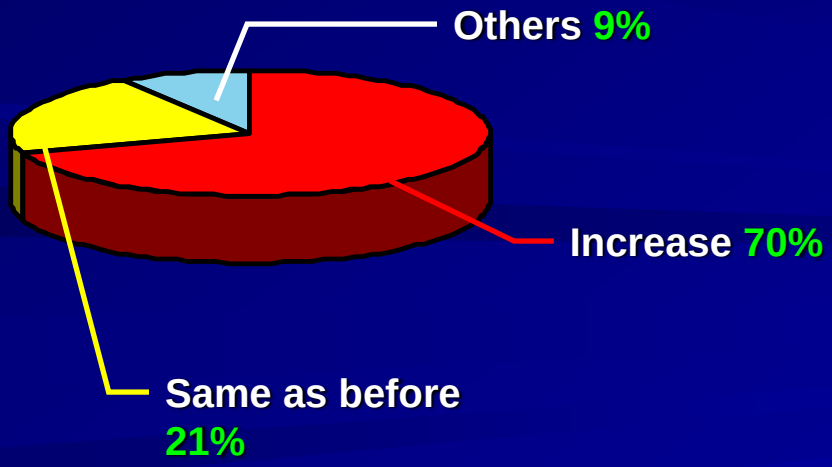
Juvenile study



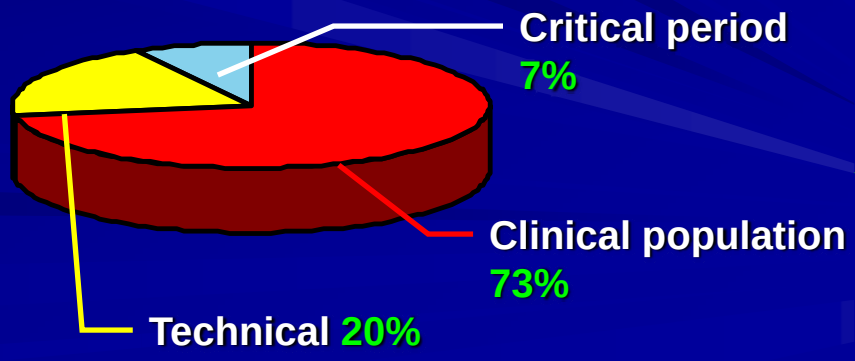
Reason for Juvenile study



Request from PMDA

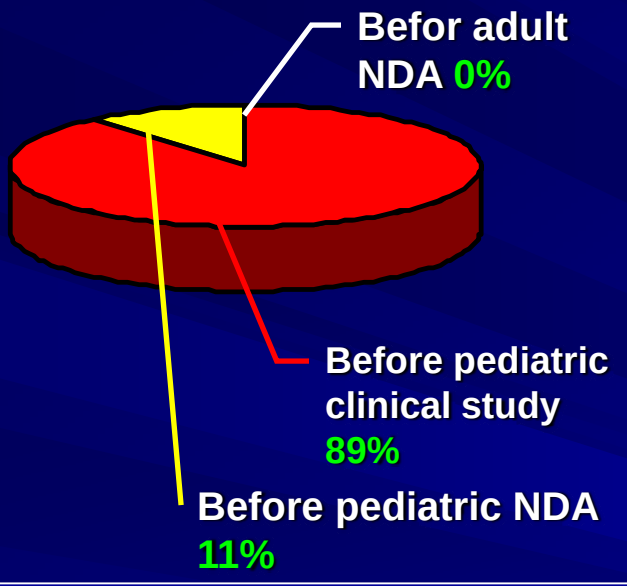


Selection for dosing period

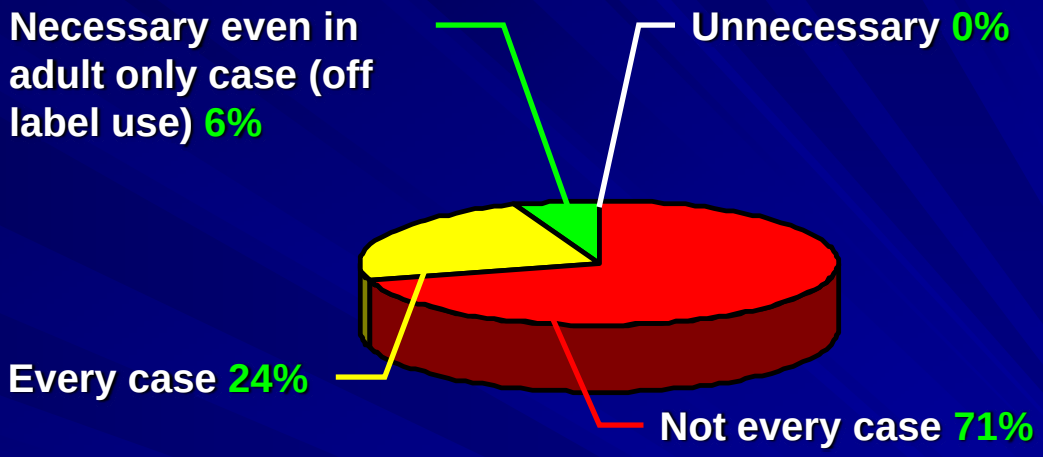


Future prospects (2)

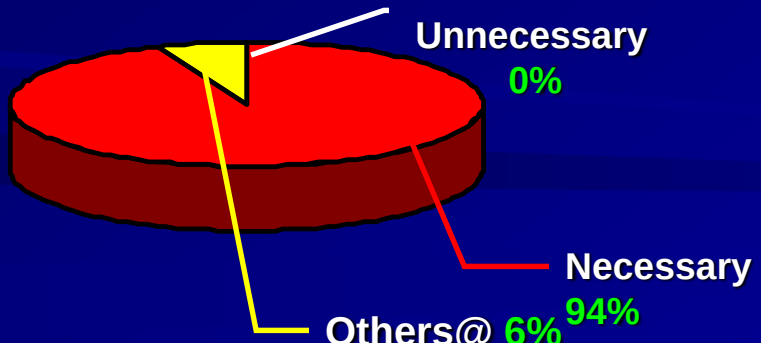
Timing of Juvenile study



Necessity of juvenile study



Juvenile study guidance in Japan



@: Study design could not included in guidance because juvenile studies may conduct by case by case basis

Guideline for Juvenile Study

2000 ICH-E11

USA	2003	Draft
	2006	Finalized
EU	2001	Concept paper
	2005	Draft
	2008	Finalized
Japan		?

(2007 JPMA)

JPMA Guidance (1)

1. Prolusion

- Introduction
- Purpose
- Background
- Application

2. Necessity of study

- Considerations
- Necessary case
- Not necessary case

3. Protocol

- Purpose
- Considerations
- Study type
- Animals
- Dosing
- Examinations
- TK

4. Timing of study

5. Utilization of results

Study design example

JPMA Guidance (2)

Screening Study design example

Animals: Rat, Male Female, n=20, Culling on PD4: Male 4, Female 4

Dosing: from PD1 to 6W old, once daily, intended clinical route

Group: Control, Low, Middle, High

General Observations: Clinical signs, Body weight, Food consumption

Physical development: Pine unfolding, Incisor eruption, Eye opening

Sexual maturation: Balano-preputial separation, Vaginal opening

Reflex: Righting reflex

Sensory function test: Pupillary reflex, Corneal reflex, Preyer's reflex

Behavior: Motility test, Learning test

Fertility: Sperm examinations, estrus cycle

Function test: Renal function etc.

Urinalysis, Hematology and biochemistry:

Necropsy: 7 and 13 W, Organ weight, Microscopy, Tibia length

TK: PD7 and 21, 1, 4, 24 h after single dose, n=5

Request from PMDA (1)

Pediatric indication: Antifungal drug

Testicular toxicity was observed in

- **9M repeated dose study in dogs**
- **Fertility study in rats**

4W repeated dose juvenile study in rats (PD4)

PMDA: Is it adequate?

Applicant: No testicular toxicity was noted in the juvenile study. Low risk for fertility.

Request from PMDA (2)

PMDA: Disagreed

No detailed investigation for testicular toxicity.

Not enough dosing period.

Applicant:

9M repeated dose juvenile study with 3M recovery study in dogs were conducted additionally.

(from assessment report of PMDA)

Conclusion

Many scientific meetings about Juvenile study are held in Japan.

Juvenile study is learning by doing now.

Japanese guidance is requested.

Concrete directionality is not yet shown by PMDA.

Alignment among 3 regions (US, EU, Japan) is important.