

Discussion Points for Panel Discussion

<Reproductive Toxicity Studies for Biopharmaceuticals>



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Reproductive Toxicity Studies for Biopharmaceuticals

- (Monkeys, Transgenic Animals or Homologous Proteins)
- *****
- Do monkey data meet regulatory requirements?
- What are technical limitations?
- How about alternatives?
 - Transgenic animals
 - Homologous proteins

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Problems of Reproductive Toxicity Studies with Biopharmaceuticals

- 1) Rats (Mice) and Rabbits Studies for GL
- 2) Production of Neutralizing Antibody
- 3) Animals with Pharmacological/Biological activities
- 4) Any other animals
- Monkey (Cynomolgus, Rhesus), Hamster, etc.
- 5) Transgenic animals
- (No example for New Drug Application in Japan.)
- 6) Homologous protein

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Monkey Reproductive Toxicity Studies at Contract Research Organization (CRO) :Number of Each Study

Stages	CRO Laboratories		
	A (1994-)	B (2001-)	C (1990-)
I (Fertility)	0	Cy:2 ^{a)}	25 ^{b)}
II (Pre- and Post-natal)	Cy:14	Cy:3	2
III (Embryo-Fetal Development)	Cy:75 CM:1 ^{c)}	Cy:6	62

a) Cy: Cynomolgus Monkey, b) Cynomolgus or Rhesus Monkey, c) CM: Common Marmoset

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Points of Monkey Studies

- 1) Low Pregnancy rate (30-41%) ^{a)}
- 2) Low amount of Back Ground Data
- 3) Long Test Period
- 4) Single Fetus
- 5) Abortion rate (13-16%) ^{a)}
- 6) Rhesus Monkey: Seasonal Reproduction
- a) Data from 3 CROs (2007/04)

Reference: IYAKUJIN KENKYU, 34(9)616(2003).

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Case Reports using Monkey Reproductive Toxicity Studies (Examples)

No.	Medicine	Stages			Pmda Web site
		I	II	III	
1	Trastuzumab (トラスツズマブ) N=	Cy 5/6	Cy 8	Cy 12/13	2001/4
2	γ IFN-α Con1 (IFNアルファコン-1) N=	Hm	---	Rhe 2/3	2001/10
3	Basiliximab (バシリキシマブ) N=	---	---	Cy 12	2002/1
4	PEG-IFN (ペグインターフェロン・アルファ-2a) N=	Rhe 4-6 ^{a)}	---	Rhe 8/9	2003/10
5	Tocilizumab (トシリズマブ) N=	Rat	---	Cy 10 Rat	2006/4

a) : 2 studies, Cy : Cynomolgus Monkey, Rhe : Rhesus Monkey, 2007/08/10 Hm : Hamster

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Case Reports using Other animal (Mice) for Reproductive Toxicity Studies (Homologous protein)

No.	Medicine	Stages			Pmda Web site
		I	II	III	
1	Infliximab (インフリキシマブ) N= O Mice TNF α MC Ab	Mice 25	---	Mice 17-22	2002/1

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Summary

Several Proposal regarding Reproductive Toxicity Studies with Biopharmaceuticals

○ Each biopharmaceutical has each strategy for reproductive toxicity studies.

- Rat, Rabbit, Mouse, Monkey, Hamster, etc.
- Homologous proteins

○ Enhance scientific assessment for new biopharmaceuticals based on case by case concept with scientific consideration.

○ The historical control data of new experimental animals would be very important to assess the results of Reproductive toxicity studies for Biopharmaceuticals

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1 Day



3 Months

Thank you very much for your attention.

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