Japanese Practices in Non-clinical Safety Assessment of Biopharmaceuticals

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Agenda

1. Introduction
   - Benefits from ICH-S6
2. JPMA questionnaire survey
   - Implementation of ICH-S6
3. “Points-to-consider”
   - Species differences
   - Differences between biopharmaceuticals and NCEs
   - Types of biopharmaceuticals
4. ICH safety brainstorming about ICH-S6
5. Conclusion

Concerns/Questions prior to ICH-S6

- Fewer toxicity observed in less responsive animals
- Decreased toxicity after repeated administration
- Value of genotoxicity studies
- Value of antigenicity studies
- Value of ADME studies with radiolabeled proteins

Historical Background

- ICH-S6 (1997)
- Japanese translation of ICH-S6 (2000)
- JPMA questionnaire survey on ICH-S6 implementation (2000)
- Japanese “Points-to-consider” (2002)
- Update and English translation of Japanese “Points-to-consider” (2004)

Answers from ICH-S6

- Species differences
  - Fewer toxicity observed in less responsive animals
- Antibody production
  - Decreased toxicity after repeated administration
- Genotoxicity sometimes not relevant
  - Value of genotoxicity studies
- Antigenicity not relevant
  - Value of antigenicity studies
- Use of radiolabeled proteins sometimes not relevant
  - Value of ADME studies with radiolabeled proteins

Principle of ICH-S6

- Appropriate safety test for each product
  - Relevant animal selection
- Flexible description, not to be checklist
  - Decision making based on “case-by-case”
- Toxicity test based on biological activity/PK

  1) Predict testing scheme

  2) Testing doses based on biological response

  3) Testing doses based on clinical usage

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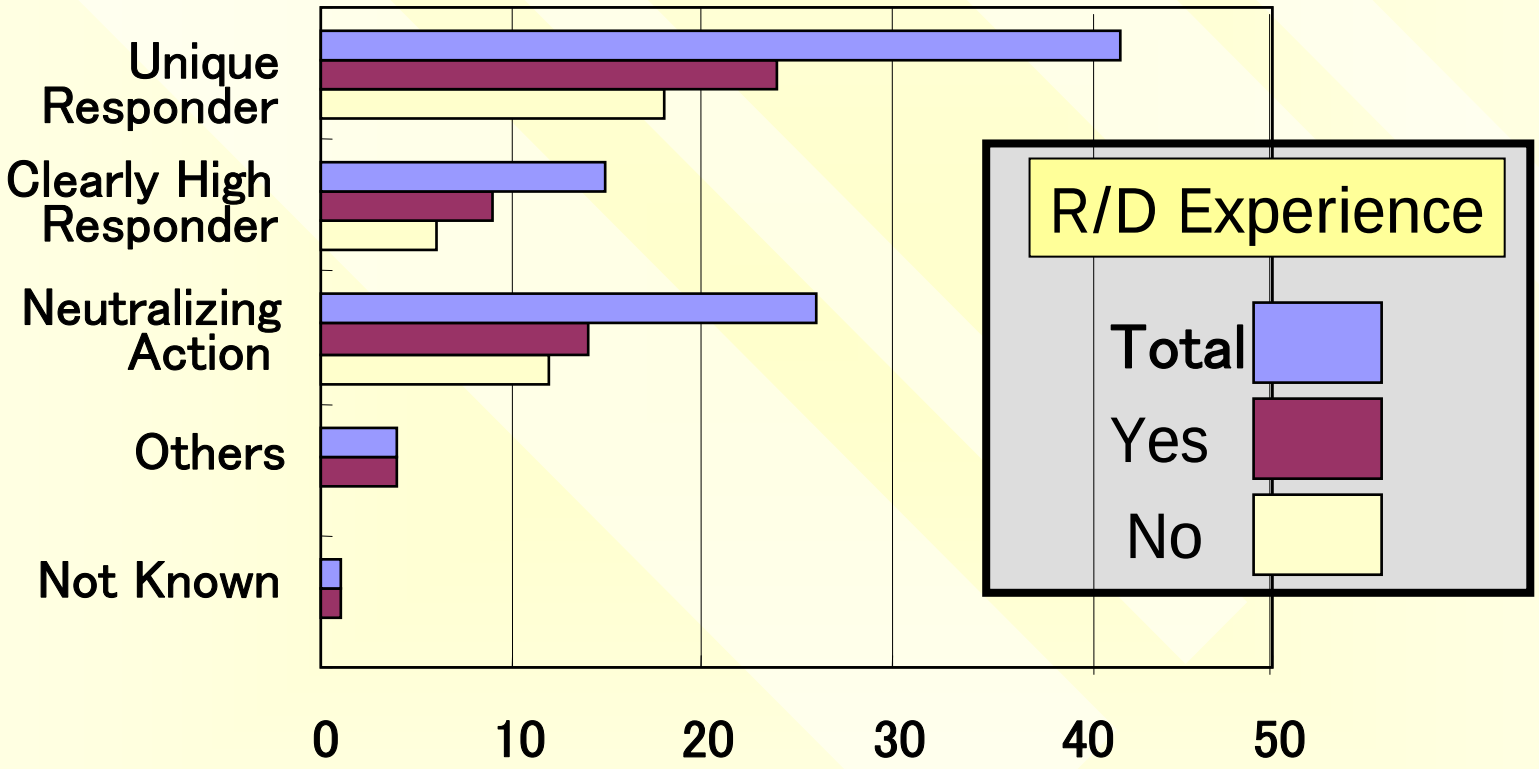
Selection of Animal Species

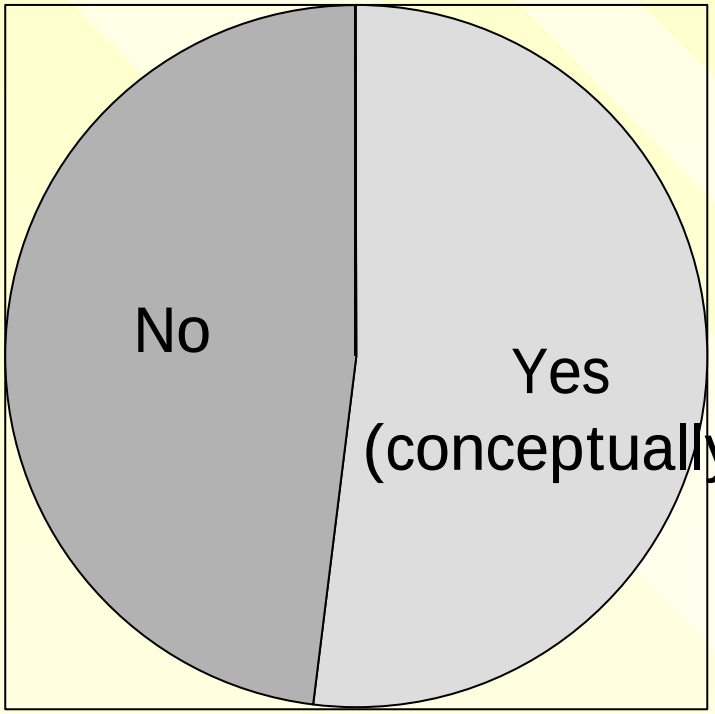


Genotoxicity and Antigenicity

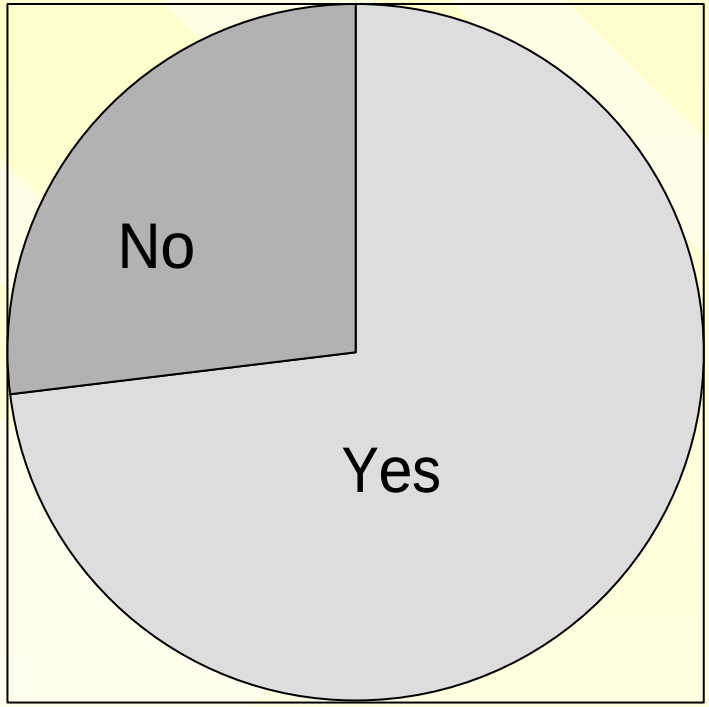
	Conducted	Intentionally not conducted
Genotoxicity	**16/34**	**11/34**
Antigenicity	**12/34**	**15/34**

Examined 34 biopharmaceuticals in total

Compliance with ICH-S6 Concepts



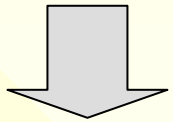
Prior to ICH-S6



After ICH-S6

Benefits from ICH-S6

- Better understanding of safety assessment of biopharmaceuticals
  - Decrease of inappropriate studies
  - Responsibility in establishing further relevant system



Further need to define what “relevancy” is

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Intention of “Points-to-Consider”

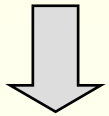
- Not government opinion
  - Iyakuken Hirinsyou Kenkyukai (Collaboration group among JPMA, PMDA and NIHS)
- Not requirement
  - Encouraging scientific discussion for scientists’ better understanding of ICH-S6
- Not requesting a new study
  - Aligned with ICH-S6

Clarification of “Case-by-Case”

- Species differences
  - Maximum dose, homologous proteins, transgenic animals
- Differences between biopharmaceuticals and NCEs
  - Genotoxicity, *in vitro* cardiac electrophysiology, neutralizing antibody, carcinogenicity, radio-labeled proteins for ADME studies
- New types of biopharmaceuticals
  - Bioconjugates and protein analogs with non-natural aminoacids
  - Therapeutic antibodies
  - Glycoprotein analogs

Species Differences

- Non-relevant animals would be
  - Non-responsive
  - Less responsive
  - Over responsive
  - Differently responsive
- Appropriate maximum dose
  - Results at a high dose do not always predict toxicity



Need to know how much relevant the test system used is

Homologous Proteins and Transgenic Animals

- Useful alternatives
  - Provide helpful information when no relevant animals available
- Limitation
  - Not the final product (H)
  - Difficult to estimate the safety margin (H, T)
  - Few background data (T)

Genotxicity Studies

- Rationale for human type protein
  - It is not expected that these substances would interact directly with DNA or other chromosomal material.
  - The expected consequence of metabolism of biopharmaceuticals is the degradation to small peptides and individual amino acids.
- Cause for concern
  - The presence of an organic linker molecule in a conjugated protein product

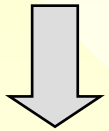
Bioconjugates

- Fragment including organic linker

- How to ensure the safety of bioconjugate regarding genotoxicity and/or potential QT prolongation
  - Scientific rationale
  - Relevant test system

Therapeutic Antibodies

- Novel mechanism of action
- Highly species-specific action
- Action on immune system



  - Cytokine release syndrome
  - MABEL

See Dr. Shinoda's presentation

Safety Brainstorming Session
(ICH Yokohama Meeting, June 2006)

■The Steering Committee agreed to initiate a scientific discussion on this topic.

- During the October meeting of the SC, a plenary meeting should be held of all present nonclinical experts "**to discuss in detail the way in which this scientific discussion should be held.**"
- Suggestions to be considered included a scientific discussion might be held in cooperation with other organisations such as SOT or DIA.

JOINT S2/M3 Session
(ICH Chicago Meeting, Oct 2006)

- Regional meetings (2007)
  - –USA DIA Annual Meeting (Jun)
  - –Japan Drug Evaluation Forum (Aug)
  - –EU Immunotox “summer school” (Oct)
- Central meeting (2008)
  - – Discussion with results from regional meetings
  - – A concept-paper as the outcome

Central Themes

- Predictive value of the nonclinical studies, what is the clinical outcome experience?
- Data should be presented and discussed, *e.g.* TGN1412
- Where does the S6 guideline “work” and where not?
- Focused expertise

Potential topics for ICH-S6

- Carcinogenicity testing. *E.g*. with hormonal growth factors. The need for *in vivo* studies, and the value of *in vitro* studies.
- Use of transgenic models and homologous products
- Timing and need for preclinical testing before the entry into humans (also contact M3), appropriate dose levels and starting dose
- Use for non-human primates in reproduction toxicology
- The risk assessment with monoclonal antibodies.
- *In vitro* cardiac testing
- Antisense nucleotides/ SiRNA
- What is the scope of biologics in development?

Conclusion

- Safety assessment of biopharmaceuticals on the basis of “case-by-case” concept
  - Consider species differences
  - Consider differences between biopharmaceuticals and NCEs
  - Consider the type and nature of each biopharmaceutical

⇨ Be responsible for seeking relevant approach!

- New approaches will be discussed at Drug Evaluation Forum

Acknowledgements

- Pharmaceutical industries that answered JPMA questionnaire
- JPMA
- PMDA
- NIHS