Values and Challenges for ICH S6 Guideline

Takahiro Nakazawa
JPMA / Eli Lilly Japan

Agenda

- Background
  - History
  - Scope of ICH S6
  - Principle of ICH S6
- Values and challenges for ICH S6
- Questions to guide

ICH Safety Guidelines

- S1A (1995)
- S1B (1997)
- S1C(R1) (1994, 1997, 2005)
- S2A (1995)
- S2B (1997)
- S3A (1994)
- S3B (1994)
- S4 (1998)
- S5(R2) (1993, 1995, 2000, 2005)
- S6 (1997)
- S7A (2000)
- S7B (2005)
- S8 (2005)
- M3(R1) (1997, 2000)

Biopharmaceuticals in scope?
Black: excluded
Red: included
Blue: unclear

Local Documents

- Japan
  - PTC for biopharmaceuticals (2002, 2004)
- EU
  - PTC on carcinogenic potential of insulin analogues (2001)
  - PTC on reproduction toxicity of insulin analogues (2002)
  - Guideline for FIH risk identification and mitigation (2007)
- US
  - PTC on mAb (1997)
  - Draft guidance for PTH (2000)
  - Draft guidance for biopharmaceuticals (Pending, 2007)

Scope of ICH S6

- In scope
  - Biotechnology-derived proteins/peptides of the same primary sequence as natural (human) proteins/peptides
  - (Human) protein/peptides analogs
    - Consisting of natural amino acids but different primary sequence from natural proteins/peptides
    - Containing of non-natural amino acid
    - Bioconjugates
  - Diagnostic and therapeutic antibodies
- Out scope
  - Biological pharmaceuticals
    - Vaccines, antibiotics, allergen extracts, vitamins, etc.
  - Oligonucleotide medicines (S6 basic principle applicable)
    - Antisense, ribozyme, RNAi
  - Peptidemimic (S6 basic principle applicable)

Basic Principle of ICH S6

- "Case-by-case" approach
  - Appropriate safety test for each product
  - Flexibility in designing the best safety assessment possible
    - Not to be checklist
- Toxicity test based on pharmacological/biological activities
  - Relevant animal selection
  - Testing dose selection

"Case-by-Case" Approach
Further Clarification for Biopharmaceuticals

- Species differences
  - NHP, homologous proteins, transgenic animals
- Differences between biopharmaceuticals and NCEs
  - Genotoxicity, *in vitro* cardiac electrophysiology, neutralizing antibody, carcinogenicity, radio-labeled proteins for ADME studies
- Types of biopharmaceuticals
  - Human proteins
  - Protein analogs
    - Different primary sequence from human protein
    - Replacement w/ non-natural amino acids
  - Bioconjugates
  - Antibodies

General Principle

Item	Value	Challenge
Basic principle and scope	▪Case-by-case approach ▪Scope: Biotechnology-derived Proteins/peptides and their analogs	▪New types of biologics ▪Bioconjugates and therapeutic antibodies ▪Antisense and RNAi
Species selection	▪Relevant species selection based on pharmacological and/or biological activities ▪Decrease of unnecessary animal studies ▪Appropriate safety evaluation ▪Transgenic animals and homologous proteins	▪No relevant animals available in some cases ▪No clear guidance on when/how to use transgenic animals and homologous proteins

General Principle (Cont'd)

Item	Value	Challenge
Dose selection	▪Dose selection in light of PK/PD and expected clinical dose	▪Little predictive value of starting dose for FIH from animal data in some cases ▪TGN1412 ▪Disharmony on the need of observable toxicological endpoint at highest dose ▪Exaggerated pharmacology

Individual Studies

Item	Value	Challenge
Single dose tox studies	▪Unnecessary	
Repeat dose tox studies	▪Measurement of neutralizing antibody ▪One species for long-term tox study, when appropriate	▪Disharmony among regulatory requirements on the duration of non-rodent repeat dose tox study ▪6 Mo vs. 9 Mo vs. 12 Mo

Individual Studies (Cont'd)

Item	Value	Challenge
Repro/dev tox studies	▪Flexible study design	▪Unavailable conventional animals in many cases due to lack of pharmacological response or neutralizing antibody production ▪Some technical limitations for monkey repro/dev tox studies ▪Homologous proteins or transgenic animals?

Individual Studies (Cont'd)

Item	Value	Challenge
HERG assay		▪No description in ICH S6 and unestablished justification for biopharmaceuticals
Genotoxicity testing	▪Unnecessary for most biopharmaceuticals	▪Unestablished scientific justification for bioconjugates

Individual Studies (Cont'd)

Item	Value	Challenge
Carcinogenicity studies	▪One species for carcinogenicity study ▪Concern about mitogenicity rather than mutagenicity ▪Utility of *in vitro* promotion assay	▪Unavailable rodents in many cases due to lack of pharmacological response or neutralizing antibody production ▪Unestablished scientific justification for growth factors and immunosuppressants

ICH S6 Discussions

- ICH Brussels meeting in 1997 (Step 4)
- ICH Yokohama meeting in June, 2006
- ICH Chicago meeting in Oct, 2006
- Regional meetings in 2007
  - DIA (US, June)
  - Drug Evaluation Forum (Japan, Aug)
  - Summerschool of Immunotoxicology (EU, Oct)
- Central meeting in Spring, 2008
- Next step?

Questions for Discussion

- Predictive value of preclinical studies?
  - Initial dose selection for FIH from preclinical data
- Where ICH S6 "works" and where not?
  - Individual studies
- Scope of ICH S6?
  - New types of biologics
- Update of ICH S6 guideline?
  - Sections to be updated