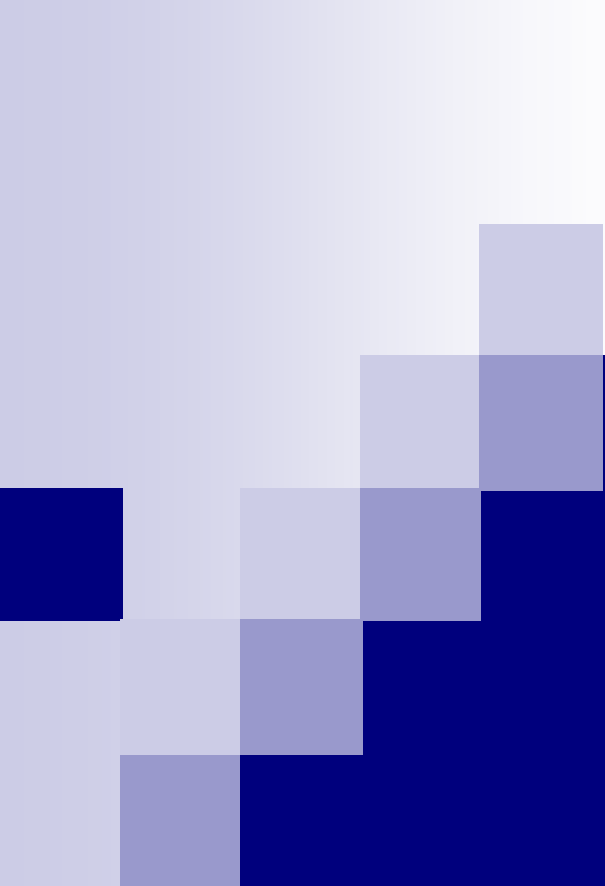




Update the guidance of ICH S6

Dr Jennifer Sims, Novartis Biologics, Switzerland

EFPIA (Rapporteur)

International Conference on Harmonisation of Technical
Requirements for Registration of Pharmaceuticals for Human Use



Parties represented during the meeting

- MHLW
- JPMA
- FDA
- PhRMA
- EU
- EFPIA

Observers:

- Health Canada,
- EFTA (not present)

Interested parties:

- BIO
- WSMI, IGPA (not present)



ICH Meeting June 2008: Concept Paper

- 5 topics selected for update via an addendum to S6
 - ☐ Species Selection
 - ☐ Study design
 - ☐ Reproductive/developmental toxicity
 - ☐ Carcinogenicity
 - ☐ Immunogenicity
- November 2008: 5 topics discussed in EWG, new information presented by external experts

Topic 1: Species Selection

- Default position in S6 is need for 2 species, where 2 relevant species exist for the **clinical candidate**.
 - Clarification: Does not mean NHP with clinical candidate AND rodent studies with surrogate product
 - For further discussion: Under what circumstances may testing in **only** one relevant species be considered sufficient?
- Clarify critical factors to qualify a surrogate/homologue for use in toxicity testing if no relevant species exist for clinical candidate

Topic 2: Study Design

- Rationale to support dose selection and need / duration for recovery may benefit from PK/PD approaches
 - Proposal under discussion: high dose in toxicity studies is maximum pharmacological dose and provides a 5-10 fold exposure multiple versus the therapeutic dose
 - **For mAbs, increasing this high dose in the toxicity study beyond this maximum pharmacological dose will increase the duration of effect NOT the magnitude of the effect**
 - Proposal under discussion: Recovery groups not required in all dose groups – based on PK/PD approaches to enable assessment of reversibility of findings if needed – NOT detection of immunogenicity
 - Rationale to support 6 months duration for chronic toxicity study:
 - For further discussion: based on PK-PD approaches and continuous max pharmacological effect as intended in clinical use
 - For products active only in NHP, FIH supportive studies are conducted in sexually immature animals: Lack of histology in reproductive organs in sexually mature animals may be a potential issue for Japan
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Topic 3: Reproductive / developmental toxicity

- For products pharmacologically active only in NHP
 - Proposal for discussion: Developmental toxicity hazard detection study with a single cohort of gestationally exposed animals
 - All animals allowed to deliver, no C-section
 - Single dose group and control
 - Consensus that a separate EFD study is of little or no value for large molecular proteins
 - This ePPND study design has an impact on timing of these studies in clinical development (cross-talk with M3)
- Further discussion needed on the value of surrogate data in rodents in place of NHP with clinical candidate

Topic 4: Carcinogenicity

- Consensus in S6 EWG:
 - Life time rodent bioassay for therapeutic proteins does not provide useful information.
 - Alternative approaches are more appropriate to assess carcinogenic potential in accordance with S6
- But, high proportion of FDA Divisions will expect life time rodent bioassay with either clinical candidate or surrogate
- EWG is still considering whether further clarification is useful, or whether this is just an implementation issue



Topic 5: Immunogenicity

- First draft completed
- Clarification: purpose of immunogenicity is to assist in the interpretation of results of toxicity studies
 - Circumstances when ADA testing may not warranted
 - Although assessment of neutralizing activity can be addressed using a separate neutralizing antibody assay, other approaches can also be valid and may be more robust

Impact on 3R's if consensus reached on the following aspects

- Enhanced PPND study design involves holistic assessment of all developmental toxicity endpoints in a single cohort of gestationally exposed animals
 - Reduces need for 2 separate studies (EFD and PPND studies)
 - One treated group and control will reduce numbers further
 - Inclusion of fertility aspects in chronic toxicity studies – no need for separate studies
 - Use of only one relevant species for chronic toxicity studies even if 2 relevant species – if circumstances can be defined when this would be sufficient
 - Recovery groups not required for all treatment groups
 - Only 2 repeat dose studies required for non-oncology products: FIH-supporting and 6 months chronic
 - Lifetime bioassays in rodents not required
 - Use of a surrogate in order to avoid use of NHP e.g. for reprotox
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Way Forward

■ Expert Working Group

- Start in November 2008 with discussion of various topics, presenting the background data
- Drafting of 5 sections with small working groups for each section – first draft of Immunogenicity section completed
- Preliminary draft of all 5 sections end Q109, distributed for comments by May 09 and discussion in June 09
- June/November 2009: Step 2
- Consultation period: 6 months
- Step 4 in June 2010

Rapporteurs

- For step 2: EFPIA
- For step 4: EU