Update the guidance of ICH S6

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EFPIA (Rapportuer)

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 asessment 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

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

ICH

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