Hypothesis based testing in pharmaceutical development

Dinesh Stanislaus
GlaxoSmithKline
WHAT DOES IT MEAN ?

Understanding the pharmacology, toxicology and the clinical use of the drug when designing the testing strategy…

Considering the effect of target/off-target engagement on embryo-fetal development

Consideration of clinical hypothesis
  Clinical PK profile and its relevance to embryo-fetal development
WHY IS IT IMPORTANT?

Standard battery of reproductive toxicity testing is good at hazard identification and risk assessment.

However using a hypothesis when testing can …

- Prevent unnecessary testing and reduce animal use
- Prevent inadequate risk assessment when clinical use/hypothesis is taken into consideration
- Avoid a missed signal when the biology is taken into consideration
Three case studies to stimulate your thinking...
1. Unnecessary testing and animal use

Anti-cancer drug testing

• Current ICHS9
  • If embryo-fetal hazard identified in one species, testing in a second species may not be necessary as hazard has been identified

• Evolved approach to the current guideline
  • Target = embryo toxicity
    • Would a DRF-type embryo-fetal study to test the hypothesis be sufficient to test the hypothesis and confirm the hazard?
  • 3R implications and resource savings
2. When clinical use/hypothesis is not taken into consideration

Clinical drug exposure profile of a dermal drug

- **Clinical efficacy needs 24 h target engagement**

Two dosing paradigms in a rabbit S.C. study – conducted to maximize exposure to the fetus: exposure profile

*Which dosing schedule gives more confidence in identifying and detecting a hazard?*
2. When clinical use/hypothesis is not taken into consideration

**Outcome:**
- Target = Some evidence to suggest human genetic defects producing craniofacial malformations
- Dose at which malformations identified in QID study did not Produce malformations in the BID study
- BID dosing produced single digit safety multiples but QID didn’t

*Understand the clinical use and pharmacokinetic profile when designing studies*
3. Not clearly understanding the biology can lead to a missed signal

When the abnormal development could be only assessed during post-natal period
  • Target = could play a role in mammary gland development
  • Could a standard rat EFD study identify a hazard?
    • What hypothesis driven adjustments are needed on a standard EFD study?
      • Is addressing this hazard potential necessary?
      • Risk management considerations

*Impact on informed consent; potential for expedited reporting*
3. Not clearly understanding the biology can lead to a missed signal

- A missed signal leading to inadequate risk mitigation steps in the clinic
  - Target = present in $2^0$ follicles
  - Could a standard rat fertility study identify a hazard?

- What hypothesis driven changes are needed to standard EFD study?
  - Why addressing this potential necessary?
    » Risk management considerations

Impact on the duration of contraception requirements after the end of in clinical trials

McGee and Hsueh 2000; Endocrine Reviews
Final points for consideration

• Understand the target and off-target biology for safety and efficacy
• Understand what a standard study can detect and not-detect
• Design studies based on a hypothesis and test that hypothesis

But
• Beware of missing a signal as unknown biological interactions can lead to surprises!