Overview of Toxicology Evaluations

Presentation date: November 2017
Presented by: Toxicology Section, Scientific Evaluation Branch
Presented at: Therapeutic Goods Evaluation Panel Information Sessions
What do we do?

- Evaluate nonclinical (pharmacology and toxicology) data submitted to support clinical trials or registration of medicines (prescription, over-the-counter and complementary) and medical devices in Australia;

- Report on the nonclinical data submitted; and

- Assess and make recommendations for sections of the Product Information that contain nonclinical data, including Use in Pregnancy and pregnancy categorisation.
Goals of nonclinical studies

- To identify starting dose and dose escalation for clinical trials;
- To identify potential target organs; and
- To identify toxic effects that cannot be discerned from clinical studies
Contents of an Evaluation Report

Nonclinical Evaluation Report
Genericdrugname [TRADENAME®]

Submission No: PM-2015-00000-1-0
Sponsor: Drug Company Pty Ltd
January 2016
Evaluation Content – Main Body

• Pharmacology

  – Primary Pharmacology
    ✈ *In vitro*: Mechanism of action and potency;
    ✈ *In vivo*: Efficacy in an animal model;

  – Secondary and Safety Pharmacology
    ✈ Pharmacological effects other than primary therapeutic effects
    ✈ Unwanted effects on major organ systems & exaggerated pharmacological effects
Evaluation Content – Main Body

- **Pharmacokinetics (ADME)**
  - **Absorption** (IV: $V_d$, $C_l$, $t_{1/2}$; PO: $C_{max}$, $T_{max}$, $F$, single & repeated dose)
  - **Distribution** (organ concentration, autoradiography)
  - **Metabolism** (plasma, urinary, biliary & faecal metabolites)
  - **Excretion** (urine, faeces, expired air, carcass; time course)
  - **Interactions** (plasma protein binding, CYP450 drug interactions, transporters)

Are animals used in the studies good models for human?
Evaluation Content – Main Body

• Toxicity (1)

  – Acute/Single dose toxicity
    - Single dose, mortality & signs, 14 days observation

  – Repeat dose toxicity
    - Dose, duration, species, sample size, route, toxicokinetics;
    - Mortality, bodyweight gain, food & water consumption, clinical signs, ECG, ophthalmology, haematology, clinical chemistry, urinalysis, organ weight;
    - Includes detailed microscopic examination of an extensive set of tissues;
Evaluation Content – Main Body

• Toxicity (2)

  – Carcinogenicity
    - Near lifetime studies in two rodent species
    - Applicability to humans

  – Genotoxicity
    - Gene mutation
    - Chromosomal damage
    - DNA damage
Toxicity (3)

- Reproductive and developmental toxicity
  - Fertility and early embryonic development
  - Embryo-foetal development (teratology)
  - Pre- and post-natal development

- Local tolerance
  - IV, inhalation, eye, skin injection site effects after IV, IM, SC

- Other Toxicity studies
  - Antigenicity/immunotoxicity
  - Studies with impurities
Evaluation Content – Assessment

• Integration & critical assessment of data
  (http://www.tga.gov.au/industry/pm-euguidelines.htm)

• Consider overall quality of submission
  – Highlight inconsistencies or concerns;

• Deficiencies & their significance for human risk
  – Relevant studies not conducted;
  – Deficiencies in conducted studies;

• Positive findings & their significance for human risk
Recommendation

Registration/variation to existing registration:

• supported;
• supported with reservations or restrictions
  (this may refer to recommended changes to the proposed Product Information);
• not supported by nonclinical data
Evaluation Content – Product Information

• A concise summary of all information about the drug relevant to its clinical use

• Sections containing nonclinical data
  - Pharmacodynamics/mechanism of action
  - Pharmacokinetics and drug interactions
  - Genotoxicity and carcinogenicity
  - Effects on fertility
  - Use in pregnancy (Aus categorisation: A, C, B1-B3, D, X)
  - Use in lactation
  - Interactions with other medicines
Conclusions

• Evaluation of nonclinical (toxicological) data is an integral part of prescription medicines registration;

• Animal to human: Identification of potential adverse effects in humans;

• Key areas of nonclinical toxicological concern;

• See “real-life” evaluations in the Australian Public Assessment Report (AusPAR) for prescription medicines: