



Drug Development: Building Confidence in Safety

Chudy Nduaka, DVM.,MS.,Ph.D.,DABT
President, The Africa Education Initiative (NEF)



Toxicology:

adverse effects of chemicals or molecules

All substances are toxic. The dose makes the difference



Objective:

To identify and characterize toxicity

What? Dose

Where? Organ system

When? Acute, subchronic or chronic

How? Toxicology study design



Confidence in Safety Strategy

- Operating plan: outline development plan
- Review literature: what is known? What is unknown?
- Select appropriate testing species
- In silico approaches: DEREK, SAR databases
- Rule out potential genotoxicity: Ames, in vitro micronucleus
- Early in vivo toxicity studies
- Mechanistic assays: ocular, hepatotoxicity, renal



Plan for Success

- ❑ Create Project Teams and Project Operating Plans
- ❑ Teams should be multidisciplinary: Toxicology, PDM, Biology, Chemistry, Regulatory, Project Manager
- ❑ Scientists working together will Enhance Project Understanding of Biology and Identify Potential Risks
- ❑ Project team will evaluate potential risk and weigh against anticipated benefit



Manage attrition

- Identification of risk earlier will help manage attrition
- Early termination of compounds due to unacceptable adverse events saves resources
- Prepare summary Reason for termination (RFT) document to capture learnings for the future



Driving Success

- Identify and validate preclinical biomarkers of safety and efficacy (serum/urinary enzymes, clin path, imaging)

- Validated preclinical biomarkers provide options for use in clinical studies



Early Toxicology Study Design

Species	RAT
Dose	0.5,5,50,500 mg/kg
Duration	4-7 days
Parameters examined	Clin observation Body wt Food consumption Clinical chemistry Gross and anatomic pathology
Route of admin	Oral gavage



Rank order New Molecular Entities (NME)

- Therapeutic index (TI): ratio of toxic dose to efficacious dose
- Pharmacokinetics: C_{eff}, AUC, T_{1/2} and clearance
- Potency
- Toxicity profile
- Cost of goods: CMC



Summary

- Early identification of risk is paramount to the success of Program
- Toxicity bioassays help in the rank ordering process
- Preclinical target organ identification and characterization provide general guidance to the clinician during clinical trials
- Project operating plans are very useful in building confidence in safety