NON CLINICAL DEVELOPMENT FOR FIM
Evaluation of Risk

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Predicting the potential severe adverse reactions for the first-in-human use of a drug, involves the identification of the factors of risk

Drug discovery →				PreClinical
TARGET SELECTION	**CHEMOTYPE**	**SELECTION**	**COMPOUND SELECTION**	
Pick the target (eg- enzyme or receptor) to be modulated	Develop in vitro potency hits to yield 2 lead series that have in vivo pharmacology and systemic exposure	Optimize series for in vivo potency, selectivity, PK and safety	Select Candidate w/ credentials to pursue regulatory toxicology and clinical testing	Conduct Regulatory Toxicology package to understand human safety risks and write NCO. Make clinical quality drug substance and formulation for administration to Humans. File IND/CTA with Authorities to permit FIH
Evidence that target can be dosed safely	Target localization and function to predict potential for adverse pharmacology	What is dose-limiting adverse effect and is it due to activity at primary target or a non-specific mechansim	If tox is due to activity at primary target, is TI sufficient to proceed	

Regulatory environment

- **Drug development is harder and more complicated than before**

- **With a very important regulatory environment :**
  - Local
  - National
  - Regional
  - Global

- **… And prescriptive guidances**
  - Guidelines are becoming « mandatory instructions ,» not only recommandations

Factors of risk : (1) knowledge on Mode of action

- Nature and intensity (extent, amplification, duration, reversibility) of the effect on the specific target and non-targets and subsequent mechanisms

- Type and steepness of the dose response measured in experimental systems

✓ When analyzing risk factors associated with the mode of action, aspects to be considered may include:

- Previous exposure of human to compounds that have related modes of action.
- Evidence from animal models (including transgenic, knock-in or knock-out animals) for the potential risk of serious, pharmacologically mediated toxicity
- Novelty of the molecular structure of the active substance

Factors of risk : (2) knowledge on Nature of the target and off-target

- Extent of the available knowledge on the structure, tissue distribution, cell specificity, disease specificity, regulation, level of expression, and biological function of the human target including “downstream” effects, and how it might vary between individuals in different populations of healthy subjects and patients

- Description of polymorphisms of the target in relevant animal species and humans, and the impact of polymorphisms on the pharmacological effects of the medicinal product (if possible)

- Nature of the target : specific investigations / biomarkers to be tested in addition to the classical safety parameters as per guidances

Factors of risk : (3) Relevance of Animal Species & Models

- Comparison of the available animal species to humans taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects

- Instrumental for Pharmacological and Toxicological assessment in animal studies to:

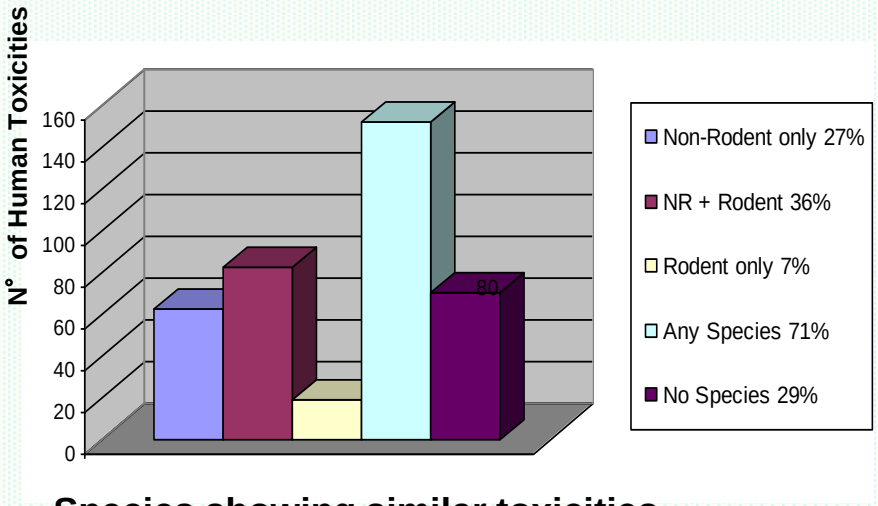
  – Reproduce the intended pharmacological effect in humans
  – Lead to relevant interpretation of pharmacokinetic (PK profile, metabolites, tissue to plasma ratio etc…) and pharmacodynamic results
  – Identify relevant toxic effects

    > studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals, providing scientific justification

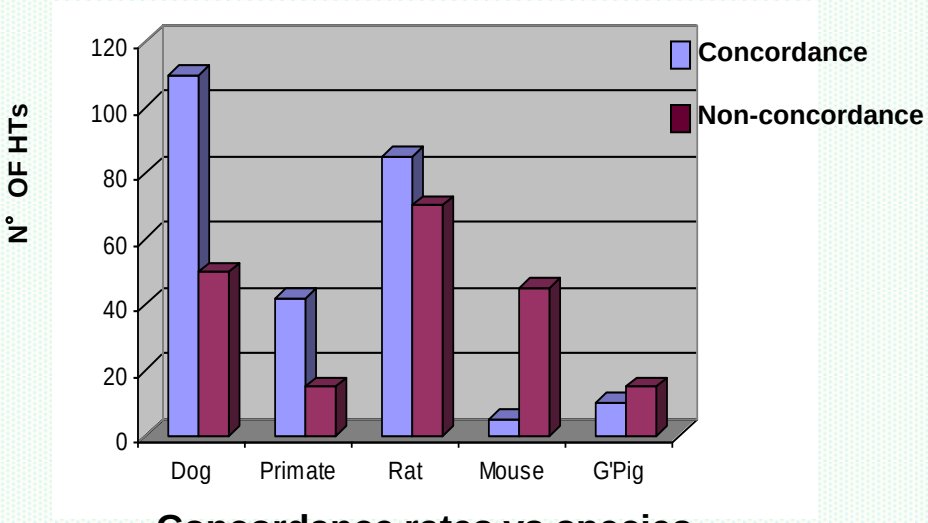
Concordance of Human Toxicity from Animals (ILSI Workshop : 12 Companies – 221 Human Toxicities – 150 drugs)

From Regul Toxicol & Pharmacol 32:56-67 (2002)

- ✓ Good but imperfect models ➔ 29% human findings not found by in vivo models



Species showing similar toxicities



Concordance rates vs species

NR only: Dog (49), NHP (7), or both (1) R only: rat (10), mouse (3), GP (3), rabbit (2)