Basic principles of the safety assessment of drugs

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Outline of presentation

Safety assessment in the discovery and development of drugs

Target
Lead chemistry
Cmpd selection

Cmpd characterisation / regulatory documentation / risk assessment

New indications, formulations, combinations, impurities, degradation products, patient populations, paediatrics etc
Target Safety Assessment

Some components

• overall target function/biology in health and disease
  • pathway mapping/interaction with other pathways
  • information from ko/ transgenic models
  • human target variations - implications

• target distribution
  • explicitly not only confined to intended pharmacological tissue/ organ
  • identifying relevant species for toxicological characterisation
  • in health and in disease

• functionally / structurally related targets
  • selectivity (off target pharmacology)

→ critical issues addressed experimentally when possible

→ build/refine safety plans moving forward
Chemistry Safety Assessment

Components of early avoidance of chemical structure safety liabilities:

• chemical structures are analysed continuously *in silico* for possible structure-related safety concerns:
  
  • genotoxicity
  • hERG channel blockade
  • reactive metabolite formation
  • phospholipidosis
  • bone marrow toxicity
  • structural similarity to problematic molecules
  • DMPK properties
  • and more ……

→ experimental follow up of potential issues
→ build/refine safety plans moving forward
Optimisation of lead compounds

Screening *in vitro* for e.g.

- Genotoxicity
- hERG and other ion channels
- Cyto tox
- Immunotox
- Hepatic tox
- Bone marrow tox
- Transporters
- Metabolism/CYPs
- Reactive metabolites
- Off target pharmacology/secondary pharmacology
- Cross-species comparisons where applicable

Fit for purpose *in vivo* studies, e.g.

- To early address target or chemistry related safety concerns identified
- To extract relevant safety information as part of PK/PD characterisation in *in vivo* (disease) models
- To build confidence in safety before expanding into larger regulatory animal studies

**Internal decision making up to this point**
Safety characterisation of candidate drug

Objective
- Provide and assess safety information relevant for conducting safe clinical trials and supporting marketing applications.

Animal data generally more in focus at:
- First dose to man (healthy volunteers, patients)
- Increased duration/doses
- First dose to women of childbearing potential
- First dose to children
- Assessing reproductive and carcinogenic risks

Clinical safety data evolve during development and eventually override some of the toxicology data

Drug safety surveillance of marketed drugs continues for the life-time of the products
Regulatory guidelines - framework

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- ICH M3(R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

- And many more detailed international and regional guidances
Considerations selecting animal species

• Pharmacologically responsive?
  • To address concerns around exaggerated pharmacology

• Appropriate local and systemic exposure to the drug
  • Ensure adequate exposure margins in the relevant tissues/compartments is achievable using the proposed route of administration in man.
  • Supplement by alternative route if needed and feasible
  • Take into account local vs systemic exposure, half-life, exposure profiles, max/min levels, protein binding etc.

• Coverage of human relevant metabolites?
  • Compare cross-species including man
  • Microsomes
  • Hepatocytes
  • *In vivo* data

Chromatograms obtained from analysis of Human, Rat and Dog steady state plasma samples
Safety Pharmacology

Studies that investigate the potential **undesirable pharmacodynamic effects on physiological functions** at exposures in the therapeutic range and above

- Studies on the mode of action and or effects in relation to the **desired therapeutic target**
- Studies on the mode of action and/or effects **not related to the desired therapeutic target** (with focus on vital functions such as CV, Respiratory, CNS)
- Usually single dose/short-term studies in rodents and non-rodents

- **Identify** undesirable pharmacodynamic properties relevant to human safety
- **Evaluate** adverse pharmacodynamic effects observed in toxicology and/or clinical studies
- **Investigate mechanisms** of adverse pharmacodynamic effects
General toxicity studies

One rodent and one non-rodent species
- Generally rats and dogs
- Duration equal or longer than intended clinical trial (up to 6 months in rodents and 9/12 months in non-rodents)

Dose levels:
- Relevant route of administration
- Therapeutic up to Max Tolerable/Limit/Fesible Dose
- Exposure rather than dose levels
- Generally 1 control and 3 treatment groups (+ recovery)

Aim:
- Systemic exposure levels
- Target(s) of toxicity
- Incidences and severities
- Dose-dependency
- Time-dependency
- Species specificity
- Reversibility
General toxicity studies continued

Evaluations - endpoints

- clinical signs
- body weight
- food & water consumpt.
- ophthalmoscopy
- ECG (non-rodents)
- toxicokinetics
- clinical pathology
  - haematology
  - blood chemistry
  - urinalysis
- pathology
  - necropsy/gross pathology
  - organ weights (12-20)
  - microscopic pathology (40-45 different tissues from each animal)
- ad hoc as appropriate
  - non std biomarkers
  - special stainings
  - male fertility
  - explorative samples
  - Met ID
  - safety pharm endpoints
**Genetic toxicology**

**Drug:**

*in vitro assays*
- Ames Test (bacteria) – gene mutation
- Mouse Lymphoma TK locus test or Chromosomal aberrations in human lymphocytes (mammalian cells)  – chromosomal damage
- +/- metabolic activation system

*in vivo assays*
- Micronucleus assay (rats or mice, bone marrow)

**Genotoxic Impurities:**
- *In silico* and *in vitro* assessment of Potential Genotoxic Impurities (PGI) from manufacturing route or degradation processes
- Control under Threshold of Toxicological Concern (TTC) (some times down to ppm levels of active drug)
Reproductive toxicology

- **Fertility** – dosing of males and females before and during mating, but also evaluation of reproductive organs in general tox studies: usually in rats

- **Embryofoetal development** – dosing of females during major organ development – evaluation of offspring: usually in rats and rabbits

- **Peri and postnatal development**: including reproductive performance of offspring (2nd generation)

- Generally, studies on fertility and embryofoetal development before inclusion of women of childbearing potential although exceptions do exist
Carcinogenicity

• Studies in rodents with life time exposure ~ 2 years
  • Usually rats and mice (2 studies)
  • 500-600 animals/study
  • Tumour incidence – histopathological evaluation of most tissues
  • Performed at a late stage of development – takes ~3 years to complete
  • Options for alternative tests, eg 6 month test in transgenic mice models sensitive to tumour development
    • Can replace one of the studies
  • ICH S1 revision under discussion
Phototoxicity

Assessment for potential phototoxicity part of the standard package

- Does the cmpd absorb UV/VIS light in significant amounts (MEC>1000)?
- Does it distribute to tissues exposed to sunlight?
- In vitro assessment
- In vivo assessment

Apply precautions if needed in clinical trials
Safety margins - Risk assessment

Estimated pharmacodynamic response (Human, fri fraction 13%)

Toxicological response (dog, fri fraction 10%)

Safety margin: 10x
Correction free fraction (unbound): 7.5x
### Primary PK parameters in animals (CV%)

<table>
<thead>
<tr>
<th>Animal</th>
<th>CL (mL/min/kg)</th>
<th>VDss (mL/kg)</th>
<th>t_{1/2,\lambda_2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cynomolgus monkey</td>
<td>3.6 (45)</td>
<td>87 (24)</td>
<td>19.4 (47)</td>
</tr>
<tr>
<td>Mouse</td>
<td>12 (8)</td>
<td>138 (13)</td>
<td>10.2 (12)</td>
</tr>
<tr>
<td>Rat</td>
<td>5.6 (5.4)</td>
<td>73 (9.4)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Rat a)</td>
<td>5.7 (13)</td>
<td>77 (22)</td>
<td>11 (40)</td>
</tr>
</tbody>
</table>

### Predicted human PK

<table>
<thead>
<tr>
<th></th>
<th>CL (mL/h/kg)</th>
<th>Vss (mL/kg)</th>
<th>t_{1/2,\lambda_2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human*</td>
<td>1.5</td>
<td>53</td>
<td>29</td>
</tr>
</tbody>
</table>

* Predicted from allometric scaling

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**Example prediction of human exposure at FTIM**

Pharmacokinetic models – allometric scaling – predictions to man

![Graph showing predicted human exposure vs animal parameters](image)

\[ y = 0.741x + 0.643 \]
What is an appropriate safety margin/exposure limit?

Some general considerations:

- Patient population, indication
- Human relevance or not
- Human vs animal sensitivity
- Exaggerated pharmacology or unspecific toxicology
- Adaptive vs. degenerative
- Reversibility
- Biomarker sensitivity and predictivity, if available

- Risk to occur in the study population at suggested dose levels?
- Potential consequences if it occur?
- Risk/benefit for the patients?
- How to detect, predictive or diagnostic markers available?
- How to act if it occur, recovery following drug withdrawal, antidotes?

Acceptable safety margins and exposure limits set case-by-case

Risk assessment not only for next clinical trial but also for "line of sight"
Concordance of toxicity: animal vs man

Olsson et al., Regulatory Toxicology and Pharmacology 32, 56-67 (2000)
Sola dosis facit venenum

“The dose makes the poison”