Preclinical studies needed in the development of human pharmaceutical drugs - role of toxicology and risk assessment

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Preclinical studies needed in the development of human pharmaceutical drugs

Pharmacology
- primary pharmacodynamic studies: studies on mode of action and/or effects of a substance to its desired therapeutic effects
- secondary pharmacodynamics: effects of a substance not related to its desired therapeutic target
- Safety pharmacology
Pharmacokinetics and metabolism
Toxicology

Factors affecting development strategy

- Guidelines
- Novelty
- Acceptable risk/Benefit
- Drug supply
- Expected market value
- Type of compound
- Ethics

Clinical studies

Phase 1
Who: Normal volunteers or special populations (renal or hepatic impairment)
Why: Safety, biological effects, metabolism, kinetics

Phase 2
Who: Selected patients
Why: Therapeutic efficacy, dose range, kinetics, metabolism

Phase 3
Who: Large sample of patients
Why: Safety and efficacy. Compare to golden standard

Goals of non-clinical safety evaluation

- To be as sure as possible (within reasonable limits) that the products we develop are not harmful to man at clinically relevant doses
- To identify target organs or biomarkers that need to be followed-up in clinical studies
- To fulfill the regulatory requirements for registration of the products
- To improve our understanding of the biological effects of specific drugs
- To develop safer drugs in the future
Predictive value of non-clinical safety evaluation

From Greaves et al., Nature Drug Discovery, March 2003

Regulatory requirements in different regions in the world

- There were big differences between regulatory requirements between USA, Japan, and Europe.
- These differences are nowadays less.
  - Europe is more interested in mechanistic type of studies and more open for new types of studies/study designs
  - Japan: large focus on No-effect Levels, excipients and impurities.

International Commission on Harmonisation – guidelines (www.ICH.org)

S1A Guideline on the need for carcinogenicity studies of pharmaceuticals
S1B Testing for carcinogenicity in pharmaceuticals
S1C Guidance for dose selection for carcinogenicity studies of pharmaceuticals (+ S1C(R): Addendum)
S2A Genotoxicity: Specific aspects of regulatory genotoxicity tests
S2B Genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals
S3A Toxicokinetics: Guidance on the assessment of systemic exposure in toxicity studies
S3B Pharmacokinetics: Guidance for repeated dose tissue distribution studies

S4 Single dose toxicity tests
S4A Duration of chronic toxicity testing in animals (rodent and non-rodent)
S5A Detection of toxicity to reproduction for medicinal products
S5B(M) Reproductive toxicology: Male fertility studies
S6 Safety studies for biotechnological products
S7A Safety pharmacology studies for human pharmaceuticals
S7B Safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals
M3 Timing of pre-clinical studies in relation to clinical trials
Safety pharmacology studies for human pharmaceuticals - ICH S7

- Core battery:
  - Effects on CNS system
    - Motor activity, behavioral changes, coordination, sensory/motor reflexes, i.e., Modified Irwin test, Functional Observation test
  - Cardiovascular system
    - Blood pressure, heart rate, and electrocardiogram
    - Preferably use conscious animals (telemetry models)
  - Respiratory system
    - Respiratory rate and tidal volume

- ICH S7B: safety pharmacology for assessing the potential for delayed ventricular repolarization (QT interval prolongation)

- QT interval is dependent on heart rate and should therefore be corrected for heart rate (QTc)
- Long QT syndrome is QTc > 440 ms
- QT prolongation can lead to arrhythmias and/or Torsade de pointes
  - Antihistamines
  - Antidepressants
  - Anticonvulsants
  - Antiarrhythmic agents
  - etc

- HERG assay
  - HERG is a Human Ether-a-go-go gene Related Gene
  - Transfected in human cells (human embryonal kidney cells)
  - Codes for a K+ channel
  - Measurements on individual cells by action potential clamp techniques

Pharmacokinetics and metabolism
Why is it important to know the pharmacokinetics of new drugs?

- Interpret toxic findings and side-effects
- Maximum concentration and total exposure
- Predict drug-drug interactions
- Are drugs metabolized by the same enzymes (P450 3A)?
- Predict influence of diseases on drug use
- Liver diseases can lead to reduced drug metabolism
- Predict influence of age and gender on drug use
- Activity phase 1 drug metabolizing enzymes is reduced in elderly people
- Design dosing regimens

ADME

Quantitative whole-body autoradiography

- Test article labeled with an appropriate radioactive isotope
- Administration to animals
- Animals killed at different time points, and frozen
- Slices prepared by whole-body microtome
- Freeze-dried sections exposed to storage phosphor screens, which are scanned using a phosphor imager.

Quantitative whole-body autoradiography 14C glucose

Toxicology

- Single dose toxicity
- Repeat dose toxicity
- Local tolerance
- Genetic toxicity, in vitro + in vivo
- Reproductive toxicity
- Carcinogenic potential
- Immunotoxicology
- Special studies
**Single dose toxicity**

- **ICH** - 2 mammalian species
- **EU** - 2 mammalian species
- **FDA** - 2 mammalian species, justify if not dog
- **MWH** - rodent + non-rodent other than rabbit

- DRF (to lethal / limit dose)
- Single dose via intended clinical route + i.v.
- Minimum 3 doses + control
- 14 Day observation
- Body weight
- Necropsy
- Target organ weight
- Target organ histology
  - (clinical pathology)

**Repeat dose toxicity**

- Normally preceded by Dose Range Finding study
- 2 species - rodent + non-rodent
- Duration of studies dependent on duration of human treatment
- Toxicokinetics required to document exposure and aid to interpretation
- Recovery period to investigate reversibility of findings

**Role of toxicological risk assessment**

- Due to a new chemical synthesis of the drug substance to be used in clinical trials a new impurity is found in the drug product:
  - Question to the toxicologist: Can we use this batch of drug product in clinical trials
- During migration studies using a new type of plastic bottle a new impurity is observed in a marketed drug product
  - Question to the toxicologist: can we release this product in this new bottle to the market.

**Permitted Daily Exposure**

- \[ \text{PDE (mg/day)} = \text{NOEL or LOEL (mg/kg)} \times \text{human body weight (50 kg)} \times F1 \times F2 \times F3 \times F4 \times F5 \]
  - \( F1 \): Interspecies differences,
    - mouse:human = 12
  - \( F2 \): Inter-individual differences
    - 10
  - \( F3 \): Duration of exposure
    - 10 short-term exposure
  - \( F4 \): Severity of toxicity
  - \( F5 \): Quality of data
    - 1 (NOEL determined)

**Toxicological risk assessment in pharmaceutical industry**

- Perform new toxicology studies to qualify the impurity
- Study own documentation: was this impurity present in batches used in safety testing
- Perform literature study and try to find No-effect levels
Permitted Daily Exposure

- PDE (mg/day) = NOEL or LOEL (mg/kg) x human body weight (50 kg) / F1 x F2 x F3 x F4 x F5
- PDE = 24 mg/kg x 50 kg / 12 x 10 x 10 x 1 x 1 = 1 mg/day

Theoretical Maximum Exposure

- The theoretical maximum exposure [TME] to an impurity = maximal dose of drug product x concentration of the impurity in drug product.
- Risk assessment:
  - Divide Permitted Daily exposure with Total Maximum exposure and determine safety factor.