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

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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

Safety pharmacology

- 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 Swim test, Functional Observation battery
  - 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 I drug metabolizing enzymes is reduced in elderly people
- Design dosing regimens

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.

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.

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
• F1: Interspecies differences,
  - mouse:human = 12
• F2: Inter-individual differences
  - 10
• F3: Duration of exposure
  - 30 short-term exposure
• F4: Severity of toxicity
• F5: Quality of data
  - 1 (NOEL determined)
Permitted Daily Exposure

- PDE (mg/day) = NOEL or LOEL (mg/kg) x human body weight (50 kg)
  \[ \frac{F1 \times F2 \times F3 \times F4 \times F5}{12 \times 10 \times 10 \times 1 \times 1} \]

- PDE = 24 mg/kg x 50 kg = 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