General introduction to non-clinical toxicity testing of pharmaceuticals

Dr. Weir– Charles River Laboratories, USA

General Introduction to Non-Clinical Toxicity Testing of Pharmaceuticals

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Biopharmaceutical/Pharmaceutical Practice

Presentation overview

Overview of the Food and Drug Administration
Potential safety concerns identified in non-clinical studies
Correlation between non-clinical and clinical toxicities
Overview of drug development from the non-clinical perspective
Considerations for using non-clinical data to support safe drug development

Overview of the Food and Drug Administration

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Role of the Food and Drug Administration (FDA) in drug development

In the United States (US), it is illegal to test new drugs in humans or to market new drugs for human use without approval from the FDA.

FDA ensures clinical trials are safely conducted and that drugs are approved for marketing.

Elixir of sulfanilamide

Sulfanilamide in tablet and powder form as safely used in the US prior to 1937.

In 1937, F.E. Massengill Company prepared an elixir by dissolving the drug in diethylene glycol, a renal toxicant.

1937 drug laws did not require safety testing.

Resulted in >100 deaths.

Hastened the enactment of the 1937 Federal Food Drug and Cosmetic Act.

Thalidomide tragedy

Prescribed to pregnant women during late 1950s and early 1960s as an anti-emetic.

From 1956-1962, over 9000 children in Europe & Africa were born with severe deformities, including phocomelia.

Impact minimal in US - Frances Kelsey of the FDA refused to approve the drug due to lack of sufficient safety data.

Resulted in the passing of Kefauver-Harris Amendment to ensure drug efficacy and greater safety.

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Elixir of sulfanilamide and thalidomide

US FDA

US FDA

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Non-clinical pharmacology and toxicology at FDA/CDER

- ~140 non-clinical pharmacology and toxicology reviewers within FDA/CDER
- Assigned among 16 review divisions
- Each division has 1/2 pharmacology/toxicology team leaders and a variable numbers of reviewers
- Generally hold a PhD in pharmacology, toxicology or other life science

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Testing of new drugs for safety and efficacy

- FDA/CDER does not test new drugs
- Sponsors and/or their contractors conduct studies (e.g., non-clinical, clinical and CMC) needed to support drug development
- Sponsors submit study reports to FDA/CDER for review

Sponsors

- Pharmaceutical and biopharmaceutical companies
- Academic institutions
- Government institutions

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Submissions to the FDA/CDER

Investigational New Drug Application (IND)

New Drug Application (NDA) or Biologics Licensing Application (BLA)

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Submissions to the FDA/CDER
Investigational New Drug Application (IND)
- Documents that sponsors submit to FDA/CDER to support drug development
- Includes reports and protocols for non-clinical and clinical studies and CMC and other information

New Drug Application (NDA) or Biologics Licensing Application (BLA)
- Documents that sponsors submit to FDA/CDER to support approval to market a new drug or biologic
- Includes reports for non-clinical, clinical and CMC studies and other information

Overview of drug development from the non-clinical perspective

Non-clinical studies
- Pharmacology and toxicology studies conducted using in vitro systems and laboratory animals
- Intended to support the safety of new drugs during the drug development process and for marketing

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Drug development process

Drug development process

Non-clinical

Phase 1, 2 and 3 Clinical Trials

Pre-IND

IND

NDA/BLA

Regulations and guidance

Regulations

• Provide plans for following/enforcing laws
• Legally binding
• Defined in Code of Federal Regulations (CFR)

Guidance

• Provides direction and a course of action
• Not legally binding

Regulations

Code of Federal Regulations (CFR)

http://www.ecfr.gov/cgi-bin/ECFR?page=browse

(click link below)

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**FDA/CDER guidance documents**
- Generally prepared by a committee of scientists and/or other experts
- Address a range of topics and concerns

**Examples of non-clinical topics covered in the ICH guidance documents**
- Carcinogenicity
- Genotoxicity
- Duration of chronic toxicity studies in non-rodents
- Reproductive toxicology studies
- Biotechnology-derived pharmaceuticals
- Safety pharmacology
- Immunotoxicity
- Non-clinical studies needed to support clinical trials
- Anti-cancer pharmaceuticals
- Phototoxicity

**Examples of topics covered in the CDER non-clinical guidance documents**
- Non-clinical safety evaluation of reformulated drug products and products intended for administration by an alternate route
- Non-clinical safety evaluation of drug combinations
- Non-clinical safety evaluation of pediatric drug products
- Estimating the safe starting dose in clinical trials in normal healthy volunteers
- Investigational enzyme replacement therapy products: Non-clinical assessment

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Types of non-clinical studies

- Pharmacokinetics
- General pharmacology
- Pharmacology
- General toxicology
- Genetic toxicology
- Reproductive toxicology
- Carcinogenicity
- Immunotoxicology
- Phototoxicology
- Juvenile toxicology

Guidance documents address when and if these studies are needed in the drug development process.

Clinical trials

Phases of clinical investigation

Phase 1  Phase 2  Phase 3

Clinical trials

Phase 1

- Initial introduction of a new drug into humans
- Closely monitored
- Safety, pharmacokinetics, drug metabolism and mechanism of action
- Healthy volunteers or patients
- Generally 20 to 80 subjects

Starting a Phase 1 clinical trial is a major milestone for a sponsor

- Unrealistic timelines
- Promises to investors
- Impact on stock value

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Clinical trials

Phase 2
• Evaluate effectiveness of a new drug for a particular indication in patients with the disease
• Define doses for Phase 3
• Determine short-term risks and side effects
• Closely monitored
• No more than several hundred subjects

Clinical trials

Phase 3
• Performed after preliminary evidence of efficacy has been demonstrated
• Intended to gather additional information on safety and efficacy
• Evaluate risk vs. benefit
• Several hundred to several thousand subjects

Basic relationship between non-clinical and clinical development

• Clinical plan (e.g., route of administration and dosing frequency) needed to design an appropriate non-clinical safety program
• Role of non-clinical data in drug development
  – Define safe starting dose for Phase 1 trials
  – Define endpoints for clinical safety assessment
  – Assess safety concerns that cannot be readily addressed in clinical trials (e.g., reproductive toxicity, carcinogenicity)

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Potential safety concerns identified in non-clinical studies

Questions answered through non-clinical studies

- What are the toxic doses in animals?
- What are the target organs?
- How do the toxic doses compare to the effective/clinical dose(s)?
- Can the toxicities be monitored in patients in the clinical trials?
- Are the toxicities reversible?

Safety concerns (ref. 2)

- Steep dose response curve
  - Slight changes in dose can lead to large changes in toxicity
- Severe toxicities
- Non-monitorable toxicities
  - Histopathological changes in animals

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Safety concerns (ref. 2)

- Toxicities without premonitory signs
  - Difficult to know when toxic doses are being approached in humans
- Variable bioavailability
  - Can lead to underestimating toxicity in humans
- Irreversible toxicity
  - Suggests possibility of permanent injury in humans

Safety concerns (ref. 2)

- Unexplained mortality
- Large variability in doses or plasma levels eliciting effects
  - Reduces ability to predict toxic doses in humans
- Nonlinear pharmacokinetics
  - Reduces ability to predict human toxicity in relationship to dose

Safety concerns (ref. 2)

- Inadequate dose-response data
  - Reduces ability to predict toxic doses in humans
- Novel therapeutic targets
  - Increase uncertainty of relying on animal data
- Animal models with limited utility

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Addressing concerns identified in non-clinical studies

- Modify the clinical trial
  - Lower the clinical dose
  - Change dose escalation
  - Decrease patient enrollment
  - Increase patient monitoring
  - Change inclusion/exclusion criteria

- Conduct additional non-clinical studies
  - Define reversibility
  - Identify no-observed-adverse-effect level (NOAEL)
  - Explore mechanism of action

Considerations for using non-clinical data to support safe drug development

Differences between laboratory animals and humans (ref. 3)

<table>
<thead>
<tr>
<th></th>
<th>Animals</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Young adults</td>
<td>All ages</td>
</tr>
<tr>
<td>State of health</td>
<td>Healthy</td>
<td>Generally sick</td>
</tr>
<tr>
<td>Genetic background</td>
<td>Generally homogeneous</td>
<td>Heterogeneous</td>
</tr>
</tbody>
</table>
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Differences between laboratory animals and humans (ref. 3)

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<thead>
<tr>
<th></th>
<th>Animals</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose magnitude</td>
<td>Therapeutic to toxic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Housing</td>
<td>Uniform, optimal</td>
<td>Variable</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Uniform, optimal</td>
<td>Variable</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>Generally, never</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

Differences between laboratory animals and humans (ref. 3)

<table>
<thead>
<tr>
<th></th>
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<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal contact</td>
<td>None</td>
<td>Extensive</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>Clinical lab</td>
<td>Standardized</td>
<td>Individualized</td>
</tr>
<tr>
<td>Necropsy</td>
<td>Almost always</td>
<td>Exceptional</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Extensive</td>
<td>Exceptional</td>
</tr>
</tbody>
</table>

Correlation between non-clinical and clinical toxicities
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Correlation between non-clinical studies and clinical trials (ref. 3)

Concordance of the Toxicity of Pharmaceuticals In Humans and in Animals

- Multinational pharmaceutical company survey
- 150 compounds from multiple therapeutic classes
- 221 human toxicity events
- Events classified as a human toxicity resulted in at least one of the following:
  - Termination of clinical development
  - Limitations on the dosage
  - A need for drug level monitoring/dose adjustment
  - Restriction of the target patient population

Correlation of human and animal toxicities (ref. 3)

- Non-rat only
- Non-rat = rodent
- Rodent only
- Any species
- No species

221 human toxicities were reported for 150 compounds
Correlation of human and animal toxicities (ref. 3)

- Hematological, gastrointestinal and cardiovascular toxicities had the best correlation.
- Cutaneous/hypersensitivity and hepatotoxicity had the poorest correlation and most often led to termination of clinical development.
- 94% of the animal toxicities that correlated with human toxicities were detected in preclinical studies ≤ 1 month in duration.

Presentation summary

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Acknowledgements

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  Regul. Toxicol. Pharmacol. 32, 56-67

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