Ensuring Safety in Exploratory Development: Preparation for First in Human studies

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Content

1. Introduction to Exploratory Development
2. Preparing for First in Human
Quest for the Pharmaceutical Industry: Large investments at low(-er) Probability of Success

Some reasons:
- Less validated targets
- Long-term efficacy goals for complex diseases
- Safety issues

Post approval withdrawals for safety

80-90s
90s >
BETWEEN PHASE SUCCESS RATES FOR ACTIVE SUBSTANCES ENTERING PHASE 1999-2005 BY THERAPEUTIC AREA - CMR METHODOLOGY

Success rate

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Figure 3 | Reasons for attrition (1991–2000). PK, pharmacokinetics.
Clinical Pharmacology & Therapeutics (1997) 61, 275–291; doi:

Learning versus confirming in clinical drug development* Lewis B. Sheiner MD1
Objectives of Exploratory Development

- To identify the relationship between dose and plasma (or other) concentrations and describe the absorption and disposition. Including the influence of polymorphisms in metabolic pathways (CYP enzymes) when indicated.

- To define the shape and location of the dose - concentration - response curves for both desired (therapeutic) and undesired (tolerability and safety) effects using surrogate (biomarker) or clinical endpoints.

- On the basis of these curves, to identify the range of dosage / concentrations producing maximum benefit with least undesirable effects (therapeutic window).

- To describe the relation between dose – concentration and desired / undesired effects in a mathematical model allowing predictions about optimal designs and choice of doses for future studies.

- Exploratory Development should generate the information required for early go - no go decisions on the value of targets and early phase compounds, ultimately at Proof of Concept. The latter usually in a well defined population of patients with the target disease. This information should be fed back to Discovery.
Curves for desired and undesired responses

- Preclinical: window between wanted pharmacology and unwanted toxicology
- Clinical: window between activity / efficacy and unwanted side effects

![Therapeutic Index diagram](image)
Content

1. Introduction to Exploratory Development
2. Preparing for First in Human
General Principles

- Pre-clinical testing should be appropriate for intended duration of clinical trial and indication in ED (see ICH, esp M3-R2)
- It is important to generate sufficient PK data in both relevant animal (disease) models as well as in pre-clinical safety studies to establish a PK-PD model. Such model can be used to help set First in Human (FiH) dose and guide dose escalation

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodents</td>
<td>Non-rodents</td>
</tr>
<tr>
<td>Up to 2 weeks</td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Between 2 weeks and 6 months</td>
<td>Same as clinical trial&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>6 months&lt;sup&gt;b, c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Guidelines to identify and mitigate risks for First in Man studies

EMEA: Guideline on strategies to identify and mitigates risks for First-in Man human clinical trials with investigational medicinal products (CHMP - Sept. 2007)

FDA: Guidance for Industry - Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers (CDER - July 2005)

Scope
- Assist sponsors in transition from non-clinical to early clinical development
- Identification of factors influencing risks for new IMPs
- Consideration of quality aspects, non-clinical and clinical testing strategies and designs for FiM studies
- Strategies for mitigating and managing risks when starting FiM including calculation of first dose, subsequent dose escalation and conduct of clinical trial
History of EMEA 2007 guidance on mitigation of risk for First in Man trials

- March 8, 2006: TeGenero trial commences
- Soon after 6/8 vols became seriously ill, MHRA established Expert Scientific Group (ESG)
- Gordon Duff (Prof in Molecular Medicine) ±20 academics, ±6 MHRA officials, ±10 observers (eg FDA), ± several Stakeholders
- 6 Group meetings, many Stakeholder meetings etc.
1. To consider what may be necessary in the transition from pre-clinical to first-in-man Phase I studies, and in the design of these trials, with specific reference to:
   - Biological molecules with novel mechanisms of action;
   - New agents with a highly species-specific action;
   - New drugs directed towards immune system targets.

2. To provide advice in the form of a report to the Secretary of State for Health for the future authorisation of such trials with an interim report to be provided within three months”
**ESG: ‘Higher risk medicines’**

- Attention is given to ‘higher risk medicines’ where these criteria apply:
  - Species-specificity of action creating challenges for pre-clinical development;
  - Agonistic activity on targets within a biological amplification cascade;
  - Immune System targets;
  - Multifunctional molecules, eg antibodies with potential to activate FcR-bearing cells as well as primary target cells;

- **Potency:**
  - Increased affinity, occupation or signalling effect on target receptor compared with natural ligand (eg “superagonist antibody”);
  - Prolonged exposure to target via normal (eg antibodies) or altered pharmacokinetics (eg pegylation);
  - Multivalency allowing cross linking of target molecules.
ESG Summary recommendations

1. The strategy for preclinical development of a new medicine and the experimental approaches used to assemble information relevant to the safety of phase one trials must be regarded as science-based decisions, made and justified case-by-case by investigators with appropriate training.

2. Developers of medicines, research funding bodies and regulatory authorities should expedite the collection of information on unpublished preclinical studies and phase one trials, and explore the feasibility of open access to this database.

3. Regulatory authorities should consider ways to expedite the sharing between regulators worldwide of information on Suspected Unexpected Serious Adverse Reactions (SUSARs) in phase one trials, and explore the feasibility of open access to this data.

4. A broader approach to dose calculation, beyond reliance on ‘No Effect Level’ or ‘No Adverse Effect Level’ in animal studies, should be taken. The calculation of starting dose should utilise all relevant information. Factors to be taken into account include the novelty of the agent and its mechanism of action, the degree of species-specificity of the agent, the dose-response curves of biological effects in human and animal cells, dose-response data from in vivo animal studies where relevance to human has been validated, the calculation of receptor occupancy versus concentration and the calculated exposure of targets or target cells in humans in vivo. The ‘MABEL’ approach is a good option for achieving this.

5. If different methods give different estimates of a safe dose in humans, the lowest value should be taken as the starting point in first-in-man trials and a margin of safety introduced.

6. When it is likely that preclinical information, for any reason, may be a poor guide to human responses in vivo, the starting dose in first-in-man trials should be calculated to err on the side of caution.

7. Careful consideration should be given to the route and the rate of administration of the first dose in first-in-man trials. with careful monitoring for an exaggerated response.
EDA is prepared in collaboration between relevant Discovery Labs (safety, pharmacology, metabolism) and Global Clinical Pharmacology & Exploratory Development in line with the scope of FDA/EMEA guidelines i.e. to identify and mitigate risks when starting early clinical studies.

“The EDA provides a final account on behalf of the company whether critical data on the investigational medicinal product (IMP) are sufficient for passing a clinical milestone in a safe and ethical manner. Milestones are first dosing in man, females or children and first administration of an i.v. formulation. For this purpose, the document should refer to regulatory guidances and indicate that these are accomplished. In addition, the document should provide a prediction for the pharmacological active exposure, a recommendation for the clinical starting dose and address safety and provide safety measures on anticipated safety aspects in relation to intended drug exposures.”
Algorithm for starting dose estimations

**Dose-based approach**
Step 1: Calculate MRSD\textsubscript{tox} from NOAEL
Step 2: Calculate MRSD\textsubscript{pharm} from PAD
Step 3: Determine MRSD\textsubscript{fim} as recommended starting dose from MRSD\textsubscript{tox} and MRSD\textsubscript{pharm}

**Simulation-based approach**
Step 4: Predict human exposure at recommended starting dose
   - Apply simulation methods (allometric scaling/PBPK) using animal PK and physiochemical properties
Step 5: Compare predicted human exposure with exposures arrived by dose-based approaches (MRSD\textsubscript{tox}, MRSD\textsubscript{pharm}) and consider dose showing lowest exposure as starting dose

MRSD – Maximum recommended starting dose
PAD – Pharmacologically active dose
Example of starting dose estimation for oral antidiabetic

- **Step 1: Calculate MRSD$_{tox}$ from NOAEL**

- 4 w repeated dose studies: NOAEL rat=30 mg/kg; NOAEL dog=3 mg/kg
- HED rat = 30 mg/kg (NOAEL) x 0.16 (BSA-CF) = 4.8 mg/kg
- HED dog = 3 mg/kg (NOAEL) x 0.54 (BSA-CF) = 1.62 mg/kg
  - HED dog as most sensitive species is chosen = HED$_{tox}$
  - Safety factor: no specific points to consider (such as steep DRC, severe toxicity, non-monitorable tox, non-linear PK, exposure variability species etc)
  - Apply default safety factor 10

- MRSD$_{tox}$ = 1.62 mg/kg (HED dog) x 1/10 (safety factor) x 60 kg
  = ~ 10 mg/man
Example of starting dose estimation for oral antidiabetic

- **Step 2: Calculate MRSD\textsubscript{pharm} from PAD**

- Sign. reduction postprandial glucose after single p.o. administration of 1 mg/kg (normal ICR mice)
  - 1 mg/kg is lowest dose tested showing sign. reduction (0.3 mg/kg not sign.)
  - no species differences anticipated on agonistic activity in human, mouse, rat (CHO cells expressing target)

- PAD in mice judged to be 1 mg/kg
- \( \text{HED}_{\text{pharm}} = 1 \text{ mg/kg (PAD) x 0.08 (BSA-CF) x 60 kg} = 4.8 \text{ mg} \)
  - Safety factor: no high risk compound (clinical experience with competitors)
  - Apply default safety factor 10

- \( \text{MRSD}_{\text{pharm}} = 4.8 \text{ mg (HED}_{\text{pharm}}) x 1/10 \text{ (safety factor)} = \sim 0.5 \text{ mg/man} \)
Example of starting dose estimation for oral antidiabetic

- **Step 3:** Determine $\text{MRSD}_{\text{fim}}$ as recommended starting dose

  - $\text{MRSD}_{\text{tox}} = \sim 10 \text{ mg/man}$
  - $\text{MRSD}_{\text{pharm}} = \sim 0.5 \text{ mg/man}$
  - use lowest value
  - $\text{MRSD}_{\text{fim}}$, i.e. recommended starting dose FIM is 0.5 mg/man
Example of starting dose estimation for oral antidiabetic

- **Step 4: Predict human exposure at recommended starting dose**
- Human exposure prediction at 0.1 mg/man and 0.5 mg/man (recommended starting dose)
  - rat/dog PK + physiochemical properties oral antidiabetic

<table>
<thead>
<tr>
<th>Species</th>
<th>Administration route</th>
<th>Dose (mg/kg)</th>
<th>Reported*</th>
<th>AUC\textsubscript{ref} (ng·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allometric scaling (estimated)</td>
</tr>
<tr>
<td>Dog</td>
<td>p.o.</td>
<td>0.03</td>
<td>270±63</td>
<td>259</td>
</tr>
<tr>
<td>Dog</td>
<td>p.o.</td>
<td>0.1</td>
<td>886±245</td>
<td>865</td>
</tr>
<tr>
<td>Dog</td>
<td>p.o.</td>
<td>0.3</td>
<td>2603±754</td>
<td>2594</td>
</tr>
<tr>
<td>Dog</td>
<td>i.v.</td>
<td>0.3</td>
<td>2757±711</td>
<td>2594</td>
</tr>
<tr>
<td>Rat</td>
<td>i.v.</td>
<td>3</td>
<td>4419</td>
<td>4593</td>
</tr>
<tr>
<td>Human</td>
<td>p.o.</td>
<td>0.1 mg</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>Human</td>
<td>p.o.</td>
<td>0.5 mg</td>
<td>NA</td>
<td>157</td>
</tr>
</tbody>
</table>
Example of starting dose estimation for oral antidiabetic

- **Step 5:** Compare predicted human exposure with exposures arrived by dose-based approaches ($MRSD_{tox}, MRSD_{pharm}$)

- Highest predicted human $AUC_{inf}$ value for the recommended starting dose (0.5 mg/man) is 150-160 ng*h/ml
  - At PAD in mice (1 mg/kg), total $AUC_{inf} = 1269$ ng*h/ml
  - Extrapolation mouse exposure to human plasma total $AUC_{inf} = 1404$ ng*h/ml
  - Highest predicted $AUC_{inf}$ value for starting dose of 0.5 mg/man (150-160 ng*h/ml) is about 9-times below predicted $AUC_{inf}$ leading to minimal pharmacological activity in humans (1404 ng*h/ml)

- **Starting dose for FIM can be recommended to be 0.5 mg/man**
# Antidiabetic: Risk Minimization Plan

<table>
<thead>
<tr>
<th>Target organs</th>
<th>Potential risks</th>
<th>Risk minimization action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-intestinal tract</td>
<td>Vomiting, salivation soft, mucous, or watery stool</td>
<td>Close monitoring the subjects’ symptoms (e.g. nausea, abdominal discomfort)</td>
</tr>
<tr>
<td>Hematopoietic system</td>
<td>Decreases in erythrocyte counts, hemoglobin concentrations, hematocrit values, platelet counts, reticulocyte counts</td>
<td>Measurement of standard hematological examination</td>
</tr>
<tr>
<td>Liver</td>
<td>Increases in AST, ALT</td>
<td>Monitoring of liver function</td>
</tr>
<tr>
<td>Kidney</td>
<td>Decrease in urine osmolality. Increases in blood creatinine, urea nitrogen. Decreases in blood potassium, calcium</td>
<td>Measurement of Standard blood biochemistry and urinalysis</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Transitional cell hypertrophy in the mucosa</td>
<td>Examine urine sediment in fresh urine samples for the presence of crystals (to confirm the rat specificity of the crystal formation and the absence of this risk is humans)</td>
</tr>
<tr>
<td>Exocrine pancreas</td>
<td>Mild single cell necrosis in the acinar cells</td>
<td>Monitor exocrine pancreatic enzymes (e.g. blood amylase, lipase)</td>
</tr>
</tbody>
</table>
Safety Monitoring Process starting before FiH!
Back-up
MABEL approach (NPAD+)

Schematic diagram for determination of MRSD for FIH trials based on MABEL and NOAEL. Steps 1–4 (toxicity/exposure) encompass steps 1–4 of the FDA guideline. 1) The NOAEL is determined from relevant animal species, 2) this is then converted to a HED to give 3) the HED at the NOAEL for the most sensitive species. 4) A 10-fold safety factor is applied to this HED (MRSD*). Step 5 gives focus to characterization of the pharmacological active dose and extrapolation between species, encompassing step 5 of the FDA guideline and defined here as the MABEL. A dose/concentration-effect curve is derived from experimental (animal or ex vivo) data. Extrapolation from animal to human is performed, using mechanistic data (e.g., relative affinity/potency) and MABEL is the dose/exposure that corresponds to the minimal PD effect in humans. A minimal PD effect can be defined as a biological effect, or some meaningful surrogate such as either ligand suppression or receptor occupancy. Solid lines: experimental (measured) dose response (animal PD—red/toxicity—blue); dashed lines: predicted dose response (human PD—red/toxicity—blue). The abscissa is expressed as either dose or exposure, although exposure is likely to be more relevant in most circumstances. The MRSD is calculated based on both NOAEL (MRSD*) and MABEL (MRSD**).