First Dose in Humans

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Clinical Trial Guidelines - ICH

- **ICH M3**  Non-clinical safety studies for the conduct of clinical trials for pharmaceuticals (Original 1996, R1 2000, R2 draft 2008)
- **ICH S6**  Preclinical safety evaluation of biotechnology-derived pharmaceuticals (1995)
- **ICH S7A**  Safety pharmacology studies for human pharmaceuticals (2000)
- **ICH S7B**  Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (2005)
Traditional Non-Clinical Package - Prior to “First in Man”

- Safety Pharmacology
  - Cardiovascular
  - CNS
  - Respiratory
- Toxicokinetic and Pharmacokinetic Studies
- Single dose toxicity
- Acute toxicity in two mammalian species
- Repeat dose toxicity
  - Two mammalian species (rodent and non-rodent)
  - Clinical route of administration
  - Range of dose levels (no effect to MTD)
- Genotoxicity
- Reproductive toxicity
Clinical Trial Guidelines - FDA

- Content and format of investigational new drug applications (INDs) for phase 1 studies of drugs, including well-characterised, therapeutic, biotechnology-derived products (1995)
- Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers (2005)
- Exploratory IND studies (2006)
Clinical Trial Guidelines - EMEA

- Position paper on the non-clinical safety studies to support clinical trials with a single micro dose (2003, R1 2004)
- Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medical products (2007)
- Non-clinical studies required before first clinical use of gene therapy medicinal products (draft 2007)
Why new guidelines?

- Revision of current guidelines
- Limited guidance for clinical trials with products derived from biotechnology/gene therapy/advanced therapies
- Limited guidance for clinical trials with high risk products
- Impact of TGN412 in EU
- Critical path initiative in US
Non-Clinical Studies

- “the available clinical and nonclinical information on an investigational product should be adequate to support the proposed clinical trial”
- “clinical trials should be scientifically sound, and described in a clear, detailed protocol.”
- *ICH M3* Non-clinical safety studies for the conduct of clinical trials for pharmaceuticals *provides a starting point to assess the adequacy of the non-clinical package*
ICH M3 Non-clinical safety studies for the conduct of clinical trials for pharmaceuticals

- Provides general guidance for drug development
- Applies to situations usually encountered during the conventional development of pharmaceuticals
- Recognises that it does not apply to novel therapeutic agents
- Recognises an abbreviated approach may be relevant for some products
- Does not consider clinical trial design or dose
- Focuses on toxicity
First In Human Dose

- No Observable Adverse Effect Level (NOAEL) – safety window based on toxicological threshold

- Minimum Anticipated Biological Effect Level (MABEL) – safety window based on pharmacological threshold
Maximum Recommended Starting Dose based on NOAEL

- Step 1:
  - Determine NOAEL (mg/kg body weight) in each species
  - highest dose that does not produce a significant increase in adverse effects that are biologically significant
  - based on overt toxicity, surrogate markers of toxicity or exaggerated pharmacodynamic effects
  - not NOEL, LOAEL or MTD
Maximum Recommended Starting Dose based on NOAEL

- Step 2:
  - Convert NOAEL to a Human Equivalent Dose (HED) based on Body Surface Area (BSA)
  - *toxic endpoint are usually assumed to scale between species when doses are normalised to body surface area $(W^{0.67})$*
  - sometimes mg/kg or local concentrations are appropriate
Maximum Recommended Starting Dose based on NOAEL

- Step 3:
- Select HED in most appropriate species
  - Generally the most sensitive species, however, consider:
    - differences in ADME
    - class experience
    - expression of relevant receptors
Maximum Recommended Starting Dose based on NOAEL

- Step 4:
- Divide HED by factor for inter-species variability to allow for:
  - possible enhanced pharmacodynamic sensitivity in humans
  - difficulties in detecting some toxicities in animals
  - differences in receptor density or affinity
  - unexpected toxicities
  - differences in ADME
Maximum Recommended Starting Dose based on NOAEL

- Increasing the factor:
  - steep dose response curve
  - severe or irreversible toxicities
  - toxicity not easily monitored or unexplained
  - toxicity without premonitory signs
  - variable bioavailability or nonlinear PK
  - inadequate dose response data
  - novel therapeutic targets
  - poor animal models
Maximum Recommended Starting Dose based on NOAEL

- Decreasing the factor:
  - moderate to shallow dose response curve
  - reversible toxicities
  - toxicity easily monitored and predictable
  - similar PD, PK and toxicity profiles across species, including humans
  - extended duration of toxicity studies
Maximum Recommended Starting Dose based on NOAEL

- **Step 5:**
- Influence of pharmacologically active dose (PAD)
- *Repeat steps 1-4 but using the lowest dose tested in an animal species rather than the NOAEL*
- *If PAD << NOAEL it may be appropriate to lower the starting dose*
• Although The NOAEL approach involves some consideration of PK/PD properties, its focus is on the estimation of the highest “safe” dose.

• An alternative approach involves a consideration of the lowest dose thought to be “active”.
Minimum Anticipated Biological Effect Level (MABEL)

- Utilises all in vitro and in vivo information from PD/PK data, for example:
  - target binding and receptor occupancy in vitro in target cells
  - concentration-response curves in vitro and dose/exposure-response in vivo
  - exposures at pharmacological doses in relevant species
Minimum Anticipated Biological Effect Level (MABEL)

• Integrate data using a PK/PD modelling approach
• Consider applying a further factor when considering first dose in humans
Selection of Relevant Species for Safety Assessment?

- Criteria for pharmacologically relevant species:
  - Pharmacological activity in vivo
  - Pharmacological activity in vitro – activity/potency compared to human
  - Receptor binding affinity, occupancy and on/off rates compared to human
  - Target – sequence homology, receptor or epitope expression
If Non-Relevant Models are used

- Not reproduce the intended PD effect in humans
- Will lead to misinterpretation of PK and PD studies
- May miss relevant toxic effects
- Lead to poor clinical trial design
Demonstration of Relevance

- Includes:
  - Comparative pharmacodynamics
    - Target structure
    - Binding
    - Target occupancy
    - Functional consequences (incl cell signalling)
  - Comparative pharmacokinetics
  - Cross-reactivity studies using human and animal tissues (mainly MAbs)
If NO Relevant Species exist

- Consider the use of transgenic animals expressing the human target
- Consider the use of homologous proteins
TGN 1412 – a “superagonist” that resulted in a severe cytokine storm in Phase 1 trial at a dose of 0.1 mg/kg
Pharmacological activity of TGN 1412 and its surrogate in rhesus and cynomolgus monkeys at 2.5 – 25 mg/kg
NOEL of 0.3 mg/kg in normal and arthritic rats using the rat CD28-specific homologous antibody.
Optimal PD responses between 0.3 and 1 mg/kg
MABEL 0.5 mg/kg
Safe starting dose 5 µg/kg, based on safety criteria for trials with a single microdose
• The minimally effective concentration for the in vitro stimulation of human T cells by murine parent of TGN 1412 (5.11A1) was 0.1 µg/mL.

• To obtain this concentration immediately post dose in humans would require a dose of 3 µg/kg.
Receptor occupancy
- 90% receptor occupancy may be appropriate for an antagonist (increasing doses will have minimal impact on the extent of suppression, only duration)
- 10% receptor occupancy may be acceptable for an agonist
- Estimates of 90% receptor occupancy for TGN 1412 at a clinical dose of 0.1 mg/kg
- 10% receptor occupancy estimated at a dose of about 1 µg/kg
Overall pharmacology and receptor occupancy calculations give a MABEL of 1-5 µg/kg - 20-100 fold less than the dose of 0.1 mg/kg used in the trial.
Other Considerations

- Route and rate of administration eg slow infusion may be more appropriate than a slow bolus
- Dose escalation scheme should take into consideration risk factors identified in the non-clinical studies and information from preceding dose in humans
- Stopping rules and decision making should take into consideration risk factors identified in the non-clinical studies
Summary: MABEL Approach

- Together NOAEL and MABEL may be used to define an anticipated safety window.
- Appropriate safety factors may be incorporated, based on potential risk, to estimate the “Maximum Recommended Starting Dose”.
Dose Escalation

- **MABEL** may be used to calculate a safe starting dose
- At some stage dose escalations will enter the pharmacological dose range
- Need to build non-clinical dose/response data into model and refine model with initial human PK and PD data
- Refine subsequent doses appropriately
Revision of Guidelines: Draft ICH M3(R2)

- Incorporation of “Exploratory IND Studies” and “Clinical Trials with a Single Microdose” approaches into the toxicity package
- Requirement of the toxicity package to support first use in humans
- Need to keep single dose toxicity studies as a fixed requirement prior to first human exposure
- Defining the role of M3 in the development of biotechnology derived pharmaceuticals
Revision of Guidelines: Draft ICH M3(R2)

- Exploratory Clinical Investigations 1
- Total dose $\leq 100 \, \mu g$, max 5 administrations and total dose $\leq \frac{1}{100^{th}}$ NOAEL and $\leq \frac{1}{100^{th}}$ pharmacologically active dose
- Target/receptor profiling. Characterisation of pharmacology in relevant species.
- Extended single dose toxicity study in one species
- Genotoxicity studies not generally conducted
Revision of Guidelines: Draft ICH M3(R2)

- Exploratory Clinical Investigations
  - Total dose $\leq 500 \mu g$, max 5 administrations and each dose $\leq 100 \mu g$; total dose $\leq \frac{1}{100}^{th}$ NOAEL and $\leq \frac{1}{100}^{th}$ pharmacologically active dose
  - Target/receptor profiling. Characterisation of pharmacology in relevant species.
  - 7 day toxicity study in one species
  - Genotoxicity studies not generally conducted
Revision of Guidelines: Draft ICH M3(R2)

- Exploratory Clinical Investigations 3
- Single sub-therapeutic or intended therapeutic dose. Max dose can be that yielding up to \( \frac{1}{2} \) NOAEL
- Characterisation of pharmacology in relevant species. Core battery of safety pharmacology studies
- Extended single dose toxicity dose toxicity studies in both rodent and non-rodent species
- Salmonella genotoxicity study
Revision of Guidelines: Draft ICH M3(R2)

- Exploratory Clinical Investigations 4

- Single or repeated dose (up to 14 days) into the therapeutic range but not to evaluate MTD. Starting dose 1/50\textsuperscript{th} NOAEL. Max dose can be that yielding up to the lowest NOAEL.

- Core battery of safety pharmacology studies
- Standard 2 week repeat dose toxicity studies in rodent and non-rodent species
- Salmonella and clastogenicity studies
Revision of Guidelines: Draft ICH M3(R2)

- Exploratory Clinical Investigations

- Single or repeated dose (up to 14 days) into the therapeutic range but not to evaluate MTD. Starting dose $\frac{1}{50}$ NOAEL. Max dose can be that yielding up to the AUC at the NOAEL in the non-rodent or $\frac{1}{2}$ the AUC at the NOAEL in rodent, whichever is lower.

- Core battery of safety pharmacology studies
  - Standard 2 week repeat dose toxicity study in rodent confirmatory study in non-rodent species at rodent NOAEL exposure with a duration of at least the intended clinical study duration but a min of 3 days.
  - Salmonella and clastogenicity studies