Clinical trials – preclinical requirements

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Clinical trials - legislation

• Directive 2001/20/EC
  “Clinical trial directive”
• Article 9(8):
  In consultation with Member States, the Commission shall draw up and publish detailed guidance on:
  (a) the format and contents of the request referred to in paragraph 2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator’s brochure;
4.1.6.1.2 Non-clinical pharmacology and toxicology data

“The studies needed as a basis for the non-clinical section of the IMPD are outlined in the relevant Community guidelines. In particular, applicants are referred to the Community guideline (CPMP/ICH/286/95). These and other relevant guidelines are available from the EMEA website www.emea.eu.int.

All studies should be conducted according to currently acceptable state-of-the-art protocols. In addition, they should meet the requirements of Good Laboratory Practice guidelines where appropriate. The sponsor should justify any deviations from these guidelines and provide a statement of the GLP status of all studies.

The test material used in the toxicity studies should be representative of that proposed for clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material should be subject to appropriate controls to ensure this and thus support the validity of the study.”
4.1.6.1.4 Overall risk and benefit assessment

“The aim of the non-clinical pharmacology and toxicity testing is to indicate the principal hazards of a new medicinal product. The sponsor should use the relevant pharmacology, toxicology and kinetic results as the basis of extrapolation to indicate possible risks in humans. As a guide to what may occur in humans, the sponsor should integrate all the available data, analyse the pharmacological and toxic actions of the IMP and use the results to suggest possible mechanisms and the exposure required to produce them. Where appropriate, they should discuss safety margins in terms of relative systemic exposure to the investigational medicinal product, preferably based on AUC and Cmax data, rather than in terms of applied dose. They should also discuss the clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials.”

Scientific guidelines (I)

- ICH = The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
  - brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration
  - produces guidelines on quality, safety and efficacy topics
Scientific guidelines (II)

- CHMP - Committee for Medicinal Products for Human Use
  - Assessment of EU Market Authorisation Applications for medicinal products
  - Assistance to companies researching and developing new medicines (Scientific Advice)
  - Preparation of scientific and regulatory guidelines for the pharmaceutical industry
- SWP – Safety Working Party
  - Provides recommendations to CHMP on non-clinical matters
  - Drafting guidelines on non-clinical topics
Support to first dose in human (I)

- Primary Pharmacology
  - Rationale
    - animal model
    - clinical evidence
  - Dosing scheme and dose selection
  - Selection of relevant species for toxicology studies
  - Safety concerns related to pharmacology
- Safety Pharmacology
  - vital functions; CNS, cardiovascular, respiratory

Support to first dose in human (II)

- Pharmacokinetics and toxicokinetics
  - Systemic exposure data
  - In vitro metabolism – relevance of animal model
  - Plasma protein binding
Support to first dose in human (III)

• Single dose toxicity
  – Studies on acute toxicity to determine lethal dose are not required
  – Single dose toxicity studies with extended observation time may be sufficient to support certain trials

Support to first dose in human (III)

• Repeat dose toxicity
  – Two species (rodent and non-rodent)
  – At least 2 weeks duration
  – Duration should match duration of trial
  – Dosing to maximum tolerated dose
Support to first dose in human (IV)

• Genotoxicity
  – Study on mutagenic potential (Ames test) sufficient for single dose study
  – For multi-dose trial clastogenic potential should be addressed

• Local tolerance
  – If possible addressed as part of general toxicity studies
  – For certain cases (topical administration etc.) the clinical formulation should be studied

Support to first dose in human (V)

• Reproductive toxicity
  – Males and non-fertile women
    • reproductive organs in general toxicity studies
  – Women of child-bearing potential
    • developmental (teratology) toxicity studies
    • short, well-controlled studies may be performed without developmental toxicity studies
**Biotechnology-derived proteins**

- ICH S6 - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
  - Species selection – the agent should be pharmacologically active
  - May require use of primates.
  - If no relevant species exists, use of "surrogate molecule" (e.g., an antibody binding to the homologous target in the rat) or transgenic animals

**Exploratory clinical trials (I)**
(ICH M3)

- Conducted early in Phase I, involve limited human exposure, have no therapeutic intent, and are not intended to examine clinical tolerability
- Investigate a variety of parameters such as PK, PD and other biomarkers, which could include PET receptor binding and displacement.
- Can be performed with a limited preclinical program
Exploratory clinical trials (II)

- Microdosing
  - a total dose of ≤ 100 μg
    - extended single dose toxicity study in one species
    - no genotoxicity required
  - dose ≤ 100 μg, up to 5 administrations
    - 7-day repeated dose toxicity in one species
    - no genotoxicity studies required
- Single dose and multiple dose trials in sub-therapeutic range or into the anticipated therapeutic range
  - general toxicity studies in rodent and non-rodent but these may be of less duration and/or dose intensity than is required for "standard" clinical program
"Risk mitigation guideline"

- Produced in response to the TGN1412 accident
  - An agonistic monoclonal antibody against CD28 intended for treatment of cancer and autoimmune disease
  - No important safety issues identified in primate toxicity study
  - First in human trial, 6 individuals experience severe adverse events, linked to cytokine release syndrome

"Risk mitigation guideline" (II)

- Executive summary
  - Intended to assist sponsors in the transition from non-clinical to early clinical development
  - It identifies factors influencing risk for new investigational medicinal products and considers quality aspects, non-clinical and clinical testing strategies and designs for first-in-human clinical trials.
  - Strategies for mitigating and managing risk are given, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the conduct of the clinical trial.
"Risk mitigation guideline" (III)

- Special attention if concerns due to particular knowledge or uncertainties on:
  - Mode of action and/or
  - Nature of the target
  - Relevance of animal models

Anti-cancer products

- ICH S9 – Nonclinical evaluation for anticancer pharmaceuticals
  - Guideline in preparation. Step 2 document (= draft for commenting) has been published
  - To support the development of anticancer pharmaceuticals in patients with advanced disease and limited therapeutic options
  - Allows for a less comprehensive study program
**Advanced therapy**

- Advanced therapy medicinal products (ATMPs) are medicinal products for human use, and are based on gene therapy, somatic cell therapy or tissue engineering
- Regulation (EC) No 1394/2007 on advanced therapy medicinal products
- CAT – Committee on Advanced Therapies

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**Early drug development – key issues**

- GLP compliant safety studies
  - GLP – Good Laboratory Practice, a set of rules to ascertain the integrity of achieved data
  - May need identification of appropriate CRO
- Drug substance
  - No formal GMP requirement but:
  - Should be representative for clinical material
Scientific advice

• CHMP Scientific Advice
  – focus on late development, requirements for marketing
  – decisions on clinical trials are made nationally
  – costly (but discount/fee waiver given to small companies and/or orphan drugs)

• National Scientific Advice
  – informal discussion on all aspects of drug development
  – Medical Products Agency (Sweden): ~ 200 advice/year
  – Many advice meetings with small companies / academy groups on early clinical development

Useful links

• EU pharmaceutical legislation

• Scientific guidelines (ICH & CHMP)
Some non-clinical guidelines (I)

**Safety pharmacology**
- ICH S 7 A - Safety Pharmacology Studies for Human Pharmaceuticals (CHMP/ICH/539/00)
- ICH S 7 B – Non-clinical Evaluation of Potential for delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (CHMP/ICH/423/02)

**Pharmacokinetics and Toxicokinetics**
- Pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A)
- ICH S3A - Toxicokinetics: the assessment of systemic exposure in toxicity studies (CPMP/ICH/384/95)
- ICH S3B - Guidance for repeated dose tissue distribution studies (CPMP/ICH/385/95)

Some non-clinical guidelines (II)

- **Repeat dose toxicity**
  - Repeated dose toxicity CPMP/SWP/1042/99
  - Duration of chronic toxicity testing in animals (ICH S4A; CPMP/ICH/300/95)
- **Genotoxicity**
  - ICH2A - Specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/141/95)
  - ICH2B - Genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95)
- **Reproductive and developmental toxicity**
  - ICH S5A - Reproductive toxicology: Detection of toxicity to reproduction for medicinal products including toxicity to male fertility (CPMP/ICH/386/95)
Some non-clinical guidelines (III)

- **Carcinogenicity**
  - ICH S1B - Carcinogenicity: testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95)
  - ICH S1A - Need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95)
  - ICH S1 C (R1) - Dose selection for carcinogenicity studies of pharmaceuticals & Limited Dose (CPMP/ICH/383/95)

- **Immunotoxicity**
  - ICH S8 - Immunotoxicity studies for Human Pharmaceuticals (CHMP/ICH/167235/04)

- **Biologics**
  - ICHS6 - Preclinical safety evaluation of biotechnology derived pharmaceuticals (CHMP/ICH/302/95)

Thanks for your attention!!

Questions?