Federal Agency for Medicines and Health Products (FAMHP)

Timelines, missing aspects in dossiers, reasons for delays, questions to applicants, how to improve the process

MANAGING CHALLENGES IN EARLY DRUG DEVELOPMENT: BIOLOGICALS AND SMALL MOLECULES, Lyon

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Approval of clinical trials in Belgium

- The Institutional Ethics Committee reviews the protocol and medical/ethical aspects. It approves the conduct of a clinical trial.
- The Federal Agency for Medicines and Health Products reviews the quality and pre-clinical data and can raise major or minor concerns and may refuse the start of a trial.
- Although EC and CA act independently, mutual consultation may be desirable.

Timelines for phase I trials

- Law of 7 May 2004:
  - 15 calendar days for review after receipt and validation.
  - If major concerns exist: clock stop for maximally 1 month.
  - Company must respond within 1 month, remainder of the time for review.
  - Exploratory clinical trials with limited exposure of humans (duration, dose, number of participants) are possible.

Exploratory clinical trial applications: Presubmission meeting

- More time may be needed for evaluation: more substances involved, new targets, consultation of experts in the evaluation (EC)
- Written procedure, electronic, teleconference, formal meeting
- Not always required
- After submission of the actual CTA: 15 days

Quality of the product for exploratory studies and regular phase I trials

- GMP adapted to the early phase: to be harmonised in EU
- Guideline CHMP/QWP/185401/2004
- Drug substance may be synthesised in pilot lab for exploratory trials
- Radiochemicals to be used according to existing guidelines
- Requirements for NIMP's: to be harmonised in EU, GMP, purity

Preclinical data to initiate a clinical study

- Requirements for NIMP's:
  - Safety of participants must be guaranteed
  - Marketed medicine, known or new
- Requirements for IMP's:
  - Information needed depends on the phase of the trial
  - ICH guideline M3 indicates what preclinical information should be available to initiate clinical trials.

Preclinical requirements for exploratory trials

- ICH M3 revision: under discussion
- In Belgium guidance developed in concert with EC, phase 1 units, industry to gain experience
- Learning: evaluation and adaptation if needed

Preclinical requirements for exploratory trials

- In general the Belgian guidance is very similar to ICH M3 under revision
  - ➢5 administrations 100 µg in total
  - ➢5 administrations 100 µg/dose
  - ➢Two possibilities to support pharmacologically active doses for maximally 14 days

Preclinical requirements for exploratory trials

- Primary pharmacology (species justification), in-vitro profile
- Safety pharmacology (part of toxicology study)
- Adequate genotoxicology depending on exposure (TTC)
- Extended single dose or 7-day repeat dose rodent study to support a microdose study

Preclinical requirements for exploratory trials

- To support clinical trial of max. 14 days:
  - ➢ Repeated dose of 14 days (rodent)
  - ➢ Confirmatory study with at least the duration of clinical exposure in non-rodents with exposure at least equal to exposure in rodents at NOAEL

Preclinical requirements for exploratory trials

- If rodent and non-rodent equally important:

➢ If no toxicity in rodents and non-rodents during 14 days, the animal limit dose should result in an AUC that is 10-fold the intended human exposure.

Preclinical requirements

- Single dose exposure at subtherapeutic or therapeutic range supported by extended single dose study in 2 species: to be discussed

Preclinical data to start phase I studies

- Main guidance ICH M3
  - Experiments indicative of therapeutic action and exposure required
  - Safety pharmacology (ICH 7A, 7B)
  - Repeated dose toxicity studies in two species of which one non-rodent with minimal duration of 2 weeks exposure

Preclinical data to start phase I studies

- Main guidance ICH M3
  - Pharmacokinetic and toxicokinetic data
  - Local tolerance
  - Genotoxicity in vitro and if positive findings also in vivo test
  - Immunological effects

Preclinical data to start phase I studies

- Reproductive toxicity
  - ➢No male fertility required in phase I but male reproductive organs should be studied in the repeated dose studies
  - ➢Women of non child bearing potential can be included without reproduction toxicity testing if female reproductive organs studied in the repeated dose studies

Preclinical data to start phase I studies

- Reproductive toxicity
  - Women of child bearing potential can be included if assessment of embryo-fetal development has been completed
  - Deviations need to be justified

Preclinical data to start phase I studies

- Other ICH safety guidelines
- Similar type of data for anti-tumor and anti-viral agents but specific requirements (resistance, cross-resistance, interaction)
- For pediatric trials additional juvenile studies may be needed but in the first place data in adult humans are required

Justification of the dose

- Based on conversion of mg/kg in animals at NOEL or NOAEL using classical scaling
- Preferentially based on actual exposures at effective doses or doses causing adverse effects in animals
- Prediction of human exposure from animal PK data, adjusted with PK data in humans during dose escalation

Justification of the dose

- Starting dose: MABEL- or NOAEL-based
  - ➢Safety factor should be justified and not be used to compensate lack of data
- Maximal dose: NOAEL-based and adjusted according to effects and PK in humans

Flexibility

- Exploratory Clinical Trials
- Deviation from existing guidelines if scientifically justified (company data or literature data, practical issues related to substance, target, disease)
- Pending changes in guidelines may already be taken into account if scientifically justified

Flexibility

- Scientific advise is possible
- Presubmission meeting (exploratory CTA)
- Deviation from guidelines may require consultation between CA, Ethics Committee and external experts
- More time may be needed to allow evaluation of a CTA if a more flexible approach is requested

Non acceptability

- If a CTA is considered not acceptable, one or more major concerns are raised
  - ➢18.3 % of cases (total)
  - ➢14.3 % of cases (exploratory)
  - ➢24.3 % of cases (phase I, first in human)
  - ➢15.5 % of cases (phase I)

Reasons to raise major concerns

- Doubts about GMP compliance
- License to manufacture drug product at the site
- Quality issues
- Deviation from guidelines that is not sufficiently justified
- Lack of data or unclear presentation or interpretation of data
- Species not sufficiently justified

Reasons to raise major concerns

- Starting or maximal dose is not sufficiently justified
- Safety during dose escalation should be clarified
- Safety margin appears small: depending on potential therapeutic benefit, medical need, kind of adverse effect expected and its reversibility the risk/benefit analysis should be sufficient: interaction with EC
- Monitoring measures and risk management seem inadequate: interaction with EC

Reasons to raise major concerns

- Most sensitive assay (pathology animal model) was not used to calculate MABEL (study in healthy volunteers)
- One or more animals dying from unknown reasons close to NOAEL.
- Sloppy presentation of data
- Non-commercial studies: lack of minimal data (e.g. dose justification often not done, adverse effects to be expected not indicated)

Contact

- Further details: www.fagg-afmps.be/human use/Research and Development/Orientation Documents/Exploratory clinical trial guidance
- Questions: CT.RD@fagg.be