Non-clinical assessment of early phase clinical trials
General aspects

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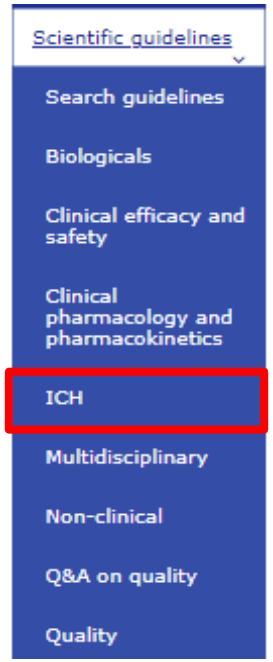
- Non-clinical assessment of clinical trial application
  - Pharmacology
  - PK / ADME
  - Toxicology
- Early phase trials: dose selection and risk mitigation
- Conclusions

Human medicines : regulatory framework



ICH guidelines

Share

The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH guidelines are provided for:

- Quality
- Safety
- Efficacy
- Multidisciplinary
- Considerations

➔ **ICH M3 (R2)** ***Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals***

ICH: safety

Share

The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

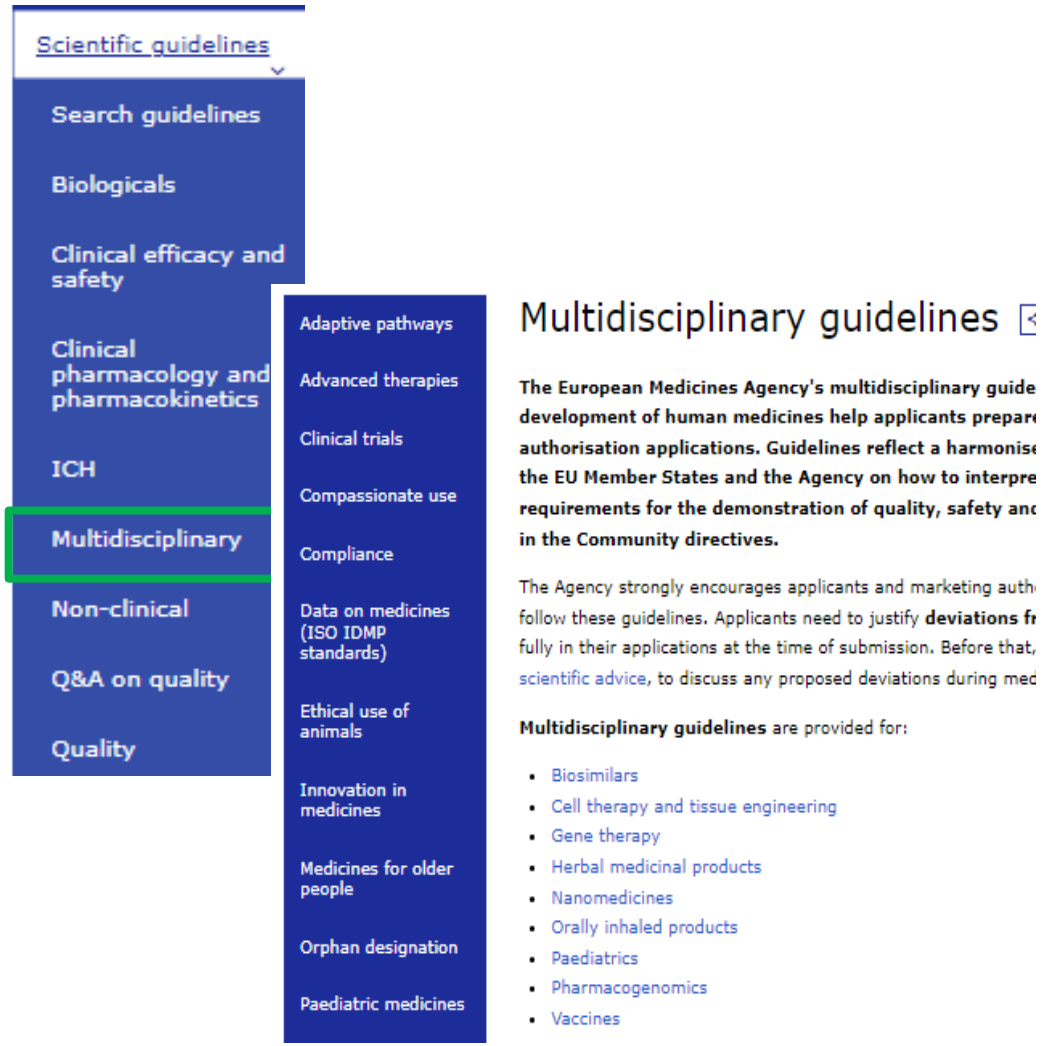
For a complete list of scientific guidelines currently open for consultation, see Public consultations.

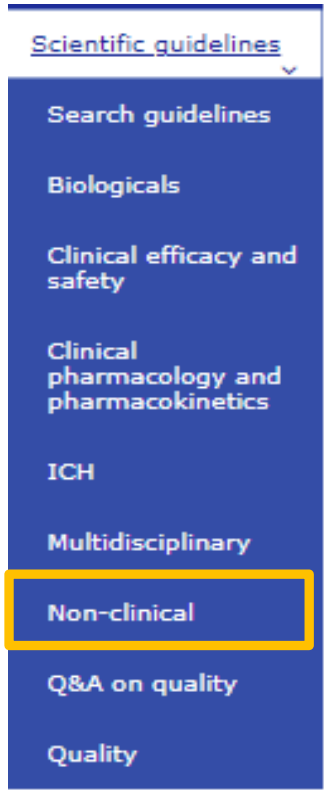
- Nonclinical safety in paediatric medicines
- Carcinogenicity studies
- Genotoxicity studies
- Toxicokinetics and pharmacokinetics
- Repeat-dose toxicity
- Reproductive toxicology
- Biotechnological products
- Safety pharmacology studies
- Immunotoxicology studies
- Therapeutic area-specific
- Photosafety evaluation

➔ **ICH S6 (R1)** ***Preclinical safety evaluation of biotechnology-derived pharmaceuticals***

➔ **ICH S9** ***Non-clinical evaluation for anticancer pharmaceuticals***

Human medicines : regulatory framework





ICH guidelines + EMA's specific guidelines

e.g. ATMP, genotoxic potential of ASO, dependence, mechanistic studies …

EMEA/CHMP/SWP/28367/07 Rev. 1
Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.

Non-clinical assessment of clinical trial application

- **Pharmacology**
- **PK (ADME)**
- **Toxicology**

Pharmacology
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions

Pharmacokinetics
- Analyt. Methods and Validat. Reports
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies

Toxicology
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Local Tolerance
- Other Toxicity Studies (Immunotoxicity, Antigenicity, Dependence, Metabolites, Impurities/excipients, Photosafety testing)

Type of toxicity studies depends on:

- **phase** of development;
- **duration** of treatment;
- **nature of product**, e.g. chemical (**ICH M3(R2)**) vs biotech-derived (**ICH S6(R1)**);
- **therapeutic indication** e.g advanced cancer (**ICH S9**).

Safety PD & pivotal toxicity studies must be **GLP compliant!** (→ **deviation should be justified**)

* *http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf*

Non-clinical assessment - Pharmacology

1. The primary pharmacodynamics

What are the reasons to believe that the product will have a therapeutic effect?
How is the pharmacology translatable to human?
Are the in vitro/in vivo PD studies a valid POC for the intended indication/population?

Primary PD studies are crucial:

- to address the MoA in relation to its intended therapeutic use ➔ **POC**;
- to acknowledge the IMP's interaction with the intended target;
- to help in the selection of the **PD relevant animal species** for the toxicity studies;
- to help in the selection of the FIH starting dose, dose escalation steps and the maximum dose.

➔ **Details on the PD experiments should be included in the NC package.**

Non-clinical assessment - Pharmacology

In vitro studies

- Small chemicals: (IC50, ED50 …).
- Biotechnology-derived pharmaceuticals.

Interspecies comparison (animal vs human):

➔ significant impact on the selection of the starting dose (additional safety factor!).

In vivo studies

- Relevant animal models, if available.
- Biotechnology-derived pharmaceuticals : if no PD relevant species ➔ transgenic animals or homologous proteins.

Combination of IMPs

- **Data** to support a **rationale** for the intended combination should be provided.
- **Oncology** ➔ see ICH S9 and Q&A.

*A rationale to support the combination should be provided, which can include in **vitro or in vivo PD data or a literature** assessment. If there is **no or very limited human safety data** for one of the combination components, **a NC pharmacology study of the combination should be provided/considered.***

Non-clinical assessment - Pharmacology

2. The secondary pharmacodynamics

→ To identify potential mode of action and/or effects NOT related to desired therapeutic target.

Small chemicals:

- screening to a broad panel of receptors, ion channels, transporters … ;
- potential interaction with related target molecules.

Biotechnology-derived pharmaceuticals

- TCR, Cytokine release assay, CDC, ADCP, ADCC (if not intended MoA).

- **To address the potential for off-target effects.**
- **To discuss the relevance in relationship with the planned clinical exposure.**
- **To include in the protocol risk mitigation measures, and specific safety monitoring, if necessary.**

Non-clinical assessment - Pharmacology

3. The Safety Pharmacology studies

→ Potential undesirable PD effects on physiological functions at therapeutic range and above.

Small chemicals

In vivo: standard core battery: CNS, respiratory & CV systems → **ICH S7A.**

In vitro: electrophysiology (QT prolongation assessment) → **ICH S7B.**

Anticancer pharmaceuticals (**ICH S9**) & **biotechnology-derived pharmaceuticals** (**ICH S6(R1)**)

Usually, no stand-alone studies but specific endpoints as part of the pivotal toxicity studies.

- **Which endpoints & when ? → to be described in the NC package** (ECG at Tmax, tidal volume …).
- Discussion on **exposure multiple** as compared to the anticipated human exposure.
- **GLP-compliance.**

Based on the nature (and tox profile) of the IMP, additional safety PD studies need to be considered, e,g. hERG assay for the payload of a drug conjugated antibody.

Non-clinical assessment – PK/ADME

ICH M3(R2)

In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data (ICH S3A, Ref. 7) in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials.

PK/TK parameters (ICH S3A) *TK : A guidance for assessing of systemic exposure in toxicology studies.*

PK profile: species-effect, gender-effect, juvenile/adult, potential for accumulation.

→ Non-linear PK : limits the ability to predict dose-related toxicity.

Dissociation systemic exposure/PD effects.

If applicable, impact of ADAs on exposure.

➔ **Importance to describe the analytical methods and their validation.**

Non-clinical assessment – PK/ADME

Distribution (small chemicals)

- Plasma protein binding: ≠ among species, adult vs. juvenile → impact on free drug exposure & FIH.
- Blood/plasma partitioning → Impact on the analytical method.
- Additional considerations (e.g. brain penetration).

Metabolism (small chemicals)

In vitro studies

- Qualitative & quantitative overview of **human vs animal** species metabolite(s) **(table, as %)**
  → selection of the **relevant species** for the toxicity studies.
- Characterisation of metabolites with an identified cause for concern (e.g. unique human M).

Non-clinical assessment – PK/ADME

Potential for drug-drug interactions

Not fully elucidated at early stage but **in vitro data** (metabolism, inhibition/induction of CYPs, interaction with drug transporters) may be **of high relevance.**

- Example: trial in patients (interaction with concomitant medications, background therapies…).
- Example: early phase trial with a combination of new IMPs.

If uncertainties ➔ appropriate restrictions/recommendations should be included in the protocol.

Non-clinical assessment – Toxicology

Toxicity studies to support clinical trials ➔ ICH M3(R2)

- List of mandatory studies.
- Doses, regimen, number of species, duration.
- Timing.
- Route of administration.
- Standard parameters.
- …

Quality aspects of the IMP:

- material used in pivotal non-clinical studies should be representative of the material used in early phase CT;
- adequate level of quality characterisation (heterogeneity, degradation profile, product- and process-related impurities) – suitability & qualification of the methods;
- reliability of very small doses.

Non-clinical assessment – Toxicology

- **Justification for the relevance of the animal species used in toxicity studies should be provided (incl. 3Rs).**
- **Sufficient information regarding the pivotal safety studies should be included in the NC package to allow a thorough review.**
- **GLP-compliance** should be addressed (a general statement is not sufficient).

Extended SD and/or RD toxicity studies

AIMS:

- characterisation of the toxic effects (target organs, severity, incidence, **dose dependence**, steepness, onset, reversibility…);
- to help in selection of starting dose, dose escalation range, and maximal dose;
- to implement safety monitoring plan.

Non-clinical assessment – Toxicology

Small chemicals ICH M3 (R2)	Biotech-derived ICH S6 (R1)	Anticancer pharmaceuticals (small & biotech / advanced disease) ICH S9
 **Dose resulting in no adverse effects** **What is adverse?** • Exaggerated PD. • Change in lab parameters but not in histo. • Few animals. • one species only. • Class effect. • Reversibility. •…		 **Toxicity studies to determine a NOAEL or NOEL ⇨ not essential to support onco trials** **If not identified:** ***Small molecules*** Common approach for starting dose : **1/10 STD10** (rodents) or **1/6 HNSTD (non-rodent).** ***Biotech-derived*** MABEL approach to be considered for the starting dose.

Non-clinical assessment – Toxicology

- The **NOAEL** should be **scientifically justified**, based on **ALL** the toxicological data.
- The **exposure data** (Cmax, AUC) of **ALL** the doses tested in the toxicity studies (incl. NOAEL) should be provided (preferably in tabular form).
- **Exposure multiples (at the NOAEL)** in relationship with the **planned human exposure range (starting → max dose) should be addressed.**

Genotoxicity studies (**ICH S2**) required for small chemicals (except products under ICH S9).

Phototoxic potential assessment (**ICH S10**) required for small chemicals (**including** those under ICH S9).

➔ If **uncertainties** or potential risk: **mitigation measures** (skin & eyes) should be described in the protocol.

Non-clinical assessment – Toxicology

Reproductive and developmental toxicity studies (ICH S5 (R3))

Not required at early stage **BUT:**

- if **adverse findings** in **reproductive organs** ➔ potential **impact on fertility.**
- **benefit/risk ?**
  - Safety margins; reversibility; population: healthy volunteers vs patients, M/F.
  - Risk mitigation (sperm and/or oocyte cryopreservation).

Effect on **pregnancy and embryo-fœtal development** usually **not known.**

Inclusion of WOCBP or male partner of WOCBP feasible **BUT:**

➔ "Recommendations related to contraception & pregnancy testing as defined of the CTFG guidance should be implemented in the protocol".

HIGHLY effective contraceptive measures **≠ effective,** duration of contraception, frequency of pregnancy testing, definition of WOCBP/postmenopausal state.

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

Non-clinical assessment – Toxicology

Local tolerance:

- when applicable, as part of the general toxicity studies.

Other toxicity studies:

- immunotoxicity, antigenicity, abuse liabilities, metabolites, impurities/excipients, combination drug toxicity testing (early stage entities).

  ➔ Case by case

Early phase trials and dose selection

Golden rules

All available NC data (PD, PK and Tox) should be taken into consideration for:

- the calculation of the safe starting dose, dose escalation steps and maximum exposure.

  ➔ The starting dose, dose escalation steps, and **maximum dose** should be thoroughly **justified** and **outlined in the protocol.**

- implementing safety monitoring and risk mitigation strategies.

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products:

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

Early phase trials and dose selection

Human starting dose

Why start with the highest dose you think is safe? NOAEL
Better to start with the lowest dose you think is active.

Toxicology Endpoints

1: determination of the NOAEL

2: calculation equivalen

3: selection appropriate species

4: application of safety factor

5: consideration of the pharmacologically active dose

NOAEL

FIH starting dose

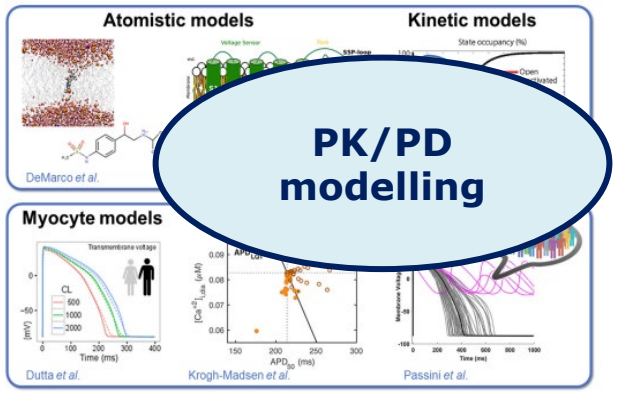
Pharmacology Endpoints

exposure-effect data (in vitro/in vivo)

- Adjust for anticipated exposure in human;
- include anticipated duration of the effect;
- interspecies difference in affinity/potency vs human?
- Available biomarkers?
- …

MABEL
In human

Estimation of the **pharmacologically active dose (PAD)**
and/or the **anticipated therapeutic dose range (ATD)** in humans
and modelling.



PK/PD modelling

Early phase trials and dose selection

MABEL approach

- There is no "standardized" way for calculating the MABEL.
- Does not incorporate R/B when population = patients, e.g. oncology.
- MABEL-based approaches do not address unknown safety risks.

The methods used and calculations on how doses and estimated exposure levels were determined, including methods for modelling (e.g. PK/PD and physiologically-based pharmacokinetic (PBPK)) should **be included in the protocol** and may be summarised in the IB.

Early phase trials and dose selection

Human starting dose

Healthy volunteers

- When the methods of calculation (e.g. NOAEL & MABEL) give different estimations → **lowest value** should be used**, unless justified.**
- The starting dose for HV should be a dose expected to result in an **exposure lower than the PAD, unless robust scientific rationale provided for a higher dose.**

Level of uncertainty
(animal relevance,
knowledge of the target …)

→

Safety Factor (SF)
FDA GL: x10
EMA GL: no range

➔ **A scientific rationale** for the starting dose and the selected SF should be detailed in the **protocol** and in the **IB.**

Patients

- Safe dose expected to have a min PD effect (nature/severity of the disease).

Early phase trials and dose selection

Dose escalation

- Criteria for dose increases should be outlined in the protocol.
- Should be **guided** by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the NC studies and adapted following **review of emerging clinical data** from previous cohorts.
- Deviations from the prespecified dose escalation and decision-making criteria would warrant the submission of (a) substantial amendment(s).

Early phase trials and dose selection

Maximum exposure and dose

Healthy volunteers

- The maximum exposure and dose should be **within the estimated PAD dose range.**

  If 100 % target occupancy, increasing the dose may not lead to a better therapeutic effect, although the duration of occupancy may still be critical.

➔ Escalating beyond this point **may be acceptable** but **should be thoroughly justified.**

  - Reaching an exposure that is predicted to eliminate the cause (e.g. anti-infective agents).
  - Uncertain exposure or PD effect needed to obtain a therapeutic effect.

- MTD inappropriate !

Patients

- The maximum tolerated dose (MTD) (if applicable) should be clearly defined and not be exceeded once it has been determined.
- B/R balance to be considered.

Early phase trials and dose selection

Maximum exposure and dose:

- should be **pre-defined** in the protocol (for each study part);
- should be justified;
- should not be exceeded without approval of a substantial amendment.

Moving from single to multiple dosing

Dosing interval and duration of dosing based on:

- PK and PD characteristics of the IMP;
- available NC safety data and all data from subject in previous SD cohorts;
- expected exposure at MAD should have been covered during preceding SAD parts/trials.

A maximum duration of dosing should be stated in the protocol for every cohort.

Early phase trials and Risk mitigation

Non-clinical assessment and impact on the protocol ?

- Study population (inclusion/exclusion criteria).
- First/starting dose, maximum dose and exposure, maximal duration of treatment.
- Sequences and intervals (subjects/cohort).
- Need for a sentinel approach based on non-clinical triggers ?
- Dose escalation increments.
- Decision-making criteria.
- Stopping rules.
- Safety monitoring.
- Length of the follow-up period.
- Emergency procedures.

Conclusions

Transition from nonclinical to FIH/early phase trial = most challenging step in drug development.

- FIH & early phase: concept of **uncertainty.**
- Material used in the pivotal NC studies = representative to the one to be used in clinic.
- GLP-compliance of the pivotal NC safety studies.
- Rigorous interpretation of ALL non-clinical data (PD, PK, and toxicity) and (ongoing) clinical:
  - rationale for the chosen efficacy models (POC), toxicology study design elements (route, species, endpoints …);
  - how doses will be extrapolated from in vitro/in vivo animal studies to the clinic;
  - additional info (comparator, DDI, literature, class-effect …).

➔ **Rationale for the decisions made in the design of the drug development NC programme.**

Conclusions

- Guidelines ➔ **GUIDE**: harmonized approach for Q, S and efficacy & do not replace the science-based approach.
- Products are becoming more complex while the GLs are not product-specific.
- Gaps/deviations are possible but must be scientifically justified.
- **Presentation of the data:**
  - **don't force the reviewer to connect the dots or guess your meaning;**
  - **complete & clear** (effective use of tables and figures).
- Uncertainties and risks must be identified and integrated within the design of the trial.
- Safety monitoring, risk mitigation measures, stopping rules, incl./excl. criteria consistent with the NC data and clearly identified in the protocol (not left to the discretion of the investigator).
- The NC package to support FIH/early phase trial is not "standardized" but depends on the nature of the drug, the target population and the intended indication.

Conclusions

Challenges: increasing uncertainties and risks

New drugs are more complex:

- from a quality point of view: e.g. bi/multi-specific antibodies, nanomedicines, ATMP, siRNA, ASO;
- from a PK point of view: e.g. persistence in the body for a long period of time, accuracy of the analytical methods;
- from a PD point of view: e.g. complex mechanism of action, lack of model disease, etc.

New drugs are more "human" specific:

- no relevant animal species: FIH trial acceptance based on in vitro/in silico results;
- first-in-class molecules

New FIH/early phase trial designs are becoming more complex:

- integrated design, combination of numerous drugs, complementary or additive/synergic MoA … ;
- increasing risk of drug/drug interaction and impact on safety;
- accelerate transition from healthy volunteers to patients while complete dataset not available.

Wide range of sponsors

Non-clinical studies frequently outsourced (facilities outside EU): GLP issues.

Conclusions

Opportunity: scientific advices

➔ **All aspects: quality, non-clinical, clinical, methodology, regulatory:**

- questions should focus on specific points;
- concise briefing package;
- not a pre-assessment;
- not a guarantee of CTA approval;
- at any stage of medicine's development.

➔ **National and/or EU levels**

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https://www.famhp.be/en/human_use/medicines/medicines/scientific_technical_advice

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

Thank you for your attention!

Questions?

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