towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course: Phase1 Trial Development Course

Lecture: Evaluation of non-clinical trials related to Phase 1 trials

Speaker: Jun Sato, MD, PhD

Jun Sato

Physician of Department of Experimental Therapeutics

Education

- M.D. (Tokyo Medical and Dental University, 2009)
- PhD. (Juntendo University Graduate School of Medicine, 2019)

Professional Positions

- 2022–present Staff Physician/Department of Experimental Therapeutics (NCC)
- 2020–2022 Reviewer/Office of New Drug V (PMDA)
- 2019–2020 Staff Physician/Department of Experimental Therapeutics (NCC)
- 2017–2019 Senior Resident/Department of Internal Medicine (NCC)
- 2014–2017 Resident/Department of Internal Medicine (NCC)

Area of Expertise

- Early drug development
- Thoracic oncology

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Role of Phase I clinical trials in drug development

Phase III clinical trials

Confirmatory study
・Comparison of study treatment versus standard treatment
・ Investigate superiority, inferiority of efficacy, and safety

・Primary endpoint: Overall survival time, etc.
・Main study design: Randomized controlled trial
・Number of cases: 200–3000 cases

Phase II clinical trials

Exploratory study
・Confirm clinical significance and therapeutic effect of study drug
・Consider propriety of conducting a Phase III trial

・Primary endpoint: Response rate, etc.
・Main study design: Single-arm study
・Number of cases: 60–100 cases

Phase I clinical trials

Toxicity confirmation study
・Confirm adverse drug reactions and investigate maximum tolerated dose (MTD)
・Determine recommended dose

・Primary endpoint: Toxicity (MTD, DLT, etc.)
・Main study design: Dose-escalating study, etc.
・Number of cases: 15–30 cases

MTD: maximum tolerated dose
DLT: dose limiting toxicity

Guidelines for clinical evaluation of anti-cancer drugs [PSEHB/PED Notification No. 0331/1 31 March 2021]

Basic framework of Phase I clinical trials

Target patients

- Patients with cancer who are **refractory to standard treatment** (with some exceptions)
- Patients with adequate organ reserves, who are relatively healthy and have a **stable general condition**

Administered drug

- New drug (**drug not approved in Japan**)
- Combination of approved drugs but **the combination is new**

Primary endpoint

- **Tolerability evaluation (estimation of DLT incidence)**, determine **MTD**, and recommended Phase II dose (**RP2D**)
- Pharmacokinetic considerations
- Exploration of therapeutic effects and biomarkers

Study design

- Dose escalation cohort (3+3 design, etc.)
- Expansion cohort
- (Safety lead-in cohort)

Terminology used for safety evaluation

Adverse event

“An unexpected medical problem that occurs during treatment with a drug or other therapy. (Omitted) may be caused by a factor other than the drug or therapy being given.”

Adverse drug reaction

“A problem that occurs when treatment affects healthy tissues or organs.”

DLT (Dose limiting toxicity)

“Side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment.”

MTD (Maximum Tolerated Dose)

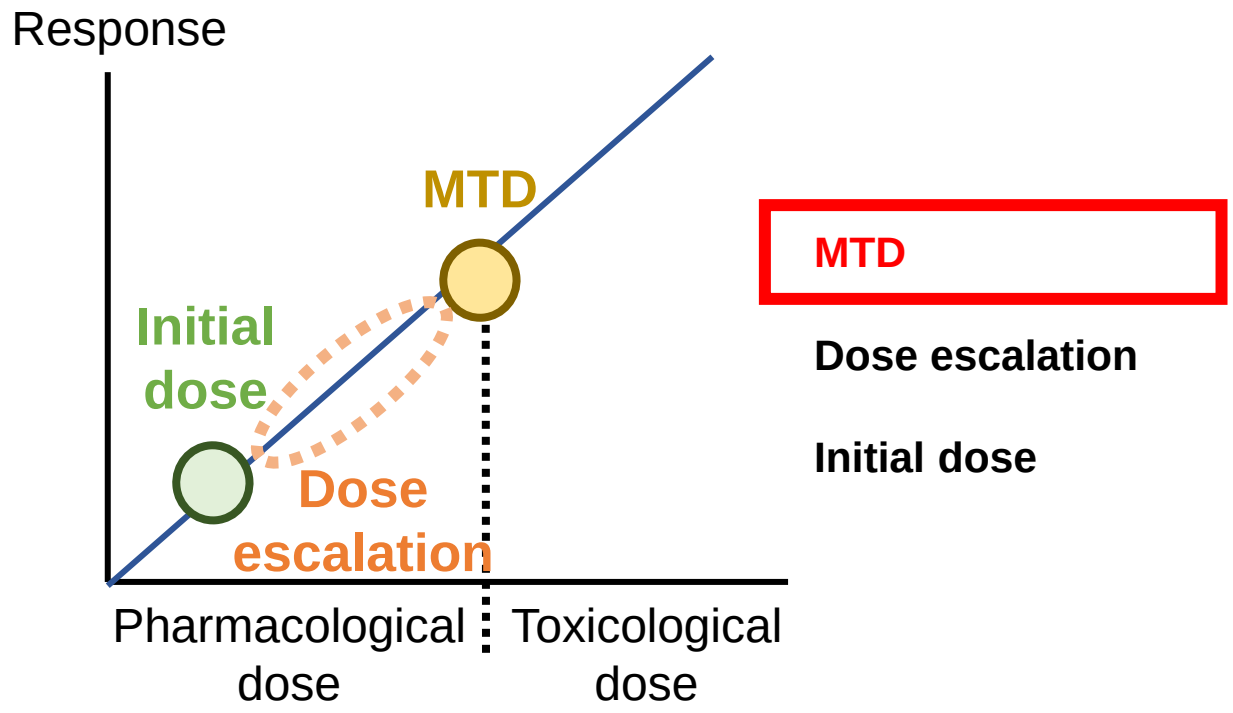
“The highest dose of a drug or treatment that does not cause unacceptable side effects. The MTD is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.”

NCI dictionaries：https://www.cancer.gov/publications/dictionaries/cancer-terms/def/dose-limiting

Validation in Phase I clinical trials

Paracelsus (1493–1541)

"All things are poison, and nothing is without poison; the **dosage alone** makes it so a thing is not a poison."



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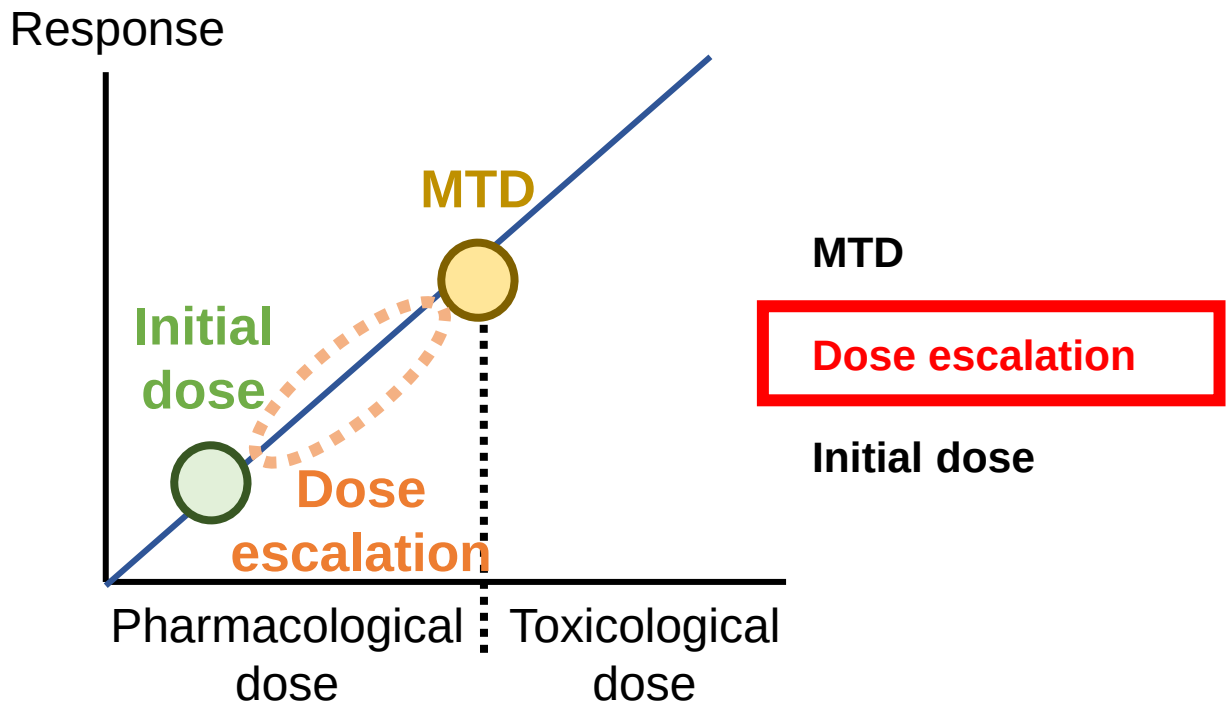

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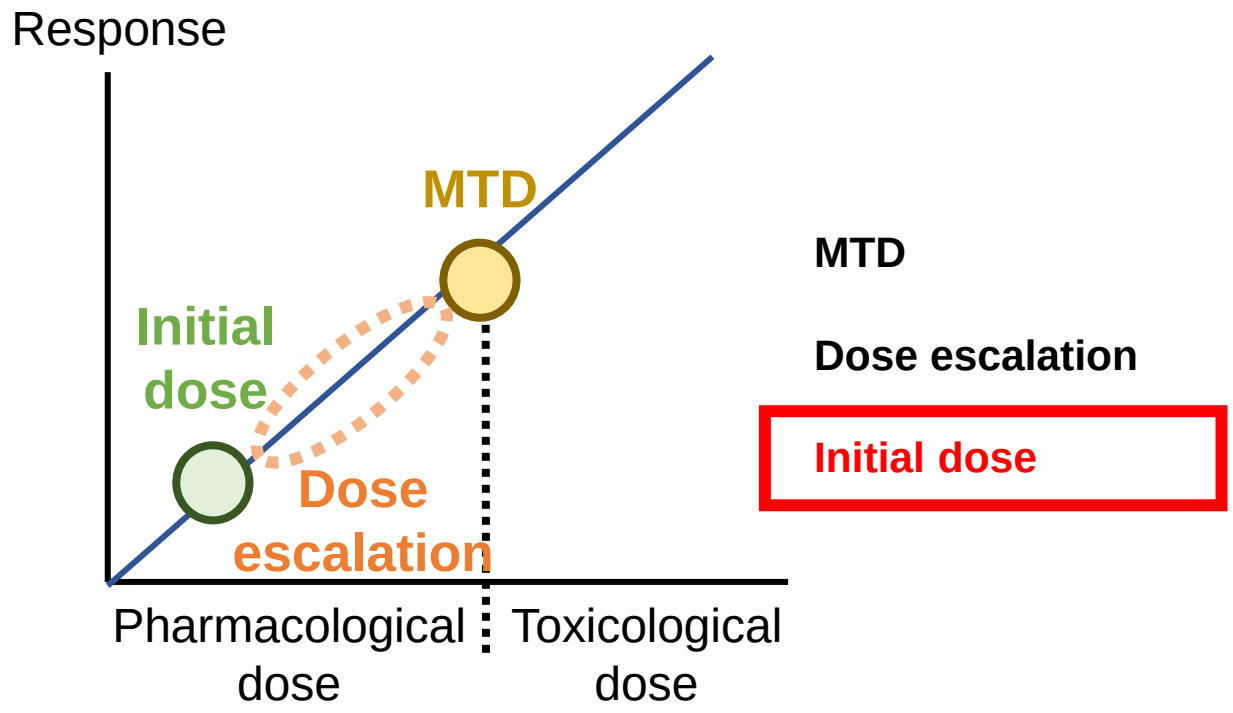

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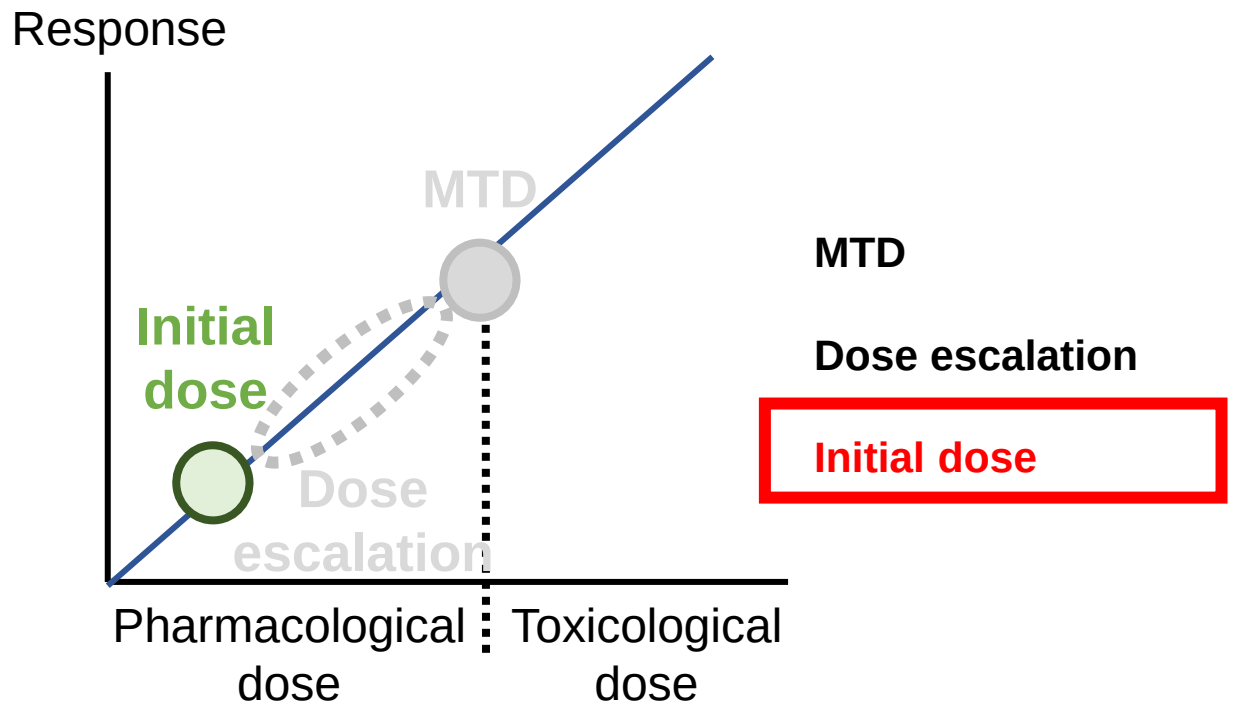

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ICH safety-related guidelines (What is ICH?)

- **What is ICH?**
  - ICH is an abbreviation of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

  - ICH is an initiative that strives for international unification and standardization of criteria for review of new pharmaceutical products by the regulatory authorities in each region, with the aim of making high-quality pharmaceutical products available for patients as soon as possible. ICH was established in April 1990 by six regulatory authorities and industry bodies in Japan, the United States, and Europe.

ICH safety-related guidelines

S1A-S1C:	Carcinogenicity studies
S2:	Genotoxicity studies
S3A-S3B:	Toxicokinetics and pharmacokinetics
S4:	Toxicity Testing
S5:	Reproductive toxicology
S6:	Biotechnological products
S7A-S7B:	Safety pharmacology
S8:	Immunotoxicology Studies
S9:	Non-clinical evaluation for anticancer pharmaceuticals
S10:	Photosafety evaluation
S11:	Non-clinical paediatric safety
S12:	Non-clinical biodistribution considerations for gene therapy products
Q3A&B:	Impurities

Dec 2022: ICH official web site

ICH safety-related guidelines (What is ICH-S9/ICH-S6?)

- **What is ICH-S9?**
  - Standards related to non-clinical trials that are required when starting first-in-human trials
  - Mainly establish criteria for chemically synthesized low-molecular-weight drugs
  - This guideline describes the types and timing of non-clinical studies using animals related to development of anticancer pharmaceuticals

- **What is ICH-S6?**
  - Standards related to non-clinical trials that are required when starting first-in-human trials handling biotechnology-derived pharmaceuticals
  - There are limitations to confirming efficacy and safety in experiments using animals for biotechnology-derived pharmaceuticals with high human selectivity

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Investigating safety in non-clinical studies

Hazard × **Safety margin** = **Risk assessment**

- **Hazard identification**
  - ➢ **STD_{10}**, **HNSTD** and **NOAEL** in animals
  - ➢ **Toxic organ/tissue** in animals

The following investigations are conducted in non-clinical studies before administration to humans:

① Estimation of initial dose
② Estimation of potential adverse events in human trials

etc.

STD10: Severely toxic dose in 10%
NOAEL: Non-observed adverse effect level
HNSTD: Highest non-severely toxic dose

Investigating safety in non-clinical studies

Hazard × **Safety margin** = **Risk assessment**

- **Hazard identification**
  - ➢ **STD_{10}**, **HNSTD** and **NOAEL** in animals
  - ➢ **Toxic organ/tissue** in animals

The following are calculated with non-clinical studies (typically a 4-week repeated dose study):

① **STD_{10}** in rodents (mice)

② **HNSTD** in non-rodents (commonly monkeys and dogs)

1/10 of STD_{10} is used as the reference dose for evaluating the initial dose if rodents are the most appropriate species, and **1/6 of HNSTD** is used if non-rodents are the most appropriate species.

STD_{10}: Severely toxic dose in 10% of animals
HNSTD: Highest dose level that does not produce serious toxicity (lethality, life-threatening toxicities or irreversible findings)
NOAEL: Maximum exposure level with no toxicological toxicity

Investigating safety in non-clinical studies

Hazard × **Safety margin** = **Risk assessment**

- **Hazard identification**
  - ➢ **STD_{10}**, **HNSTD,** and **NOAEL** in animals
  - ➢ **Toxic organ/tissue** in animals

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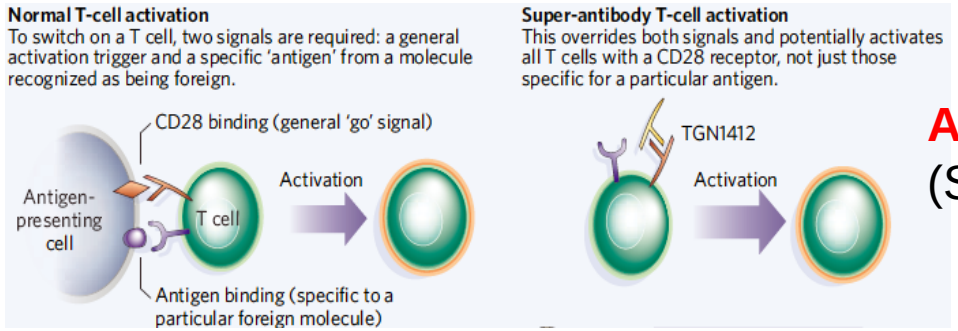
$$\text{Human equivalent dose (HED) mg/kg} = \text{animal dose (mg/kg)} \times \frac{(\text{animal weight (kg)}/\text{human weight (kg)})^{0.33}}{\text{Human 60 kg; Rat: 6.2, Dog: 1.8, Monkey: 3.1}}$$

TGN1412 case

- **Phase I clinical trial for MoAb drug TGN1412 in England (2006)**



Activate T cells
(Super-antibody)

28 days repeated-dose toxicity-study in monkeys (0, 5, & 50 mg/kg)
NOAEL: **50** mg/kg

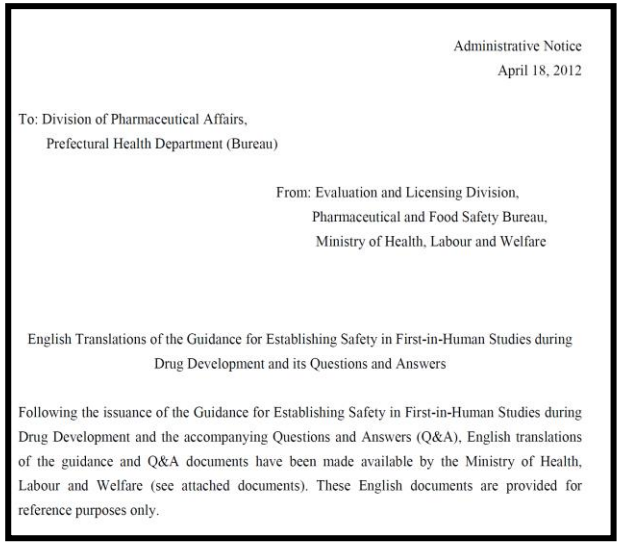
1/500

Starting dose: **0.1** mg/kg

Headache, fever, pain, multiple organ dysfunction, possible long-term disruption to immune systems

Guidance for first-in-human (FIH) studies

- **PMDA (Japan)**
  - Guidance for Establishing Safety in First-in-Human Studies during Drug Development (2012 Administrative notice)
- **FDA**
  - Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005)
- **EMA**
  - Guideline on Strategies to Identify and Mitigate Risks for First-in Human Clinical Trials with Investigational Medical (2007)→2017



Administrative Notice
April 18, 2012

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

English Translations of the Guidance for Establishing Safety in First-in-Human Studies during Drug Development and its Questions and Answers

Following the issuance of the Guidance for Establishing Safety in First-in-Human Studies during Drug Development and the accompanying Questions and Answers (Q&A), English translations of the guidance and Q&A documents have been made available by the Ministry of Health, Labour and Welfare (see attached documents). These English documents are provided for reference purposes only.

Estimation of the toxicity profile/initial dose of biopharmaceuticals

Characteristics of toxicity profile

- Overexpression of pharmacological effect/on-target effect, but a biological reaction occurs due to pharmacological effects at sites of action outside the target organ
- Less likely to cause off-target effects

Consider estimation of the initial dose using the minimum anticipated biological effect level (MABEL approach) based on the following risk factors:

① Mechanism of action
② Characteristics of target molecule
③ Validity of animal used in animal studies or *in vitro* model

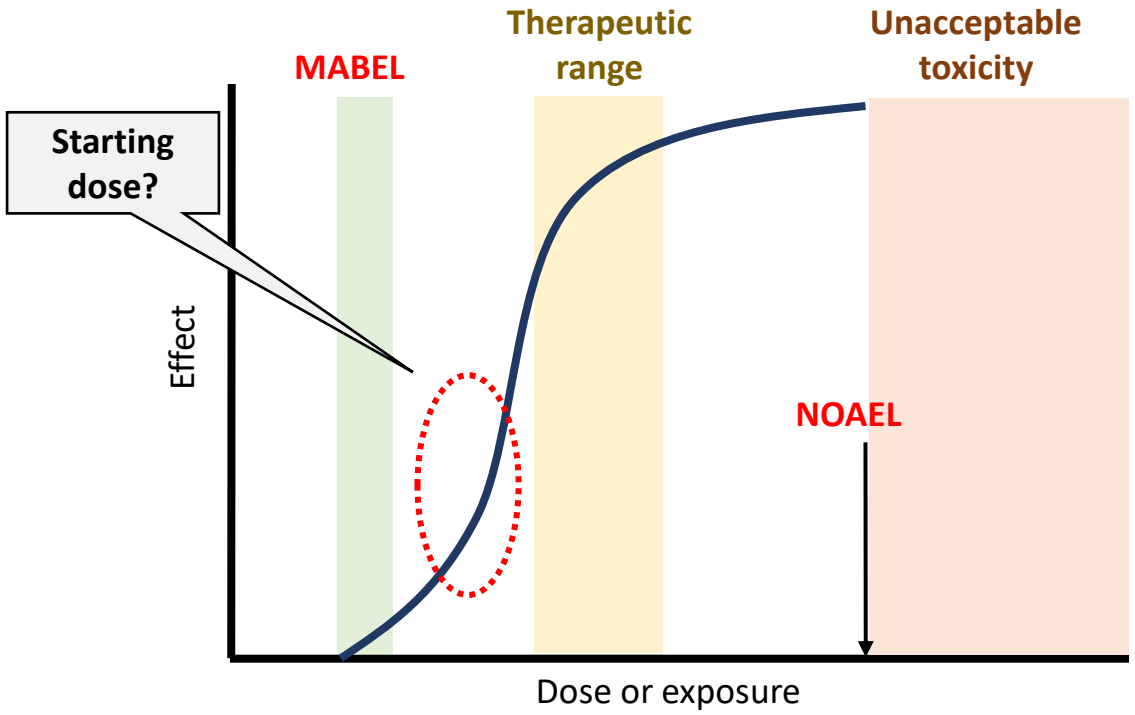
Estimation of MABEL

- Dose with the minimum pharmacological effect in animals (close to ED_{10} value)
- Concentration at which the minimum pharmacological effect is observed *in vitro* using human tissue (close to EC_{10} value)
- Dissociation constant in receptor binding studies

MABEL: Minimum Anticipated Biological Effect Level

Estimation of FIH initial dose

- **Pharmaceutical with 'obvious risks'?**
  - **Yes**: Pharmacological approach (**MABEL**)
  - No: Toxicological approach (NOAEL, etc.)



Obvious risk

- No information about target molecules
- Target molecule activates/blocks multiple signal transduction pathways
- Target molecule is widely expressed (e.g., immune system)
- Pharmacological action may develop beyond the ability of a host (e.g., cytokine release via action of super-agonist to CD3 or CD28)

ADC: Antibody-drug conjugate

Guideline on Strategies to Identify and Mitigate Risks For First-In-Human Clinical Trials With Investigational Medical Products (EMA, July 2007)

Estimation of FIH initial dose

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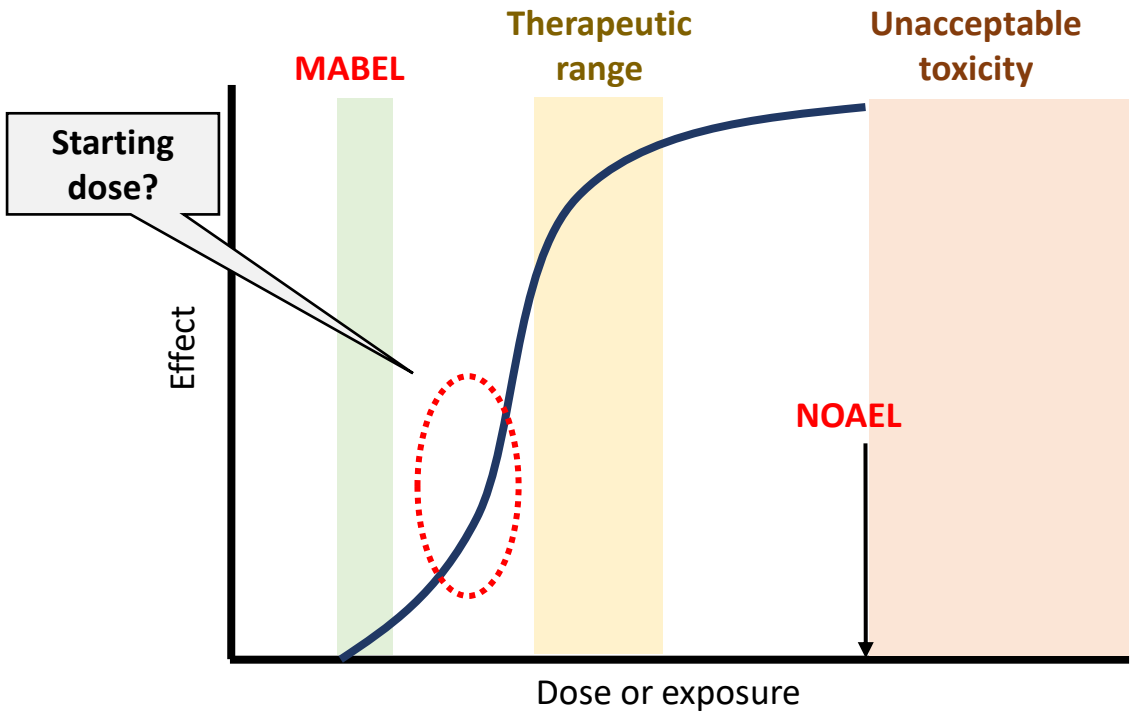
  - Yes: Pharmacological approach (MABEL)
  - **No**: Toxicological approach (**NOAEL, etc.**)



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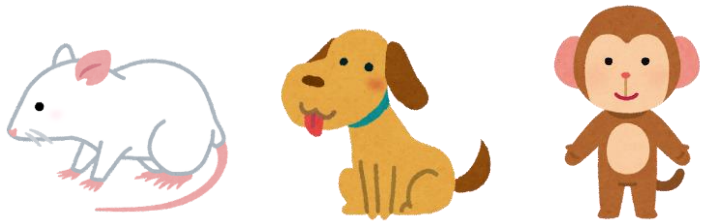
Single-dose studies (confirmation of acute toxicity)

- **Purpose**
  - Predicting **acute effects of an overdose**
  - **Lethal dose** (NOT for determining the LD_{50})
  - Dose selection for repeated dose toxicity studies
- **Animal species**
  - Rodents & non-rodents (excluding rabbits)

- **Dosage**
  - Intended clinical route
- **Observation**
  - **14 days** after dosing (evaluating recovery and/or tardive toxicity)

Repeated-dose study (confirmation of chronic toxicity)

- **Purpose**
  - Identifying **systemic toxicity** (**target organs**)
  - Recovery of the toxicity
  - Obtaining **NOAEL, STD_{10}, and HNSTD** and predicting **safety margin**
- **Animal species**
  - Rodents & non-rodents (excluding rabbits)

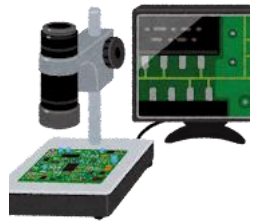


- **Dosage**
  - Intended clinical route, and **3 doses or more**
- **Duration**
  - Depending on clinical use (rodents: up to **6 mo**; non-rodents: up to 9 mo)
- **Observation**
  - General signs, body weight, food intake, ophthalmology, hematology, etc.

Local tolerance

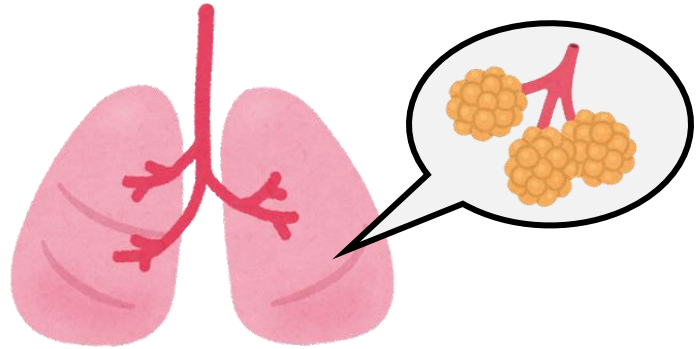
- **Purpose**
  - ➢ Detecting local tolerance of drugs used to treat the **vein**, **eye**, **dermal tissue**, and **mucosa tissue**, etc.
- **Animal species**
  - ➢ Rabbit (eye), mini-pig (dermal), hamster (oral mucosa), etc.

- **Dosage**
  - ➢ Clinical route, formulation, and concentration
- **Observation**
  - ➢ Macroscopy and histopathology at the site



Safety pharmacology

- **Purpose**
  - Detecting potential undesirable pharmacodynamics effects on physiological functions in the therapeutic range



  - Target organ: central nerve, cardiovascular, respiratory system

Conclusion

- Phase I clinical trials are a valuable opportunity to verify the efficacy and safety of multiple drug doses in humans
- Non-clinical studies conducted before starting FIH studies conform to guidelines such as ICHS6 and S9
- Non-clinical studies are conducted to investigate the initial dose and to predict adverse events that may occur in humans
- Initial doses are investigated using the STD10/HNSTD/NOAEL approaches for drugs such as low-molecular-weight compounds and ADC preparations, whereas the MABEL approach is often applied for immune system biopharmaceuticals
- Adverse events in clinical trials in humans are predicted based on findings in single-dose studies, repeated-dose studies, and evaluation of organ toxicity