Risk mitigation in early phase clinical trials

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Risk mitigation in early phase clinical trials

Luc Van Bortel

nothing to disclose

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Risk mitigation in early phase clinical trials

Question 1.
The pharmaceutical industry (sponsor of a clinical study) is responsible for the patients'/volunteers' safety in the clinical study.

Yes (green)
No (red)

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Question 2.
The aim of a first-in-man (FIM) study is to find the therapeutic dose.

Yes (green)
No (red)

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Question 3.

The risk for a healthy person participating in an early phase study of being hospitalized for drug related adverse events is higher than for accidents during the study period.

Yes (green)
No (red)

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Risk mitigation in early phase clinical trials

1. Facts on drug development

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Drug development

- >20.000 molecules → 1 medicine
- Development cost >1 billion Euro
- Development time: 12-15 years
- Phases of drug development
  - Preclinical (6 years)
    effect and toxicity on cells, organs, animals

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Drug development

- >20.000 molecules → 1 medicine
- Development cost >1 billion Euro
- Development time: 12-15 years
- Phases of drug development
  - Preclinical (6 years)
  - Clinical phase (6-9 years)

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D.R.U.G.
Drug Research Unit Ghent

Phases of clinical drug research

registration	phase		goal	volunteers	
	new	old		type	number
pre	early phase	1	Max. Tolerable Dose (MTD)	Healthy or patient	small
pre		2	dose range effect + AE	patient	small
pre	late phase	3	treatment effect + AE	Patient	large
post		4	Post Marketing Surveillance (PMS)	patient	very large

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Risk mitigation in early phase clinical trials

1. Facts on drug development
2. Guidelines for clinical drug development

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GCP/ICH

GCP: good clinical practice
ICH: international conference on harmonisation

AIM

- Preserve rights of healthy/patient volunteers
- Improve quality of clinical studies

In EU Directive 2001
To be implemented by EU member states 2004

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Some important GCP/ICH rules

- Studies to be approved by Ethics committee (EC)
- Studies to be approved by the country's competent authority (CA; representing EMA)
- Persons willing to participate in a study have to be informed orally and in writing
- Subjects can withdraw from study without obligation mentioning reason and without any consequence for his/her treatment
- The sponsor is owner of study data and responsible for submission of study to EC & CA
- The investigator is responsible for the safety of the subjects participating in the study

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ICH-GCP
Investigator's responsibilities

2.1 Clinical trials should be conducted **in accordance with** the ethical principles that have their origin in the **Declaration of Helsinki**, and that are consistent with GCP and the applicable regulatory requirement(s).

Declaration of Helsinki: avoid damage to volunteers by all means

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be **responsible for all trial-related medical** (or dental) **decisions**.

Investigator is responsible for healthy subjects'/patients' safety

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Risk mitigation in early phase clinical trials

1. Facts on drug development
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3. How to choose the first dose in man

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Non-clinical data

ICH Topic M3 (R2), June 2009

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

Goals of nonclinical safety evaluation:

-characterization of toxic effects
-dose dependency
-relationship to exposure (AUC) & Cmax
-reversibility

Information is used to:

-estimate safe starting dose
-estimate dose range for human trials
-identify parameters for clinical monitoring of potential AEs

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Non-clinical data needed for full development

Pharmacology studies

-Core battery of safety pharmacology studies includes effects on **cardiovascular, central nervous, respiratory** systems
-mode of action/effect on therapeutic target

Genotoxicity studies

-phase-I single dose: assay for gene mutation (AMES test)
-phase-I multiple dose: tests for chromosomal damage in mammalians

Phase-II: complete battery of tests for genotoxicity

Carcinogenicity studies

For clinical trials only needed if significant concern of carcinogenic risk

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Non-clinical data needed for full development

Repeated-dose toxicity studies in 2 mammalians, at least 1 is a non-rodent

max duration of clinical trial	recommended min duration of repeated-dose toxicity studies	
	rodents	non-rodents
≤ 2 weeks	2weeks	2 weeks
2 weeks-6 months	= clinical trial	= clinical trial
> 6 months	6 months	9 months

Selection of Maximum Recommended Starting Dose

for drugs administered systemically to normal volunteers

Step 1 — **Determine NOAELs (mg/kg) in toxicity studies**

Is there reason to believe that toxic doses do not scale by body surface area?

- Yes → HED (mg/kg) = NOAEL (mg/kg) (or other appropriate normalization)
- No → **Step 2** — Convert each animal NOAEL to Human Equivalent Dose (HED) (based on body surface area)

Step 3 — Pick HED from most appropriate species

Step 4 — Choose Safety Factor and divide HED

Maximum Recommended Starting Dose (MRSD) → Consider lowering dose based on a variety of factors, e.g., the PAD — **Step 5**

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Step 1: No observed adverse effect level (NOAEL) determination

- NOAEL:
  The highest dose level that does not produce a significant increase in adverse effects
- Adverse effect:
  Statistically significant or clinically significant

Step 1: No observed adverse effect level (NOAEL) determination

- Three types of findings to determine NOAEL:
  - overt toxicity (e.g., clinical signs, macro- and microscopic lesions)
  - surrogate markers of toxicity (e.g., serum liver enzyme levels)
  - exaggerated pharmacodynamic effects

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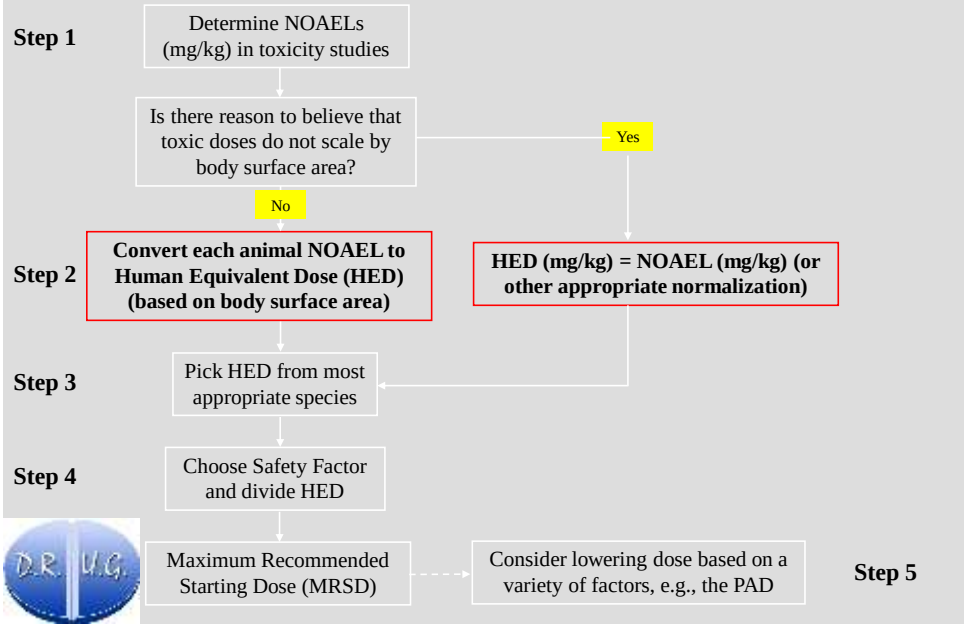
Selection of Maximum Recommended Starting Dose

for drugs administered systemically to normal volunteers



Step 2: Human Equivalent Dose (HED) calculation

- Aim: to correct for species differences in metabolism/drug elimination
- Conversion based on Body Surface Area
- Conversion based on mg/kg (if in all species NOAEL occurs at same mg/kg
- Approach based on PK: AUC (and Cmax)

Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area

Species	To convert animal dose in mg/kg to dose in mg/m^2, multiply by km below:	To convert animal dose in mg/kg to HED in mg/kg, either:	
		Divide animal dose by:	Multiply Animal dose by:
Human	37	---	---
Child(20 kg)	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54

Conversion: example

Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area

Species	To convert animal dose in mg/kg to dose in mg/m^2, multiply by km below:	To convert animal dose in mg/kg to HED in mg/kg, either:	
		Divide animal dose by:	Multiply Animal dose by:
Human	37	---	---
Rat	6	6.2	0.16

Conversion of dose in mg/kg to dose in mg/m^2

Human: 1 mg/kg ~ 37 mg/m^2 (60kg ~ 1.70m^2)

Rat: 1 mg/kg ~ 6 mg/m^2 (0.15kg ~ 0.03m^2)

Conversion of animal dose in mg/kg to HED in mg/kg

6.2 mg/kg in rats is equivalent to 1 mg/kg in humans

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Step 3: Most appropriate species selection

- In the absence of data on species relevance the most sensitive species is chosen (i.e., the species with the lowest HED)
- Obligatory: tox data (2 weeks) in 2 species:
  1 nonrodent
  (often dog and rat/mouse)

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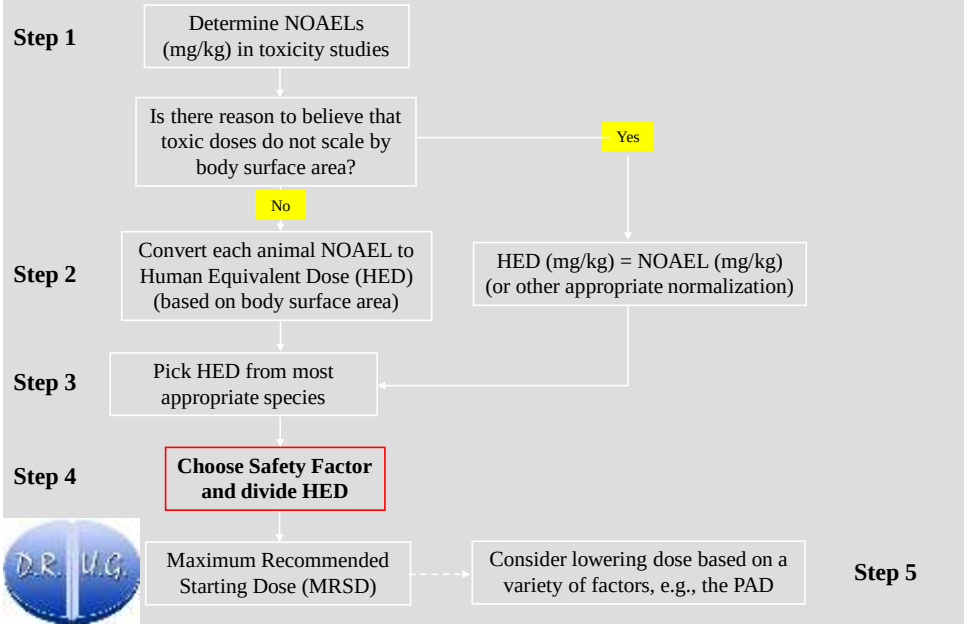
Selection of Maximum Recommended Starting Dose

for drugs administered systemically to normal volunteers



Step 4: Application of safety factor

- A safety factor is applied to provide a margin of safety because
  - uncertainties due to enhanced sensitivity
  - difficulties in detecting certain toxicities in animals
  - differences in receptor densities or affinities
  - unexpected toxicities
  - interspecies differences in ADME
- The default safety factor is 10
- The default safety factor may be increased or decreased using all available information

Increasing the safety factor

- Steep dose response curve
- Severe toxicities
- Nonmonitorable toxicity
- Toxicities without prodromal indicators
- Variable bioavailability
- Irreversible toxicity
- Unexplained mortality
- Large variability in doses or AUC levels eliciting effect
- Questionable study design or conduct
- Novel therapeutic targets
- Animal models with limited utility

Decreasing the safety factor

- The toxicologic testing is of the highest caliber in both conduct and design
- Most of the time, candidate therapeutics for this approach are members of a well-characterized class with
  - administration by the same route, schedule, and duration
  - similar metabolic profile and bioavailability
  - similar toxicity profiles across all species tested including humans
- Toxicities produced by the therapeutic
  - easily monitored
  - reversible
  - predictable
  - shallow dose-response relationship across the tested species
- NOAEL based on toxicity studies of longer duration compared to the proposed clinical schedule in healthy volunteers (assumption of cumulative toxicity)

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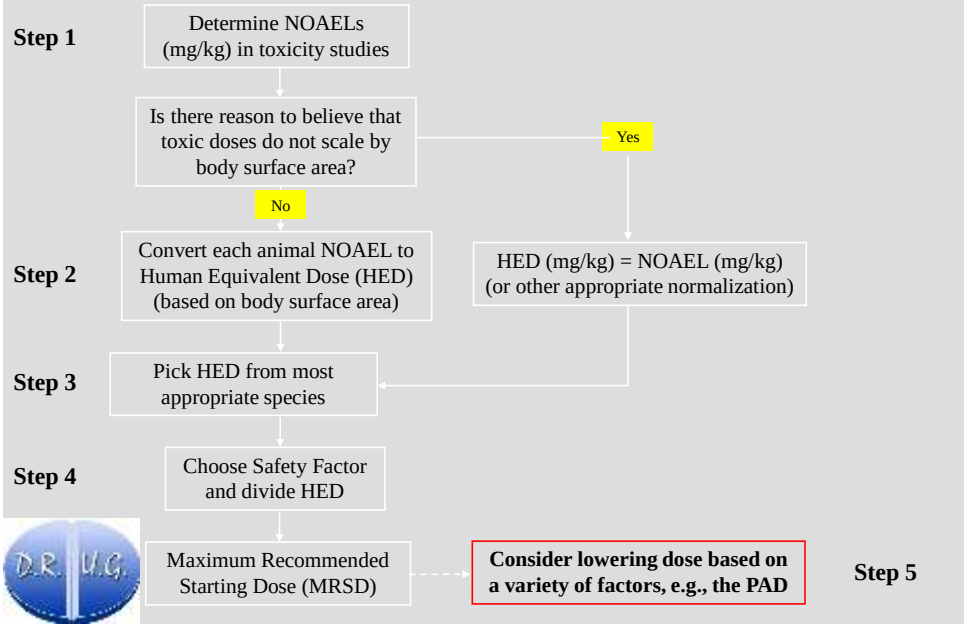
Selection of Maximum Recommended Starting Dose

for drugs administered systemically to normal volunteers



Step 5: Consideration of the pharmacological active dose (PAD)

- Compare maximum recommended starting dose (MRSD) to the pharmacologic HED derived from pharmacodynamic models
- If MRSD is higher than this pharmacologic HED, it may be appropriate to decrease the clinical starting dose
- MABEL: minimal anticipated biologic effect level

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Safety rules for First in Man dosing

- Don't give a dose in man → plasma concentrations that were not safe from preclinical data (lowest NOAEL)
- NOAEL based on exposure (AUC) and Cmax
- If no human PK available → correct NOAEL to HED
- If human PK available → guidance on plasma conc (AUC & Cmax)
- Take into account safety factor (10 fold) ~ nature of tox (serious? monitorable?)
- Consider appropriate dose escalation (linear PK?)
- First dose should not be pharmacologically active
- Don't administer doses in ambulatory setting resulting in concentrations that were not proven safe in house

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First in man studies

- First study: single ascending dose study (SAD)
- First dose = single dose, pharmacologically not active (lower than MABEL), often <1/50 of NOAEL/HED
- Example of dose steps: 1-2-5-10-25-50-100 mg
- Postdose: In-house observation of 24 h (more if needed)
- Standard safety analysis: blood, urine, blood pressure, electrocardiogram, reported adverse events …
- Decision to move to next higher dose step based on complete safety analysis of previous step

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First in man studies

Stopping criteria

- Important adverse events
- NOAEL reached
- Withdrawal of volunteer

After single ascending dose study, 1-2weeks multiple ascending dose study (MAD)

Take possible drug accumulation into account

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First in man studies

Study design

- Double blind, randomized, placebo-controlled
- Cohorts of 8 subjects (6 active, 2 placebo)

For innovative mode of actions including biologicals

- Start with 1 active (+1 placebo)
- Low starting dose
- Take large safety factor if drug is targeting the immune system, particularly if it is an agonist (cfr Tegenero)

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Serious adverse events (SAEs) in early phase studies

Survey in Belgian early-phase units 2009-2014

Number of volunteers in studies	**18995**
Number of possibly drug related SAEs	**6**
	0,032% (3,2/10.000)

Possibly drug related SAEs

- Hallucinations/psychosis 2
- Cardiac arrhythmia 1
- Arthritis 1
- Mild renal function decrease 1
- Steven-Johnson 1

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Survey in Belgian early-phase units 2009-2014

Number of volunteers in studies		**18995**
Number of SAEs		
possibly drug related SAEs	**6**	**(0,032%)**
non drug related SAEs	**70**	**(0,4%)**

Risk for hospitalisation during early phase study is > 10 x higher for a non drug-related reason than for possibly drug related SAEs

Serious adverse events (SAEs) in early phase studies

Survey in Belgian early-phase units 2009-2014

Number of volunteers in studies		**18995**
Number of SAEs		
possibly drug related SAEs	**6**	**(0,032%)**
not drug related	**70**	**(0,4%)**
non disease related SAEs	**11**	

- Traffic accidents 5
- Alcohol intoxication 1
- Assault at home 1

Fractures (falling) 3
Knee injury at work 1

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5. Involvement of hospital pharmacist

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Involvement of hospital pharmacists

- Keeping randomization lists
- Member of ethics committee
- Drug storage
- Drug packaging and blinding
- Drug manufacturing according to GMP
- Drug delivery (more in later phase studies)

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Yes (green)
No (red)

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Yes (green)
No (red) the investigator is responsible

Risk mitigation in early phase clinical trials

Question 2.
The aim of a first-in-man (FIM) study is to find the therapeutic dose.

Yes (green)
No (red)

Risk mitigation in early phase clinical trials

Question 2.
The aim of a first-in-man (FIM) study is to find the therapeutic dose.

Yes (green)
No (red) find the maximal tolerable dose (MTD)

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The risk for a healthy person participating in an early phase study of being hospitalized for drug related adverse events is higher than for accidents during the study period.

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Yes (green)
No (red) in Belgian survey 6 versus 11 accidents

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