PreClinical Safety (PCS) Consultants Ltd

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AGAH Workshop February 28, 2018
First-in-human trials – What you need to know

Which answers do we need from non-clinical pharmacology and toxicology prior to the first human exposure?
How to derive the human starting dose?

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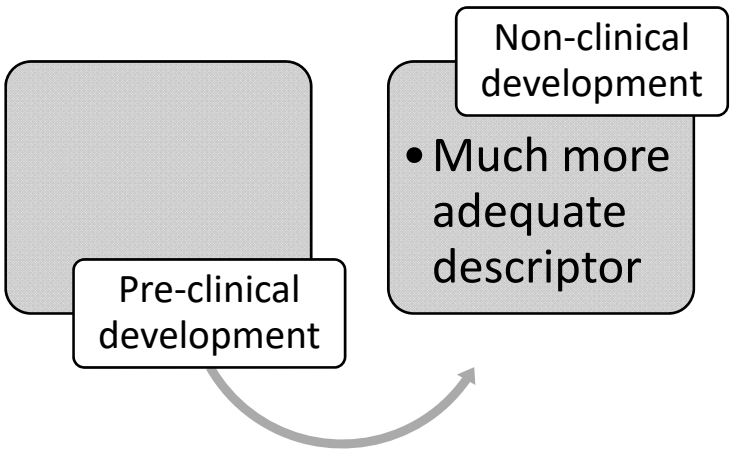
PCS – The Integrated Drug Development Company

Preclinical and clinical development are closely intertwined from start to end



Outline part I

- Principles of early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Example CNS drugs

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Principles of early compound characterisation

Screening strategies to select most promising candidates

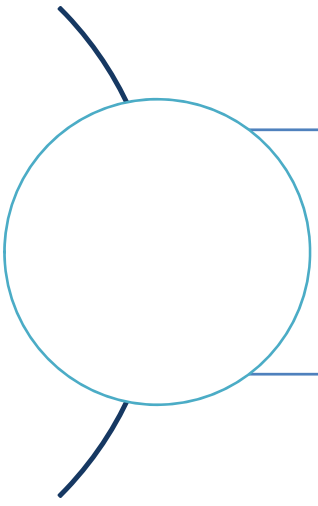
In silico (computational)

Physical screening (miniaturised formats)

Capturing many features of classes of molecules and of individual representatives

Should select the most promising candidates

RISK: Drug and/or target promiscuity



Aim: assess binding affinity and functional activity at unintended targets ("off-target")

- More recent approach: Computational prediction
- Drug and target promiscuity
- Further reading: Lounkine 2012 Nature 486(7403): 361–367

Outline part I

Principles of early compound characterisation

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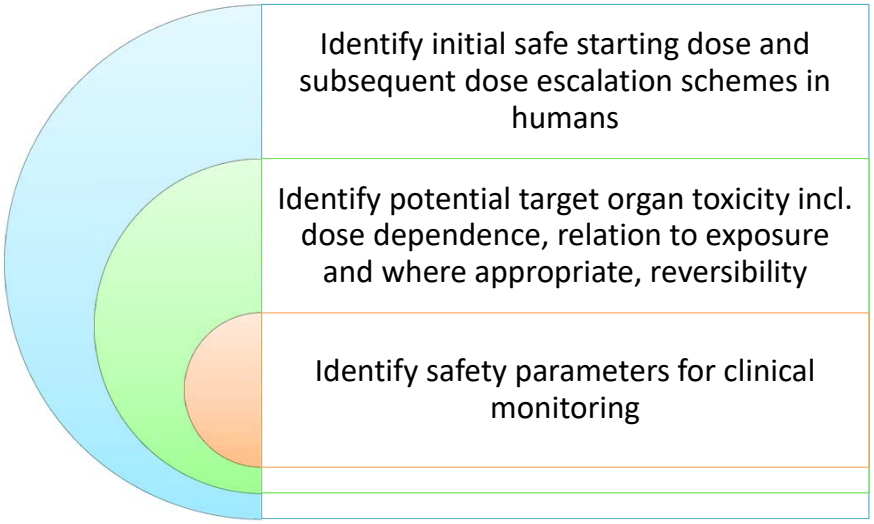
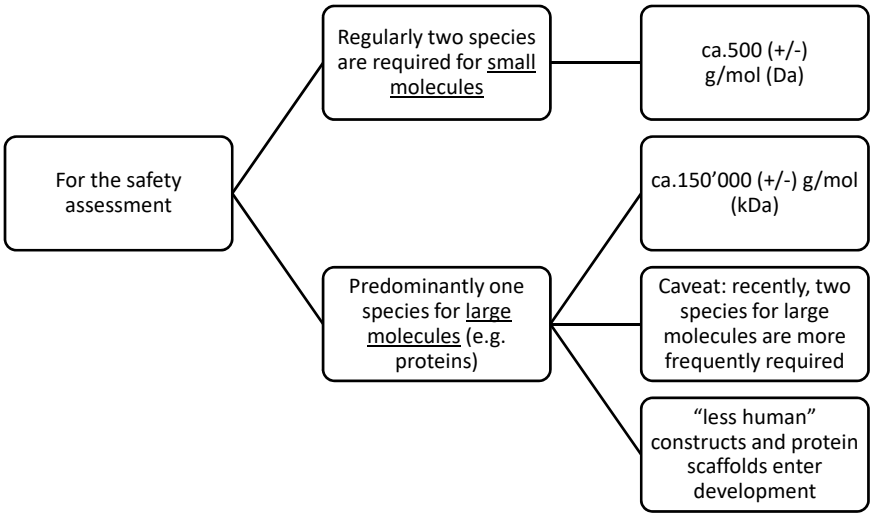
Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

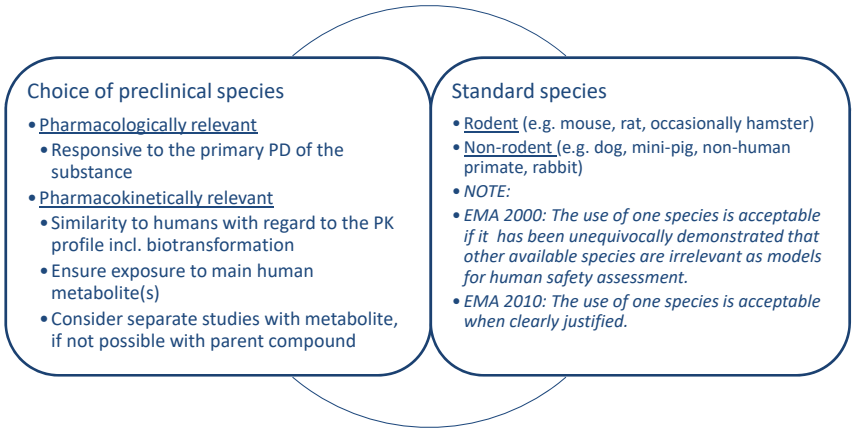
ICH M3(2): Key objectives



Principal aspects testing strategy



Principal decisions



Preclinical studies *in vivo* (1)

Pivotal studies to be conducted under GLP

- Good Laboratory Practice
- In GLP-certified facilities
  - In house
  - Contract Research Organisations (CROs)

GLP is a prerequisite

- Absolutely essential
- But not sufficient for the conduct of robust preclinical studies

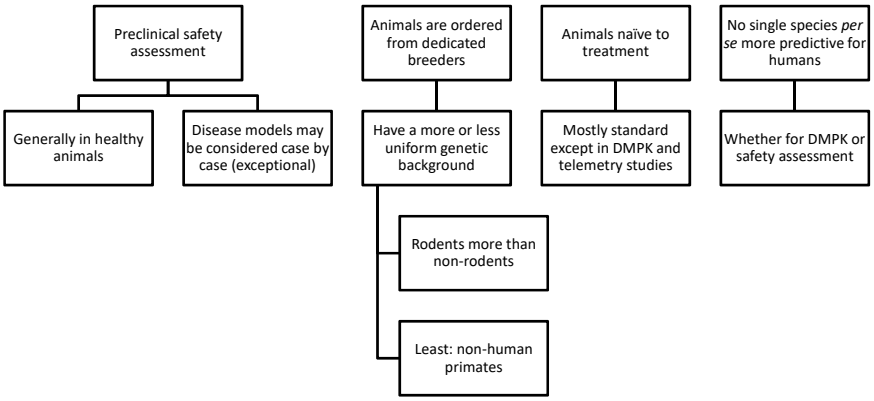
Preclinical studies *in vivo* (2)

Equally important

- Experience, experience, experience!!
- Historical background data over recent years due to genetic shift
- Scientific knowledge

Quality precipitates in many ways!!!

Practical considerations



Practical considerations (2)

Group sizes follow established rules

- Depending on study type and design
- Should be "sufficient to allow meaningful scientific interpretation" EMA 2010

Generally four treatment groups

- Control (vehicle)
- 3 dose groups
  - Ideally low (NOAEL) – mid (LOAEL) – high (MTD) dose
  - No – Lowest Adverse Effect Level – Maximum Tolerated Dose

Route of administration generally same as intended in humans except

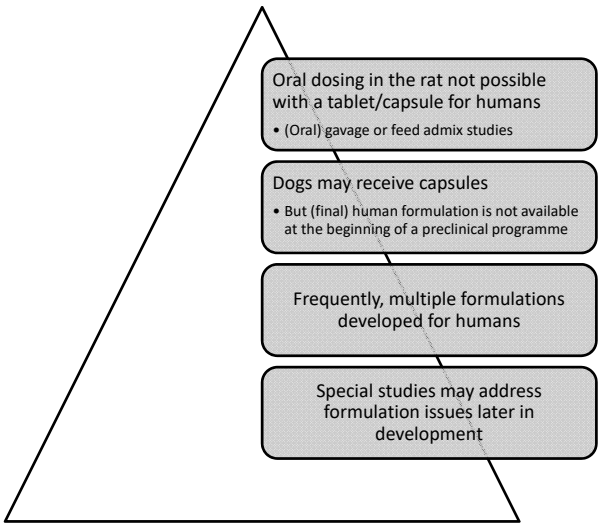
- For dedicated studies
- Where insufficient exposure or other limitations
  - E.g. rabbits notoriously challenging

Practical considerations (3)

Mostly, formulation not the same as in clinical studies

- New drug substance
- But not new drug product studied
- Synonyms for new drug substance:
  - NCE = New Chemical Entity
  - NME = New Molecular Entity
  - API = Active Pharmaceutical Ingredient

Practical considerations (4)



Outline part I

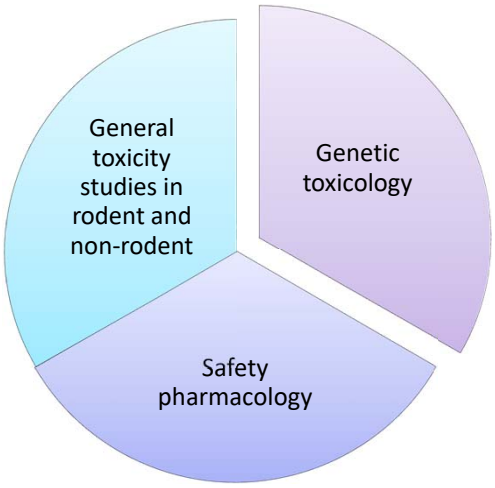
Principles of early compound characterisation

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

Minimum requirements



Principal Aims (1)

- Characterise dose-response over time frame studied
- Establish NOAEL (No Observed Adverse Effect Level)
- Establish MTD (Maximum Tolerated Dose)
- Identify target organs of toxicity
- Identify parameters for clinical monitoring for potential adverse effects

Principal Aims (2)

- Potentially characterise reversibility of effects observed
- Provide information on systemic (and tissue) exposures
- Provide basis for dose selection in subsequent preclinical studies in the species studied
- To identify initial safe starting dose and dose range for subsequent human trials (in context with other studies)

Key parameters in safety assessment

SR/MoE
- Safety ratio
- Multiples of exposures

NO(A)EL
- No observed adverse effect level
- Other parameters may be more appropriate to set starting dose in humans **(e.g. MABEL, PAD)**

MTD
- Maximum tolerated dose

Key parameters in safety assessment

Anticipated therapeutic dose range

MABEL
- Minimal anticipated biological effect level

PAD
- Pharmacologically active dose

NO(A)EL
- No observed adverse effect level

MTD
- Maximum tolerated dose

Safety Ratio (SR) – multiples of exposure

Parameter to estimate relative safety

- Usually based on AUC
- However, Cmax may be more relevant (CNS/CVS)

Comparison of systemic drug exposures

- In patients at therapeutic doses up to the maximum recommended human dose (MRHD)
- With those in animals at the no-observed-[adverse]-effect level (NO[A]EL)

For NCEs

- SRs (i.e. multiples of exposures at NOAEL) normally at least 20
- but SRs may even be less than 1

NOAEL = No Observed Adverse Effect Level

Toxicities in the animals may depress the NOAEL

= dose level at which no adverse effects were observed

Room for interpretation

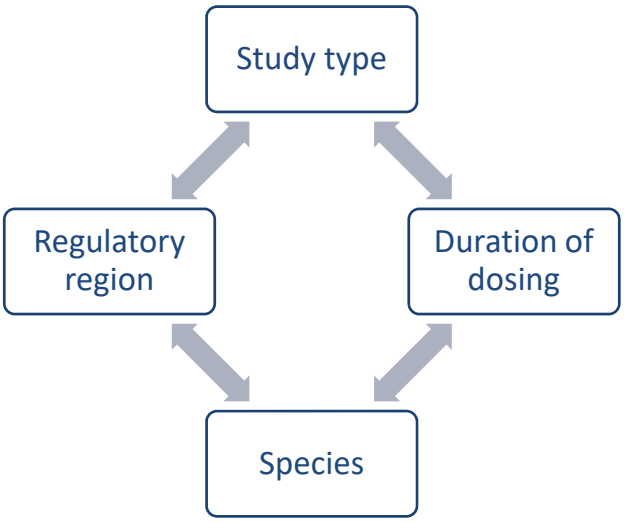
- What is considered adverse?

Altered SRs may result from

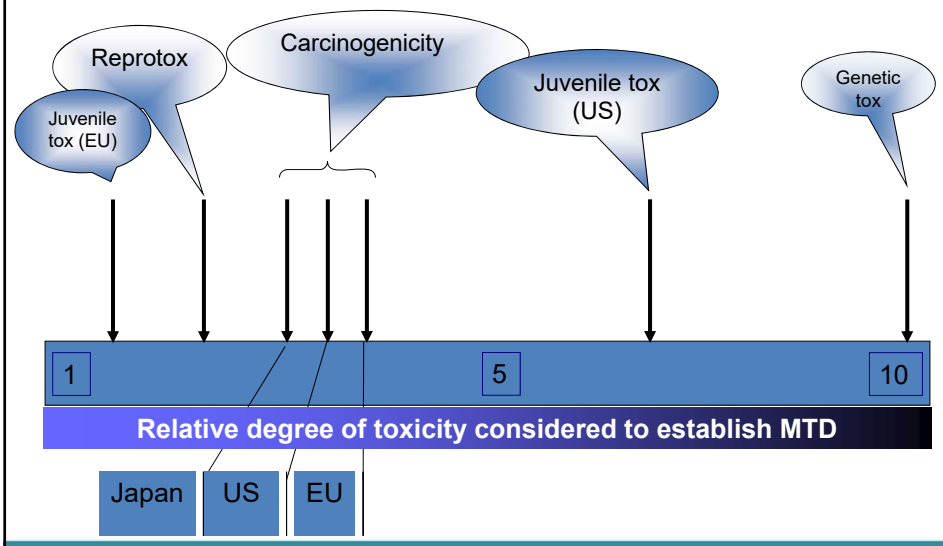
Changes in NOAEL

Changes in human exposure

MTD = maximum tolerated dose is a function of



Study type and regulatory region



Safety pharmacology

Investigate effects on vital functions

Cardiovascular	Respiratory	Central nervous systems

Core battery of tests

Any follow-up/
supplemental studies based on cause for concern

General toxicology

Key elements

- Selection of relevant species
- Dose range finding studies (non-GLP)
- Pivotal GLP studies

Primary objectives

To characterise the general toxicological profile of the test item

- Investigation of effects of the drug in development on the organism of the test species
- Following single – repeated dosing

To provide information for human risk assessment

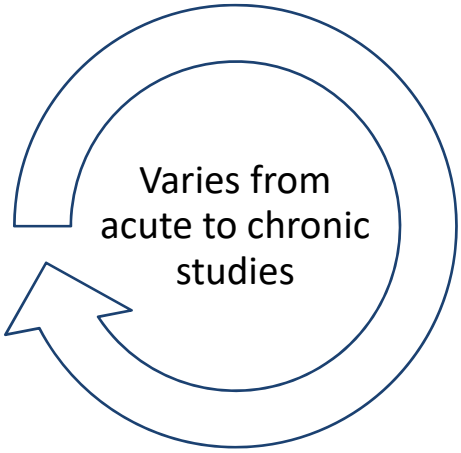
To support specific studies in humans

To support marketing authorisation

Dose range finding (DRF) studies

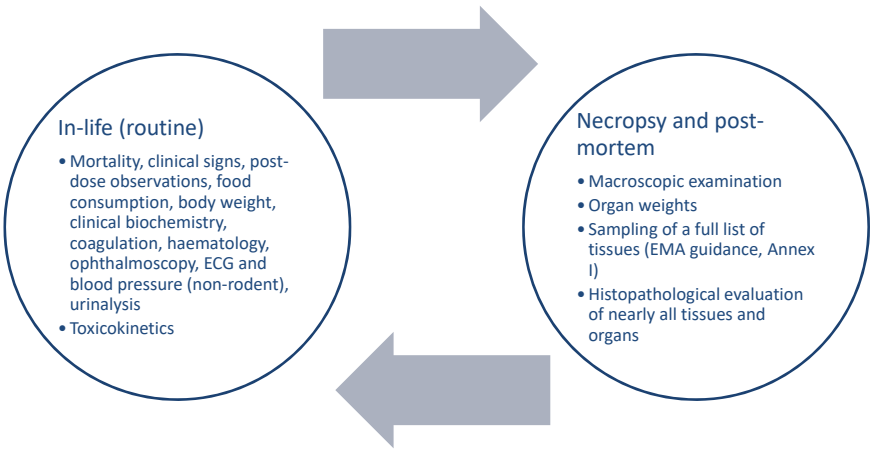
Objectives	**Not uncommon to see mortality at doses > MTD**
Identify Maximum tolerated dose (MTD) for main studies	Particularly for CNS, CVS or other drugs targeting vital functions for which the prevailing findings are dominated by exaggerated pharmacological effects

Treatment duration pivotal studies

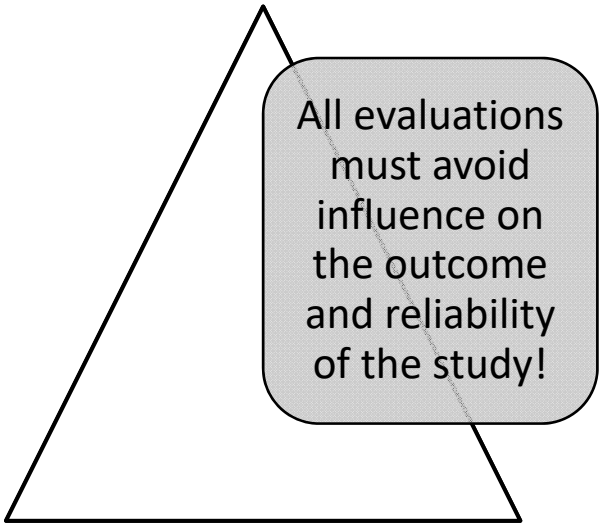


- 1 day up to 6 months (rodent) to 9 months (non-rodent)
  - Duration of treatment in chronic toxicity studies see ICH S4

Endpoints



In life observations



Additional investigations

- "If immunologic effects are anticipated with the compound or if there is evidence of immunologic activation or inhibition in repeated dose toxicity studies, immunotoxicity of the compound should be explored in accordance with the *Guideline on Immunotoxicity of Human Pharmaceuticals* (CPMP/ICH/SWP/167235/2004; ICH S8)."
- Neurotoxicity
  - FOBs can be included – i.e. following repeated dosing
- Additional sub-sets of animals
  - Interim and recovery animals to be added

Outline part I

Principles of early compound characterisation

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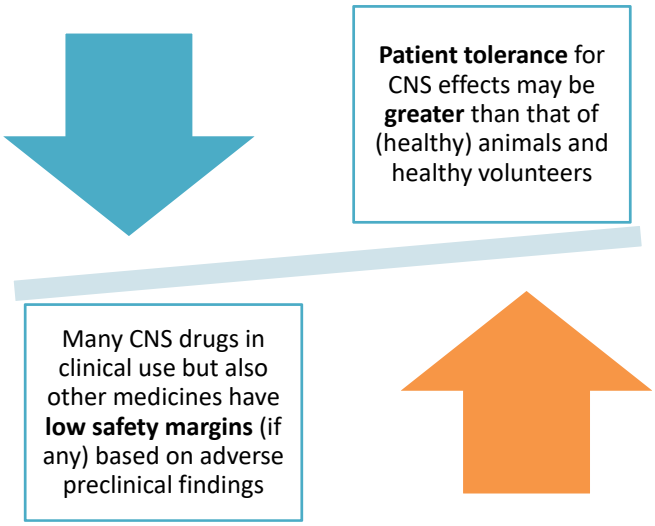
Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

Example: CNS active drugs



Low safety margins – typical causes

Clinical (in-life) intolerance

e.g. CNS clinical signs in one or more laboratory species (rat, dog, non-human primate, rabbit etc.) often consistent with exaggerated pharmacology

Target-organ toxicity

e.g. liver, kidney, lungs, CNS, eyes, endocrine (e.g. (pituitary) and cardiovascular systems (heart, blood vessels) etc. consistent with on and/or off-target effects

Clinical intolerance - typical profile

Steep dose-response

CNS-symptoms

- Such as tremor, altered activity, altered posture, ataxia, recumbency etc., reduced body temperature (rodent), convulsions at high(er) doses
- Typically transient and reversible
- Often strong correlation with systemic Cmax

Mortality may be seen at low multiple of those doses with first mild CNS signs

- May even occur at doses only 2-3 fold the NOAEL and/or MRHD (based on HED = human equivalent dose on mg/m^2 basis)

No histopathological findings in the brain

Typical features of target organ toxicity

CNS active drugs must be able to pass the blood-brain barrier

Physico-chemically characterised by high(er) lipophilicity

May undergo extensive metabolism

May therefore adversely affect any other organ system in the body

Doses in non-rodents not uncommonly limited by clinical tolerance

Rodents may show greater clinical tolerance
- Identification of target organs other than CNS more likely in these species

Exceptional changes

Adverse CNS effects are commonly
- Functional
- Not morphological

Morphological alterations in the brain
- Exceptional

Observed e.g. for drugs interacting with the NMDA receptor such as
- Phencyclidine (PCP) (Olney, Science 1989)
  - «Angel Dust»
  - «Olney's lesions» – neuronal vacuolation
- MK-801 (Auer, Stroke 1996)
- Memantine (Creeley, Neurobiology of Aging 2008)

Safety assessment

Mostly not marketed

Unless perhaps if they were reliably identifiable by a biomarker indicating a fully reversible functional stage well preceding any changes at the histopathological level

- How to identify?
- How to translate from animals to humans?
- Safety margins?

Outline part II

Determination of a safe starting dose for FIM

- FDA and EU concepts

Case study

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Determination of a safe starting dose for FIM

- FDA and EU concepts

Case study

Safety evaluation in ICH regions

Focus EU	Focus US (FDA)
• Exposure and target organs/adverse findings	• Target organs/adverse findings and exposure

Considerations regarding dose levels

NOAEL

- US – exaggerated pharmacology and absence of adverse effects
- EU – absence of adverse effects and exaggerated pharmacology

MTD

- US – tend to expect more severe toxicity to accept an MTD
- EU – various concepts support lower levels of toxicity to establish MTD

NOTE:

- Biologics are NOT dosed up to an MTD
- Dose levels are generally based on exaggerated (on-target) pharmacology

Setting a maximum recommended starting dose (MRSD)

FDA guidance provides factors for conversion of animal dose into Human Equivalent Dose

- mg/kg
- mg/m^2

→ HED must be based on NOAEL in the most sensitive species (i.e. lowest HED derived)

Following extrapolation of the HED, an additional safety factor has to be applied → Standard factor = 10

NOAEL definition used in FDA guidance

Several definitions of NOAEL exist, but for selecting a starting dose, the following is used: the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group.

The definition of the NOAEL, in contrast to that of the NOEL, reflects the view that some effects observed in the animal may be acceptable pharmacodynamic actions of the therapeutic and may not raise a safety concern.

Increasing the safety factor to > 10

- Steep dose-response
- Severe toxicities
  - CNS explicitly mentioned
- Non-monitorable toxicities
  - Example: histopathological changes in animals that are not readily monitored by clinical pathology markers
  - Note: such a biomarker would have to reliably precede the adverse manifestation and allow for definitive prevention in humans (see next point)!
- Toxicity without pre-monitory signs
- Variable bioavailability
- Irreversible toxicity

Increasing the safety factor (2)

Unexplained mortality

Large variability in doses or plasma drug levels eliciting effect

Non-linear pharmacokinetics

Inadequate dose-response data

- Based on poor study designs (too few animals, too wide a dose-range)

Novel therapeutic targets

Animal models with limited utility

Decreasing the safety factor

A safety factor smaller than 10 could be justified when

- the NOAEL was determined based on toxicity studies of longer duration compared to the proposed clinical schedule in healthy volunteers.

This assumes that toxicities are cumulative, are not associated with acute peaks in therapeutic concentration (e.g., hypotension), and did not occur early in the repeat dose study.

MABEL concept

EMA guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products first issued in 2007 - after TeGenero (TGN1412)

- Introduced new additional MABEL concept = Minimal Anticipated Biological Effect Level concept outlined in EMA guidance
- Revised guideline (2018) addresses concerns arising from events in Rennes (Bial)
- Guideline now reads: "risks for first-in-human and early clinical trials"

PAD concept

FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers issued in 2005 before TeGenero

- PAD (Pharmacologically Active Dose) outlined in FDA guidance
- However, FDA focus on dose selection (steps 1-4)
  - Defining a dose that causes toxicity and the No Observed Adverse Effects Level (NOAEL)
  - Secondary focus (step 5) on a dose that causes pharmacological activity (PAD).
- In addition, the focus is on defining a safe dose level rather than a safe level of exposure

FDA Guidance Step 5

However, once the MRSD has been determined, it may be of value to compare it to the PAD derived from appropriate pharmacodynamic models.

If the PAD is from an in vivo study, an HED can be derived from a PAD estimate by using a BSA-CF (Body surface area conversion factor).

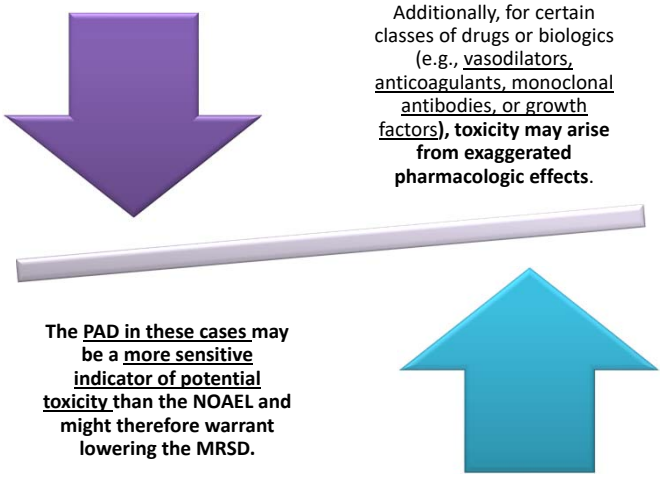
FDA Guidance Step 5

This HED value should be compared directly to the MRSD.

If this pharmacologic HED is lower than the MRSD

It may be appropriate to decrease the clinical starting dose for pragmatic or scientific reasons.

FDA guidance step 5 (2)



Additionally, for certain classes of drugs or biologics (e.g., vasodilators, anticoagulants, monoclonal antibodies, or growth factors), **toxicity may arise from exaggerated pharmacologic effects**.

The PAD in these cases may be a more sensitive indicator of potential toxicity than the NOAEL and might therefore warrant lowering the MRSD.

Outline part II

Determination of a safe starting dose for FIM

- FDA and EU concepts

Case study

TMP137: LD_{50} in rodents

Indication: Add-on therapy for mild to moderate headache and migraine

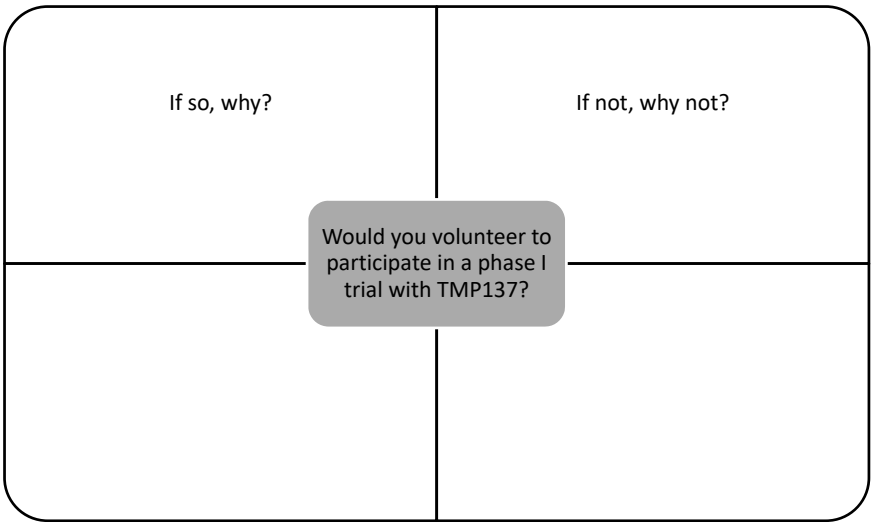
Human dose: 400 mg/day

Species	LD_{50} mg/kg	HED factor	HED mg/kg	mg/person (60kg)	SF based on 400 mg/day
Rat	200-400	x 0.162	32-65	1920-3900	4.8-9.8
Mouse	185	x 0.081	15	900	2.3
FDA guidance on estimating the maximum safe starting dose in initial clinical trials, 2005					

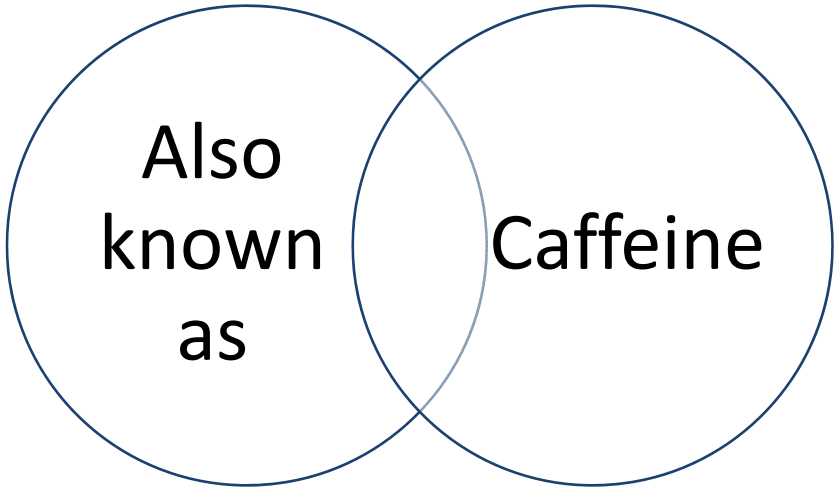
TMP137: Effects in dogs

Dog dose (mg/kg)	Effects in dogs	HED multi-plication factor*	HED (mg/kg)	Human Dose (mg/ 60 kg person)	SF based on 400 mg/day
20	- ↑ heart rate - hyperactivity	x 0.541	11	660	1.7
45	- ↑ blood pressure - cardiac arrhythmias	x 0.541	24	1440	3.6
60	- tremor - seizure - death	x 0.541	32	1920	4.8
FDA guidance on estimating the maximum safe starting dose in initial clinical trials, 2005					

Question to think about



TMP137: 1,3,7-Trimethylpurine-2,6-dione



Caffeine

- Lethal dose in human: 10 000 mg
- Pharmacological dose: 400 mg
- SF: 25

- 1 cup of coffee has about 100 mg caffeine
- Lethal dose would be 100 cups of coffee
- 250 mL water x 100 cups = 25 L
- Water intoxication (hyponatremia) occurs at about 6 L

➢ Conclusion: The dose makes the poison
(Paracelsus 1493-1541)

Special considerations for oncology compounds (1)

Nonclinical evaluation for anticancer pharmaceuticals

(ICH S9)

- Patients with advanced disease
- Higher acceptability for toxicities of new therapeutics

Oncology compounds (2)

- Toxicology studies to determine a NOAEL are not needed
- The potential to recover from toxicity should be evaluated, however demonstration of complete recovery is not considered essential
- Genotoxicity studies are not needed for clinical development, but to support marketing
- The clinical schedule should be evaluated in toxicology studies
- Treatment can continue according to the patient's response and can continue beyond the duration of the completed toxicology studies

Oncology compounds (3)

- Highest dose of exposure tested in the nonclinical studies does not limit the highest dose in cancer patients
- Non-clinical data to support Phase 1 are sufficient for moving in Phase 2
- Phase 1 studies should avoid exposing too many patients to sub-therapeutic doses
- Starting dose should have pharmacological effects and be reasonable safe

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Further reading (selection)

1. E.Koch and S. Plassmann. Critical Aspects of Integrated Non-Clinical Drug Development: Concepts, Strategies and Potential Pitfalls in: A Comprehensive Guide to Toxicology in PreClinical Drug Development. Editor Ali S. Faqi. 2nd edition (2017)
2. Waring JM et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nature Reviews Drug Discovery 14:475-486 (2015)