PreClinical Safety (PCS) Consultants Ltd

Eufemed Conference London, May 2017

Pre-Conference Workshop
Toxicological risk assessment for early medicines development: case studies & discussion

Dr. med. vet. Stephanie Plassmann

Outline

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Example: CNS Drugs
- Example: Interpretation of equivocal findings
- Resources and communication
- Possible outcomes and success rates
- Conclusions and take home messages

Outline

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Example: CNS Drugs
- Example: Interpretation of equivocal findings
- Resources and communication
- Possible outcomes and success rates
- Conclusions and take home messages

Early compound characterisation

Screening strategies to select most promising candidates

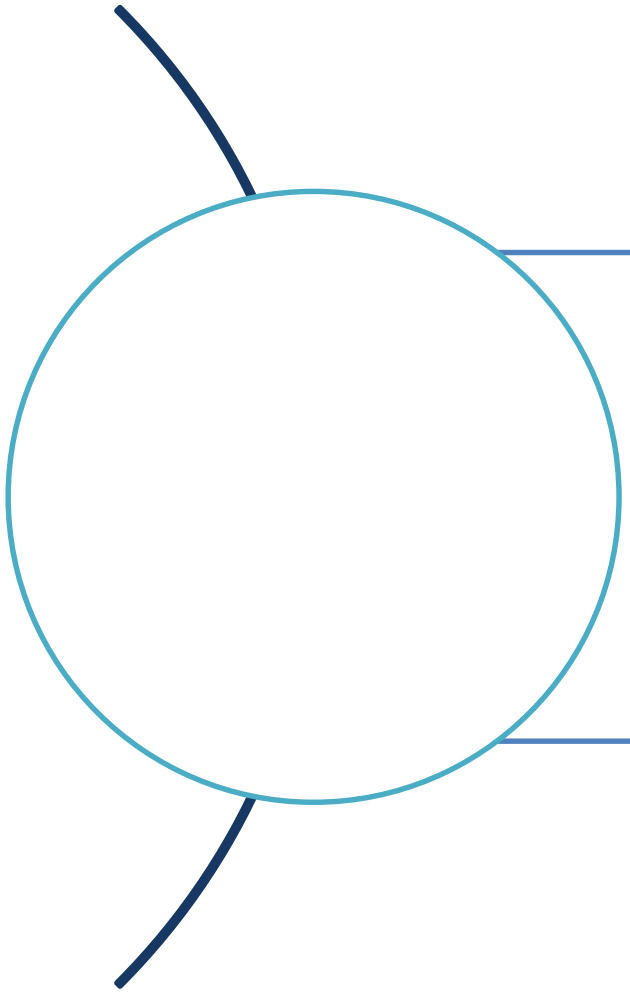
In silico (computational)

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

Early compound characterisation

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

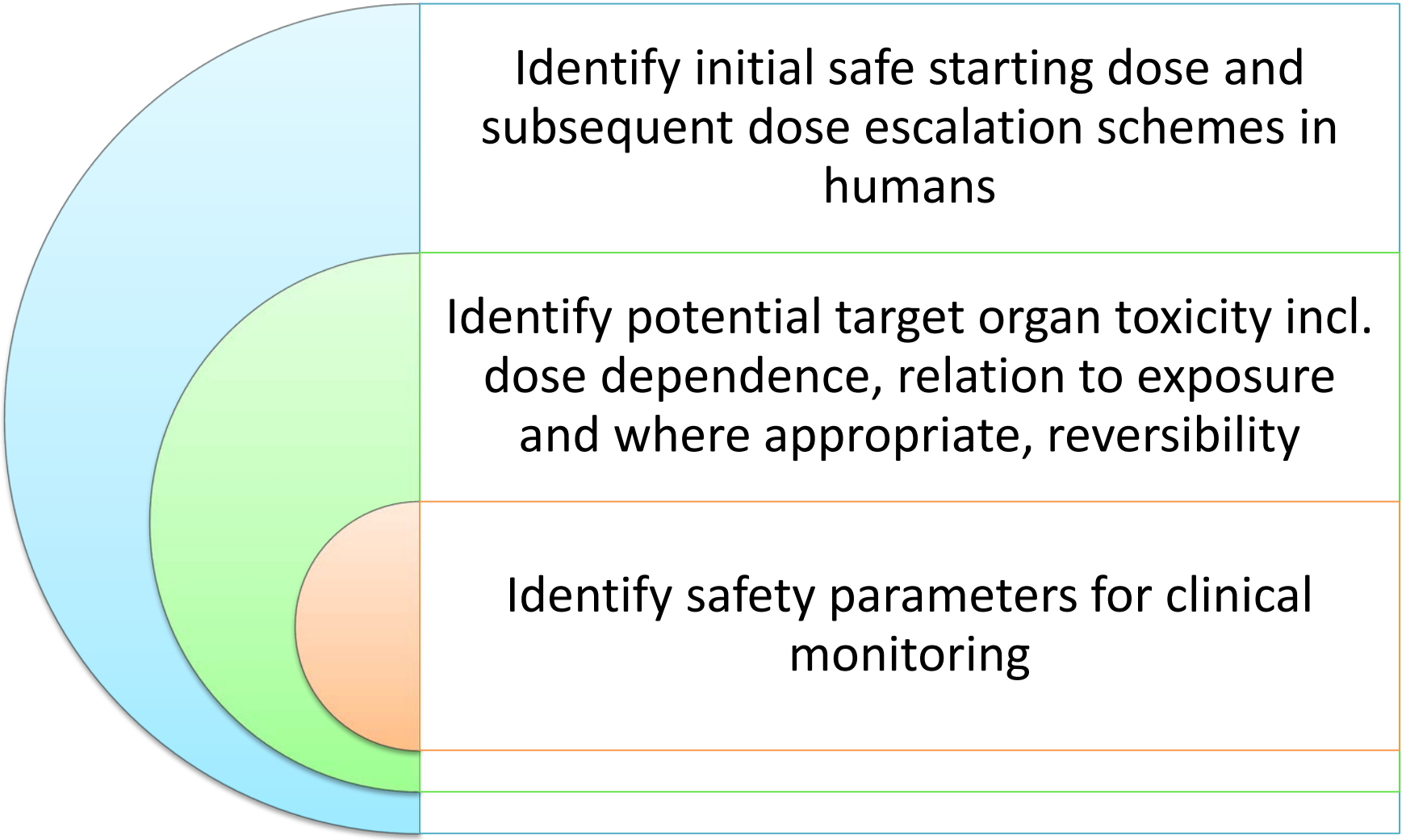
Example: Interpretation of equivocal findings

Resources and communication

Possible outcomes and success rates

Conclusions and take home messages

Key objectives



Outline

Early compound characterisation

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

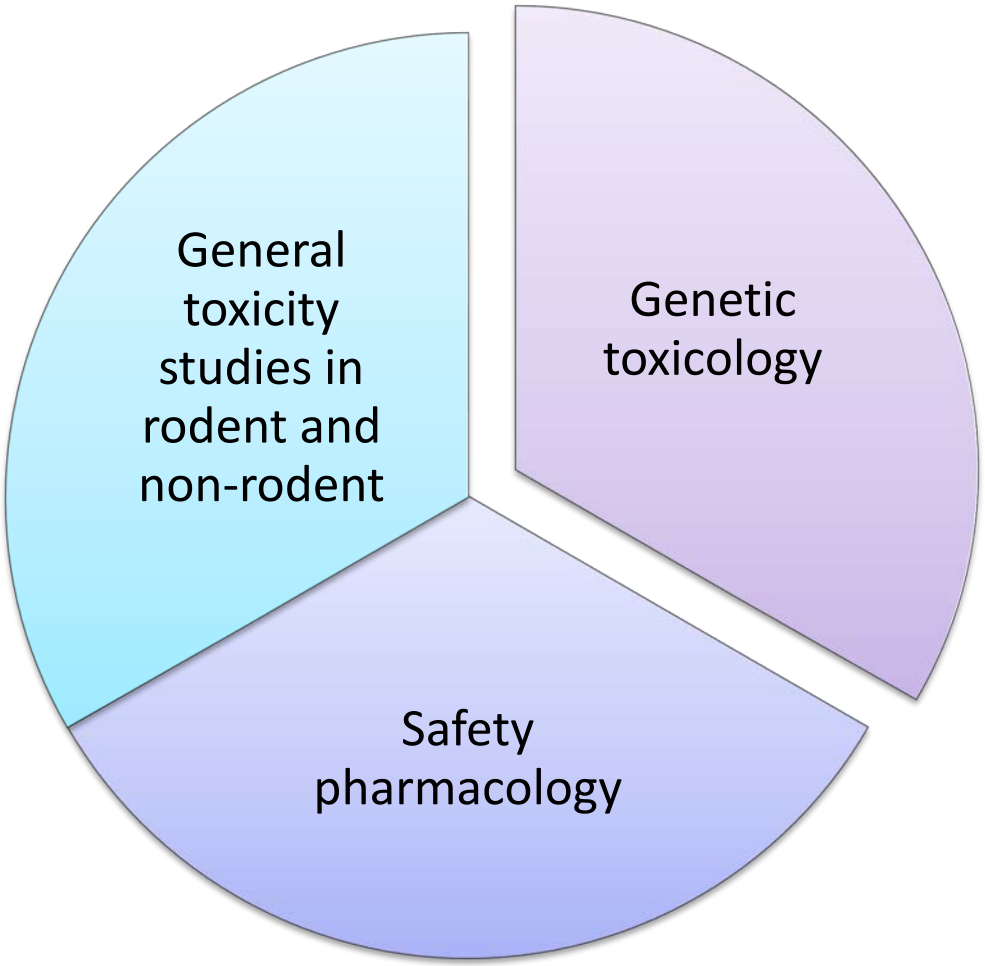
Example: Interpretation of equivocal findings

Resources and communication

Possible outcomes and success rates

Conclusions and take home messages

Minimum requirements



Key parameters in safety assessment

SR

- Safety ratio

NO(A)EL

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

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

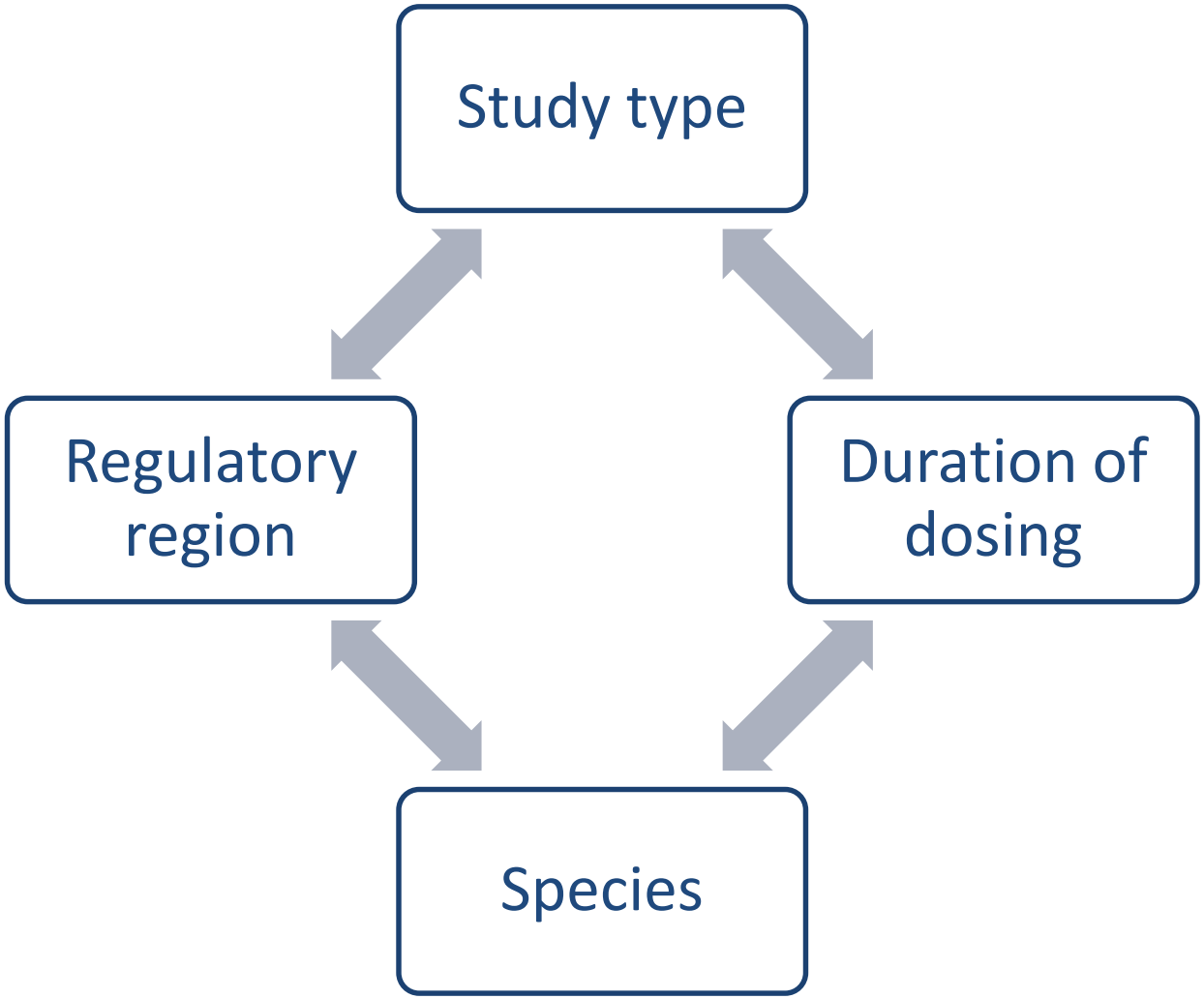
- What is considered adverse?

Altered SRs may result from

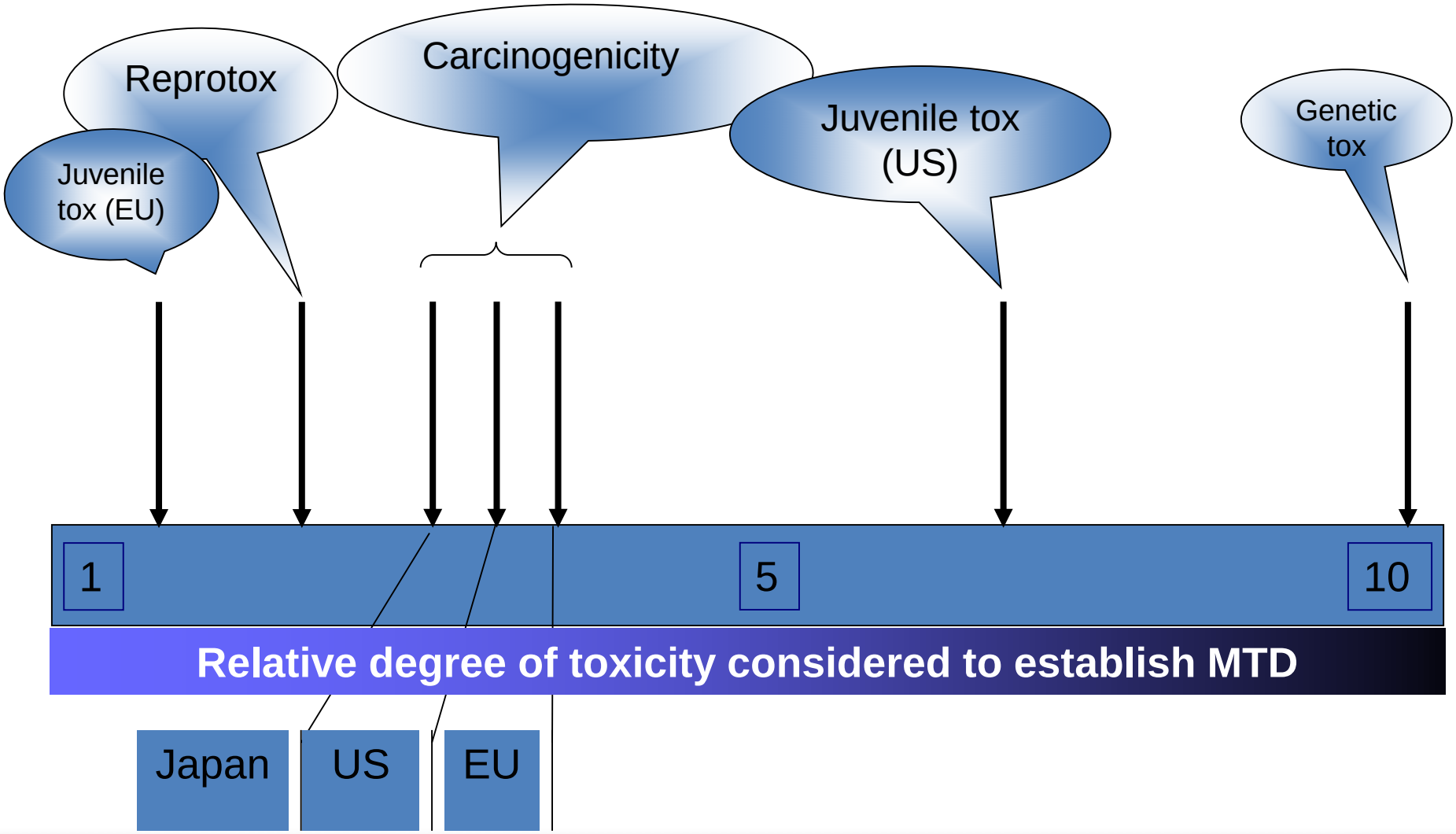
Changes in NOAEL

Changes in human exposure

MTD = maximum tolerated dose is a function of



Study type and regulatory region



Safety pharmacology

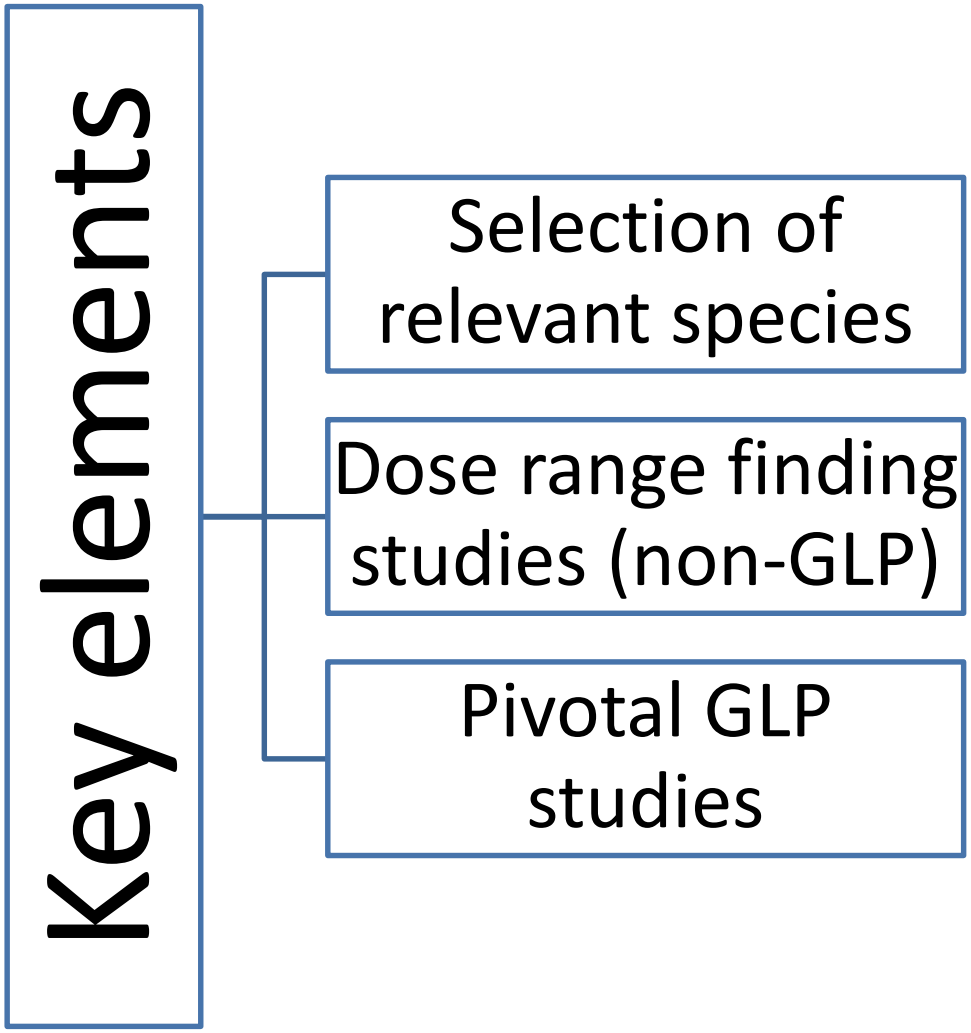
Investigate effects on vital functions

Cardiovascular	Respiratory	Central nervous systems

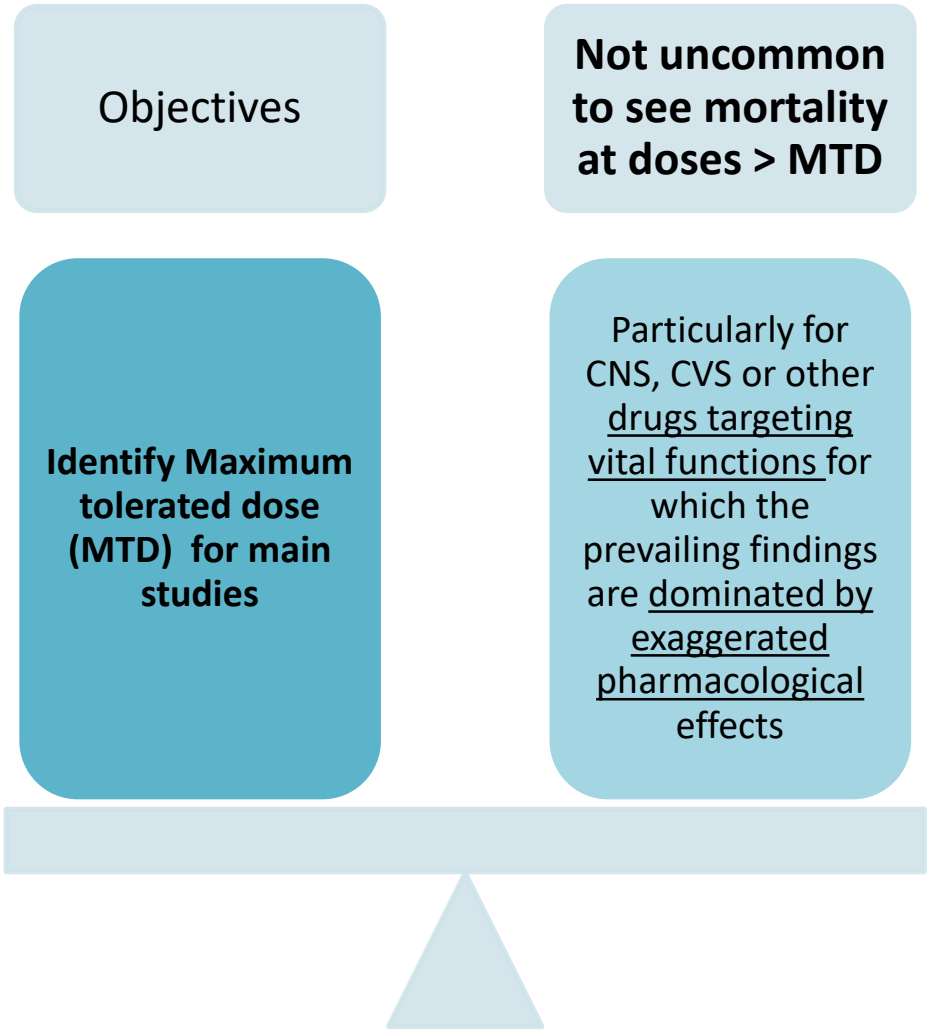
Core battery of tests

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

General toxicology



Dose range finding (DRF) studies



Outline

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- **Example: CNS Drugs**
- Example: Interpretation of equivocal findings
- Resources and communication
- Possible outcomes and success rates
- Conclusions and take home messages

Example: CNS active drugs

Patient tolerance for CNS effects may be **greater** than that of (healthy) animals and healthy volunteers

Many CNS drugs in clinical use but also other medicines have **low safety margins** (if any) based on adverse preclinical findings

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

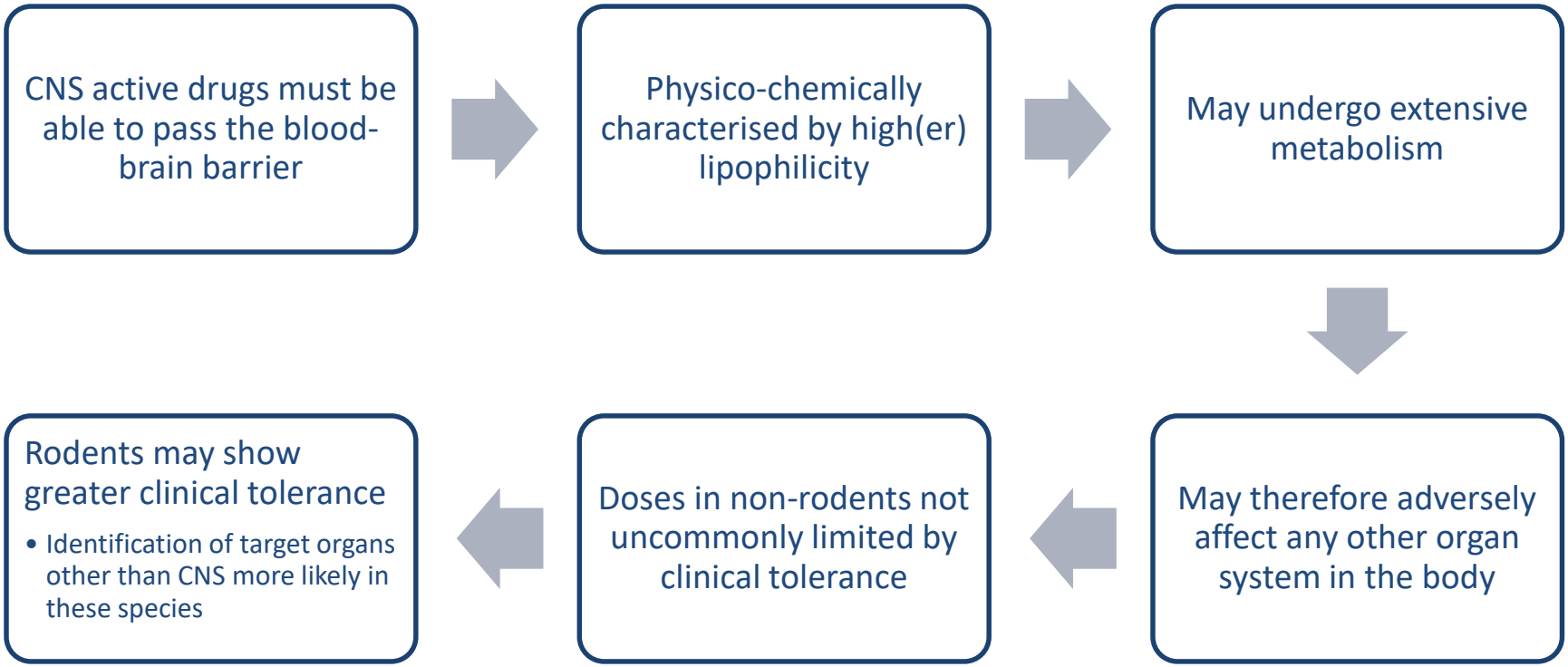
- Such as tremor, altered activity, altered posture, ataxia, recumbency etc., reduced body temperature (rodent), convulsions at high(er) doses
- Typically transient and reversible
- Often strong correlation with systemic Cmax

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

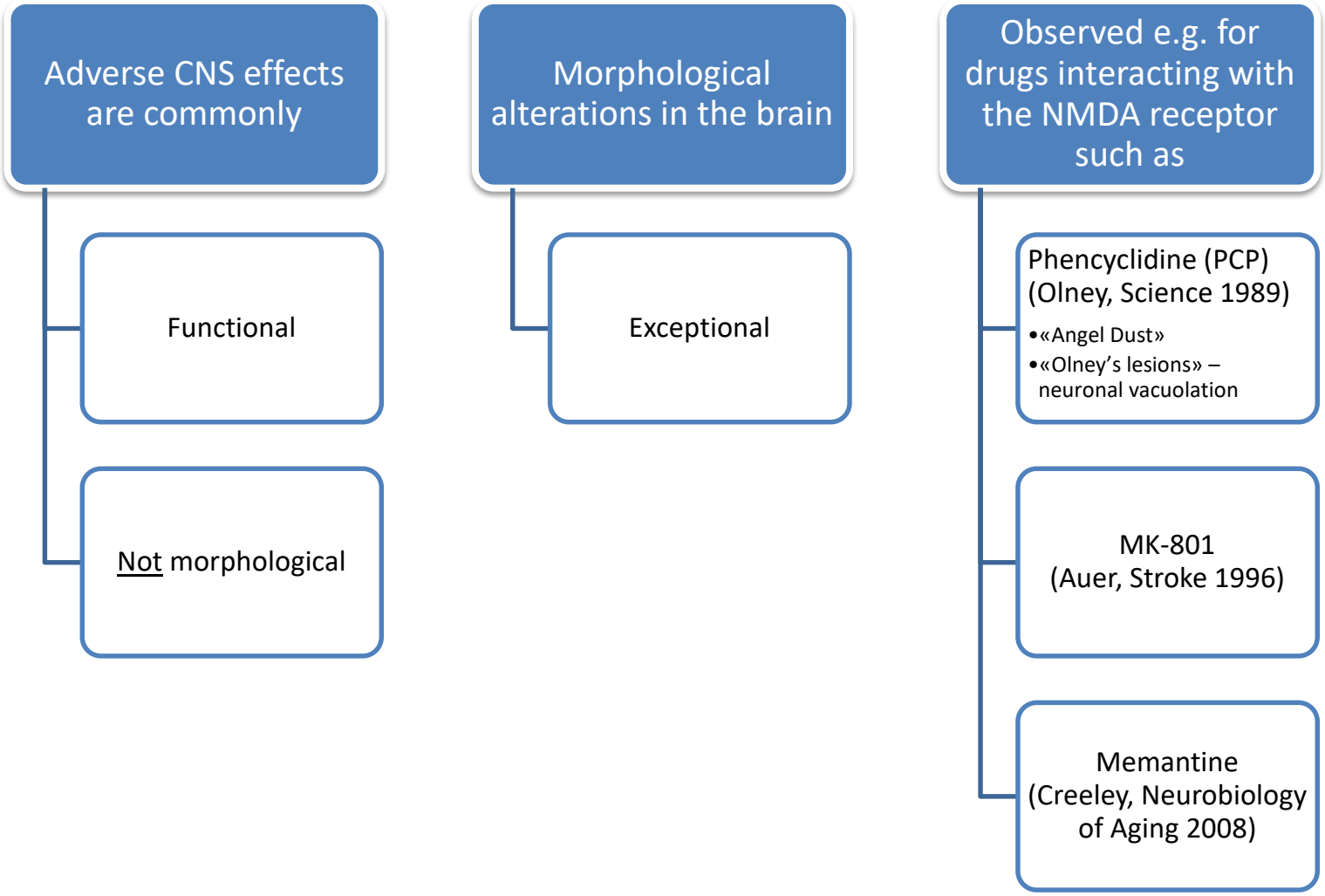
- May even occur at doses only 2-3 fold the NOAEL and/or MRHD (based on HED = human equivalent dose on mg/m^2 basis)

No histopathological findings in the brain

Typical features of target organ toxicity



Exceptional changes



Safety assessment

Mostly not marketed

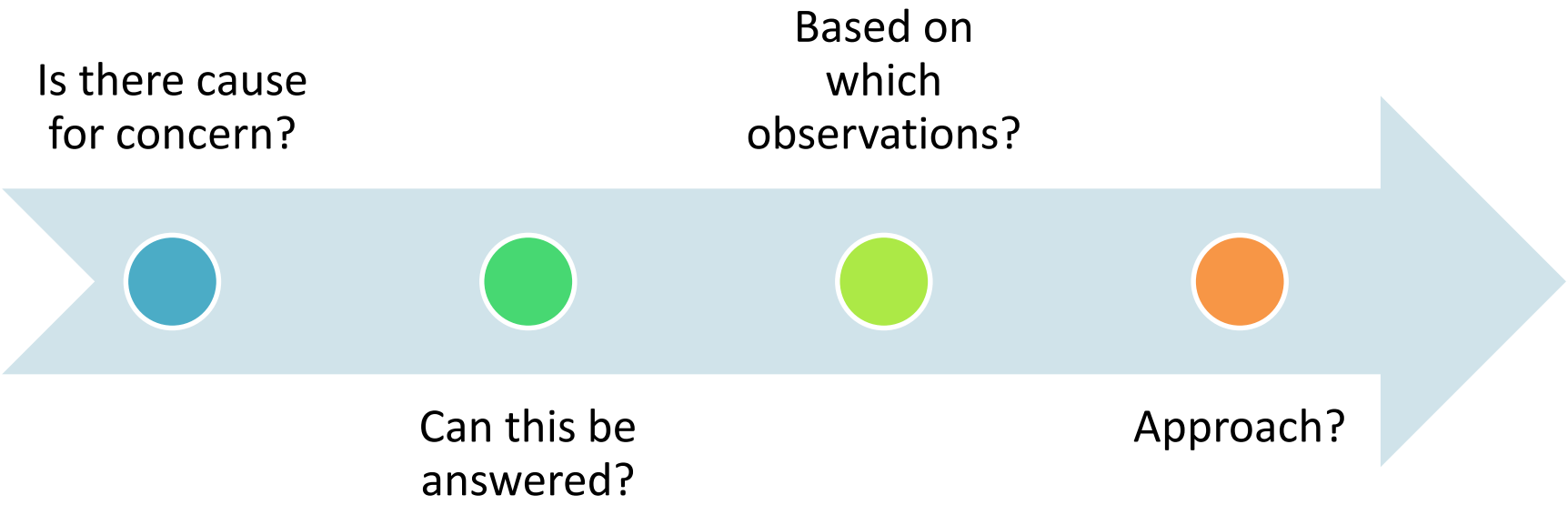
Unless perhaps if they were reliably identifiable by a biomarker indicating a fully reversible functional stage well preceding any changes at the histopathological level

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

Outline

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Example: CNS Drugs
- **Example: Interpretation of equivocal findings**
- Resources and communication
- Possible outcomes and success rates
- Conclusions and take home messages

Interpretation?



Mortality – end of story?

Not necessarily - principle of Paracelsus does apply!
Interpretation of other findings at dose levels > MTD?
Consistent with mode of action?
Consistent with kinetic profile?
Coherent between species?
Any (apparent) species differences?
Functional effects only?
Morphological changes?
Adverse?
Individuals affected or dose-related increase in incidence and severity?
If individuals only – context?

Issue identified - stop development?

Not immediately!

Address observation to establish answers to the following questions:

- Real observation or artefact?
- Nature of observation?
- Exacerbation of spontaneous finding?
- Known class finding?
- Individuals only affected?
  - Could it be a chance finding?
  - Outlier?
  - Or is it representative for the group?
  - Specifically susceptible?
  - Is more than one species affected?
  - Signal for same organ system in other studies?
  - Strength of signal?

Issue identified - stop development?(2)

What are the (predicted) safety margins?

Are the safety margins a reliable tool to estimate/mitigate and/or manage human risk or do additional factors have to be taken into account?

Could the finding be species-specific?

- Does species-specificity truly mean a difference in specificity or rather sensitivity?
- If the latter – are humans less sensitive? If so, how much?
- Can this be answered at all?

Issue identified - stop development?(3)

Is the observation reversible?

Does the finding deteriorate with ongoing treatment – perhaps to an irreversible stage?

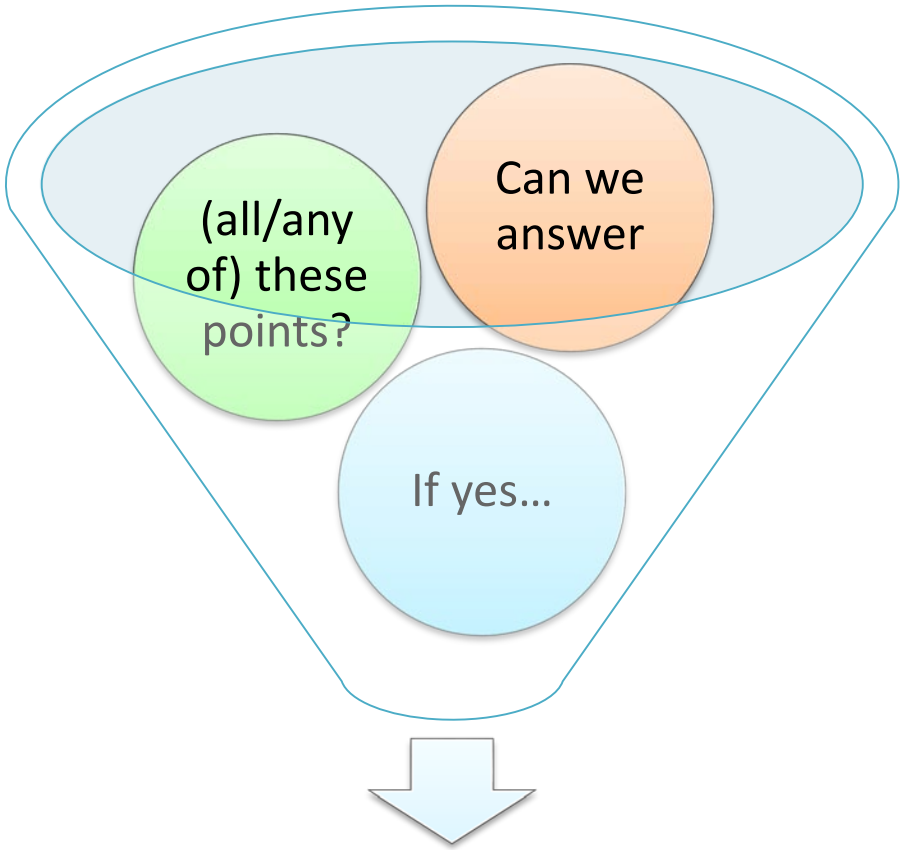
What is the degree of severity?

Finding monitorable in the clinic?

Finding considered predictive or relevant for humans?

Can this question be answered at all (at this stage)?

Question to be answered



Is there cause for concern?

Outline

Early compound characterisation

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

Example: Interpretation of equivocal findings

Resources and communication

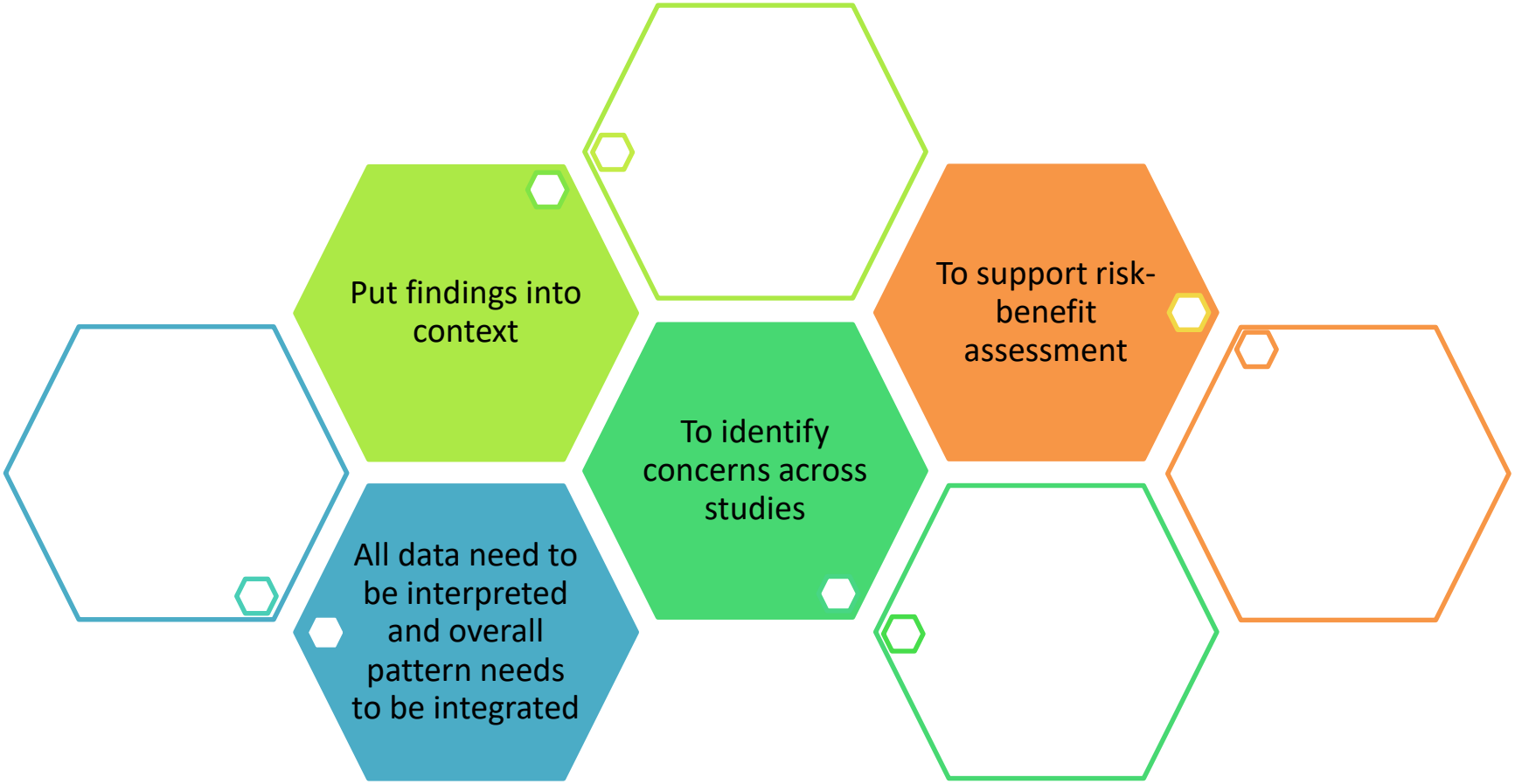
Possible outcomes and success rates

Conclusions and take home messages

Some thoughts

Sponsor taking overall responsibility of a given programme	Experts involved in a single study	Minimum package of a total of about 10 studies to be assembled
• Responsible toxicologist – study monitor • A senior supervisor • Project teams composed of experts from all disciplines involved • Management	• Study director • Technicians to support all investigations • including clinical observations, body weight, food consumption, blood samples for TK, clinical biochemistry, haematology, ECGs, ophthalmoscopy, necropsy, macroscopy • Pathologist to undertake histopathological assessment of a full list of tissues • Peer review of pathology phase	• All in one place? Several test facilities/test sites (CRO/Sponsor) involved?

Objectives of preclinical risk assessment



Which support could help achieving these?

Communication across disciplines

- Key requirement to support this process effectively

Helpful approaches may include – but not be limited to –

- Critical assessment of findings across all studies to integrate information
- Independent pathological peer review across studies

Outline

Early compound characterisation

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Example: CNS Drugs

Example: Interpretation of equivocal findings

Resources and communication

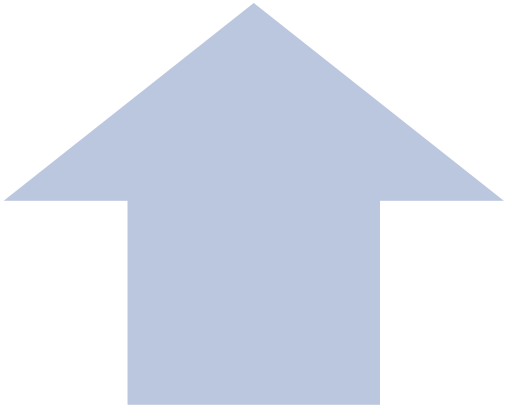
Possible outcomes and success rates

Conclusions and take home messages

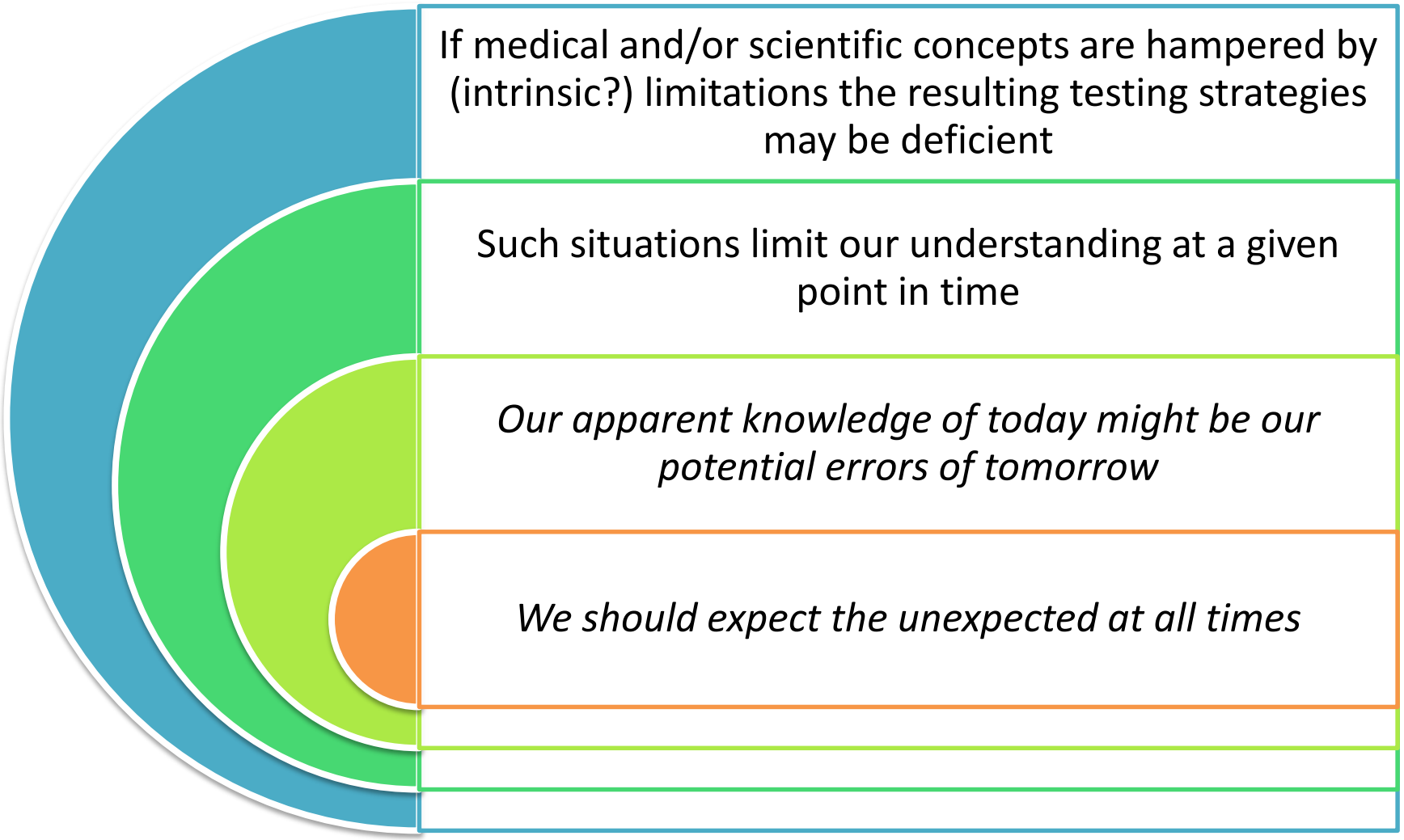
Final aim for any assessment

Transform information into knowledge

Beware: Testing concepts current at a given point in time determine resulting testing strategies!



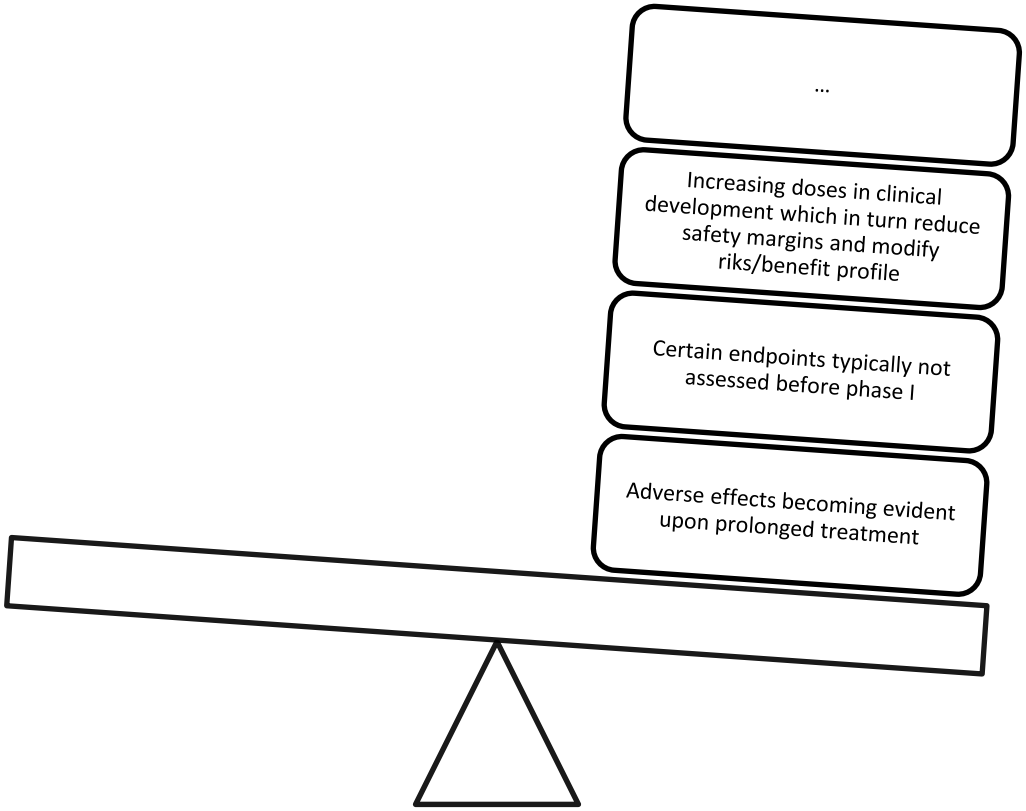
Limitations



Possible outcomes and success rates

Approximately 60% of compounds are terminated before entering phase I trials due to unfavourable risk/benefit profiles

Processes therefore work reasonably effectively with a remaining proportion being missed due to



Outline

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Example: CNS Drugs
- Example: Interpretation of equivocal findings
- Resources and communication
- Possible outcomes and success rates
- Conclusions and take home messages

Conclusions

There is a potential gap between information and knowledge

Identification of such gaps might not be straightforward

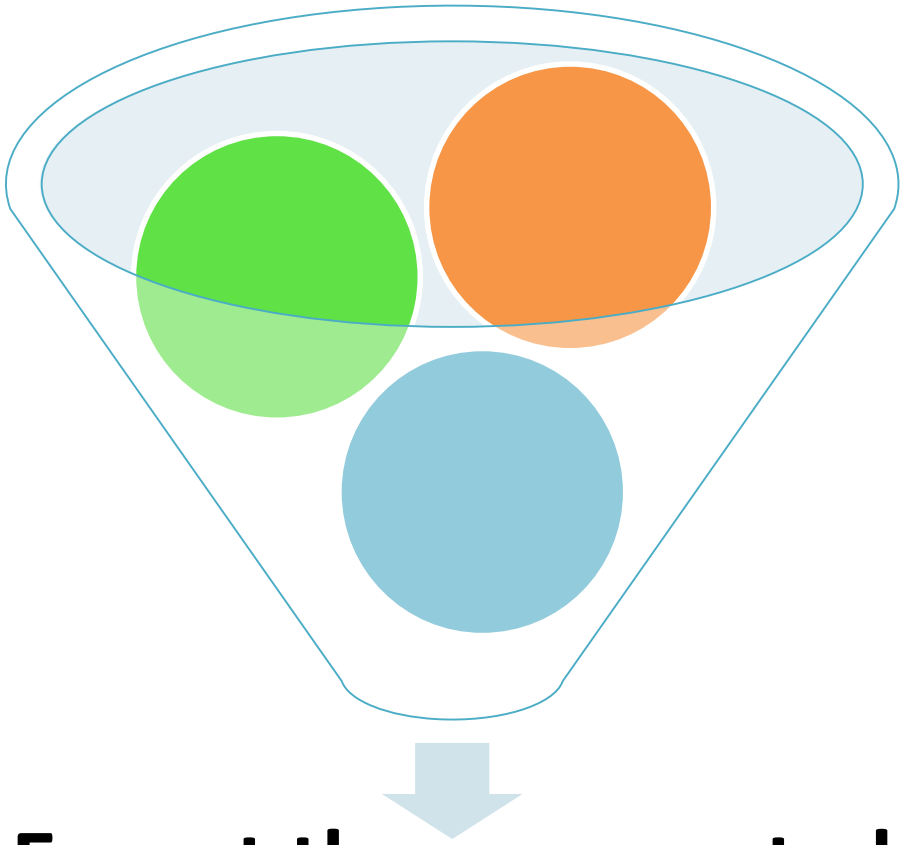
There is always a risk of failure

Timely communication between all disciplines involved is mandatory to support successful medicine development

Preclinical and clinical development remain closely intertwined from start to end

Ongoing risk assessments should be undertaken to integrate all data as they become available, including from other sources, such as from the public domain

Take home message



Expect the unexpected at all times!

Thank you very much for your attention!

PreClinical Safety (PCS) Consultants Ltd

Nauenstrasse 63A

CH-4052 Basel

Switzerland

Website: www.pcsconsultants.com

Dr. med. vet. Stephanie Plassmann

Veterinary Surgeon

Board Certified Specialist in Veterinary Pharmacology and Toxicology

Eurotox Registered Toxicologist

Senior Expert in Non-Clinical Development

Tel: +49 8133 908896

e-mail: stephanie.plassmann@pcsconsultants.com

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)