AGAH

Arbeitsgemeinschaft
für angewandte
Humanpharmakologie e.V.

Potential risks for human subjects associated with inadequate non-clinical safety assessment

AGAH Discussion Forum Bonn
11th of November 2019

Dr. Lutz Wiesner,
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn

Dr. Stephanie Plassmann
PreClincal Safety (PCS) Consultants Ltd, Basel

AGAH

There are
RISKS
associated with
INADEQUATE presentation of the
data in the IB!

What does „inadequate“ mean?

ICH E6 (R2) - Guideline for good clinical practice

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

- ✓ Species tested
- ✓ Number and sex of animals in each group
- ✓ Unit dose (e.g., milligram/kilogram (mg/kg))
- ✓ Dose interval
- ✓ Route of administration
- ✓ Duration of dosing
- ✓ Information on systemic distribution
- ✓ Duration of post-exposure follow-up

ICH E6 (R2) - Guideline for good clinical practice

- ✓ **Results, including the following aspects:**
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

ICH E6 (R2) - Guideline for good clinical practice

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

Layout recommendations

- Tabular format:

Species/ Study ID/ GLP	Duration/ Route/ Number/ Sex/Group/ Recovery	Dose	Exposure Cmax AUC	Noteforthy findings	NOAEL/ Safety margin*

* Exposure margin to planned clinical e.g.

- Starting dose
- Highest dose
- Threapeutic dose

Examples

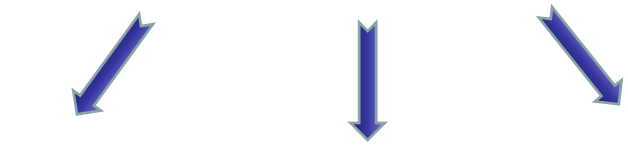
Relevance of:

- PD-models
- Species
- Off-targets
- Findings in non-clinical safety studies

→ ***Missing!***

- Condensed presentation of the IB
- Study reports submitted, but not discussed and presented in the IB and protocol
- …no signs of toxicity in mice, rats, dogs and monkeys up to the NOAEL…
- …one dose was fatal otherwise no other findings…
- … we have defined a safety margin…

Discussion on non-clinical data e.g. reference to literature, other compounds …



Risk/benefit **Protocol**

Guidance for Investigator

Question which should be answered before…
What are the certainties und the uncertainties?

Outline

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Key parameters to support (any) clinical study

Interpretation of critical findings

Resources and communication

Adequate IBs to support human risk assessment

Conclusions and take home messages

Outline

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Key parameters to support (any) clinical study

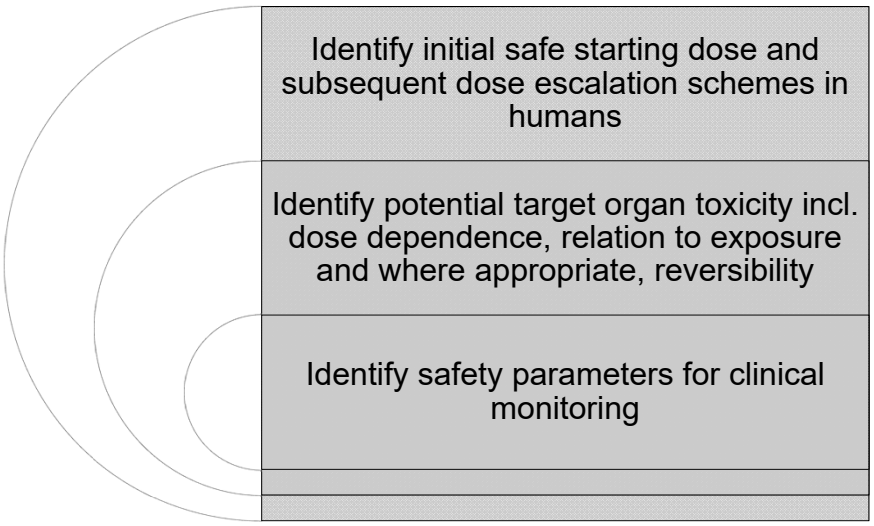
Interpretation of critical findings

Resources and communication

Adequate IBs to support human risk assessment

Conclusions and take home messages

Key objectives



All these points need to be covered in the IB

How can we achieve this?

Outline

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

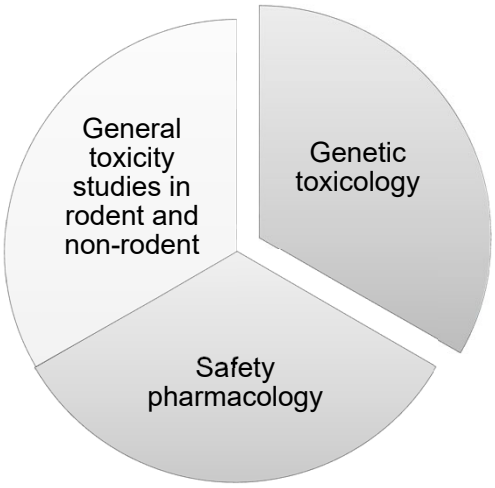
Interpretation of critical findings

Resources and communication

Adequate IBs to support human risk assessment

Conclusions and take home messages

Minimum requirements



Safety pharmacology

AGAH

Investigate effects on vital functions

Cardiovascular	Respiratory	Central nervous systems

Core battery of tests

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

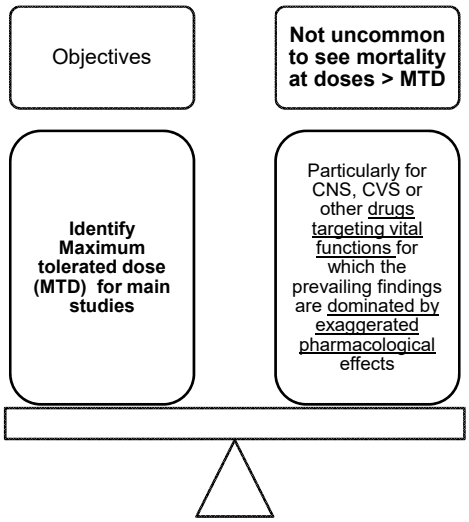
General toxicology

AGAH

Key elements

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

Dose range finding (DRF) studies



Outline

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Key parameters to support (any) clinical study

Interpretation of critical findings

Resources and communication

Adequate IBs to support human risk assessment

Conclusions and take home messages

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

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) ideally at least 10-fold
- but SRs may even be less than 1

NOAEL = No Observed Adverse Effect Level

NOAEL

= dose level at which no adverse effects were observed

Room for interpretation

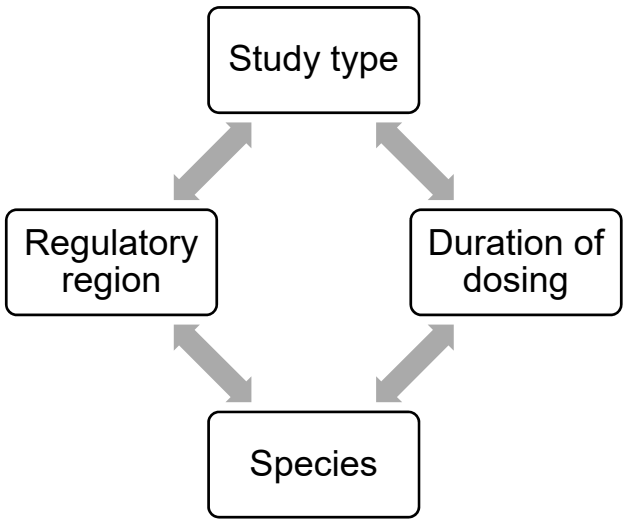
- What is considered adverse?

Altered SRs over time may result from

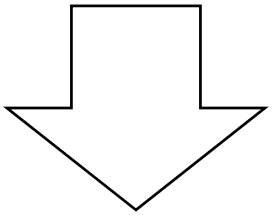
Changes in NOAEL

Changes in human exposure

MTD is a function of



Dose response curve

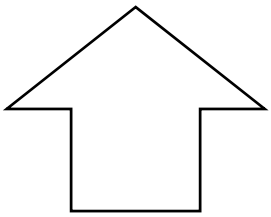


May be flat

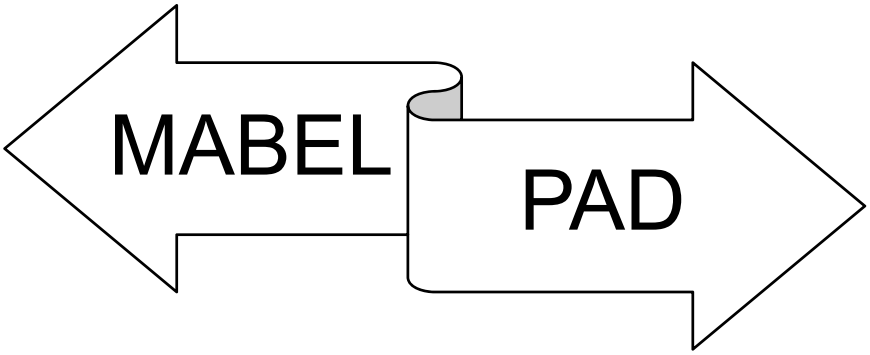
- MTD may never be reached

Or may be very steep

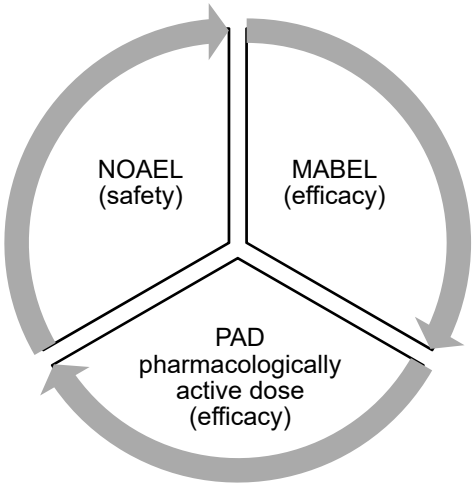
- With a factor as low as 2 fold between NOAEL and MTD



New concept of "Anticipated therapeutic dose range" – ATD



Parameters to set starting dose



Outline

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Key parameters to support (any) clinical study

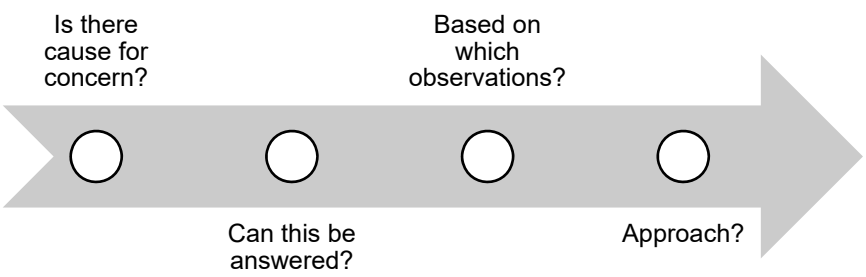
Interpretation of critical findings

Resources and communication

Adequate IBs to support human risk assessment

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!	Review finding in detail to answer 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 have additional factors 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?

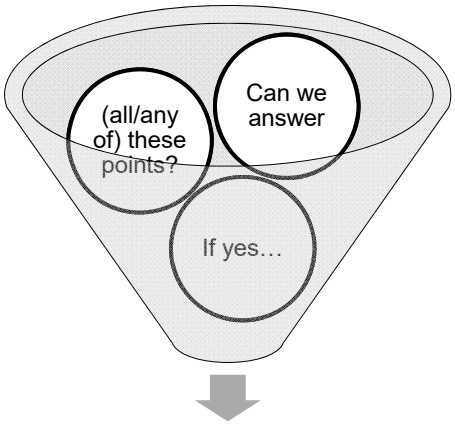
What is the degree of severity?

Finding monitorable in the clinic?

Finding considered predictive or relevant for humans?

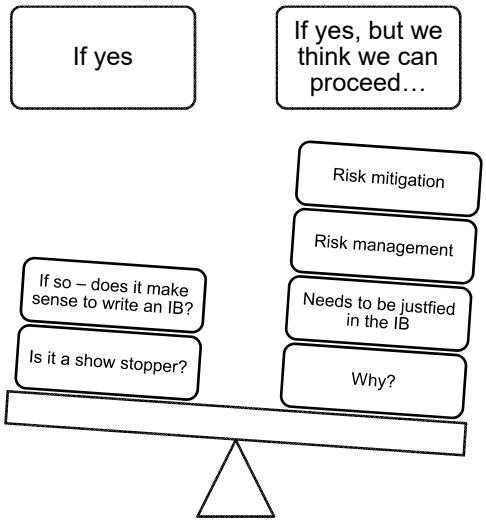
Can this question be answered at all (at this stage)?

Key questions to be answered in an IB



Is there cause for concern?

Cause for concern?



IB needs to clearly assess any findings and put them into context to guide all parties involved in decision making

Outline

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Key parameters to support (any) clinical study

Interpretation of critical findings

Resources and communication

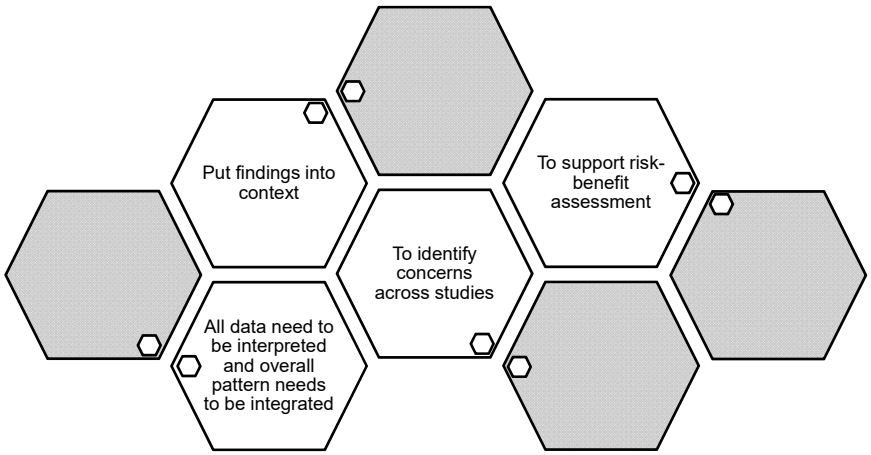
Adequate IBs to support human risk assessment

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



Outline

- Early compound characterisation
- Key objectives of preclinical safety programme
- Minimum (typical) preclinical package to enable FIH studies
- Examples
- Interpretation of critical findings
- Resources and communication
- Adequate IBs to support human risk assessment
- Conclusions and take home messages

What we should achieve

AGAH

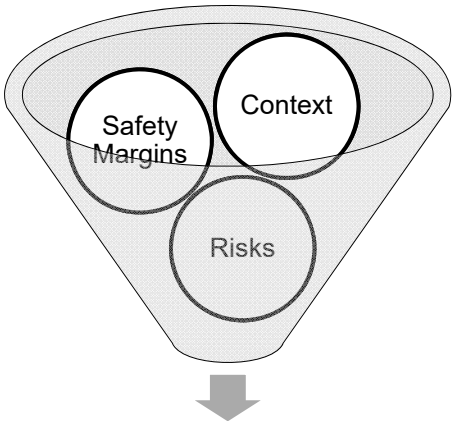
Transform information into KNOWLEDGE

Communicate knowledge to everybody who needs to UNDERSTAND potential risks for humans

Principal Investigators, Ethical Review Committees, Regulators…

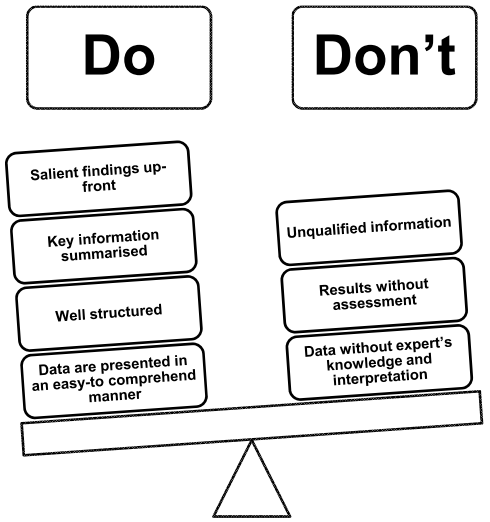
How do we best communicate?

AGAH



One of the most important tools is an adequate IB!

Dos and Don'ts for adequate IBs



Criteria for adequate IBs

Make patterns visible – tell the story of your compound!

Present all information for human risk assessment such that it stands out

Safety margins	Target organ systems?	Risks? If so – which?	Monitoring parameters?

Don't let the reader search for information in a maze where the exit is hidden!

Comprehensive risk/benefit assessment

Will be based on

- Good data
- Thorough evaluation with expert‘s knowledge
- Clear presentation of the information
- Meaningful interpretation
- Translation to humans
- Clear guidance for the Investigator

Outline

Early compound characterisation

Key objectives of preclinical safety programme

Minimum (typical) preclinical package to enable FIH studies

Examples

Interpretation of critical findings

Resources and communication

Adequate IBs to support human risk assessment

Conclusions and take home messages

Conclusions

If we don‘t clearly convey the key messages for human risk assessment they will not be understood

There is always a risk for failure but it shouldn‘t result from insufficient IBs

The IB is an expert document which requires a lot of time and resources to be well-written

It will accompany a drug‘s development for its life-time

Sufficient time and resources need to be allocated to write and update IBs with emerging information from all disciplines involved to keep it up to date

Conclusions (2)

The Sponsor‘s job is to digest all the data, describe and assess them in the IB so that it can serve its primary purpose

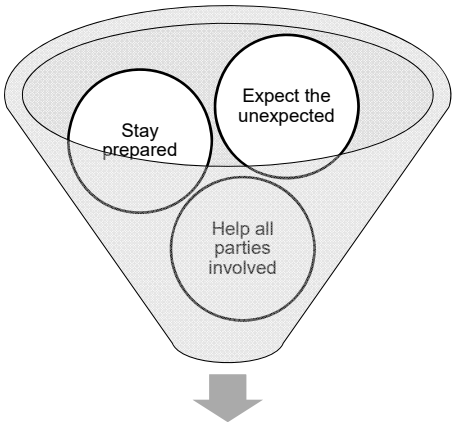
Use of the IB should be made to bridge potential gaps between information and knowledge!

Identification of such gaps might not be straightforward – provide context!

Preclinical and clinical development remain closely intertwined from start to end which is reflected in the IB

Ongoing risk assessments involving all disciplines should be undertaken to integrate all data as they become available, including from other sources such as from literature, into the IB

Take home message



Write smart IBs which easily guide the way through the maze!

Thank you very much for your attention!

Bundesinstitut für Arzneimittel und Medizinprodukte
Kurt-Georg-Kiesinger Allee 3
53175 Bonn

Dr. Lutz Wiesner
Lutz.wiesner@bfarm.de

PreClinical Safety (PCS) Consultants Ltd
Nauenstrasse 49
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 preclinical Development
Tel: +49 8106 9976670
e-mail: stephanie.plassmann@pcsconsultants.com

Further reading (selection)

1. E.Koch and S. Plassmann. Critical Aspects of Integrated preclinical 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)