PreClinical Safety (PCS) Consultants Ltd

Mastering the New Time Pressure on Human Pharmacology
4th Eufemed Conference
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Session 1
How to Assess Risk from Pre-clinical to Clinical Research More Efficiently – Experiences and Suggestions
The Pre-Clinical Perspective

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PCS – The Integrated Drug Development Company

Outline

- Principal aspects of risk assessment
- Key objectives of non-clinical safety assessment
- What do we need to be efficient?
- How can things go wrong? Where do we lose the time?
- Low solubility
- High dosage selection
- Resources
- Disease models

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How to assess risk more efficiently?

- What does it mean to be **efficient**?
- What is risk in this context?
- The theme of this annual conference refers to the time pressure we are all under
- So more efficient risk assessment implies to be faster
- When we say **faster** – we refer to an aim we want to achieve in a certain period of time
- What is our aim?
- To support a **robust risk assessment**
- That can only be done when **taking the benefits into account**
- **Entirely driven by the clinical indication**

Support a sound risk/benefit assessment

Key objective of non-clinical development

- To support human studies
- Initially, human pharmacology studies / first in human studies
- Any subsequent clinical studies

These processes remain closely intertwined

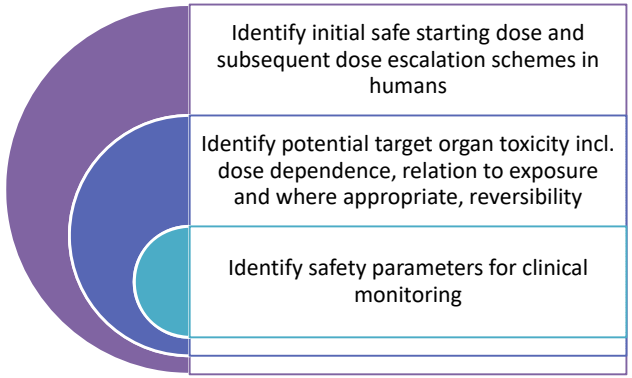
- There is no "pre"-clinical development – it is "non"-clinical and only undertaken to support clinical studies
- There is no other purpose for these studies
- **Bridging from bench to bedside**
- Non-clinical development is one of the cornerstones of drug development
- Summarised in the IB
- The IB is of utmost importance to effectively communicate risk and benefits

Efficient risk/benefit assessment

Any clinical study with a new medicine in development can only start when adequately supported by non-clinical data

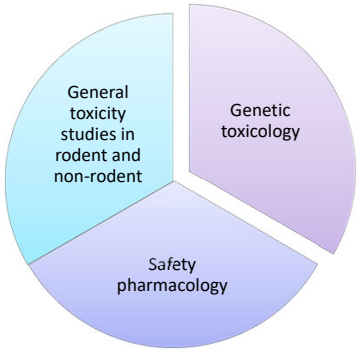
Outline

ICH M3(R2): Key objectives



Minimum requirements to support FIH studies

In a standard setting



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

Identify Maximum tolerated dose (MTD) for main studies

Not uncommon to see mortality at doses > MTD

Particularly for CNS, CVS or other drugs targeting vital functions for which the prevailing findings are dominated by exaggerated pharmacological effects

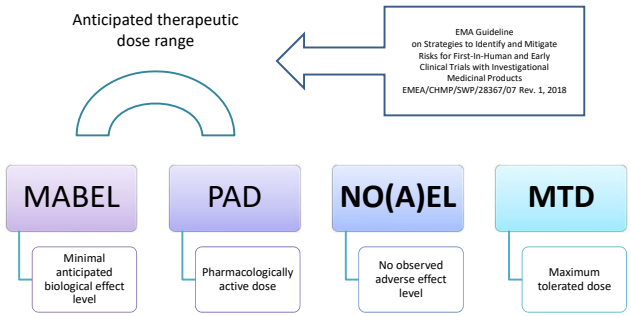
Principal aims general toxicology (1)

- 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 general toxicology (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



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What do we really need to be efficient?

Bringing drugs on the market in the shortest possible time while maintaining the highest quality standards

- Sound science is key
- Robust processes
- Expertise
- Experience
- Wise planning

Proactive process management on all ends

- Set a clear goal at the beginning
- Target drug profile must lead the way
- What do we need to achieve this?
- Consider key aspects at the start such as
  - Route of exposure?
  - Solubility?
  - Systemic bioavailability?
  - What are acceptable risks in a given indication?
  - Competitor profiles?

Operational implementation

- Physicochemical properties
- Upscaling/CMC
- Non-clinical testing of early drug candidates
- Screening – liabilities
- Make the right choices early on
- Define your objectives
- Develop adequate testing strategy
- Implement operationally
- Do it right first time
- Do it fast – plan your programme well in advance

Outline

How can things go wrong? Where do we lose time?

Compound supply

- Often insufficient amounts available to initiate non-clinical studies
- Dosage levels too low due to restricted amounts of test item
- Toxicology studies typically require large g or kg amounts
- Often the quality is insufficient for pivotal toxicology studies
- Must be GLP or GMP (OECD 19) or another defined standard

Formulation for non-clinical studies

- Not done by CMC experts
- Will be covered by CROs or experimentally by sponsor
- Can be a major hold-up because
  - Solubility – is a major issue for most compounds
  - Dosage levels in toxicology studies exceed those in human by far
  - As soon as it is a parenteral route can become a severe limitation

Outline

Example solubility

Solubility may be 0.5 mg/mL

Oral dosing in rats = maximal 10 mL/kg

Maximal dosage = 5 mg/kg

However, we need to treat up to the **maximum tolerated dose (MTD)**

Unknown at this stage

Oral suspension is possible as long as it can be formulated homogenously

- CMC
- Rape seed oil
- Some other vehicles

Dosages
- in the event of no MTD as high as 2000 mg/kg (limit dose)

What if it is a parenteral route?

IV bolus dosing in rats maximal 5 ml/kg

Must be solution – so limited to 2.5 mg/kg

Alternative might be continuous infusion but changes the PK completely

Maximal volume in non-rodents lower

E.g. 2 ml/kg in dog – maximum dose 1 mg/kg

If it is not toxic – how do you achieve relevant overdosage to establish a safety margin?

Potential consequences of low solubility

Low solubility may make it impossible to achieve the objectives of ICH M3(R2)

A new medicine may not be adequately characterised

Maximum feasible dosage?

Limit dose?

Multiples of human exposure?

All of those concept require significant overdosage compared to humans

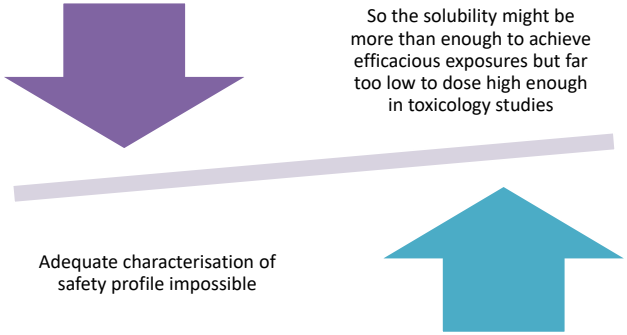
Very difficult to defend

Impossible (up to 2000 mg/kg/day or in most cases 1000 mg/kg/day)

At least 50-fold (ICH M3(R2) – for the US less acceptable)

Unlikely achievable with low solubility

Potential consequences of low solubility (2)



So the solubility might be more than enough to achieve efficacious exposures but far too low to dose high enough in toxicology studies

Adequate characterisation of safety profile impossible

Physico-chemical properties

- Can be the reason for a major delay to initiate any safety studies or worse (show-stopper)
- The target determines the principal structure of the molecule
- The chemical space is limited by the target and other chemical properties
- Targets may be “undruggable”
- Targets may be “promiscuous” – bind to different molecules
- Drugs may be “promiscuous” – bind to different targets
- Off-target effects may cause “dirty” drug profiles with increased liability for unwanted side effects

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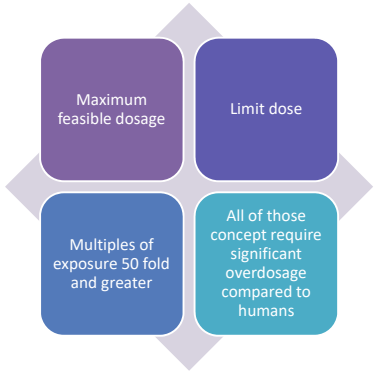
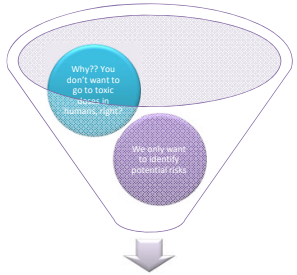
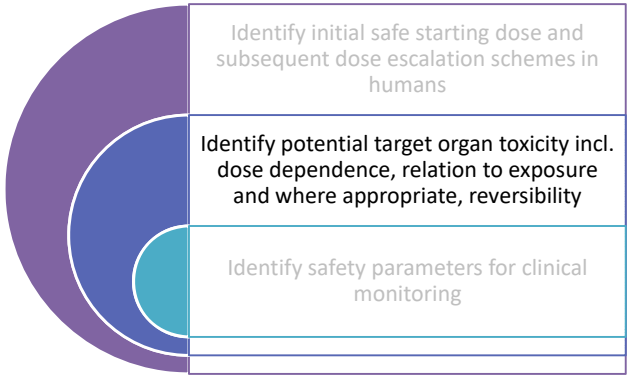
Concepts other than MTD





But…

ICH M3(R2): Key objectives



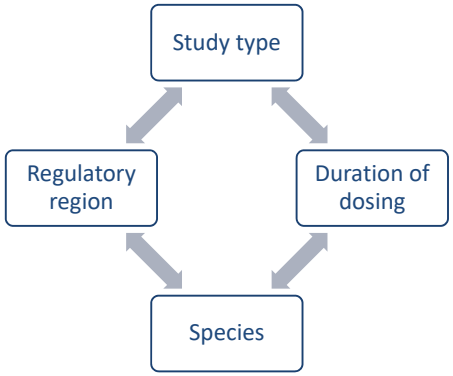
How do we know have identified them all?

- We don't know before we know (in humans)
- However - we aim to do the best possible to identify them all by
  - Assessing two species, where possible and meaningful
  - Testing up to the highest possible dose – preferably the MTD (small molecules)
- All other dosage concepts have limitations
  - Not the least of which is that important toxicities might not be identified in the animal species
- Possible failure to identify potential risks in humans
- Humans may show specific toxicities
  - TGN-1412
- Humans may be more sensitive than animals
  - Thalidomide
  - BIA-2474
- The MTD concept offers the most robust approach for human risk assessment

MTD concept

- What constitutes an MTD?
  - How to establish the MTD, if solubility does not prevent us from escalating high enough?
  - This is not trivial
  - Senior expertise required
- We are regularly involved in projects where the MTD was not robustly identified
- Studies may not be accepted by national competent authorities (NCA)
  - Full or partial clinical hold
  - Repeat of studies
- Prior to FIH means a delay of at least 9 months (if timing is ideal)
- Initiate study again
  - Book a slot – first! You might have to wait months at present
  - Do you have enough compound to repeat it? At higher dosages?
- Study will take a minimum of 6-8 months if everything goes according to plan
- Update all documentation
- Submit and wait for approval of the trial

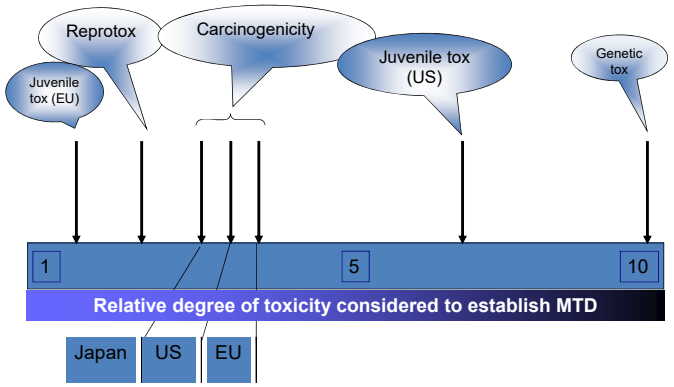
MTD = maximum tolerated dose is a function of



What is an MTD?

- Senior expertise and experience required to correctly determine
  - Less and less available in CROs
- Drain of resources
- Important to design the MTD/DRF and subsequent GLP studies robustly to generate relevant information
- If not characterized correctly will inevitably limit the interpretation of your non-clinical toxicology studies
  - That is the issue that we see most frequently
- May require a repeat of the studies
- Or if not repeated may increase the risk for humans

Study type and regulatory region



"We have a non-toxic compound"

You should be seriously concerned!

The likeliest explanation is that the dosage levels selected were too low for various possible reasons

- Not enough compound available
- Solubility too low to dose high enough
- Lack of systemic absorption
- Lack of experience to design the study???

This is one of the main reasons for possible delays

May mean you have to repeat the study or several studies

In very rare cases are compounds non-toxic when tested up to the highest possible dosage (limit dose) in the absence of an MTD

Outline

Availability of resources

- CROs are overcommitted
  - Long lead-in times
- Limitation of animals – currently monkeys in particular
  - Price of a single monkey currently in the range of nearly 40’000 USD
- Often monkeys the only option for testing of biopharmaceuticals
  - Selection of species must be based on pharmacological relevance
  - Use of monkeys is high – vaccine development (pandemic), biopharmaceuticals
- Small molecules
  - Selection of species based on DMPK comparable to humans
  - Pharmacological relevance is easier to achieve and not a must in each species
- Use of alternative non-rodent species highly encouraged
  - E.g. the minipig
  - Issue: compound supply – much heavier than dogs or monkeys
- Compound supply can be limiting to initiate human trials

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Principal aspects of risk assessment

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High dosage selection

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Disease models

Proof of principle

Disease models

Specific for each clinical condition

Attrition rates are high

Might help to identify suitable biomarkers

However, often of limited value

Or impossible – endpoints may be post-mortem such as histopathology

PK/PD modelling…? Ideal for antibiotics

Studies may demonstrate target engagement

Studies may show proof of principle

However, animal disease models have principal limitations

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