“EXPLORATORY MEDICINES DEVELOPMENT: INNOVATION AND RISK MANAGEMENT”

The updated EMA guideline on strategies to identify and mitigate risks in First-in-Human clinical trials with investigational medicinal products
Overview

Guideline: Timelines for implementation and Scope
Guideline: Objectives and Legal Context
Risks versus Uncertainties

Rules for dose selection, escalation and maximal dose
Clinical aspects and monitoring: Toxicity and Stopping Rules
Managing Risk: Checklists and Treatment Algorithms

Conclusions
Guideline: Timelines and Scope

**Timelines:**
- **End of consultation**: 28 February 2017 (600 pages of comments)
- **Implementation expected in 2017**

**EMA Workshop 28 March, London:**

- **Introduction** (Harald Enzman)
- **Non-clinical aspects** (Jan Willem van der Laan)
- **Dose selection, escalation and maximal dose** (Ulla Wändel Liminga, David Jones)
- **Clinical aspects and monitoring** (Kirsty Wydenbach, Elke Stahl)

**Scope**

Small molecules & Biological Medicines

[Advanced therapy medicines are not included]

First single or ascending dose trials

Early trials with very limited knowledge on the substance, with very limited experience in humans, i.e. uncertainties

Integrated protocols combining a number of different studies in one trial
**Guideline: Objectives**

**Objective**

The **safety** of study participants
[not **scientific value** of trial, **speed** of drug development or marketing authorisation]

**Draft guideline text:**

“The **exact** nature of the proposed assessments **and their timing** should be provided.”

“The **time intervals** [between cohorts] should be stated in the protocol.”

“**Evaluable subjects** should be defined and it is expected that these are subjects who have completed **all** planned study visits”

“For studies with multiple parts, consideration may be given to submitting an **interim report** to the CAs for review as **substantial amendment prior to the start of further dosing phases”**

“The members of the group should also be sufficiently **independent from IMP administration** and monitoring”

**Scientific value and/or speed** of integrated adaptive protocols **should not be hindered**, unless there are compelling reasons

**Respondents said:**

The protocol should specify minimum requirements **and maximum adaptability**

The interval between cohorts is determined by data requirements from previous cohort(s) rather than time.

Minimum data requirements in terms of “**evaluable subjects**” should specify the number of subjects from a cohort and the minimum data post-dose required for decision making

Unnecessary, if trial runs within the boundaries set by an adaptive protocol and if there is no increase in risk and no approved toxicity/stoping rules have been met; would cause significant delays.

Principal Investigator should be involved in decision making (data usually reviewed blinded)
Guideline: Legal Context

Applicants are expected to choose wisely from the guideline, and to justify their choices where applicable

Legal Status
EMA’s FIH Guideline is a recommendation
[Not legally enforceable
Not binding for national clinical trial authorisation decisions
Not crucial for benefit risk assessment by CHMP
Not always feasible]

Respondents raised concerns about varying levels of expertise amongst investigators and sponsors, competent authorities and ethics committees

Inadequate and/or disproportionate application of the guideline

Training of all parties

Scientific Advice pre-CTA submission
There are known knowns; there are things we know that we know.

and...unknown knowns; the things that we know, but are unaware of, untapped knowledge, knowledge that is not shared.

There are known unknowns; that is to say, there are things that we now know we don't know.

But there are also unknown unknowns – there are things we do not know we don't know.”

(Donald Rumsfeld, 2002)
Unknown unknown:
We have two roads, we don’t know where either of them leads; both roads may be good or bad.

Known unknown:
We have two roads, one is good, one bad; we don’t know which is which.

The risk is to make the wrong choice
Dealing with uncertainties

paralysis

over-elaboration

addressing uncertainties

ignorance

You can not be certain about uncertainty

( Frank Knight)
Rules: Dose selection, escalation and maximal dose/exposure

We constantly review emerging data and collect evidence
UNCERTAINTY decreases

**Unknown unknowns:**
*Uncertain*
Very potent, off target, and damaging to vital organs

**Known Unknowns:** Some degree of uncertainty
Predictable/anticipated PK/PD profiles through
- mode of action
- non-clinical data
- modelling
- emerging human data

**Known Knowns:**
Limited uncertainty
Emerging human data confirms and/or adjusts PK/PD modelling

**Starting dose**

**Dose/exposure range**

**Maximum dose/exposure**
Rules: Dose selection, escalation and maximal dose/exposure

We constantly review emerging data and collect evidence

UNCERTAINTY decreases

Unknown unknowns:

*Uncertain*

Very potent, off target, and damaging to vital organs

Starting dose

Risk mitigation

Safety Factor

Good non-clinical package identifying all potential targets; NOAEL, MABEL

Some points for discussion

Use of NOAEL *and* MABEL always required?
Are PD effects at starting dose permitted?
Most sensitive vs most relevant species
Patient vs healthy volunteers
Rules: Dose selection, escalation and maximal dose/exposure

We constantly review emerging data and collect evidence
UNCERTAINTY decreases

Known Unknowns: Some degree of uncertainty
Predictable/anticipated PK/PD profiles through
- mode of action
- non-clinical data
- modelling
- Emerging human data

Dose/exposure range

Risk mitigation
- Dose range guided by anticipated therapeutic range
- Maximum dose increments
- Sentinel dosing
- Adjustment of anticipated doses in line with emerging PK, PD, safety & tolerability data

Some points for discussion
Can anticipated therapeutic dose range be exceeded?
- to account for uncertainty what the actual range is
- to cover exposures for TQT, DDI and impairment studies and vulnerable populations
- to cover potential clinical use, variability in patients in less standardised conditions and overdose
Rules: Dose selection, escalation and maximal dose/exposure

We constantly review emerging data and collect evidence

UNCERTAINTY decreases

Known Knowns:
Limited uncertainty
Emerging human data confirms and/or adjusts PK/PD modelling

Risk mitigation

Set individual and mean exposure limits

Review limits in line with emerging data

Some points for discussion

Is PK data always required for decision making?
Are individual exposure limits always required?
Can PK exposure limits exceed NOAEL based on
  • Monitorability,
  • Reversibility,
  • Seriousness & severity of potential toxicities &
  • Margin of NOAEL to AEL
Known Knowns:
"Expected" ADR
Solid Reference Safety Information (RSI) available
Potential risks’ nature, occurrence and impact are known
Limited uncertainty

Unknown unknowns:
Potential risks are unpredictable and uncertain

Known Unknowns: “Predictable/anticipated” ADR
Little or no RSI available
Potential risks’ nature, occurrence and impact are predictable *with some degree of uncertainty* through
- mode of action
- non-clinical data
- anticipated pharmacokinetics and –dynamics
- class effects

Known Knowns: “Expected” ADR
Solid Reference Safety Information (RSI) available
Potential risks’ nature, occurrence and impact are known
Limited uncertainty

Clinical aspects and monitoring
Toxicity & Stopping Rules

We constantly review emerging data and collect evidence
UNCERTAINTY decreases

Marginal Risk Fundamental
Clinical aspects and monitoring
Toxicity & Stopping Rules

We constantly review emerging data and collect evidence
UNCERTAINTY decreases

Unknown unknowns:
Potential risks are unpredictable and uncertain

Use simple and short template rules and emergency algorithms
Managing Risk: Checklists and Treatment Algorithms

US Airways flight 1549:

Normally, crews follow checklists in emergencies. There were two applicable:
1. Ditching
2. Loss of thrust

Chesley Sullenberger (pilot):
“Not only did we not have time to go through a ditching checklist, we didn’t have time to even finish the checklist for loss of thrust in both engines. That was a three-page checklist, and we didn’t even have time to finish the first page. That’s how time-compressed this was”.

Time between “engines dying” and landing in the Hudson: 3 min 32 sec

“In many ways, as it turned out, my entire life up to that moment has been a preparation to handle that particular moment.”

Captain Sullenberger highlights the importance of having an expert team rather than a team of experts.
Clinical aspects and monitoring

Toxicity & Stopping Rules

We constantly review emerging data and collect evidence

UNCERTAINTY decreases

**Known Unknowns: “Predictable/anticipated” ADR**
- Little or no RSI available
- Potential risks’ nature, occurrence and impact are predictable (with some degree of uncertainty) through
  - mode of action
  - non-clinical data
  - anticipated pharmacokinetics and –dynamics
  - class effects

**Known Knowns: “Expected” ADR**
- Solid Reference Safety Information (RSI) available
- Potential risks’ nature, occurrence and impact are known
- Limited uncertainty

**Uncertainty**

- Simplify rules based on RSI
- Be cautious, consider worst case scenario for fundamental risks

© U Lorch
Clinical aspects and monitoring
Toxicity & Stopping Rules

We constantly review emerging data and collect evidence
UNCERTAINTY decreases

**Known Unknowns: “Predictable/anticipated” ADR**
- Little or no RSI available
- Potential risks’ nature, occurrence and impact are predictable (*with some degree of uncertainty*) through
  - mode of action
  - non-clinical data
  - anticipated pharmacokinetics and –dynamics
  - class effects

**Known Knowns: “Expected” ADR**
- Solid Reference Safety Information (RSI) available
- Potential risks’ nature, occurrence and impact are known
- Limited uncertainty

Be cautious, consider worst case scenario for fundamental risks

Simplify rules as ADR likely less predictive for overall risk than RSI

**Respondents Comments:** The guideline needs to permit consideration of
- Extent of current knowledge and uncertainty on fundamental risks
- Which individual and cohort rules are required
- Whether healthy volunteers or patients are concerned
Clinical aspects and monitoring
Toxicity & Stopping Rules

We constantly review emerging data and collect evidence
UNCERTAINTY decreases

Known Unknowns: “Predictable/anticipated” ADR
Little or no RSI available
Potential risks’ nature, occurrence and impact are predictable (with some degree of uncertainty) through
- mode of action
- non-clinical data
- anticipated pharmacokinetics and –dynamics
- class effects

Be cautious, consider worst case scenario for fundamental risks

Known Knowns: “Expected” ADR
Solid Reference Safety Information (RSI) available
Potential risks’ nature, occurrence and impact are known
Limited uncertainty

Simplify rules as ADR likely less predictive for overall risk than RSI

Consider:
- Extent of current knowledge and uncertainty on fundamental risks
- Which individual and cohort rules are required
- Whether healthy volunteers or patients are concerned

- Emergency algorithms
- How ≥Grade 3 ADR should be dealt with
- Whether any low grade (1/2) ADR may indicate risk of ≥Grade 3/serious ADR
- How Grade 2 serious ADR should be dealt with
- Whether rules for Grade 2* non-serious ADR are required or unnecessary
- Whether further investigation of ADR may be needed for decision making
- Whether reactions may be signs of efficacy

© U Lorch
Conclusions

When applying the guideline we should:

...be proportionate to uncertainty and potential risk
...avoid getting stuck in marginal issues and long checklists
...allow for further investigations where appropriate
...develop and/or use simple algorithms for potentially fundamental risks

Knowledge, expertise and an expert team are essential

[the guideline is not a textbook]
Consider Training
Consider Clinical Pharmacology Unit accreditation schemes
Take advantage of Scientific Advice pre-CTA submission
Thank you!