"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

European Federation for Exploratory Medicines Development – EUFEMED

London 18 May 2017

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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

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
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ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Draft

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016

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]	**Scientific value and/or speed** of integrated adaptive protocols **should not be hindered,** unless there are compelling reasons
Draft guideline text:	**Respondents said:**
"The **exact** nature of the proposed assessments **and their timing** should be provided."	**The protocol should specify minimum requirements and maximum adaptability**
"The **time intervals** [between cohorts] should be stated in the protocol."	**The interval between cohorts is determined by data requirements from previous cohort(s) rather than time.**
"'Evaluable subjects should be defined and it is expected that these are subjects who have completed **all** planned study visits"	**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**
"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**"	**Unnecessary, if trial runs within the boundaries set by an adaptive protocol and if there is no increase in risk and no approved toxicity/stopping rules have been met; would cause significant delays.**
"The members of the group should also be sufficiently **independent from IMP administration** and monitoring"	**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

Risks vs uncertainties definitions

uncertain (unknown)	certain (known)
	" There are **known knowns**; there are things we know that we know.
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)	and…**unknown knowns**; the things that we know, but are unaware of, untapped knowledge, knowledge that is not shared.

Risks vs uncertainties definitions

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:	**Known Unknowns:** *Some degree of uncertainty*	**Known Knowns:**
Uncertain Very potent, off target, and damaging to vital organs	Predictable/anticipated PK/PD profiles through • mode of action • non-clinical data • modelling • emerging human data	*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 | **Maximum dose/exposure**

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

Clinical aspects and monitoring
Toxicity & Stopping Rules

We constantly review emerging data and collect evidence

UNCERTAINTY decreases

Certainty/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**

Marginal Risk Fundamental

Clinical aspects and monitoring
Toxicity & Stopping Rules

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UNCERTAINTY decreases

Certainty/Uncertainty

Unknown unknowns:
Potential risks are unpredictable and **uncertain**

Marginal Risk Fundamental

Use simple and short template rules and emergency algorithms

ADR/Toxicity Rules

Managing Risk:
Checklists and Treatment Algorithms

US Airways flight 1549:

Normally, crews follow checklists in emergencies.

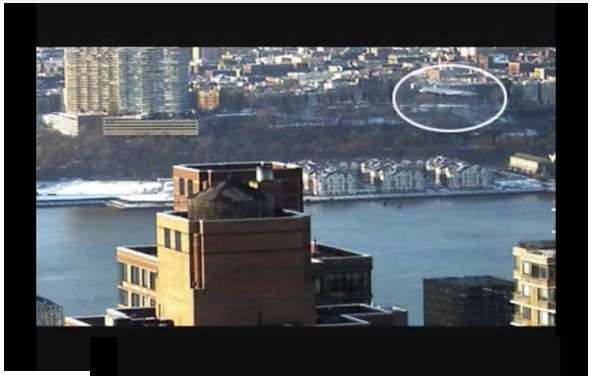
There were two applicable:

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".

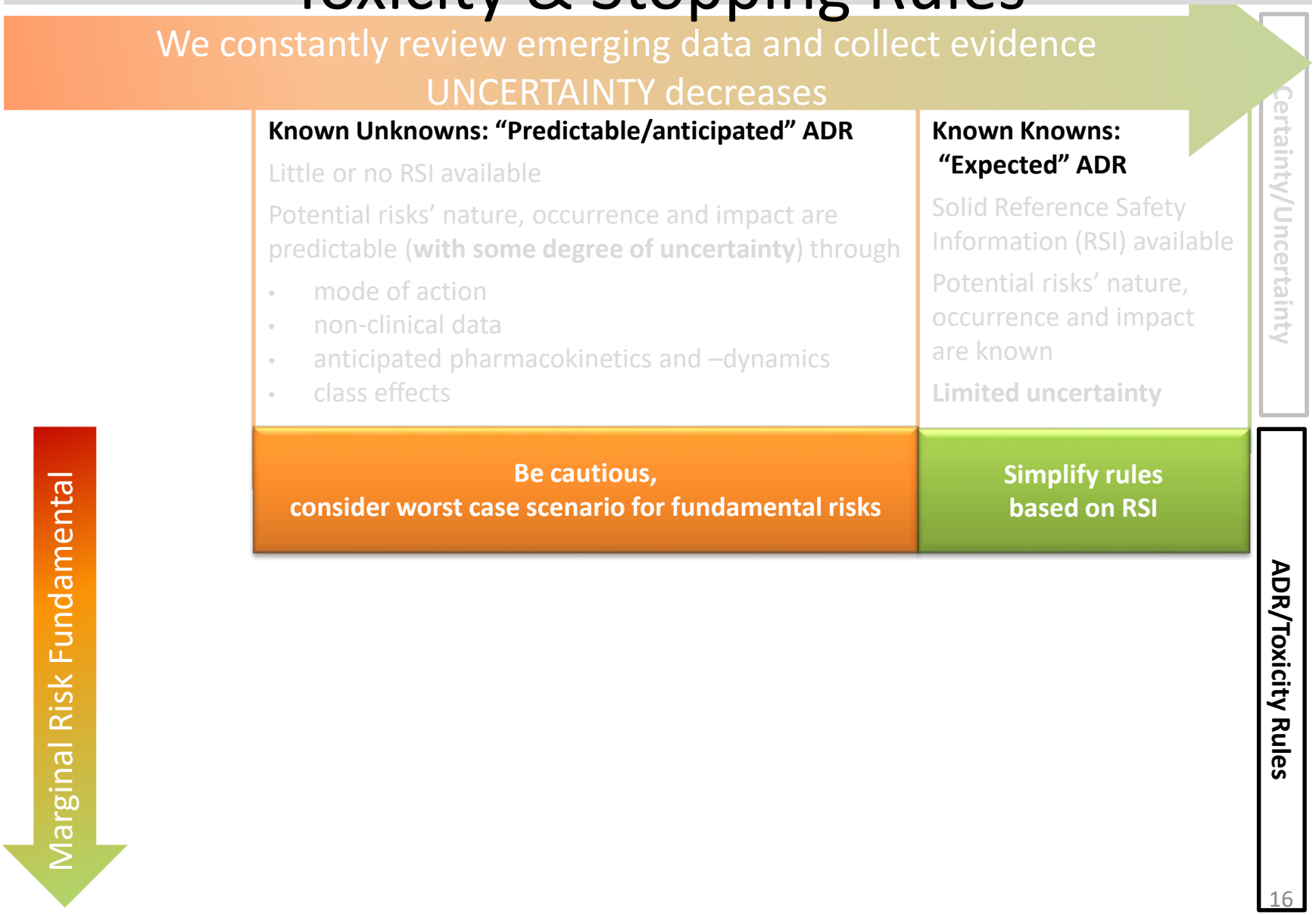
Time between "engines dying" and landing in the Hudson: **3 min 32 sec**



"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



Clinical aspects and monitoring
Toxicity & Stopping Rules

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Known Unknowns: "Predictable/anticipated" ADR	**Known Knowns: "Expected" 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	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**

Marginal Risk Fundamental

ADR/Toxicity Rules

<u>Respondents Comments:</u> 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

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Certainty/Uncertainty

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
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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

ADR/Toxicity Rules

Marginal Risk Fundamental

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

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!