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Key considerations regarding dose escalation schemes in FIH and early clinical trials

Thomas Sudhop

The Basic Principle of Toxicology

„Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding' kein Gift ist.“

"Sola dosis facit venenum“
„(only) dose makes the poison“

Philippus Aureolus Theophrastus Bombast von Hohenheim *aka Paracelsus. 1493-1541*

Severe incidents in recent drug development

TGN-1412 and BIA-10-2474

2006: TGN-1412 Incident
6 healthy volunteers (HV) suffered from a severe cytokine-release syndrome after the first (starting) dose. Not all HVs have been fully recovered yet.

2016: BIA-10-2474 Incident
1 HV died in the highest dose cohort iun the MAD part of a FIH trial. All HVs of the same cohort exposed to BIA-10-2474 suffered from cerebral hemorrhaging.

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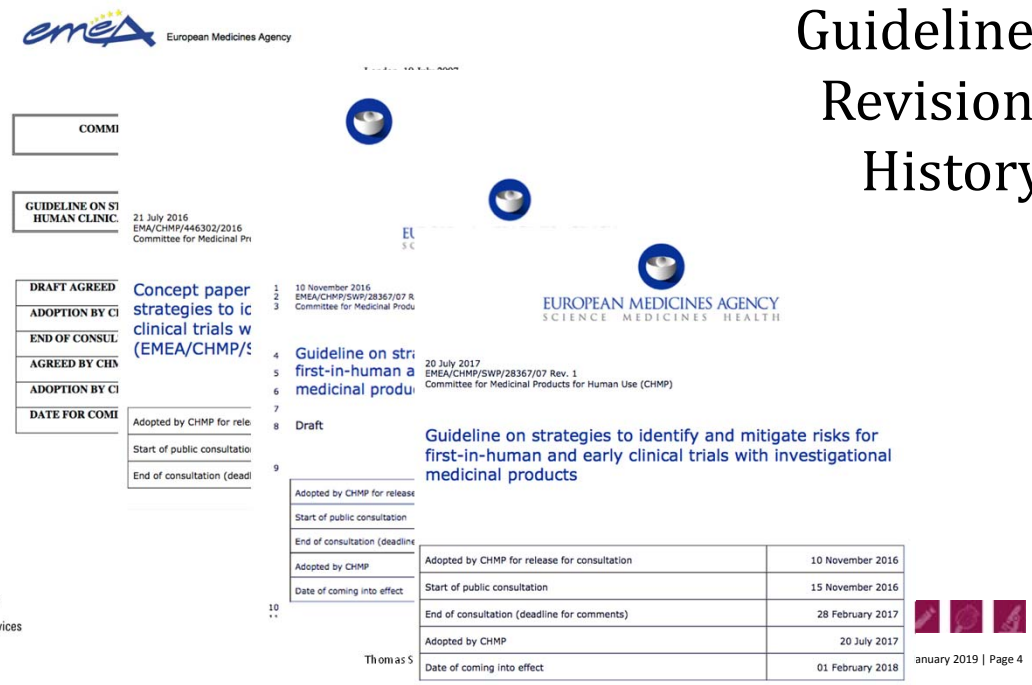
Guideline Revision History


European Medicines Agency

21 July 2016
EMA/CHMP/446302/2016
Committee for Medicinal Pr

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Draft

Adopted by CHMP for release
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Date of coming into effect

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
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

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

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Lessons learnt from the TGN-1412 and BIA-10-2474 incidents

- TGN-1412 (SAD study)
  - Safe starting dose
  - Relevance of animal model
  - Receptor occupancy …
- BIA-10-2474 (Integrated protocol)
  - Accumulation
  - Dose escalation
  - Integrated protocols …

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Dose escalation

Recommendations by the Guideline

- Safe starting dose
- Dose escalation steps
  - Provide maximum fold increase in dose (exposure) between two consecutive cohorts for each escalation step
  - Provide maximum number of cohorts
- Maximum exposure reached or **other stopping** rules apply

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Aspects to take into account for dose escalation (1/2)

- Calculated pharmacologically active dose (PAD) and the anticipated therapeutic dose range (ATD)
- Dose/exposure-toxicity and/or dose/exposure-effect relationship
  - Derived from non-clinical studies and adapted according to PK/clinical data from previous cohorts
  - Steepness of the dose/exposure-toxicity or dose/exposure-effect curves
- Reliability with which potential AEs can be monitored before potential serious/irreversible effects may develop
- Chance of non-linear PK resulting in a supra-proportional increases in exposure

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Aspects to take into account for dose escalation (2/2)

- Check if available clinical data reveal substantial differences from non-clinical or modelling/simulation data
- Consider potential saturation effects (target, PK)
- Check for plateauing of exposure

- *All changes in dose levels require a substantial amendment unless such changes are covered by predefined decision criteria in the protocol and no predefined dose/exposure limits are exceeded*

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Sentinel dosing

- Sentinel dosing in any cohort is considered the standard approach for all SAD and MAD trials
  - Provide number of patients on active drug and placebo (e.g. 1+1 approach)
  - Provide time period between sentinel sub-cohort and rest of the cohort
- If deviations from sentinel dosing considered, provide:
  - **Scientific** rationale for deviation
  - Risk analysis (risk management)
- Many protocols apply sentinel approach only for starting dose(s) without providing a rationale
  - BIA-10-2474 incident indicated that sentinel dosing would have been beneficial on any dose level

Stopping rules (8.2.9.)

- Stopping rules should be defined for each of the following:
  - Final stop to dosing and termination of the trial
  - Stopping for an individual subject, at any time in the trial
  - Stopping within a cohort
    - when subjects in a cohort are dosed staggered
    - during multiple dosing
  - Progression to the next part of the trial (integrated protocols)
  - Any dose escalation parts of the trial
- It should be specified in each rule if the stop is a final end of dosing or a temporary halt

Additional stopping rules for healthy volunteers (HV)

- Each of the following conditions should follow in an immediate stop to dosing
  - A **serious** adverse reaction* (SAR) in one HV
    - Lesson from BIA-10-2474: Each SAE in a HV should be considered as related (SAR or SUSAR) as long as the opposite cannot be assumed
  - *Severe* non-serious adverse reactions in **<u>two</u>** HVs **in the same cohort**, independent of within or not within the same system-organ-class
  - Predefined maximum clinical exposure (C_{max} or AUC) reached
    - Use maximum exposure in a single HV not the mean exposure

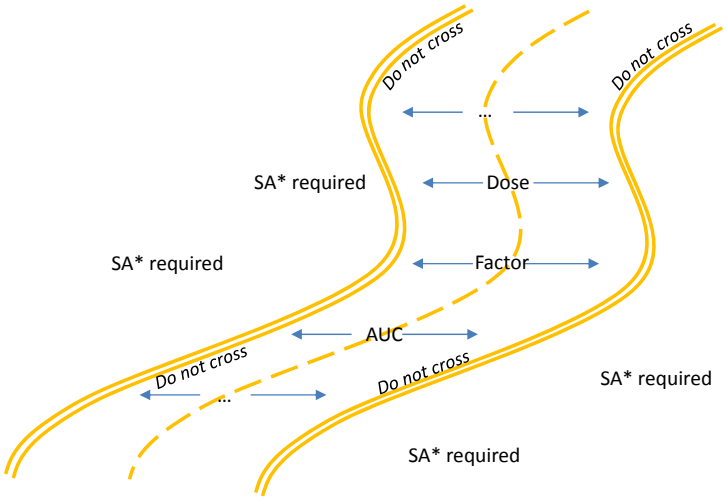
*Adverse event considered at least possibly related to the IMP administration

Restart/continuation after match of stopping criteria (8.2.9.)

- Restart is possible **without a substantial amendment** if review leads to a conclusion which is **fully within predefined conditions** for the relevant stopping criterion
  - Anticipation of the most likely stopping criteria in recommended
- Any submitted substantial amendment should include a rationale for the proposed dosing and for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable

When to submit a substantial amendment?

Predefined (Safety) Corridor



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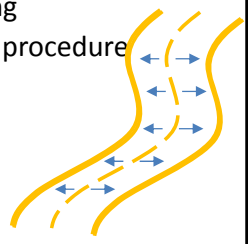
Guideline adherence and flexibility

- The Guideline describes the current state of scientific state of the art and should to be adhered to by sponsors and authorities(!)
- Deviations should not be the rule, but a scientifically justified exception
- The Guideline requires "justifications" for a certain procedure in many places
  - If justifications are missing, the BfArM will raise objections and demand them
- If a *safety corridors* is clearly pre-specified in the protocol and decision-making processes are described clearly and comprehensibly in the protocol, a staged procedure within the corridor can also be implemented without substantial amendment
- If the *safety corridor* is left or if assumptions do not apply a substantial amendment is required



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