EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07)

Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	21 July 2016
End of consultation (deadline for comments)	30 September 2016

Comments should be provided using this template. The completed comments form should be sent to FIH-rev@ema.europa.eu

Keywords	First-in-human, early phase, clinical trials, risk mitigation, integrated protocols, multiple ascending dose.

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1. Introduction

The requirements for progression from the conduct of non-clinical studies to clinical trials for investigational medicinal products in humans are extensively addressed as part of ICH M3 (R2) and the related Q&A document. In addition, in 2007, EMA published the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials (CTs) with investigational medicinal products' (EMEA/CHMP/SWP/28367/07), which is now proposed for revision.

2. Problem statement

The current guideline mainly focuses on non-clinical aspects of drug development and the use of animal data and reflects the practice at the time it was developed which focused on a single ascending dose (SAD) design for first-in-human (FIH) trials.

Since then, integration of the non-clinical data available before FIH administrations and the pharmacokinetic (PK), pharmacodynamic (PD) and human safety data emerging during a trial has also evolved. Consequently, the practice has evolved and many FIH trials are now performed with integrated protocols potentially combining a number of different study parts, e.g. single and multiple ascending doses (SAD and MAD), food interaction, different age groups and early proof of concept or early proof of principle parts. FIH and early phase CTs with multiple study parts are, therefore, increasingly being submitted for regulatory review to National Competent Authorities as part of a single CT application.

3. Discussion (on the problem statement)

Some specific discussion points have been defined (non-exhaustive) when reviewing the current guideline:

- Extension of the guidance to early phase CTs including single study or integrated protocol designs.
- Extension of the non-clinical aspects of the guideline to address:
  - better integration of non-clinical pharmacology data (including PK and PD data evaluated using current PK/PD or physiologically-based pharmacokinetic modelling) and data from the toxicology testing into an overall risk assessment for FIH and early CTs administration;
  - translation of non-clinical data to human use by extrapolation and verification of assumptions made;
  - expanding on the minimum anticipated biological effect level (MABEL) approach taking all biological effects into account;
  - the role of non-clinical data for the:
    - estimated therapeutic dose, maximum human dose level (both for SAD and MAD parts), dose escalation steps and dosing frequency and intervals;
    - definition of stopping criteria for the trial;
    - identification of safety aspects to monitor.
- Extension of the clinical part of the guideline with new guidance to address:
  - integrated CT designs and study endpoints including decision-making aspects;

- extension of the remit of the guidance beyond single ascending dose FIH trials to incorporate other early phase trials and designs;
- clarification on the choice of trial subjects;
- overall dose/exposure range and scheme including stopping rules;
- rolling review of emerging human data during the study;
- general principles on key scientific information to be included in a CT application;
- safety observations for trial participants;
- handling of adverse events in relation to stopping rules and progress to next dosing steps;
- general principles on communication to competent authorities and CT subjects.

Given the diversity in type of investigational medicinal products being developed and clinical trial designs, and considering the complexity in interpretation of relevance of animal toxicology findings for human use, it is considered that the revised guideline should continue to be followed in conjunction with all applicable national and international guidance in an integrated, risk-based approach. In addition, although already outlined in the current document, there is a need to emphasise that the guideline is applicable for all molecules and not only for biotechnology-derived proteins.

4. Recommendation

The CHMP recommends the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07). Aspects to be considered in drafting the revision include the specific points raised above.

In line with the existing guideline, it is anticipated that the revised guidance should continue to be applicable to all types of investigational medicinal products including, but not limited to, trials where specific factors of risk have been identified or are anticipated.

5. Proposed timetable

The Concept Paper will be released for public comments for 2 months. A draft version of the revised guideline is expected to be published for comments before the end of 2016.

6. Resource requirements for preparation

The preparation will mainly involve the multidisciplinary group nominated by CHMP, which includes experts from CHMP and its working parties and Heads of Medicines Agencies' (HMA) Clinical Trial Facilitation Group with consultation of relevant EMA scientific committees and working parties, in addition to the abovementioned HMA's Clinical Trial Facilitation Group .

7. Impact assessment (anticipated)

The most important anticipated impact of the revised guideline will be the enhancement of the current strategies to identify and mitigate risks for trial-participants. This is to facilitate the conduct of these trials in a safe, efficient and transparent manner to the benefit of public health and further harmonise practice in EU Member States.

8. Interested parties

Patients, physicians, academia, ethics committees, pharmaceutical industry, sponsors, investigators, contract research organisations and regulatory authorities.

9. References

Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (ICH M3 (R2), EMA/CPMP/ICH/286/1995).

ICH guideline M3 (R2) - questions and answers (EMA/CHMP/ICH/507008/2011).

Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 (R1), EMA/CHMP/ICH/731268/1998).

Nonclinical evaluation for anticancer pharmaceuticals (ICH S9, CHMP/ICH/646107/08).

Guideline for Good Clinical Practice (ICH E6 (R1), CPMP/ICH/135/95).

Questions and Answers by the CTFG on clinical trials - Answers to frequently asked questions, updated January 2012 – Head of Medicines Agencies' Clinical trial facilitation group (link).