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Press release

Revising the guideline on first-in-human clinical trials

Changes are open for comments until end of February 2017

The European Medicines Agency (EMA), in cooperation with the European Commission and the Member States of the European Union (EU), is proposing changes to its existing guideline on first-in-human clinical trials, to further improve the safety of trial participants. The revised [guideline](#) is open for public consultation until 28 February 2017. Comments should be sent to FIH-rev@ema.europa.eu using the template provided.

Clinical trials are essential for the development of medicines and without them patients cannot gain access to new potentially life-saving medicines. EU and international guidelines are in place to ensure that first-in-human clinical trials are conducted as safely as possible. EMA's existing guideline, released in 2007, provides advice on first-in-human clinical trials, in particular on the data needed to enable their appropriate design and allow the initiation of treatment in trial participants.

Between July and end of September 2016, EMA released for public consultation a [concept paper](#) which outlined the major areas that needed to be revised in the guideline, to reflect the evolution of practices in the last ten years. The review also took into account the lessons learnt from the tragic incident which took place during a phase I first-in-human clinical trial in Rennes, France, in January 2016.

The consultation of the concept paper served as the basis for the revision of the guideline, which was carried out by an EU-wide group made up of experts from the national competent authorities who authorise clinical trials in the EU. The draft revised guideline was adopted last week by EMA's Committee for Medicinal Products for Human Use (CHMP).

This revised guideline aims to address the increasing complexity of protocols of first-in-human clinical trials in recent years. While the 2007 guideline focused on the single-ascending-dose design used at that time, the practice for conducting first-in-human clinical trials has evolved towards a more integrated approach, with sponsors conducting several steps of clinical development within a single clinical trial protocol (e.g. to assess single and multiple ascending doses, food interactions, or different age groups).

Strategies to mitigate and manage risks for trial participants are outlined, including principles to be used for the calculation of the starting dose in humans, the subsequent dose escalation, and the criteria for maximum dose, as well as principles on the conduct of the clinical trial including the conduct of studies with multiple parts.



In particular, guidance is proposed on non-clinical aspects such as the better integration of pharmacokinetic and pharmacodynamic data and toxicological testing into the overall risk assessment, as well as the role of non-clinical data in the definition of the estimated therapeutic dose, maximal dose, and dose steps and intervals. Guidance is also provided on clinical aspects, including criteria to stop a study, the rolling review of emerging data with special reference to safety information for trial participants, and the handling of adverse events in relation to stopping rules and rules guiding progress to the next dosing level.

EMA will make available all comments received, both on the concept paper and the revised guideline, after the final guideline is released. The aim is to publish a final revised guideline for the conduct of first-in-human clinical trials in the first half of 2017.

Notes

1. This press release, together with all related documents, is available on the Agency's website.
2. In a single ascending dose trial, a single dose of the investigational medicine is given to each volunteer in a small group of clinical trial participants to assess the safety; if this is positive each participant in the next group receives a single dose at the next higher dose of the investigational medicine.
3. In multiple ascending dose trials, each subject is treated on multiple occasions (e.g. once a day for a week) at a given dose level. The treatment is then increased progressively to higher doses in successive groups of volunteers, provided the safety and tolerability at the previous dose is acceptable.
4. In the EU, the approval and conduct of clinical trials is within the remit of the relevant authorities of the European Member States.
5. An article co-authored by the EMA Executive director Guido Rasi in the New England Journal of Medicine (NEJM), discusses what EMA can do to help identify and minimise risks for participants in first-in-human clinical trials. ['First-in-Human Clinical Trials – What We Can Learn from Tragic Failures'](#), N Engl J Med 2016; 375: 1788-1789.
6. More information on the work of the European Medicines Agency can be found on its website: www.ema.europa.eu

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