

News from the EMA

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Revising the guideline on first-in-human clinical trials

November 15, 2016 — The EMA, in cooperation with the European Commission and the Member States of the 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 was open for public consultation until 28 February 2017.

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 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. 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.

The aim is to publish a final revised guideline

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for the conduct of first-in-human clinical trials in the first half of 2017.

Notes

- 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.
- 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.

Also see the editorial: Sergio Bonini, and Guido Rasi. *First-in-Human Clinical Trials – What We Can Learn from Tragic Failures*, *N Engl J Med* 2016; 375:1788-1789.

Opening up clinical data on new medicines: EMA provides public access to clinical reports

October 20, 2016 – The European Medicines Agency (EMA) has now given open access to clinical reports for new medicines for human use authorised in the European Union (EU).

For every new medicine, citizens, including researchers and academics, will be able to directly access thousands of pages from clinical reports submitted by pharmaceutical companies to EMA in the context of marketing-authorisation applications. Clinical reports give information on the methods used and results of clinical trials conducted on medicines. EMA is the first regulatory authority worldwide to provide such broad access to clinical data.

With EMA's proactive approach to providing access to the data, patients and healthcare professionals will be able to find out more information about the data underpinning the approval of medicines they are taking or prescribing. It will also facilitate the independent re-analysis of data by academics and researchers after a medicine has been approved. This will increase scientific knowledge, and potentially further inform regulatory decision-making in the future.

Increased transparency will also benefit innovation. The shared knowledge about a medicine helps developers learn from the

experience of others and can lead to more efficient medicine development programmes.

The publication of the clinical reports follows the adoption by EMA of a policy on the publication of clinical data for human medicines. The website, available at <https://clinicaldata.ema.europa.eu>, will include the clinical reports contained in all initial marketing-authorisation applications submitted to the Agency on or after the policy's entry into force on 1 January 2015. According to current forecasts, EMA expects to offer access to approximately 4,500 clinical reports per year.

The European Commission launches a public consultation on the Paediatric Regulation: More medicines for children are now available

November 15, 2016 — The European Commission (EC) has launched a public consultation to get views and feedback from stakeholders, to support the Commission in drafting its second report on the Paediatric Regulation after nearly ten years of implementation. The consultation launched today is based on a report prepared by the EMA and its Paediatric Committee (PDCO). The feedback received will form an integral part of the Commission's final report assessing the impact of the Paediatric Regulation on public health and the pharmaceutical industry, which is expected to be published in 2017.

The Paediatric Regulation came into force in the EU ten years ago, on 26 January 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of age-appropriate medicines for children, and by increasing available information on the use of medicines for children.

A comparison of data collected between 2004 and 2006, immediately before the regulation came into force, and data collected between 2012 and 2014, shows that the Paediatric Regulation has led to more medicines and new indications being authorised for



children in the EU. From 2004 to 2006, 31 new medicines and new indications were centrally authorised for paediatric use. From 2012 to 2014, this number more than doubled to 68 new medicines and new indications. For example, medicines to treat certain rheumatology conditions in children, infectious diseases such as chronic hepatitis C and HIV infection, hypertension and paediatric cancers like acute lymphoblastic leukaemia are now available on the basis of studies conducted in children.

By the end of 2015, the PDCO had adopted 860 opinions for paediatric investigation plans (PIP). PIPs are the main tool of the regulation to ensure that previously unmet therapeutic

needs in children are researched and appropriate medicines are developed.

Clinical trials in children initiated as part of an agreed PIP now represent about 30% of paediatric trials recorded in the EU Clinical Trials database (EudraCT). Additionally, the European Network for Paediatric Research at the EMA (Enpr-EMA) was set up to facilitate the conduct of clinical studies in children. Enpr-EMA is an umbrella network of 38 national and international networks recognised for their paediatric research experience. It acts as a platform for sharing good practices as well as a pan-European voice for promoting research into medicines for children.

Tailored scientific advice to support step-by-step development of new biosimilars

December 16, 2016 – The EMA will launch a pilot project in February 2017 to test the added value and feasibility of tailored scientific advice for the development path of biosimilar medicines. Through this new initiative, EMA aims to provide developers of biosimilars with advice on the studies/tests they should be conducting, on the basis of the quality, analytical and functional data they have already available for the medicine.

This is expected to better support the stepwise development of biosimilars that is recommended in EU guidelines. According to this approach, the extent and nature of the studies/tests required depend on the level and robustness of data already accumulated.

Biosimilars are biological medicines developed to be highly similar to another biological medicine (also known as the reference medicine) already authorised in the EU. To obtain a marketing authorisation, developers

need to establish similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

The standard scientific advice procedure can advise applicants on the proposed biosimilar development strategy, however it does not allow for a formal assessment of data. As part of this pilot, an in-depth review of the quality, analytical and functional data available will be carried out. Advice will be given on the basis of the data submitted allowing for more tailored recommendations on the studies/tests that should be carried out in the next step of the development. This will allow applicants to make a more informed decision on the development strategy once sufficient quality data has been accumulated. However this will not constitute a formal pre-assessment of the data submitted during the marketing authorisation application.

The pilot is open to all companies seeking

scientific advice for the development of a biosimilar medicine. Any type of biosimilar will be accepted in the pilot. Companies wishing to take part in the pilot will have a pre-submission meeting during which the suitability of the data package is reviewed. EMA's Scientific Advice Working Party (SAWP) will need an extra month in addition to normal scientific advice timelines to review the requests accepted in the pilot.

The pilot is planned to run until six scientific advice requests have been completed, with maximum one scientific advice request accepted per month. After the completion of the pilot, EMA will carry out an analysis of the outcome.

Scientific advice provided to developers is separate from the assessment of a marketing authorisation application which takes place later and does not pre-empt the recommendation from the CHMP on whether or not the medicine can be authorised.