Promoting Safe Early Clinical Research of Novel Drug Candidates: A European Union Regulatory Perspective

Stefano Ponzano1, Kevin Blake1, Milton Bonelli1, Harald Enzmann2 on behalf of the European Medicines Agency Committee for Human Medicinal Products “First-in-Human Guideline Drafting Group”

The European Medicines Agency (EMA) revises its guideline on minimizing risk in first-in-human trials to reflect changing practice and in light of a recent tragic incident.

The EMA Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States. These guidelines reflect a harmonized EU approach and are based on the most up-to-date knowledge. Therefore, they may require revision over time to reflect the evolution in knowledge and practices. Where major problems or unanticipated changes in scientific knowledge come to light, review may also be initiated.

Clinical trials are essential for the development of new medicines. In all clinical trials, the safety and well-being of trial subjects (be they patients or healthy volunteers) should always be the priority and EU and international guidelines are in place to ensure that they are conducted as safely as possible. Consequently, the vast majority of clinical trials are completed without any adverse impact on participants. Data from the EMA’s clinical trial database (EudraCT) shows ~14,700 phase I clinical trials (with participation of 305,000 subjects) have been conducted in the EU since 2005. These include 3,100 first-in-human clinical trials. In the same period, there have been two tragic events in a first-in-human clinical trial in the EU, i.e., the cytokine storm and irreversible consequences of the TGN 1412 trial in London, UK in 20062 and the BIA 10-2474 trial in Rennes, France, in 2016. In the latter, on January 10, 2016, a healthy volunteer who had received a fatty acid amide hydrolase (FAAH) inhibitor for 5 days was admitted to the hospital with neurologic symptoms. The participant subsequently died on January 17. Another five participants who received the same drug dose for 6 days were also hospitalized. Four of the five had similar neurologic symptoms.

In response to the first of these, in 2007 the EMA published a scientific guideline to emphasize that absolute consideration should be given to characterizing risks and putting in place appropriate strategies to minimize risks in first-in-human clinical trials.3 The second, in conjunction with the need for alignment with more current practice, triggered its revision.4 This revision included reflection throughout the guideline that every potential new medicine (investigational medicinal product (IMP)) has a unique pharmacotoxicological profile that is associated with an intrinsic level of uncertainty related to potential benefits and risks.

CHANGING PRACTICE

Crucially, the 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 trials has evolved towards the conduct of several steps of clinical development within a single clinical trial protocol. Such trials, commonly referred to as those with "integrated protocols," encompass multiple components. Each part is focused on determining aspects of the drug's profile and may explore a drug's safety, tolerability, pharmacokinetic profile, and/or pharmacodynamic effects, e.g., after single and multiple ascending doses, proof of concept into a relevant patient population, and/or interactions with food or other drugs. The EMA and the national competent authorities who authorize clinical trials in the EU consider the conduct of such trials with integrated protocols as appropriate, provided they are supported by sufficient knowledge of the drug candidate, their design is rational and science-driven, and the supportive resources (e.g., facilities, personnel, and procedures) are adequate to enable their safe conduct. It is also paramount that decisions before and during the trial should be based on a rigorous interpretation of the totality of the available data, including new and emerging data. Above all, the practice of performing initial human dosing in the context of these trials should not come with a higher degree of risk for study participants. The overall study design should justify the inclusion of each study part considering the data each will provide and the time available for integrated assessment. Safety should not be compromised in the interests of speed of acquiring data or for logistical reasons. The guideline has been significantly revised to take account of these points in relation to the practice of trials with integrated protocols.

OTHER SIGNIFICANT CHANGES IN THE REVISION

The introduction of the “level of uncertainty” concept was done to consolidate risk mitigation based on the individual uncertainty of the IMP rather than on a list of predefined factors, as were described in the old version of the guideline. This takes account of many sponsors already incorporating additional work based on scientific rationale, but now as a requirement and no longer as a “tick box” exercise. In this respect, it is important that the appropriate studies are conducted to define the intended and the unintended effects of the drug candidate. A strong target validation and an adequate characterization of selectivity of the drug candidate are crucial steps to correctly interpret toxic effects detected in vitro preclinical safety studies and, in turn, to minimize the risk for unexpected adverse events in the clinical trial setting. Predisciplinary studies should use the relevant animal species and should rely whenever possible also on in vitro methods and use of human-derived materials. In all cases, the generation of preclinical data should be supported by a clear scientific rationale in line with the International Council for Harmonisation (ICH) safety guidance documents (M3, S6, and S9), but should be well-thought through and not, as previously stated, just follow a “tick box” approach.

Importantly, a new section has been added on dose selection to support stakeholders in their transition from the nonclinical to the clinical setting. This section contains the guiding principles on the role of nonclinical data in the definition of an initial starting dose and of an estimated pharmacodynamic dose range up to a maximal dose, including dosing steps and intervals, based on the exposure of the IMP. Of note, in relation to initiation of dosing in humans, a different angle is provided as compared to the US Food and Drug Administration (FDA) guidance, which delineates an algorithm of allometric scaling for selecting a maximal starting dose for adult healthy volunteers.

The clinical section has been markedly expanded in detail. Clinical aspects now include very clear criteria or “stopping rules” for stopping a study, a study part, or a planned increase in dose to put patient safety first. These include those as a consequence to the occurrence of adverse effects. Additional guidance is also provided on the appropriate handling and communication of adverse events. Regarding principles for rolling review of emerging data with special reference to safety information for trial participants, the guide now emphasizes that the knowledge at hand before the start of clinical development is to be critically reviewed and integrated with emerging data and reused to optimally inform decision-making for the ongoing trial. These decisions might relate to initiating a new part or escalation of the dosing in sequential study parts and, in turn, go/no-go decisions on the given drug development program.

EFFECTS ON DEVELOPMENT

Clinical trial authorization is within the remit of the national competent authorities in individual EU Member States and not with the EMA. Therefore, while it is not the EMA who will make direct decisions on following the guideline, the close collaboration with the Member States in the revision of the guideline is expected to prevent significantly different decisions in different Member States. In addition, the revised guideline’s extensive list of issues may help to prepare for a smooth and efficient authorization procedure. Using it in a “checklist” approach, relevant issues are considered proactively while designing the protocol rather than late during the assessment of a clinical trial application.

CONCLUSION

The EMA has taken an overarching approach in revising the guideline, focusing on changing required practice and including, but not dominated by, lessons learned from the very few trials with serious incidents. The revised guideline, therefore, aims to address as far as possible the important issues that may need consideration during the process of designing and conducting a set of studies in a clinical development program. In line with differing uncertainty associated with individual IMPs, due to their differing pharmacological features and intended use, it is also acknowledged that parts of the guideline may be important for some IMPs and inapplicable to others. The true impact of the various aspects of the revision may never be known in terms of their prevention of incidents. This is in part because no one can know that an incident that might have otherwise occurred has been averted by a particular new recommendation or scientific approach. It is also not possible, given the intrinsic uncertainty associated with any IMP, to reduce the risk associated with clinical trials to zero. However, the EMA anticipates, even in the face of an impressive clinical trial safety record in general, that application of the principles of the revised guideline will further enhance the conduct of trials, particularly those with integrated protocols, to the extent possible based on current knowledge and practices.
CHRONOLOGY

A concept paper addressing areas for potential change underwent public consultation from July to September 2016. Subsequently, a draft revision implementing these changes was published in November 2016, and public comments were accepted until 28 February 2017. Extending the consultation with stakeholders, a workshop was held at the EMA on 28 March 2017. Individuals and organizations that had submitted comments were invited to further discuss these so that they could best be reflected in the guideline. The revised guideline was adopted by the CHMP on 20 July 2017. The comments received in the public consultations on the revision were published on the EMA website on 27 September 2017. [Correction made here after initial online publication.]

The revision was led by a drafting group including experts from the national competent authorities and developed in close collaboration with EU Member States including the involvement of the Clinical Trials Facilitation Group of the Heads of Medicines Agencies.

MEMBERS OF THE EUROPEAN MEDICINES AGENCY COMMITTEE FOR HUMAN MEDICINAL PRODUCTS “FIRST-IN-HUMAN GUIDELINE DRAFTING GROUP”

Jan-Willem van der Laan (MEB, The Netherlands); David Jones (MHRA, UK); Lutz Wiesner (BfArM, Germany); Ulla Wändel-Liminga (MPA, Sweden); Kirsty Wydenbach (MHRA, UK); Elke Stahl (BfArM, Germany); Walter Janssens (FAGG, Belgium); Dominique Masset (ANSM, France); Joelle El-khoury (ANSM, France); Philippe Vella (ANSM, France); Jan Welink (MEB, The Netherlands). [Correction made here after initial online publication.]

CONFLICT OF INTEREST

The authors declared no conflict of interest.

© 2017 The Authors Clinical Pharmacology & Therapeutics published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

An Industry Perspective on the 2017 EMA Guideline on First-in-Human and Early Clinical Trials

Joseph DeGeorge1, Sarah Robertson2, Lynne Butler3, Mazin Derzi3, S. Aubrey Stoch4, Dolores Diaz5, James Hartke6, Peggy Guzzie-Peck7, Elisabeth Mortimer-Cassen8, Matthew Bogdanffy9, Yvonne Will3 and Nigel Greene10

The European Medicines Agency (EMA) in 2017 issued a revised guideline on nonclinical and clinical aspects of first-in-human (FIH) and early clinical trials (CTs). External input was solicited during a draft comment phase, and although some industry suggestions were adopted, others were not. We agree that subject safety is of utmost priority, and believe that minimizing risk must be balanced with efficient and informative study designs to bring new medicines to patients.

1Bianca Holdings, Lansdale, Pennsylvania, USA; 2Vertex Pharmaceuticals, Boston, Massachusetts, USA; 3Pfizer Worldwide Research and Development, Groton, Connecticut, USA; 4Merck & Co, Inc., Kenilworth, New Jersey, USA; 5Denali Therapeutics, San Francisco, California, USA; 6Celgene, Nonclinical Development, San Diego, California, USA; 7Janssen Research and Development, Spring House, Pennsylvania, USA; 8AstraZeneca, Melbourne, Hertfordshire, UK; 9Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; 10AstraZeneca, Waltham, Massachusetts, USA. Correspondence: Lynne D. Butler (lynned.butter@pfizer.com)

doi:10.1002/cpt.984