WHITEPAPER

How the revised EMA guidance on First in Human clinical trials affects your study design

Dr Bradley Joblin
Chief Scientific Officer Q-Pharm
Q-Pharm helps clients comply with the regulatory demands while creating efficient and effective early phase clinical studies. The clinical and scientific experts at Q-Pharm specialise in efficient and effective early phase studies designs. Having designed early phase programs at global pharmaceutical companies and biotech companies, Q-Pharm staff have years of experience integrating modelling and adaptation to early phase study designs.

The advantage Q-Pharm has as a phase I clinic is that we also know which designs translate into an implementable study in the clinic. This adds confidence that the design will answer your objectives in a reliable, safe and time efficient way.

Dr Brad Joblin
Chief Scientific Officer

Brad has a doctorate from the University of Zurich. Having held senior management and director positions in clinical research at the headquarters of global pharmaceutical companies and smaller biotech companies, Brad’s experience is in clinical study implementation, early and late phase clinical study design and clinical development strategy.

Brad founded his own company providing clinical study and development advice to the clinical research community including biotech companies and medical research institutes. Brad joined Q-Pharm at the start of in 2017 to provide scientific oversight and management within Q-Pharm, as well as study design and development strategies to clients.
Introduction

“The expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were observed in animals or earlier in the study in humans, is considered more relevant than the relative dose levels between animals and humans.”

EMA FIH guidance 2017

In July 2017, the European Medicines Agency (EMA) revised its guidance on First in Human (FIH) Clinical Trials. The revised guidance provides strategies to identify and mitigate risks for trial participants. This whitepaper outlines how modern clinical study strategies can be utilised in early phase studies, to not only satisfy the new regulatory risk mitigation guidance principles, but also incorporate efficiencies in your study design and certainty of decision making. The purpose of this whitepaper is not to re-state information that has been provided in earlier FIH guidance documents, but to highlight the new recommendations being suggested.

Understanding the EMA Guidelines
The EMA’s original FIH guidelines were released in 2007. These guidelines helped sponsors to safely transition their discovery from non-clinical into early clinical development. Now, in 2017, EMA has adopted the first update to their 2007 FIH guidance. The focus on risk identification and mitigation is a consistent theme in both the original and updated EMA FIH guidance documents.

The revised EMA guidance document asks us to consider some new approaches in the development of study design and targeting of dose ranges. The revised guidance also includes strategies to mitigate risk. This is in recognition of the fact that early phase trial design now integrates multiple parts such as Single Ascending Dose (SAD), Multiple Ascending Dose (MAD), and food effect. Early phase trial design also now employs novel strategies to more efficiently achieve study objectives.

First in human (FIH) studies are critical initial investigations used to determine the safe dosing characteristics of a new investigational medicinal product. In EMA’s initial 2007 guidance document, calculations for initial doses to be administered in FIH studies were provided. Strategies for subsequent dose escalations and intervals between doses were also described. In 2007, early phase studies were designed as rigid single ascending dose studies followed by rigid multiple ascending dose studies. Numbers of cohorts were fixed and maximal tolerated doses (MTD) would cap dose escalations.

Early phase clinical trial design and drug development strategy has evolved significantly since 2007. Modern early phase clinical study designs are more integrated, and include multiple parts such as SAD/MAD/food effect and patient cohort. This integrated approach allows more questions to be answered under one ‘umbrella’ design.

Today, we are also able to understand the relationship between the drug concentration in the body (exposure) and the observed safety and efficacy effect at that concentration much earlier in development. In doing do, we can design studies that more precisely describe and predict the exposure/effect (PK/PD) relationship of our investigational drug. This increases our precision and efficiency in dose escalation designs. The new guidance document reflects the evolution of modern early phase clinical development and includes updated strategies to help facilitate modern designs whilst identifying and mitigating risks for participants in early clinical trials.
Translational research continues to improve our understanding of safe and therapeutic human doses prior to administering the IMP in FIH studies. Even so, there is always a level of uncertainty around risks and benefits when translating data of a novel drug candidate from animals to human. The new strategies recommended in the updated guideline further assist sponsors transitions from pre-clinical to early clinical development in part by making use of our improved ability to understand translation from results in preclinical research.

As such, these updates now include new recommended approaches to calculating starting doses, dose escalation intervals, rules for progressing to the next dose level and criteria for the maximum dose. In our early designs we are now asked to consider the exposure levels in animals, rather than the dose, in order to target the expected exposure in humans at a certain dose. Put simply, where the previous question was ‘at what dose?’, we are now being asked to consider all non-clinical data (PK, PD, TK profiles, dose or exposure effect profiles) to calculate “at what exposure level” we expect responses in humans. The design will then administer doses to achieve target exposure levels.

This point is clearly illustrated in the recommendations for calculating a starting dose. The updated guidelines want us to consider what exposure levels in relevant animal models can be used to ascertain the NOAEL in humans.

Another clear example of the new FIH recommendations no longer incorporating dose targeting as the recommended approach can be seen from the statement for FIH studies involving healthy volunteers. Previously, dose escalations were fixed until, at a particular dose, toxicity signals alert that the maximum tolerated dose (MTD) has been established and escalations stop. The updated recommendations state:

“**A trial design using a Maximal Tolerated Dose approach is considered to be inappropriate for healthy volunteers**”

Instead the recommended approach is to investigate higher doses for FIH studies as follows: “An expected maximum exposure level, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined in the protocol for each study part”

Understandably, as we translate from animal to humans, its logical that exposure/response (PK/PD) translations come with inherent complexities and uncertainty on the risks and benefits at each exposure level. However, the new guidelines recommend two key principles to safety mitigate this uncertainty.

“The exposures achieved at the NOAEL in the most relevant animal species used (which might not necessarily be the most sensitive species) should be used for estimation of an equivalent exposure for humans”
Adapt the design as we learn

The first principle is applicable to dose escalations and integrated protocol designs.

Typically, dose escalations administered in early phase SAD and MAD studies were fixed and based upon data collected at certain doses in relevant animal model studies. In a fixed study design approach, the key parameters determining a safe dose range are set regardless of what the information we receive during the study tells us about the accuracy of our hypothesis and assumptions. Such fixed dose escalation study designs can often result in many objectives not being reached, such as highest dose cohort being dosed without the highest tolerated doses being attained. In the new recommendations, we are asked to embrace the fundamentals of Bayesian statistics, to revise beliefs in light of new information and better inform subsequent activities as information is collected along the way. For deciding on incremental dose cohorts in SAD and MAD studies, the recommendations are to adapt within the study as data is collected from previous cohorts.

“The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the non-clinical studies and adapted following review of emerging clinical data from previous cohorts”

The recommendations to include rolling adaptations in an early phase study design is also extended to integrated protocol where a study may include many parts such as a SAD, MAD and food effect design.

“When definite doses cannot be predefined in all study parts (dose selection) criteria should be established in the protocol. These criteria should integrate data from previous study parts. Feasibility to review and adapt the planned study design based on emerging clinical data should also be considered.”

Adaptive design has been used in clinical studies, especially phase IIb and III, for almost 20 years. Adapting studies as we gather data is an indispensable tool allowing greater precision and efficiency. It allows us to refine the design, and replace prior assumptions with experience collected throughout the study. Under the new guidelines it’s important that the protocol design is written to allow for adaptations. It’s also important that decision criteria around adapting the planned dose escalation steps based on emerging data are clearly defined within the protocol. Correct wording in protocol which allows for flexibility in design is now critical as changes in dose levels may require a substantial amendment unless such changes are covered by predefined decision criteria in the protocol.
Modelling and Simulation

The second approach highlighted in the updated recommendations is the use of model based design. Model based designs estimate the exposure/event (efficacy or toxicity) relationship and assign exposure levels based on the statistical probability of seeing that event. To facilitate precision in the predictions, models and simulations integrate data from different studies (e.g. in vitro pharmacological data, in vivo pharmacokinetic and even data from different compounds with same mechanism of action). The PK/PD based models and simulation approaches recommended in the new guidelines emphasise precision when determining starting exposures, dose increments, maximal exposures and adaptations. In the case of estimating exposures for NOAEL, the new guidelines state:

“The exposures achieved at the NOAEL in the most relevant animal species used (which might not necessarily be the most sensitive species) should be used for estimation of an equivalent exposure for humans. Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using allometric factors.”

Additionally, as data is collected, knowledge of the IMP is continuously updated and dose prediction is continually informed and refined. As such, modeling and simulation is not only recommended for calculating starting exposures but also for dose increments, calculations of maximal exposures, and to inform adaptations. When applied to dose increments in a SAD study, and as data from earlier cohorts are added to a model, estimations of further safe exposures can be refined and dose increments increased or decreased accordingly. The new guidelines recommend methods for modelling that determined dose and estimated exposure levels to be included in the protocol and to be summarized in the IB.

PK/PD modelling has been incorporated in drug development since the turn of the century. It has evolved and become a powerful predictive tool used to improve the translation of preclinical findings to early clinical studies. It is also used to increase efficiencies in early phase development, and help predict dose ranges in FIH studies. In 2018 Q-Pharm will publish their second white paper describing in more detail how PK/PD modelling and simulation can help inform early phase study design.
Our understanding of disease using data, technology and innovation has led to exponential developments in translational science and in all phases of clinical development. The new EMA guidelines on FIH studies open and guide the integration of non-clinical data in PK, PD and toxicology with modern, adaptive design and modelling and simulation tools. This facilitates greater safety, precision and efficiency in early phase study designs.

European Medicines Agency (EMEA) Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products 2007
