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# Pre-clinical Data Analysis Ensuring Relevant First-in-Human Clinical Trials

The first-in-human trial (FIH) is an important milestone in the development of a potential new drug. It will already have successfully passed a whole range of preclinical tests, including pharmacokinetic and pharmacodynamics experiments and *in vivo* safety tests in animals, but there remains no way of being absolutely certain how a drug will behave when it is taken by humans.

When setting the dose, there is no substitute for experience, and even then, it can be risky. It is unusual for something to go very wrong, but when it does, it puts the industry and clinical trial procedures in the spotlight. The 2006 study carried out by Parexel for TeGenero on an immunological agent at Northwick Park hospital in London is still well remembered, more than a decade on, after six men experienced organ failure. More recently, the trial run by Biotrial in Paris for Bial on a fatty acid amide hydrolase inhibitor, being investigated as a potential pain therapy that led to one death and five hospitalisations, provided more negative coverage for FIH clinical trials. Although these were just two incidents in a decade in which thousands of other trials were conducted, they were the ones that are remembered.

The regulatory authorities are rightly concerned about the risk of the first exposure of humans to investigational therapeutic agents. The EMA's '*Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products*' was published in 2007, the year after the Parexel/TeGenero incident, and is currently being revised in the light of developments in the intervening years (draft revised version is available and will become effective from February 2018).

The FDA's guidance, '*Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers*', dates back to 2005, and sets out a process for determining the maximum recommended starting dose that is likely to prove safe for first-in-human volunteers.

That year, the FDA also recognised the exploratory IND study. These small studies, usually on fewer than 10 subjects and taking no more than a week, are designed to determine whether or not full human trials are likely to be worthwhile. Similar guidance on exploratory human studies was published by the EMA in 2008.

However, there is no one-size-fits-all approach for first-in-human trials. Every investigational drug is different, and the likely risks and uncertainties vary greatly from one to the next. Published guidelines and guidances merely describe the agencies' current thinking, and can never be a substitute for a thorough assessment of each individual case.

Regardless of the care taken in designing and running a FIH trial, there remains only about a one-in-10 chance that an investigational drug being tested in humans for the first time will reach the market. This is only likely to improve with an increasing ability to predict in advance how a drug is likely to behave in humans.

Great strides have been made in the ability to assess and predict pharmacokinetics and pharmacodynamics in recent years, but anticipated unexpected toxicity remains difficult, even though it is often closely related to the pharmacokinetic properties. The ability to more reliably assess the likelihood of a project's failure before a FIH trial is commenced would be a huge asset in reducing attrition.

At the heart of the problem is the reliance on animal models. Although they are required by the regulators, and do indeed give an insight into how a drug might behave in humans, in reality, human biology and biochemistry are very different from those of mice, rats or dogs, and the success of the translation of these results into human predictions is patchy at best.

There is a growing realisation and acceptance among industry scientists, that animal models cannot reliably predict what will happen in humans, and that the poor attrition rate is a result of this and the similar inadequacy of *in vitro* lab assays. So, how can safety and efficacy predictions be improved, when the translational success of going from preclinical to clinical results is so limited?

Simply relying on the preclinical studies required by the regulators is unlikely to give the best results. Those laid down by the EMA, FDA and their counterparts elsewhere have to be undertaken for legal reasons, but they should only be considered as guidance. Further preclinical studies, that give wider data on the likely behaviour of an investigational new drug in humans, should be carried out and the information they provide used to make those all-important go-no go decisions.

**CNS Case Study**

A drug recently being developed for a CNS indication provides a good example of why it is important to carefully consider the likelihood of success before embarking on a FIH programme.

The FIH trial was initiated, but rapidly paused by the authorities because of an unexpected non-linearity in pharmacokinetics. The regulators, quite rightly, required this observation to be explained and an adequate investigational plan put in place before the trial could be resumed.

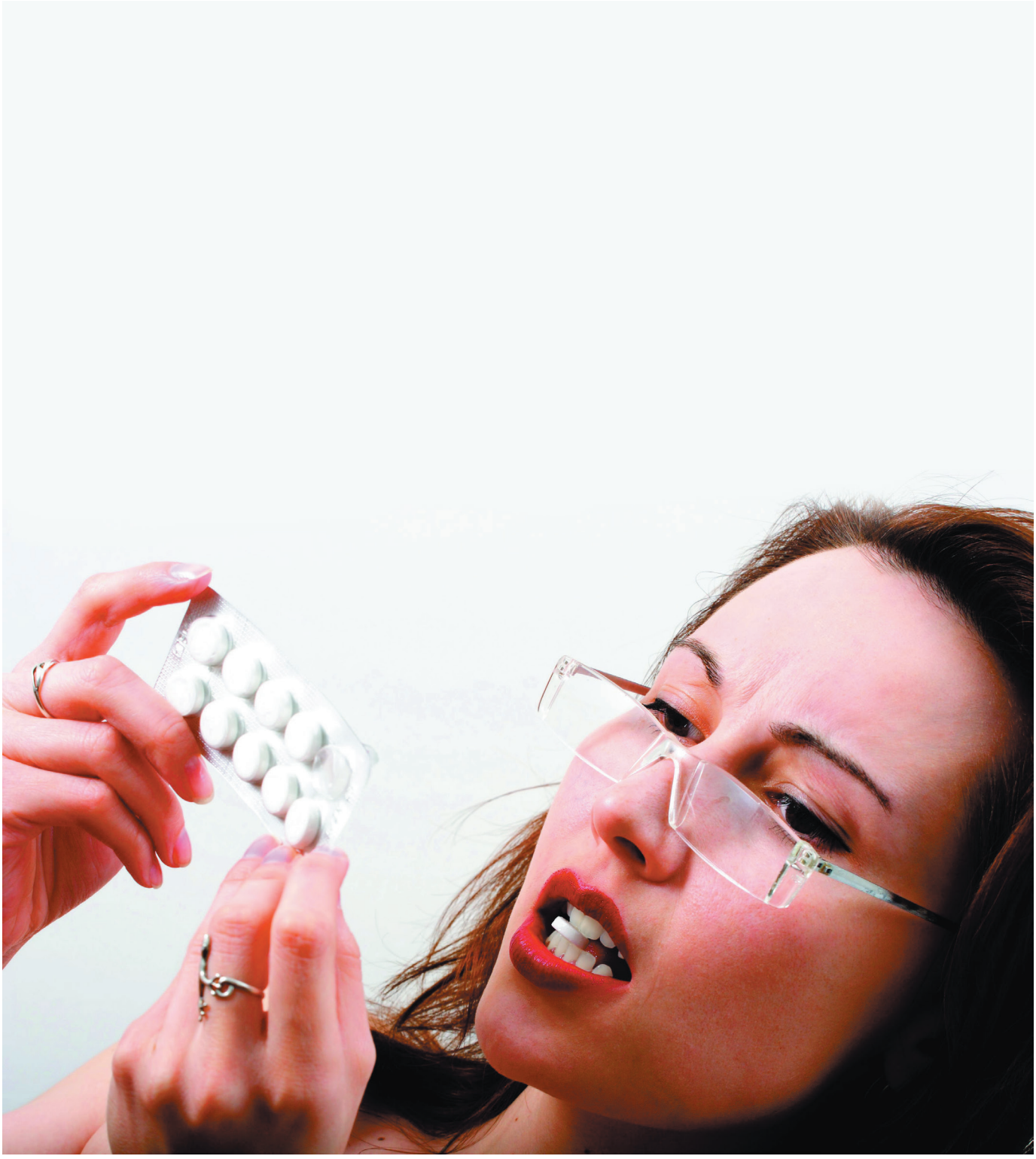
The trial had been initiated with the usual collection of data from both *in vitro* and animal studies. When this was reassessed in the light of the suspension of the FIH trial, it became clear that there

were signals in the animal toxicokinetic data that, with hindsight, showed that the non-linear behaviour in humans might have been predicted.

Further data that would have been useful to inform the FIH trial were also absent. Although the high protein binding of the major pharmacologically active metabolite had been investigated, this was not the case for the parent compound. There was no explanation of the high volume of distribution or tissue affinity that was observed. And, although enzyme inhibition and induction were studied, whether the drug or the metabolite acted as an enzyme substrate were not.

This failure to explain and collect all data led to an inadequate trial design for the FIH study. The trial being stopped because of the pharmacokinetic anomaly prevented more serious safety problems, as the potential of the agent to cause serious toxic side-effects had not been adequately investigated. Further analysis of the preclinical data also indicated that it was likely to have a narrow therapeutic index.

The decision whether to resume the trial could only be made after a full clinical development plan was made. This included a complete list of those *in vitro* and animal studies that were required, along with modelling and simulation services to aid the predictions.



Once the risk factors such as pharmacokinetics, pharmacodynamics and potential toxicities have been evaluated and a starting dose established, there are multiple other factors that will affect the trial's likelihood of success. A good deal of care and attention must be put into the design of the trial protocol in terms of both logistics and timelines.

Factors that must be considered include the number of doses that will be given to each subject, and how many participants will be dosed each day. How likely are subjects to drop out, if it is a multi-period study? Is the design sufficiently flexible to allow changes in the light of clinical data? And, should the worst happen, how well equipped is the clinical research unit to handle unexpected adverse events? These are all questions that should be addressed in collaboration with the principal investigator and other staff from the trial site, including experts in pharmacology and clinical medicine.

In most cases, the subjects recruited for a FIH trial will be healthy volunteers. There are many advantages: the recruitment speed is usually swift and cohorts can easily be scheduled, and there are no co-medications or co-morbidities to contend with. However, it is more commonplace for FIH trials of cancer drugs and those with a narrow therapeutic index to be in patient populations, and a decision to use patients instead of healthy volunteers needs to be carefully considered and justified for every individual FIH.

The starting dose is perhaps the most important decision that must be made, but also one of the most challenging. It must be sufficiently low that toxicity is unlikely, but not so low as to allow relatively rapid attainment of efficient dose in early or Phase II studies. Several strategies can be applied to determining the maximum recommended starting dose, including the 'no observed adverse effect level,' which is also referred to as the FDA approach. Alternatives include the minimal anticipated biological effect level approach, a similar drug approach, the use of modelling and simulation, and microdosing. A case-by-case approach is usually appropriate, but caution should always be applied because of the safety implications.

Once the starting dose has been given to study volunteers without incidence, attention must be turned to the dose escalation strategy. A safe multiplying factor is commonly applied, typically a factor of three for the first two or three escalation steps, a factor of two for the next two steps, and finally a factor of 1.5. Pharmacokinetic and pharmacodynamic data should be assessed throughout, and predefined criteria should support the decision to escalate to the next dose.

If an investigational drug is deemed to be particularly high risk or at high tested doses (when the safety coverage seems not to be full in terms of expected drug exposure), it can be appropriate to use sentinel subjects. By dosing a very limited number of subjects, often only one, with the active agent at the outset before the remainder of the cohort is dosed, the overall risk is much lower. Both the EMA and FDA recommend this strategy for high-risk compounds and, had it been applied, the fall-out in terms of number of patients experiencing adverse events would have been very much lower in the 2006 Parexel/TeGenero trial.

Most FIH studies are carried out in a randomised, double-blind, placebo-controlled manner. This removes the opportunity for bias in reporting adverse events and in the assessment of laboratory abnormalities while the trial is underway. Other design options will depend on the aims of the development programme and the demands of the individual agent. Alternatives include parallel, cross-over, sequential or interlocking cohorts. The decision whether to use a conventional, umbrella, adaptive or adaptive umbrella protocol must also be used. Within limits, the design should be flexible, and deliver better information more quickly and cheaply.

Statistical methodologies such as the Bayesian adaptive method have flexible numbers of cohorts, and subjects within them, and simple empirical stopping rules are applied to increase performance and facilitate implementation.

As an example, a FIH exploratory design was developed to establish safety, tolerability and pharmacokinetics for an investigational tyrosine kinase inhibitor. Healthy volunteers were deemed most appropriate as the biomarker of tyrosine kinase inhibition was measurable, there were no expected target-related safety issues, and high doses were not going to be necessary.

The maximum recommended starting dose was calculated using both the NOAEL and MABEL methods. MABEL resulted in a lower starting dose and was chosen, and a conservative dose escalation schedule was planned in the light of the expectation, made on the basis of pre-clinical toxicology studies, that it would have a narrow therapeutic index. Sentinel groups were recommended in the high single ascending dose group, and also in all multiple ascending dose groups. The length of the in-house stay was planned based on the *in vitro* plasma half-life, and also, the potential for delayed toxicities occurring based on pre-clinical studies. An adaptive umbrella design with sequential cohorts was chosen, with two different oral formulations being assessed in a cross-over manner in one of the single ascending dose cohorts.

There is a temptation to stick to what is known and to choose a protocol based on habit and experience, rather than applying a scientific rationale. The overall landscape of required, suitable and advisable pre-clinical studies will vary from compound type to compound type, and therapeutic indication to therapeutic indication. Filing an IND and carrying out FIH trials is an expensive and time-consuming process. Going ahead with something that will, in all likelihood, fail is a waste of time and money that could better be invested in something that is more likely to succeed.

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