CHMP guideline on reducing risk in first-in-man trials: how will it affect your research?

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Pharmaceutical manufacturers are producing ever more novel and sophisticated products. These medicines are often highly targeted and have complex mechanisms whose effect can vary widely between study populations and animal surrogates. The effect of these medicines in humans can be difficult to foresee, even when pre-clinical testing in animal and in vitro models predicts that the products will be tolerated. Grant Castle and Charlotte Marshall throw some light on this complex area.

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Only a few years ago, first-in-man, or phase I, research in healthy volunteers was subject to reduced or negligible regulation in many European countries. In the UK, for example, phase I research in healthy volunteers required only ethics committee approval. Even following the implementation of the Clinical Trials Directive 2001/20/EC [1], a number of Member States, such as the UK and Germany continued to offer accelerated review of phase I Clinical Trial Authorisation (CTA) requests. Regulatory attitudes to phase I research have, however, changed since the unfortunate events surrounding the TGN1412 clinical trial in March 2006.

The TGN1412 trial at Northwick Park highlighted the risk of phase I clinical trials. Nothing in the pre-clinical studies gave the investigators any indication that the six volunteers would react as they did. The animal studies for TGN1412 were encouraging and the sponsor established an initial human dose level equating to just one five hundredth of the dose that was well tolerated in cynomolgus monkeys. Even so, the subjects suffered severe adverse reactions that have subsequently caused regulators and manufacturers to examine strategies to reduce the risk to subjects in phase I trials.

One year after the Northwick Park trial, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) released a draft guideline on reducing risk in phase I trials. The CHMP has since finalised the guideline, which came into effect on 1 September 2007 ("the Guideline") [3].

The Guideline applies to relevant CTA applications and will affect the information and data that applicants submit. From 1 September, clinical trial sponsors will need to design their development programmes so that non-clinical data and other information about their investigational medicinal product (IMP) complies with the Guideline[3]. A failure to plan appropriately may result in delays and additional research expense. Similarly, sponsors must ensure that the design of their phase I clinical trials, and associated protocols, satisfy the Guideline. In general, the higher the potential risk associated with an IMP and its pharmacological target, the greater the precautionary measures the sponsor will need to incorporate into the design of its phase I study.

We consider how the Guideline will affect sponsors planning their research and submitting CTA applications. There are four principal steps to ensure compliance. Sponsors should use the criteria in the Guideline to assess the risk of an IMP (Step 1), including any quality concerns (Step 2), and appropriate non-clinical investigations that might reveal risk factors (Step 3). In light of the risks identified or raised in non-clinical investigations, the sponsor must then mitigate these risks through the design of the clinical trial (Step 4).

. . . step one: identify the risk of the IMP

The first step in complying with the Guideline is to identify features of the IMP that increase the risk of adverse reactions in trial subjects. The Guideline considers three criteria: a) the mode of action, b) the nature of the target, and/or c) the relevance of animal models. In CTA applications, sponsors should identify concerns deriving from any particular knowledge, or a lack thereof, for each of these criteria[4].

Concerns are most likely to arise where the mode of action of an IMP is novel, since knowledge of its extent, amplification, duration, and reversibility may be incomplete. For example, targets that are connected to multiple signalling pathways, or that could trigger a biological cascade or cytokine release, will result in complex and potentially unpredictable mechanisms. The Guideline also notes that the type (linear, U-shaped, bell-shaped, etc.) and steepness of the non-clinical dose response are important considerations.

An IMP will also carry a higher risk where its human target is not well studied. The risk is determined by the extent of the available knowledge of the structure, tissue distribution, cell and disease specificity, regulation, level of expression, and biological function of the target. This would include the existence and impact of polymorphisms (in animal species and humans) and variation between healthy subjects and patients.

For some IMPs, animal species/models or surrogates cannot reliably predict the pharmacological, pharmokinetic (PK) and pharmacodynamic (PD) results or toxic effects of the IMP in humans. The Guideline therefore requires the sponsor to compare the available animal species to humans, taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects.

By considering the three criteria above, sponsors might identify the level of risk associated with their IMP and can plan to mitigate any risks as far as possible.

. . . step two: assess additional concerns about quality attributes

The Guideline also expects sponsors to consider IMP quality attributes as part of the risk assessment. This will be particularly important

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where the IMP is sensitive to minor variations in manufacturing process, materials or dosage, as will be the case for many complex molecules and biological IMPs. Sponsors must demonstrate in their CTA applications that they have minimised any associated risks.

The Guideline requires sponsors to demonstrate that the material used in non-clinical studies is representative of the material they will use in phase I[5]. Using a suitable and qualified method, sponsors should characterise the active substance and product, including its heterogeneity, degradation profile and process-related impurities. If there are differences between the product used in the non-clinical studies and the IMP, or there has been a change in the manufacturing process since the non-clinical studies, the sponsor must ensure that the change is validated. This may require further non-clinical studies.

Sponsors must also show that the methods used for determination of the strength and/or the potency of the product are relevant, reliable and qualified. They must consider whether the intended formulation and route of administration of the IMP actually provides the intended dose. For instance, products at very low concentrations could be adsorbed to the wall of the container or infusion system.

. . . step three: review non-clinical investigations

The third step in complying with the Guideline is to ensure that non-clinical investigations explore and mitigate the risks associated with an IMP as far as possible. This includes assessing the limitations of non-clinical studies in predicting safety issues.

Some IMPs are highly species specific, and animal studies may not accurately predict their effect in humans. CTA applications must therefore demonstrate the relevance of the animal models they have used in non-clinical studies[6]. In particular, the Guideline requires sponsors to assess the homology between the animal model and humans and use information from in vivo, ex vivo and in vitro studies to demonstrate the predictive value of non-clinical study results[7]. PD data can also assist sponsors to identify the most relevant animal models by characterising the mode of action of the IMP and its pharmacological effects[8].

PK, PD and toxicology (including toxicokinetic) data will be reviewed as part of the CTA process. The Guideline recommends that sponsors conduct primary and secondary[9] PD studies in in vitro animal and human systems and in vivo in the animal models. Sponsors should include additional studies and end-points that mitigate the identified risks of the IMP. For instance, where IMPs target the immune system, the sponsor should investigate potential unintended effects.

The Guideline requires a dose/concentration-response curve of the pharmacological effect(s) detailed enough to identify detect significant pharmacological effects with low doses and to identify active substances with non-linear dose-response curves [10]. The sponsor will use this, and all other non-clinical information, to calculate a dose for the first-in-man trial.

Clinical trials have generally identified the No Observed Adverse Effect Level (NOAEL) from non-clinical studies and adjusted this to calculate the appropriate human dose. In the TGN1412 trial, however, subjects suffered adverse reactions despite the dose being five hundred times smaller than the NOAEL. This suggests that calculations based on NOAEL may result in a significant overestimation of dose for complex IMPs. For such IMPs, the Guideline recommends that sponsors follow the "Minimal Anticipated Biological Effect Level" (MABEL) approach, provided that the MABEL dose is lower than the NOAEL dose[11]. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans, which is calculated using all in vitro and in vivo information available from PK/PD data.

To reduce further the risk of adverse reactions, the first human dose might be only a small percentage of the MABEL. This "safety factor" should take into account all relevant information including the risks of the IMP, the shape of the dose-response curve and the degree of uncertainty in the calculation of the MABEL.

. . . step four: design the trial appropriately

Having identified the risks associated with an IMP, and mitigated these as far as possible on the basis of appropriate non-clinical data, sponsors must consider the design of the first-in-man trial. To ensure that risk factors have been addressed properly, the Guideline asks sponsors to arrange for peer review of the protocol and the associated risk factors[12].

The Guideline sets out a number of criteria for selecting the study population. Whether the sponsor chooses healthy subjects or patients, he must fully justify the decision on a case-by-case basis[13]. To comply with the Guideline, the number of patients per cohort and progression between cohorts must reflect the variability of PD and PK parameters and the trial objectives.

The route and rate of administration must also allow monitoring for adverse events and timely discontinuation where necessary. For example, in the case of an intravenous administration, a slow infusion may be more appropriate than a slow bolus.

The sequence of dosing subjects within the same cohort and the interval between dosing must minimise risks to subjects and allow identification and assessment of adverse events[14]. Sponsors will need to justify the duration of the observation period between doses.

Once the first cohort has been dosed, the protocol should pre-specify criteria to be met before proceeding to the next cohort or dose escalation[15]. The Guideline suggests that this might involve comparison of data from previous cohorts or dosing levels against non-clinical data and safety information and/or anticipated responses.

The sponsor's obligation to mitigate risk to the subjects includes planning for adverse events[16]. CTA applications should identify likely adverse reactions. Sponsors must ensure that clinical staff can identify and respond to those or any other adverse reactions. The trial protocol should describe a strategy for managing risk, including a plan to monitor for and manage likely adverse reactions and procedures and responsibilities for modifying or stopping the trial if necessary[17]. The Protocol should also include a treatment strategy where there is a "predictable risk" of a certain type of adverse reaction. The strategy should detail any antidotes and the availability of emergency facilities and staff.

The TGN1412 trial demonstrated the importance of Intensive Care Unit (ICU) facilities being readily available. Accordingly, the Guideline requires clinical research units to co-ordinate with ICUs and to have immediate access to equipment and staff for resuscitating and stabilising individuals in an acute emergency[18].

. . . conclusion

The CHMP's Guideline provides a comprehensive strategy for reducing the risk of phase I clinical trials. There are now additional obligations for clinical trial sponsors to assess and mitigate the risks associated with IMPs. This will affect research on IMPs from an early, pre-clinical stage as sponsors will need to provide a submission that complies with the Guideline when applying for a CTA.

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Provided that sponsors are aware of the Guideline at an early stage, and design pre-clinical studies and clinical trial protocols accordingly, the Guideline will enable them to reduce the risk of unexpected adverse reactions in clinical trials. This is essential to increase and maintain the confidence of volunteers, investigators and manufacturers themselves in the regulatory framework for clinical trials. ❊

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1 Directive 2001/20/EC Of The European Parliament And Of The Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

2 Guideline on strategies to identify and mitigate risks for first-in-man clinical trials with investigational medicinal products (EMEA/CHMP/SWP/294648/2007), EMEA, July 2007.

3 In addition to the principles expressed in the Guideline, some special populations such as paediatrics may deserve specific considerations. Ibid at 4.

4 Supra, note 2 at 4.1.

5 Supra, note 2 at 4.2

6 Supra, note 2 at 4.3.1. Where no relevant species exists, the use of homologous proteins or relevant transgenic animals expressing the human target may be the only option. The search for a relevant animal model should be documented and detailed.

7 A high degree of homology does not necessarily imply comparable effects. Supra, note 2 at 4.3.1.

8 Supra, note 2 at 4.3.2. Target interactions linked to functional response (e.g. receptor binding and occupancy, duration of effect and dose-response) are particularly important.

9 "Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies. Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target are secondary pharmacodynamic studies (these have sometimes been referred to as part of general pharmacology studies)." Note For Guidance On Safety Pharmacology Studies For Human Pharmaceuticals (CPMP/ICH/539/00), EMEA, June 2001 at Note 2.

10 Supra, note 2 at 4.3.2.

11 Supra, note 2 at 4.3.6.

12 Supra, note 2 at 4.4.1.

13 Supra, note 2 at 4.4.2.1.

14 Supra, note 2 at 4.4.2.4.

15 Supra, note 2 at 4.4.1, 4.4.2.5 and 4.4.2.6. The criteria must take into account the number of subjects that might have received placebo. The dose increment between two dose levels should be guided by the dose/toxicity or dose/effect relationship revealed in non-clinical studies, depending on whichever curve is steeper at the relevant dose – the steeper the increase in the curves, the smaller the increase in dose should be.

16 Supra, note 2 at 4.4.1 and 4.4.2.8

17 Supra, note 2 at 4.4.2.8. Duration and nature of monitoring should be justified on the grounds of PD, PD and safety endpoints considering any long-term consequences to physiological systems or safety problems. Sponsors must ensure that expedited reporting procedures are in place for SUSARs before the trial begins.

18 Supra, note 2 at 4.4.3. First-in-man trials should preferably be conducted as a single protocol at a single site. Trials with multiple sites must be justified and require plans for subject well-being and rapid communication between sites.

Swedish nicotine drug proposals herald break-up of pharmacy monopoly

The Swedish government is planning to submit a proposal to the legislative council (Lagradet) to break the monopolistic right of the state-owned pharmacy, Apoteket, to sell nicotine-replacement products. The move is aimed at increasing accessibility to these medicines, thereby contributing to the national action against smoking.

The proposal – part of the government's response to the European Court of Justice (ECJ) Decision to end the overall monopoly of Apoteket in area of drug sales – would allow stores, such as supermarkets to stock nicotine-replacement drugs. However, in order to do so, the store would be obliged to notify the regional municipal council. "You would not need either a licence or authorisation. If the store does not have a fixed business address in a any Swedish municipality, then we suggest that they notify the Stockholm municipality," Sara Rosenmuller, spokesperson for the health ministry told *EURALex*.

As the legal smoking age in Sweden is currently 18, the sale of nicotine-replacement products to individuals below this age will remain illegal. Those who transgress this rule could face up to six months imprisonment. The same penalty has also been suggested in the proposal for stores that fail to notify their municipal council. Although these councils will be responsible for monitoring whether stores are following the regulations, overall supervision of the system will remain in the hands of the medical products agency (Lakemedelsverket). The agency will be authorised to ban a company from the sale of nicotine-replacement products if the firm has infringed the law.

Minister for health and social affairs Goran Hagglund insisted that the proposed law was a logical step in the right direction. "Today you can buy cigarettes anywhere, but you can only buy nicotine gum and other nicotine medicines at specific times at a pharmacy. That is not good and sends out the wrong signals," he said. The aim is to enforce the law on 1 March 2008.

In terms of the wider picture and diluting the monopoly over the medicines market that is currently enjoyed by Apoteket, in December 2006, the government appointed a special expert to make recommendations on who other than Apoteket should be able to sell prescription and non-prescription medicinal products. The expert delivered a first report in August 2007, which contained proposals on how the distribution of medicines to and within hospitals should be organised and, in particular, who should be permitted to run hospital pharmacies and what services they would be able to provide.

The second and third reports are set to be delivered to the government in December 2007 and April 2008. The second report will contain proposals concerning who, besides Apoteket, will be permitted to sell prescription and non-prescription medicinal products. The last report will focus on who will be authorised to sell a limited stock of non-prescription medicinal products outside pharmacies. ❊

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