“First-in-man” studies
an update on recent EU regulatory developments

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Abstract
The TGN1412 Phase I study conducted for TeGenero last year, which resulted in very serious life threatening adverse reactions in healthy volunteers, has led to publication of reports from a number of sources. The aim of this update is to highlight the issues raised in these recent key publications and how they may impact the conduct of FIM studies with “high risk” medicinal products in the future.

There has been a great deal of publicity recently regarding the conduct of “first-in-man” (FIM) studies. This is as a direct consequence of the TGN1412 study conducted for TeGenero last year, which resulted in very serious life threatening adverse reactions in healthy volunteers. In November 2006, the Expert Scientific Group convened by the Secretary of State for Health, UK published its final report (reviewed in Regulatory Rapporteur Vol 4, No 1 January 2007). Further key publications have been released in early 2007 regarding FIM studies using potentially “high risk” medicinal products.

The relevant key publications are:
• German Authority (BfArM/PEI) proposals for FIM studies discussed at the AGAH Workshop in Bonn in January 2007.
• Committee for Medicinal Products for Human Use (CHIMP) draft guidance “Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products” (EMEA/CHIMP/SWP/28367/2007) released for consultation on March 23, 2007 with an invitation to attend a Workshop on June 12.

The aim of this update is to highlight the issues raised in these recent key publications and how they may impact the conduct of FIM studies with “high risk” medicinal products in the future.

French Agency provided first guidance
The first regulatory agency to provide some specific guidance on Phase I studies was the French Regulatory Agency (Afssaps) last year. It issued guidance on the conduct of first-in-man clinical trials focusing on the estimation of the starting dose, definition of dose progression and the healthy volunteer clinical protocol. Because it felt that there was often inadequate justification in many studies, additional guidance for sponsors was issued in July 2006, regarding the data that must be collected and taken into consideration when drawing up such protocols, and the information that the dossier must contain for these trials. This guidance can be found at: http://agmed.sante.gouv.fr/pdf/3/clinical-trial-phase1.pdf/

German regulatory proposals for first-in-man studies
A clinical pharmacology Workshop hosted by the Arbeitsgemeinschaft für Angewandte Humanpharmakologie (AGAH) was held in Bonn in January 2007. The focus of the workshop was on “lessons learned from TGN1412” and on how to improve FIM trials in the future with representatives from both industry and BfArM/PEI presenting their thoughts. The positions presented at this workshop will have also contributed to the development of the draft CHIMP guideline. BfArM presented definitions for a “high risk” monoclonal antibody (mAb) and NCE, which are consistent with the draft guideline. PEI presented their thoughts on the classification of “high risk” and IMPO requirements for biotechnologically derived products together with the possible implications for future trials. The workshop presented issues worthy of further consideration which can be viewed on the AGAH website at http://www.agah-web.de/first-in-man-trials.html&L=1/

MHRA “Applications for first time in man trials with higher risk compounds”
In February, the MHRA published on its website (http://www.mhra.gov.uk), a new process for approval of CTAs involving FIM studies with “higher risk” compounds. The MHRA proposes that, for these trials, it will
seek advice from a UK Expert Advisory Group (EAG)/Commission on Human Medicines (CHM) before approval for the trial can be given.

This will apply in particular to trials involving:

- New compounds acting (directly or indirectly) via the immune system with a novel target or a novel mechanism of action or having a secondary potential effect on the immune system via a mechanism of action which currently is not well characterised; or

- Novel compounds acting via a possible or likely species specific mechanism or where animal models are unlikely to be predictive of activity in humans. Sponsors will need to decide, based on the type of trial, whether their applications will fall within these categories. Sponsors can also seek pre-submission advice on whether or not the compound in question falls within the category of “higher risk”. A detailed procedure for how to obtain the advice and submit documents can be found on the MHRA website along with proposed dates of meetings (2007-2008) with the EAG/CHM.

The MHRA submission package requirements for the FIM studies using “high risk” compounds is identical to the normal CTA application process but requires additional documents to address the CHM required areas of discussion to be included.

The CHM areas of discussion are:

1. Function of the target in man
2. Ability of the subject to maintain a normal physiological response to challenge in the presence of the investigational product
3. Transition from pre-clinical to human testing, particularly with regard to highly species specific molecules
4. The potential for on-target and off-target effects and how this will be handled in the clinic
5. Doses used in the relevant animal species (particularly with regard to the use in the animal model of the starting dose to be administered to man)
6. Rationale for the starting dose in man (including, for example, receptor occupancy)

7. Rationale for the study population (particularly for the use of healthy volunteers)
8. Rationale for the administration schedule for the initial and subsequent cohorts. This should include the time interval between doses administered to individual subjects
9. Rationale for the dose escalation particularly with regard to potential adverse effect
10. Rationale for the proposed trial site, including the facilities available.


Following the TGN1412 trial, the Royal Statistical Society formed a Working Party with a specific objective: “to review statistical design considerations for first-in-man studies with particular reference to monoclonal antibodies and the wider class of new biologicals and biotechnologies”. The Working Party made a total of 21 recommendations, the majority of which were broadly in line with the Expert Scientific Group on Phase I clinical trials (Duff Report, December 2006), ie, provision of appropriate medical care in case of emergency; appropriate starting dose calculations; sequential dosing of subjects; general precautionary approach to study design for studies using these “higher risk compounds”.

The remaining recommendations are summarised below:

- Ensure that adequate statistical expertise relevant to research is employed by ethics committees (and MHRA) in reviewing clinical trials applications
- Ensure all participants in FIM in healthy volunteers are insured
- FIM protocols should describe the intended analysis in sufficient detail to allow protocol reviewers (and the ethics committee) to determine if the objectives, design and proposed analysis are compatible
- The design of the FIM trials should reflect realistic models of pharmacokinetic data
- The plan for blood sampling and analysis and observation of vital signs should be based on information from pre-clinical studies

- In the informed consent, all aspects of the trial design should be shared with subjects being recruited, ie, it should be open protocol, hidden allocation in design
- Public debate and research are needed about the maximum acceptable level of risk for FIM studies in healthy volunteers and about whether there should be risk-adjusted remuneration of healthy volunteers
- The regulatory authorities should provide a mechanism for the pharmaceutical industry to collect and share data on serious adverse reactions in FIM studies – to improve _a priori_ risk assessment
- Separate syntheses of study designs and of the occurrences of predicted, theoretical and unprecedented harm, either as serious adverse events or distributional changes in biomarkers should be considered for healthy volunteers and for patients, by type and novelty of compound and by _a priori_ assessed level of risk
- The MHRA should report annually on the designs of, and serious adverse events (whether for the first exposed cohort or at a dose-escalation step) in, FIM studies in healthy volunteers (versus patients) that involved administration of a biological/biotechnology product; and for those involving a chemical compound
- The MHRA should maintain a central registry of participating volunteers in the UK
- Statistical reporting of pre-clinical studies should be improved in line with ICH on the reporting of clinical trials
- Greater use should be made of numerical, as opposed to verbal, descriptions of risk and statistical variations in the submissions made to, and accepted by, regulatory authorities
- Mock applications to competent authorities convey expected standards. They should be revised to:

  - Conform with preceding recommendations on the statistical reporting on pre-clinical studies
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Focus

- Require always that a proper inter-administration interval between successive subjects is both specified and justified
- Specify the waiting time for laboratory-based results that pertain to “safety”.

A full copy of the report can be downloaded from the Royal Statistical Society’s website (http://www.rss.org.uk/first-in-man-report/)

**CHMP draft guidance “Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products” (EMEA/CHMP/SWP/28367/2007)**

The European regulatory environment for first-in-man clinical studies is in the spotlight. Following an extensive review in the UK and discussions at national and EU level into the very serious adverse reactions that occurred during the first-in-man clinical trial with TGN1412 at the Phase I Unit at Northwick Park in the UK, the national competent authorities, together with the EMEA and the European Commission, decided that it was necessary to produce an additional Community guideline as one of the measures for minimising the risk of such serious adverse reactions occurring again in Phase I trials.

The draft guideline, prepared by clinical and non-clinical experts, from the national competent authorities and the CHMP, builds on the existing principles laid down in European legislation and existing guidelines, in order to provide specific advice for “high-risk” products.

The draft guideline was released on March 23 for a two-month public consultation period. Once finalised, the guideline should assist sponsors in the transition from non-clinical into early clinical development for products (chemical or biological) considered “high-risk”.

In essence, the draft guideline reiterates the importance of step-wise, risk-based drug development with particular emphasis on current ICH guidance. But it then goes on to highlight the need for “additional” data or areas that need to be addressed or additional precautions that are needed for high-risk products.

Overall, it recommends a more precautionary approach going forward, directing the sponsor to do more risk assessment prior to making a clinical trial application; specifically to clearly identify risks/key “unknowns” and areas of uncertainty.

Theoretically, the guideline will apply to both new chemical and biotechnologically derived entities, but inevitably there will be great deal more sensitivity towards biotechnology products that target the immune system via novel mechanisms.

As part of the consultation exercise, EMEA is to hold a Stakeholder Workshop on the draft guideline on June 12, 2007. Additional feedback received at this workshop will be taken into account to ensure the clarity and acceptability of the guideline before it is finalised in July 2007.

The guideline covers the three areas of data assessment namely, Quality, Non-clinical and Clinical.

**Quality requirements for high-risk products**

The guideline identifies that quality attributes may add to the risks inherent for a FIM administration (eg, due to insufficient knowledge for entirely novel types of medicinal products or entirely novel types of manufacturing processes).

For high-risk medicinal products, it recommends that the following points be considered:

- A high degree of characterisation to be achieved even for this early stage – characterisation of product-related variants, including heterogeneity and degradation products that may have a pharmacological impact. Special consideration should be given to the suitability and qualification of analytical methods used to characterise active drug substance and drug product.
- In order to determine a safe starting dose, methods used to determine strength and (where appropriate and possible) potency, need to be relevant, reliable and qualified (eg, where the dose is based on biological activity and is expressed in arbitrary units, and the assays are not qualified and/or validated to ensure the reliability; the doses given to animals may be poorly defined and mislead the interpretation of a safe dose). The lack of a potency assay would need to be fully justified.
- Given the fact that major clinical decisions are based on the non-clinical data, it is important to show that the non-clinical data are still valid. Comparability with the non-clinical material needs to be fully demonstrated, especially for biomolecules where subtle changes may affect binding characteristics and other biological properties, with potentially clinical consequences.
- Specific issues for very small doses or very low concentrations: the risk of reduced accuracy can have clinical consequences in these situations.

**Non-clinical requirements for high-risk products**

For high-risk medicinal products, emphasis is placed on full characterisation of the primary and secondary pharmacodynamics (in vitro animal and human systems and in vivo in one or more chosen animal models). Studies should include receptor binding and occupancy, duration of effect and dose response established with sufficient titration steps to increase the likelihood of detecting distinct pharmacological effects with low doses.

Exposures at pharmacological doses in relevant animal models should be determined in addition to standard ADME studies. Although Good Laboratory Practice (GLP) compliance is not mandatory for these studies, they should still be of high quality and consistent with the principles of GLP.

The relevance of the animal model should be demonstrated since non-clinical animal studies with highly species-specific products may:

- Not reproduce the intended pharmacological effect in humans
- Give rise to misinterpretation of pharmacokinetic results
- Not identify relevant toxic effects. Therefore, additional PK/PD/cross-reactivity studies may be needed.

Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins is strongly recommended.
In addition to the core battery, additional safety pharmacology studies investigating the effects in other organ systems may be required on a case-by-case basis.

Toxicology studies should be performed with appropriate toxicokinetic analysis in relevant animal species. A scientific justification will be needed for the use of animal models of disease to support determination of safety.

**Clinical requirements for high-risk products**

Careful consideration of the risks associated with the trial and management of those risks as part of the study design (ie, a more precautionary approach) is warranted. In general the higher the potential risk associated with the medicinal product and its pharmacological target, the greater the precautionary measures that should be exercised in the study design.

Key aspects of the trial design should be evaluated and guide the choice of:

- Study population
- First dose
- Number of subjects per dose (cohort)
- Dosing interval between subjects within the same cohort
- Dose escalation
- Transition to next cohort
- Stopping rules

- Defining responsibilities for decisions with respect to subject dosing and dose escalation.

For high-risk medicinal products, an additional approach to dose calculation should be taken. The use of the “Minimal Anticipated Biological Effect Level” (MABEL) approach is recommended. The safety factors need to be justified. Where NOAEL and MABEL give different estimations of the first dose, the lower should be used.

The choice of study population should be fully justified by the sponsor on a case-by-case basis. Careful consideration should be given to the choice of route and rate of administration with careful monitoring for an adverse reaction or exaggerated response.

An initial sequential dose administration design should be employed within each cohort in order to minimise any risks. Any non-sequential dose administration within each cohort should be justified. The dosing interval should also be justified. Time intervals between doses between cohorts should be guided by existing non-clinical and clinical PK and PD data and if available, already existing experience with comparable medicinal products.

For dose escalation methodology, pharmacodynamic aspects including the shape of dose-response curve from non-clinical studies should be taken into account. Further dose increases should proceed with caution.

The Clinical Protocol should define stopping rules for the individual subject, cohort and trial. Use of an Independent Drug Safety Monitoring Board should be considered and where not appropriate, full justification should be provided.

A specific plan for monitoring for adverse events or adverse reactions should be provided. All clinical trial staff need to be trained to identify those anticipated reactions and how to respond to those or any other adverse events or reactions. A treatment strategy should be described in the protocol for anticipated risks.

The length of the monitoring period within and outside the research site should be justified as part of the strategy to manage risks in the clinical trial.

First-in-man trials with high-risk medicinal products should take place in appropriate clinical facilities (with immediate access to appropriate facilities for medical emergencies) and be conducted by medical staff with the appropriate level of training and expertise.

A copy of the draft guidance document released for consultation is available on the EMEA website (http://www.emea.eu.int/pdfs/human/swp/2836707en.pdf).

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TOPRA is aware that regulations of the food and feed additives industry are becoming more complex. There has been interest expressed in creating an email network for TOPRA members working in regulatory affairs in the area, in order to provide a forum for the discussion and exchange of information and experiences in this changing field. If you would be interested in becoming a member of the network, send your details to spin@topra.org.