New regulatory requirements for first into man studies in France

Dominique Tremblay
External Expert at the French Medical Agency
Agence Française de Sécutrité Sanitaire et des Produits de Santé

AGAH-Club Phase I Bad Homburg April 26-27 2007

CLINICAL TRIAL

- Clinical trials are regulated in France since 1988, clauses concerning the protection of the subjects taking part into a Phase I clinical trial are still in force
- Phase I clinical trials must be performed only in accredited research sites. Accreditation is given for 5 years after inspection. Conditions to be agreed are the appropriateness between the environment and the safety: staff and facilities…
- To avoid simultaneous participation of volunteers in clinical trials, they are listed in the "National Registry of Volunteers"
- Total allowance is limited to 4500 € a year by subject

CLINICAL TRIAL

- From the directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001, a clinical trial may not start without the agreement of:
  - the Ethics Committee
  - the competent authority of the Member State concerned
- In order to anticipate the adaptation on this directive to the French law, the French Medical Agency (AFSSaPS, the competent authority) decided in November 2003 to suggest (it was not a demand) to the sponsors to submit a dossier for authorising the first in man Phase I clinical trials. As part of this pilot phase, AFSSaPS drew up recommendations regarding the format and content of applications for first in man trials

CONTENT OF THE DOSSIER RELATIVE TO THE CHEMICAL OR BIOLOGICAL AND PHARMACEUTICAL QUALITY DATA AND TO NON-CLINICAL DATA CONCERNING THE INVESTIGATIONAL MEDICINAL PRODUCTS USED IN PHASE I CLINICAL TRIALS

Version 3.0 January 2004

IMPORTANT POINTS

- 1. The investigational medicinal product (IMP) used for the proposed clinical trial should be comparable to that used in the toxicity studies in terms of quantitative and qualitative impurity profile
- 2. It is preferable to provide the results in the form of summaries and tables pointing out the key points, and to provide a list of the studies performed and references from the appropriate literature
- 3. Study reports should be provided upon request

IMPORTANT POINTS

- 4. A critical analysis of the available non-clinical data should be provided, ensuring that an appropriate safety assessment was performed allowing administration to humans or justifying the lack of data in the opposite case
  The following data should be clearly presented:
  - the kinds of toxicities observed: target organs or functions, reversibility
  - the NOEL and/or the NOAEL
  - doses proposed in the clinical trials and their justification;
  - the parameters to be monitored during the clinical trials considering the available non clinical data.

IMPORTANT POINTS

- 5. Non clinical toxicology and toxicokinetics studies must be conducted in accordance with the GLP. Any deviation must be justified.
- 6. Any new recommendation published relatively to non-clinical data should be taken into account.
- 7. Any deviation from the published recommendations should be justified.

- In this document, there is no specific recommandation on the calculation of the first dose in human

The law to adapt the European Directive has been promulgated in France in 2006. Following the very serious unexpected adverse reactions that occurred in the first-in-man clinical trial of TGN1412 in March 2006, AFSSaPS issued the following document:

FIRST-IN-MAN CLINICAL TRIALS

ESTIMATION OF THE STARTING DOSE, DEFINITION OF DOSE PROGRESSION AND PROTOCOL OF ADMINISTRATION TO VOLUNTEERS

25/07/2006 reviewed 5/09/2006

FIRST IN MAN CLINICAL TRIALS

The purpose of the first administration to man (healthy or patient volunteer) of an IMP is to conduct an evaluation of its safety profile at short-term for a given dose ranging and to establish an initial PK/PD profile.

The starting dose of the IMP must not cause any detectable adverse effects in the short term.

Estimation of the starting dose

The starting dose shall be determined on the basis of data from animals (2 species), in particular, of the **NOAEL's**

However, some adverse effects may be caused by an exaggerated pharmacological effect on an organ or a target function, rather than by the intrinsic toxicity of the new active ingredient (for example: recombining proteins, monoclonal antibodies, growth factors, etc.). In this case, it is recommended to use the **NOEL**

With regard to **biotechnology products**, at least one relevant animal should be identified with the presence of the same type of receptor, effector or regulation cascade as in human. When no relevant animal species is available, the use of transgenic is recommended.

Estimation of the starting dose

Estimation of the human equivalent dose (HED)
- According to the FDA guidance from the NOAEL's
- From the AUC at NOAEL's and the clearance estimated from *in vivo* data in animal or *in vitro* using human material

The lowest HED is considered, corresponding to the most sensitive species

Starting dose = HED/safety factor

The safety factor of the starting dose (≥10) and the dose progression must be determined according to the risk factors identified from preclinical trial data

Dose progression

The progression to the next dose must be based on clinical tolerance criteria. However, depending on the risks identified during pre-clinical testing, the plasma concentrations of the new active substance may be considered. This allows a better estimation of the safety margin at each administered dose. A safety margin close to 1 or less does not necessarily force to stop the trial, but requires a slower dose progression.

The trial must be stopped in the event of adverse clinical or paraclinical observations, such as clinical symptoms, modification of biological or electrocardiographic parameters, etc...

Protocole

It is strongly recommended to conduct the clinical trial in only one research centre
The IMP and placebo will be administered to cohorts of subjects

The following must be specified and justified:

Within cohorts:

- the number of subjects simultaneously treated, the time between treatments

Protocole

Between cohorts:

- **the time between the end of treatment in one group and the start of treatment in the following group. An overlap between two groups is not recommended**
- **the criteria for administering the drug to the next group,**
- **the criteria for modifying the dose progression and the criteria used to define a new progression,**
- **the criteria for stopping the dose escalation to the next group.**

Protocole

Shall be specified:

- The criteria for stopping the administration of the IMP: stopping a dose; stopping dose incrementation; stopping the treatment of one subject; stopping the trial
- The skills of the person(s) responsible for applying monitoring criteria and taking the resulting decisions (modification of the protocol, end of dose progression, end of trial)
- The circumstances in which these people will be required to intervene.

AUTHORISATION

Aplication for clinical trial is assessed by internal assessors and if necessary by external experts.

The target is to have an opinion within 15 days and eventually request for further information at this time and make a decision within 30 days

The maximum is 60 days

In average, authorisation is given at day 38

Beside the AFSSaPS document, a lot of documents were issued, most notably:

- **Joint ABPI/BIA Report July 2006**
- **Report from UK Ministry of Health's Expert Scientific Group on Phase I clinical trials, November 2006**
- **MHRA interim measures for clinical trial applications with high-risk products**
- **BfArM draft guidance on Phase I clinical trials, September 2006**
- **Publication from scientists from Paul Ehrlich Institute: Schneider, C.K. *et al.* *Nat. Biotechnol.* 24, 493-496 (2006).**
- **Publication from scientists from the Dutch CCMO: Kenter, M.J.H. *et al.* *The Lancet* 368, 1387-1391 (2006)**

In November 2006, the EMEA decided to prepare a guidance on the assessment of Clinical Trial Applications for Phase I trials of high-risk products.

Existing documents were taken into account by the members of the drafting goup, many of them were already implicated into writing of these documents

The new guideline has been released on 22 March 2007

Doc. Ref.EMEA/CHMP/SWP/28367/2007

DRAFT

GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR POTENTIAL HIGH-RISK MEDICINAL PRODUCTS

Dead line for comments 23 May 2007

Definition of potential high-risk IMP

- IMP's are defined as potential high-risk IMP's when there are concerns that serious adverse reactions in first-in-man clinical trials may occur. These concerns may be derived from particular knowledge or uncertainties on
- (1) the mode of action, and/or
- (2) the nature of the target, and/or
- (3) the relevance of animal models.

Definition of potential high-risk IMP

The sponsor should classify its IMP as

- high-risk or
- not high-risk

The sponsor decision will be assessed by the AFSSaPS

- In the case the IMP is or could be classified high risk, it is recommended to the sponsor to meet the AFSSaPS before filling their clinical trial authorisation application

Calculation of the first dose in human

- Beside the calculation methods already described, an additional approach is recommended: the 'Minimal Anticipated Biological Effect Level' (MABEL). The MABEL is the anticipated dose level leading to a minimal biological effect level in *humans*. The calculation of MABEL should utilise all relevant *in vitro* and *in vivo* available information from PK/PD data:

  Starting dose = MABEL/safety factor

- When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used.

Protocole

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

- Study population: healthy subjects or patients
- Route and rate of administration
- Number of subjects per cohort
- Precautions to apply between doses within a cohort: an initial sequential dose administration design should be employed within each cohort

Protocole

- **Precautions to apply between cohorts: all the results from all subjects of the first cohort (and of subsequent cohorts) need to be carefully considered before administration of the first dose of the next cohort.** PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information. Any observed responses should be compared to the responses that were anticipated. Unanticipated responses may require a revised dose escalation. Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and data/results from these participants reviewed.

Protocole

- Dose escalation scheme: pharmacodynamic aspects including the shape of dose-response curve from non-clinical studies should be taken into account.
- Interval between dosing subjects within the same cohort
- Dose escalation increments
- Transition to next dose cohort
- Monitoring for adverse events/reactions
- Stopping rules and decision making process

Protocole

- Defining responsibilities for decisions with respect to subject dosing and dose escalation
- Site of the clinical trial: staff, facilities (intensive care unit)
- Long term monitoring

CONCLUSION

- The new guideline and the French recommendations are consistent
- The French recommendations are still in force in France and are reinforced by the new guideline in the case of potential high-risk IMP
- The dead line for comments on the new guideline is 23 May 2007
- The EMEA organise a public meeting on 12 June in order to have a public discussion before finalising the guideline