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**Report of the  
“International Expert Meeting on  
Exploratory Clinical Trial Applications and Microdosing”**

**15 September 2007, BfArM, Bonn (Germany)**

E. Stahl and T. Sudhop for the Chairs of the Expert Meeting\*

The drug development process with its extensive non-clinical safety testing is requiring more and more time and increasing resources. Therefore, new concepts are needed for an early “go/no-go” decision and earliest identification of the most promising candidate. Non-clinical testing requires large quantities of drug substance, which is often difficult to provide at an early stage of drug development. In order to ensure that the process of candidate selection is based on the most relevant data, it seems necessary to shift this selection process from the preclinical to the early clinical phase, where very specific questions can be addressed. The data obtained in this phase may facilitate decisions on the further direction of a drug development process and may thus help to lower the attrition rate of drug candidates in phase I and avoid wasting time and efforts in less promising candidates. In the focus of such concepts is translational research and medicine including the use and usability of biomarkers.

With its focus on standard testing batteries, the traditional regulatory non-clinical environment in phase I studies is often too rigid. By contrast, the roadmap of the EMEA and the critical pathway initiative of the FDA, both based on a risk-benefit approach, promise a more flexible approach.

The German Federal Institute for Drugs and Medical Devices (BfArM), in collaboration with the Paul-Ehrlich-Institute (PEI), initiated an international expert meeting to discuss current concepts and requirements for first-in-human clinical trials based on microdosing and exploratory clinical trial approaches. More than 50 delegates from pharmaceutical companies, European regulatory



authorities, contract organizations, professional societies, and the working party of the German Ethics Committees, participated in the meeting at the BfArM in Bonn, Germany, on 15 September 2007.

In two plenary sessions and six workshops, the participants were discussing chemical, manufacturing, and control testing (CMC), as well as non-clinical and clinical aspects of exploratory clinical trial applications (CTA). In the opening session Thomas Sudhop from BfArM gave a short introduction into current concepts and an overview of regulatory guidance documents focussing on traditional and exploratory phase I trials, such as the EMEA Safety Working Party position paper on microdosing (CPMP/SWP/2599/02), the concept paper for early phase I guidance (CHMP/SWP/91850/2006), and the FDA guidance on exploratory IND studies (<http://www.fda.gov/cder/guidance/7086fnl.pdf>). Walter Janssens from the Belgian Federal Agency for Medicines and Health Products (FAMHP) presented the national approach and guidance document on exploratory CTA concepts in Belgium. He also addressed the non-clinical prerequisites for exploratory clinical trials based on either active or inactive doses, the latter being seen as an extended microdosing concept.

Alfred P. Tonelli (Johnson & Johnson) presented key issues to identify potential exploratory phase I projects with the focus on strategy, chemistry, toxicology, and clinical markers to afford early “go/no-go” decisions. He pointed out the advantages for time and money resources but also potential difficulties with the new concepts. Bernard LeBlanc (Pfizer) reported about own experiences in microdosing and exploratory studies focussing on pharmacokinetic (PK) issues. Although the studies were investigating only very specific questions he demonstrated that these concepts were able to select drug candidates for further development faster and on the basis of fewer resources than is usual in traditional phase I concepts.

Similar experiences were presented by William T. Robinson (Novartis). He reported that even multiple dose trials were successfully conducted in exploratory settings to answer very specific pharmacodynamic questions crucial for the further development process. James McLeod (Schering-Plough) focussed on microdose and PET studies. After a short introduction into the analytical issues and methods such as accelerated mass spectrometry (AMS), he demonstrated that microdosing can be successfully applied to investigate PK, bioavailability, drug targeting, and receptor occupancy. All speakers pointed out that exploratory CTA and microdosing could be very promising in answering specific (pharmacokinetic) questions. Exploratory CTAs with their reduced non-clinical package also offer the opportunity of an early direct comparison of drug candidates. The opening session was followed by workshops discussing issues of CMC, clinical aspects, non-clinical requirements for microdosing and exploratory CTA.

### **CMC Requirements and Issues**

The current legal concepts for any clinical trial application require that production processes conform to cGMP. For the industry this is the critical point in the supply of exploratory drugs for clinical trials. Therefore, it is important for them to develop more flexible CMC conditions in exploratory settings. The regulatory representatives at the meeting pointed to the standard requirements as well as the exceptions in the current guideline for the chemical and pharmaceutical quality documentation of investigational medicinal products in clinical trials (CHMP/QWP/185401/2004). The current legal situation does not permit a general deviation from the GMP approach. However, a more flexible interpretation of the guideline requirements should be admitted for exploratory settings. All deviations should be discussed and justified in the CTA. In cases of major deviations, applicants are advised to consult the competent authority prior to CTA submission. It should be understood that regulatory authorities are also interested in fast and uncomplicated processing. Decisions on modified CMC requirements will be taken on a case-by-case basis. Concerning the nature of the investigational medicinal product, there was consensus that GMP-like material could be sufficient for small molecules, while there was a tendency to insist on full GMP-compliance in the case of material for biological products.

### **Non-clinical Requirements and Issues for Exploratory CTA**

The design of non-clinical toxicity studies in support of an exploratory CTA approach was intensively discussed. Different concepts were proposed to minimise the resources required for early phase I studies such as compound and number of animals. Rather than prescribing a fixed number of animals per group, the number chosen should be such that relevant study results are likely to be obtained. The choice should be supported by all available information about the compound or class of compounds. There was consensus that more rodents than non-rodents should be exposed. It was also discussed whether a shorter duration, e.g. 3-4 days instead of 14 days, might be suitable for short-term exploratory clinical trials. Most delegates tended to abide by the 14-day studies to increase the likelihood of toxicity manifestations. It was controversially discussed whether a dose-escalation study in non-rodents may replace the standard 14-day non-rodent study. Repeated dose studies in rodents usually work with 3-4 dose groups, while in non-rodents one group might be sufficient if no toxicity other than pharmacological effects are anticipated.

Different approaches were considered for the selection of an appropriate start dose in humans. The selection process should be based on data from the entire development program including

information derived from PK/PD analysis. It was agreed that for novel targets also the MABEL concept should be used in addition to the conventional NOAEL or NOAEL/HED concepts. If the two approaches lead to different start doses, the lower one should be taken. The exploratory CTA approach permits dosing in the lower range of the pharmacologically active doses. For higher pharmacodynamically active doses careful dose escalation is needed based on PK monitoring/verification and adjusted PK/PD extrapolations. However, neither MTD nor clinical tolerability itself is within the scope of exploratory clinical trials. This should be taken into account when selecting an appropriate dose range for exploratory CTAs.

### **Non-Clinical Requirements and Issues for Microdosing**

While the exploratory CTA concept deals with low but pharmacologically active doses, microdosing focuses on the pharmacologically inactive dose ranges (1/100 of anticipated pharmacologically active dose). The need for genotoxicity testing as required by the CPMP position paper was intensively discussed. The industry proposed to use the TTC concept (threshold of toxicological concerns) in view of the short time nature of the experiments. When this concept is used genotoxicity testing should not be required for a single microdose ( $\leq 100 \mu\text{g}$ ). There were controversial discussions about a threshold dose of  $< 10 \mu\text{g}$  for multiple dosing on up to 14 days. The Belgian guidance requires at least AMES testing, or an appropriate alternative, for multiple microdoses. There was agreement that up to five doses would be acceptable. There was consensus that i.v. toxicity testing covers oral administration in healthy subjects and vice versa as long as sufficient multiples of exposure can be ensured.

### **Clinical Requirement and Issues**

Even in traditional phase I studies the risk-benefit assessment is crucial since no direct individual medical benefit for healthy trial subjects can be anticipated. In exploratory CTAs the reduced preclinical package may require an even more intensive safety monitoring to balance the risk-benefit ratio. The sponsor should discuss why no additional risks are expected compared to a traditional first-in-human phase I study. Therefore, the rationale for the choice of an exploratory CTA should be scientifically and ethically justified in the trial protocol.

Single dose studies were considered safe as long as no steep dose-response curves are expected. No general recommendations can be given for multiple dose trials. For dose escalation 3-5 dose steps were considered sufficient. Decision on the next dose step should usually be based on online PK data. (For selection of dose see Non-clinical Issues.) As for the trial population, the opinion was that healthy volunteers rather than diseased patients should be enrolled into an

exploratory clinical trial. However, the exploratory concept should not generally exclude patients, especially not in the case of serious diseases for which no satisfactory therapeutic options are available. Populations that are not able to give informed consent, such as children, should be definitely excluded. The role of patients with minimal disease and stable conditions was discussed controversially. The use of several NCEs in one trial is covered by the Clinical Trial Directive and therefore also possible in exploratory CTAs.

## **Conclusion**

The international expert meeting was a platform for all stakeholders to identify and discuss the problems involved in exploratory CTAs. All participants agreed that this kind of clinical trials is needed to speed up translational processes for certain compounds. It was generally accepted that exploratory concepts are appropriate for small molecules (NCEs) rather than for biological products. The choice of exploratory clinical trial designs should be scientifically justified and integrated into the overall product development concept. The Belgian guidance was considered a good and pragmatic concept. Also the ongoing review of the ICH M3(M) non-clinical safety guidance deals with exploratory trial concepts including microdosing. Therefore, the German competent authorities are not considering to develop their own national guidance. However, when the review of ICH M3(M) guidance is finalised it may well be important to discuss whether additional European guidance is needed, e.g. for those clinical, CMC, and regional non-clinical requirements that are not covered by the ICH M3(M) guidance. Especially the regulatory requirement of a strict GMP compliant manufacturing process, as laid down in Article 13 of Directive 2001/20, should be discussed with a view to a stepwise, development-adapted GMP process. In the meantime the conduct of exploratory clinical trials in Germany is possible on a case-by-case basis. Applicants are recommended to seek scientific advice prior to the submission of an exploratory CTA.

\*List of chairs (in alphabetical order):

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