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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A CHMP GUIDELINE ON THE NON-CLINICAL REQUIREMENTS TO SUPPORT EARLY PHASE I CLINICAL TRIALS WITH PHARMACEUTICAL COMPOUNDS

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1. INTRODUCTION

The requirements for non-clinical safety studies to support the conduct of human clinical trials for pharmaceuticals were largely addressed by the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) Topic M3: Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95). This guidance aimed to facilitate the timely conduct of clinical trials and reduce the unnecessary use of animals and other resources. This was designed to promote safe and ethical development and availability of new pharmaceuticals.

The development of a pharmaceutical is a stepwise process involving an evaluation of both the animal and human safety information. The overall goals of the non-clinical safety evaluation include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. This information is important for the estimation of an initial safe starting dose for the human trials and for the identification of parameters for clinical monitoring for potential adverse effects. The non-clinical safety studies at any stage should be adequate to characterise potential adverse effects under the conditions of the proposed clinical trial.

It is recognised that significant advances in harmonisation of the timing of non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals have already been achieved. However, differences remain in a few areas, including toxicity studies to support first entry into man. In 2003, the CPMP released a position paper on non-clinical studies to support clinical trials with a single microdose (CPMP/SWP/2599/02). More recently, the FDA have released guidance on conducting clinical trials under an exploratory IND.

2. PROBLEM STATEMENT

The rapid expansion of new potential therapeutic targets realised through biomedical research has a great potential health benefit, but progress in achieving these benefits is impacted by the limited overall capacity to explore each target. In order to reduce the time and resources expended on candidate pharmaceutical products, new tools are needed to distinguish earlier in the drug development process those candidates that hold promise from those that do not. Existing regulations do allow some flexibility in the amount of data that need to be submitted with a Clinical Trials Application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. However, additional guidance would be useful to describe early Phase 1 exploratory approaches that maintain the required human subject protection, while allowing sponsors to move ahead more efficiently with the development of promising candidates.

This guidance is intended to facilitate a directed exploration of the physiology, pharmacology and/or pharmacokinetics of one or more candidate pharmaceutical products in humans. Such studies could optimise the selection of safer, more effective therapeutics for further development and ultimately make them available to patients sooner.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Typically, during pharmaceutical development, large numbers of molecules are generated with the goal of identifying the most promising candidates for further development. These molecules are often structurally related, but can differ in important ways. Promising candidates are often selected using in vitro testing models that usually require only small amounts of the drug.

Candidates that are not rejected during these early tests are prepared in greater quantities for in vivo animal testing for efficacy and safety. Commonly, a single or few candidate(s) is/are selected for a Clinical Trial Application and introduction into human subjects, initially healthy volunteers in most cases.

Before the human studies can commence in the EU, a Clinical Trial Application must be submitted to the relevant Competent Authority containing, among other things, information on any risks anticipated based on the results of pharmacologic and toxicological data collected during studies of the drug in animals (ICH M3). These basic safety tests are designed to permit the selection of a safe starting dose for humans, to gain an understanding of which organs may be the targets of toxicity, to estimate the

margin of safety between a clinical and a toxic dose, and to predict pharmacokinetic and pharmacodynamic parameters. These early tests are usually resource intensive, requiring significant investment in product synthesis, animal use, laboratory analyses, and time.

Many resources are invested in, and thus wasted on, candidate products that subsequently are found to have unacceptable profiles when evaluated in humans. It is known that less than 10% percent of new molecular entities (NME) progress beyond the investigational stage to submission of a marketing authorisation application.

The CHMP Safety Working Party (SWP) have discussed a revised toxicology package designed to support early clinical investigations in man. The objectives of these clinical studies would differ from the more classical phase I approach, in that they would investigate low doses and would not be designed to investigate tolerability. Instead, the trial would generate pharmacokinetic (PK)-related or pharmacodynamic (PD)-related data, possibly based on a sensitive biomarker of efficacy. These data could then be used for early decision making on whether to progress a particular compound or work on a potential therapeutic target. The clinical studies would require the administration of one or two doses that would achieve an exposure in the predicted pharmacological range, but which would be below the tolerability range. The initial dose administered to man would be very low, and the dose would be slowly escalated (using real time pharmacokinetic monitoring) until a predefined maximum exposure was achieved. Using this approach, a good understanding of dose exposure relationship in man could be obtained.

In order to maintain international harmonisation, the revised toxicology package will follow the general principles laid down by the ICH M3 guideline. However, the dose levels used in the non-clinical studies could be lower than usual, as they are only required to support the low intended clinical doses. Human safety will not be compromised by the revised package.

4. RECOMMENDATION

The CHMP SWP recommend to draft a guidance document detailing what non-clinical data are required to be included in a Clinical Trials Application for an Early Phase I study in humans. This guideline should allow for a flexibility of approaches, including those outlined in the EU Microdose guideline or the FDA exploratory IND guideline.

5. PROPOSED TIMETABLE

It is anticipated that a draft CHMP Guideline may be available 12 months after adoption of the Concept Paper to be later released for 6 months for external consultation and finalised within 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will only involve the SWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

The development of this Guideline is anticipated to standardise and facilitate the requirements for Early Phase I studies in humans for Clinical Trial Applications made to Competent Authorities.

8. INTERESTED PARTIES

Pharmaceutical Industry and individual National Competent Authorities involved in clinical trial approval.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical trials for Pharmaceuticals (CPMP/ICH/286/95).
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

CPMP Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose (CPMP/SWP/2599/02)
FDA Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies, 2006