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Three Major Factors to Consider when Moving from Preclinical to Clinical Development

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Several aspects must be considered when planning the preclinical development program of a novel investigational compound. Among them are the nature of the target, the mode of action, the choice of suitable animal models, the identification of pharmacologically effective doses levels, the design of preclinical proof-of-concept studies, and the adequate design of toxicology studies in at least two animal species that are predictive for the situation in humans, et cetera. But there are even more important aspects that are related to regulatory affairs issues. The early elaboration of a good integrated project plan offers the opportunity to identify the critical path, and an efficient project management can streamline the developmental period. This paper focusses on three major factors that should be considered to manage a smooth transition from pre-clinical to clinical research with intent to commence the clinical development program in good time and have it adequately designed to make sure the planning targets will be met.

Extent of the non-clinical program and timely completion of essential documents

A non-clinical program should be sufficient to support the conduct of clinical studies in humans. As part of this process, ensure that results are documented and presented in accordance with the requirements of IMPD.

> *A good central project coordination should be considered throughout the transition from non-clinical to clinical research*

The IMPD is an essential document that will need to be submitted to the regulatory authority BfArM at the time when the application for the first study in humans is filed. If non-clinical reports originate from different institutions, it may be useful to centrally keep track on the contents, quality, technical preparation and compilation of the documents. In other words, good central coordination across individual investigations, subprocesses, and documents should be considered during the transition from non-clinical to clinical research.

Among other things, regulatory affairs aspects and scientific/medical writing skills with regard to the production of the essential documents are important. If the investigational compound has a novel mechanism of action, it is recommended to run through a scientific advice process at the regulatory authority before launching a clinical development program. Experience has shown that this may streamline the later approval procedure of the First-in-Human (FIH) trial.

General considerations regarding the clinical development program

Identify your target product profile at an early point in time and make sure the clinical development program is appropriately designed to meet the development goals. It is important, however, not to stick to static project paradigms throughout the program, but to reevaluate them on a regular basis based on the latest research results. A possible change in the regulatory and competitive environment should also be taken into account.

For biotechnology firms and venture capital-driven companies there is usually some focus on the next milestone that needs to be reached, and the early clinical development program should be adequately tailored to achieve that goal. "Go/No-Go criteria" should be defined. The identification of the critical path in project management is always crucial to minimize the development time and related cost.

As always, scientific aspects related to the mechanism of action, disease-specific issues, aspects related to market size and pricing as well as pragmatic considerations (e.g., feasibility to conduct clinical trials in the target patient population) should be taken into account when planning the clinical development program. Even though those aspects may have limited impact on the design elements of the FIH trial, it is important to set up the clinical development plan as a whole at an early stage because there may be important issues that could interfere with some design aspects of the FIH trial (e.g., investigation of surrogate parameters as secondary objectives).

As a matter of course, the project team must be adequately staffed during all project phases with a focus on those items that are of particular importance at a certain stage.

Make use of external expertise, e.g., with regard to scientific advice, interpretation of research results, regulatory affairs issues, clinical project planning or writing of study protocols or research reports. Get in contact with an experienced contract research organization (CRO) at an early time. Apart from managing a clinical study, the ideal CRO provides valuable scientific input within the interests of the sponsor throughout the entire clinical development process. The selection of the right CRO is therefore of paramount importance.

> *Make us of external expertise*

Special considerations when planning the First-in-Human (FIH) trial

In general, FIH trials are conducted on healthy subjects. However, in certain indications, such as oncology, patients are usually enrolled in the phase-I program. Some special considerations apply to those cases. The following general recommendations apply to the standard approach, but depending on the nature of the compound, its mechanism of action, and the galenical formation, variations of the following design features are possible:

A FIH study typically follows a single ascending dose-group design (escalating single doses) with sequential subgroups of healthy subjects. There are commonly 6-9 dose steps. A placebo control is regarded as state of the art. A common ratio of active compound to placebo is 3:1.

The primary objective of the ascending single-dose study is the identification of the highest dose that is safe and well-tolerated after single dosing (or confirmation of safety and tolerability of all doses investigated, if even the highest tested dose is well-tolerated). The assessment of the systemic exposure (pharmacokinetics) of the investigational compound and relevant metabolites is also important. This should be done as a so-called online-pharmacokinetic evaluation during the course of the study to ensure there is an adequate exposure control prior to proceeding to the next dose step.

> *Make sure there is an adequate exposure control prior to proceeding to the next dose step*

Data on pharmacodynamics or biomarkers are collected, if possible. The maximum recommended safe starting dose must be calculated based on the animal toxicology study results obtained in two appropriate species taking into consideration any additional risk factors. In this context, an important issue is determining the "Human Equivalent Dose" (HED) to the "No Observed Adverse Effect Level" (NOAEL) obtained in animal toxicology studies via normalization to body surface area. A summarizing table with a simplified process chart is given below. Scaling factors are given in pertinent guidance documents. For every early development program, a concept of risk mitigation should be developed.

> *It is therefore useful, or even mandatory, to consult an expert for early clinical development*

In light of the earlier statement, only a general outline of the study design can be given here. Considering the special peculiarities of the investigational medicinal product, the specific elements and requirements for the clinical study protocol will vary.

Therefore, consulting an expert in early clinical development is essential to smoothen the transition from pre-clinical to clinical research and to design the FIH trial properly to lay a solid foundation for future clinical trials in patients, ensuring that development goals are met promptly and efficiently.

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FIH-Studies: Estimating the Maximum Safe Starting Dose in a Nutshell

(acc. to FDA Guidance for Industry)

- Determine NOAELs [mg/kg] in toxicity studies in appropriate species,
- Convert each animal NOAEL to Human Equivalent Dose (HED) based on body surface area,
- Select lowest HED, or HED from most appropriate species,
- Choose safety factor* normally “10”,
- Divide HED by that factor,
  -> Maximum Recommended Starting Dose (MRSD)
- Consider lowering the MRSD based on Pharmacologically Active Dose (PAD)
  (converted to HED, if it is from an in vivo study)

*When should an increased safety factor be applied?

- Steep dose-response curve
- Variable bioavailability
- Severe toxicities
- Non-linear pharmacokinetics
- Nonmonitorable toxicity
- Inadequate dose-response data
- Unexplained mortality in animal studies
- Novel targets
- Toxicities without advance warning
- Animal models with limited relevance
- Irreversible toxicity

Key Takeaways from this Whitepaper

- Make sure the extent of the non-clinical program is appropriate from a regulatory perspective
- Ensure good central project coordination
- Request scientific advice from a regulatory agency
- Identify the target product profile at an early stage
- Assure that the clinical development program meets the development objectives
- It is important to observe all regulatory requirements when planning the FIH study, for example, when planning the starting dose, and select design elements that will provide the greatest benefit to the research program in the future
- Engage external expertise at an early stage; more specifically, contact an experienced CRO, which can offer solutions at every stage of clinical development

About the Author

Dr. Timmer received his board accreditation in clinical pharmacology in 1999 after residencies in prestigious institutions including the department of clinical pharmacology at the University Hospital Mannheim.

For the next years, he served as project leader of early clinical development in the pharma industry, where he spearheaded the clinical development of several compounds in their early development stages. In this role he was deeply involved in the planning, organization, performance,
analysis, and reporting of some 40 clinical studies, including preparation of expert reports for submission and representation to the US FDA. Dr. Timmer gained further expertise by serving as clinical trial leader and project manager, mainly in charge of the conduct of phase II-IV clinical studies.

After this, in 2006 Dr. Timmer changed to the CRO side and since than served as CEO and Chief Medical Director, supervising the conduct of phase I (First in Human) and phase IIa (proof-of-concept) in-house trials performed in healthy subjects and patients. In this context, he reviewed numerous non-clinical data and contents of IMPDs, provided scientific advice relating to pharmacological and toxicological data, including calculation of the safe starting dose.

Moreover, he was entrusted with the interpretation of study results in collaboration with DMPK specialists and biostatisticians, and prepared and reviewed numerous study protocols and clinical trial reports.

To date, Dr. Timmer has served as principal investigator for more than 200 clinical trials and has authored more than 30 peer-reviewed papers and lectures in a wide range of scientific disciplines and therapeutic areas, which include clinical pharmacology, respiratory, allergy, diabetology, gastroenterology,
and cardiology.