Understanding the Challenges in Designing and Executing Clinical Trials for Screening Tests

Clinical trials for screening tests of a drug candidate take place at the very early clinical development, i.e. Phase I clinical study. The aim of such studies is to assess drug candidate safety, its actual fate in human body after administration (PK/PD data, metabolite identification, mechanism of elimination and excretion, etc), its tolerance threshold (dose escalating) and its adverse effects. Other items can be studied too, according to the specific part of the studies, *i.e.* food effect, impact of renal or hepatic impairment.

To perform these studies, it is thus necessary to provide an informed consent form, a study protocol, a safety plan and an SOP on the administration of it. It is also required to present CMC (chemistry, manufacturing and control) information, and PK/PD, toxicology, mechanism of action and pharmacology data.

All of that makes Phase I clinical trials crucial to the drug development process; designing and executing such clinical studies needs much preparation and planning.

Design of a Phase I study is a key step as it can later allow saving time and preventing delays. It requires taking into consideration numerous aspects and parameters, such as the dose to be delivered, number of volunteers needed, study design which will fit the objectives of the trial, but also CRO and principal investigator choice, local regulatory rules and their updates... The final objective of this step is to design an effective clinical trial protocol in the course of which humans will be exposed to a new drug substance for the very first time.

Because of incidents of unpredicted human toxicity in recent years, safety issues are dominant when identifying a clinical drug candidate. To plan human studies and to minimise risk, prerequisites are to make plausible predictions about the fate of the drug candidate in the human body after administration, to characterise its metabolic transformations in the body and identify potential toxic metabolites. On top of that, proper risk management procedures should be put in place to allow the prediction and prevention of possible side-effects, to deal with serious adverse events (SAEs) (medical emergencies, including 24/7 access to a physician). Moreover, the conditions (or "stopping rules") under which the trial must be stopped have to be defined. Lastly, a volunteer examination plan should also be defined based upon trial objectives, and expected fate and activity of the drug candidate.

The trials are usually performed in healthy volunteers, or in patients who are not expected to benefit from the drug candidate. In a Phase I clinical study, the drug candidate is mainly compared to a placebo control. However, this leads to some concerns when the drug candidate is intended for life-threatening diseases or in oncology, as it may be not ethical to use a placebo control in such cases. Therefore, a reference medicine product can be used too, but then it is necessary to choose a good reference product.

Trials are traditionally conducted in the logical sequence of single ascending dose, multiple ascending dose, examination of preliminary effect of food on exposure, and potential drug/drug interaction, but there is now an increasing trend to include all of these "sub-studies" in the first trial to generate the maximum amount of data in the shortest time. Therefore, the first clinical study often consists of a multiple study design (including single dose/multiple dose escalation study, ADME study, BA/BE study, food effect study, *etc.*) making study global design more complicated to define.

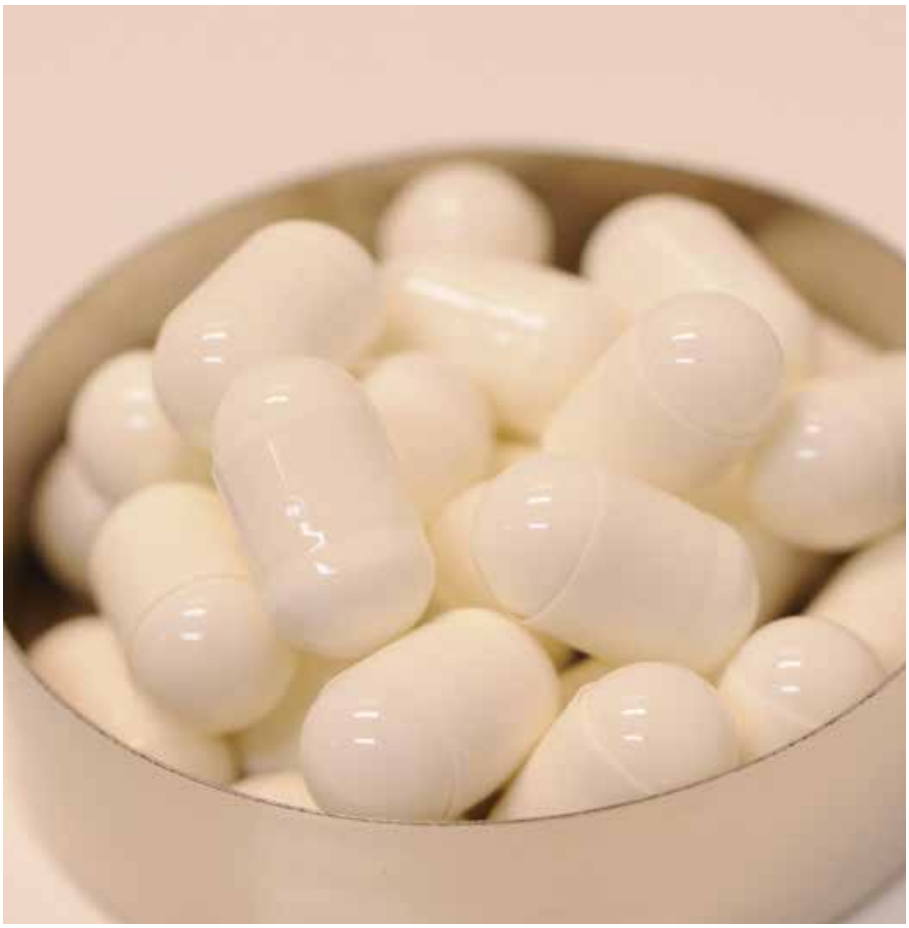
Then, one of the main challenges in clinical study design is to define the correct starting dose of the drug. This is done based on the "no observed adverse events" level (NOAEL) and on the selection of the human equivalent dose of the most appropriate pre-clinical animal model, applying a safety factor (at least 10-fold) to get the maximum recommended starting dose (MRSD), and adjusting the MRSD to the predicted drug action.

Dose escalation requirements must also be determined. Usually, a study should start with a single ascending dose design, *i.e.* different groups of subjects receive subsequentially higher doses but each subject will only get the drug once. Later, this can be changed to a multiple ascending dose design, where the same subject will receive a specific dose several times.

When required dosage strengths are defined, they have to be manufactured so that the right quantity of the investigational medicine product (IMP) arrives at the right place, i.e. the investigator sites, at the right time, i.e. before the clinical study starts to allow final setting up before first patient administration. To do that, selection of the most suitable contract development and manufacturing organisation (CDMO) is key to success! It has to be able to quickly manage different IMP and comparator formulations and process

development, including analytical methods development and validation, and stability data, with small active substance quantities, and to adhere to good manufacturing practices (GMPs) to produce batches intended to be used for clinical trials. **Synerlab Développement** (Orléans, France) is a CDMO with a proven track-record of successfully supporting sponsors with flexible supplies of IMPs for early development programmes and of optimising *in vitro* performance of drug products.

Executing a Phase I clinical study is at least as challenging as designing it, because everything rarely goes as planned! There are a number of potential unexpected situations, and staff conducting trials must be prepared for that. In Phase I research, it is necessary to always be prepared to expect the unexpected, as this is the first time a product is administered to humans. Volunteers follow-up is thus very intensive and strict, and requires strong medical teams. However, clinical trials execution has to be efficient.



Once a trial protocol has been activated, the recruitment of patients requires a significant amount of time for several reasons as they have to fit the selection criteria of the study. When patient recruitment is difficult, during oncology trials for example, the trial is delayed, sometimes by years, until the number of patients required by the study protocol can be enrolled. It can also be difficult to keep patients engaged during the study because patients may reside far from study centres, and have to leave the care of their regular doctor and receive services from unfamiliar providers, for example.

During the execution of the study, the study protocol can be amended or even broken off for several reasons: safety alert identified during the safety meeting that takes place once the first dose is administered and between dosing; occurrence of an SAE or of some unexpected findings, such as longer than expected half-life, production of a significant active metabolite, *etc*.

Therefore, to manage recruitment fluctuation and dosing switch, and minimise active substance waste, the CDMO has to be flexible and reactive in terms of manufacturing schedules to avoid any out of stock issues at the CRO. The manufacturing process has to be amenable both regarding batch size and dosage strengths range. At **Synerlab Développement**, formulation and process are designed early to offer such adjustment. **Synerlab Développement** offers state-of-the-art facilities to support an adequate supply chain with flexibility and reactivity in terms of schedules, integrating services for the development, manufacturing and testing of solid and liquid dosage forms.

Lastly, when volunteers' recruitment takes longer than expected, it is also necessary to generate a rapid update of IMP stability data supporting shelf-life extension, or to manufacture a new IMP batch to resupply the study with additional therapeutic units in order to avoid study break. This point has to be anticipated jointly by the sponsor and the CRO with the CDMO.

Phase I clinical trials are crucial for the future development of a drug, but also, for many reasons, challenging during both their design and their execution. Therefore, it is absolutely necessary for the sponsor to work with an expert CRO and an expert CDMO, which is why **Synerlab Développement** always reinforces the importance of implementing efficient interactions and continuous collaboration between the study sponsor, the CRO and its multidisciplinary scientific team of pharmaceutical development experts.

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